Fatigue and Major Depressive Disorder

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A Systematic Review of Etiology, Maintenance, Diagnosis and Treatment

Masterthesis
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Date: 23.10.2016

Abstract

Background and Objectives. Fatigue belongs to the most common experiences of human life but it often co-occurs with psychopathology as well, especially in mood disorders such as Major Depressive Disorder (MDD). Although, fatigue is often reported as symptom in MDD, rated by patients as restricting and harming, the presumably interdependent relation between both syndromes still remains unclear. This review seeks to deliver a comprehensive overview about the relationship between fatigue and MDD regarding etiological processes, maintaining factors, relevance of diagnosis criteria and treatment concepts.

Methods. A systematic literature review was conducted in 2016. The authors used differentiated search terms to bear reference to the multidimensionality of fatigue combined with the key indexing term Major Depressive Disorder and distinct search terms to answer four research questions with regard to etiology, maintenance, diagnosis and treatment.

Results. In total, 45 studies were included in the review, with various study designs, study populations and sample sizes. Firstly, a strong relationship between fatigue and MDD was found indicating that fatigue serves as a predictor of MDD and its persistence, whereby related pathophysiological processes are involved. Secondly, fatigue may reinforce the maintenance of MDD by building on a vicious cycle and enhanced by subsequent factors, due to side effects of medication or sleep disturbances. Thirdly, according to the DSM-IV fatigue-related symptoms did not fulfil alone the requirements for an MDD diagnosis, however, the overlap of symptoms of fatigue and MDD cannot be ignored. Fourthly, fatigue-related symptoms were treated with antidepressants differing in effectiveness. In addition, CBT and complementary strategies showed promising treatment results for the improvement of fatigue.

Conclusion. The relationship between fatigue and MDD is a complex and many-layered one influenced by various processes. Further, the overlap of symptoms and etiological processes, and maintaining factors of fatigue in MDD may encourage the discussion about the relevance of fatigue-related symptoms in the DSM-IV. At last, pharmacological treatment needs to be symptom-specific and requires the awareness for impeding side effects of medication.

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1. Introduction

1.1 Relevance

It is commonly known that patients suffering from chronic physical diseases like cancer, rheumatoid arthritis, fibromyalgia, anemia and multiple sclerosis also show increased symptomatology of fatigue (Aaronson et al., 1999; Agnihotri, 2007; Shapiro, 1998; Zautra, Fasman, Parish & Davis, 2007;). Not only restricts fatigue these chronic patients in their daily functioning, especially social activities or work life, it also has negative impact on their quality of life in general and can facilitate the risk for other physical or mental diseases (Tkachenko et al., 2014). Unfortunately, there is only scattered empirical information known over the relation of fatigue to mental disorders, for example depression, and, an integrated overview over empirical research considering this relation is missing. Considering the high prevalence of both syndromes and the associated serious constraints for the individual but also looking upon economic and financial costs for society (Bosmans et al., 2010) more information about this relation is needed. Gathering current knowledge about the relation between fatigue and depression could give valuable insights in etiology, diagnosis and treatment of both syndromes. Therefore, this literature review will systematically examine empirical research assessing the relation between fatigue and depression. In particular, this review will investigate causative and maintaining factors of fatigue in major depression disorder and fatigue as (residual) symptom in depression. Further, the relevance of fatigue-related symptoms in the diagnosis criteria of major depression according to the DSM IV for a diagnosis of major depression will be reviewed and, lastly, whether and to what extent fatigue during depression can be or is successfully treated with pharmacological therapy and/or psychotherapy and/or complementary treatment strategies.

1.2 Major Depressive Disorder (MDD)

Major depression disorder (MDD) is a commonly occurring and often recurrent mental disorder and affects approximately 350 million people worldwide (WHO, 2016). For example, in the Netherlands the authors of the NEMESIS-2 study found prevalence rates of 4.1% for men and 6.3% for women (de Graaf, Ten Have, van Gool, & van Dorsselaer, 2012). Further, depression is one of the main causes of disease-related disability worldwide (Busch, Maske, Ryl, Schlack, & Hapke, 2013) and comes along with serious health constraints for the individual like depressive moods, lack of interest in activities and lack of motivation. In addition, depressive patients suffer from a significant increase or decrease in weight or appetite, sleep problems (insomnia or hypersomnia), psychomotoric inhibition, tiredness or lack of energy. On a cognitive level a diminishing ability to think or concentrate and indecisiveness may arise (van der Molen, Perreijn, & van den Hout, 2007). Hereby, it should be noted that tiredness and lack of energy are related symptoms to fatigue and difficulty in concentration is also a common symptom in fatigue (Arnold, 2008). Lastly, depressive patients tend to have feelings of worthlessness and guilt which can end up in thoughts of dead or suicide (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000). In addition to these serious constraints and health/mental problems for the affected individual major depression causes concomitant financial costs for society. For example, a study by Bosman et al. (2010) found that the treatment of depression in primary health care in the Netherlands led to an adjusted annual total health care cost of 322 million Euro which represents at least 1% of the total annual health budget in the Netherlands. In addition to it, financial costs probably are higher than estimated due to absence from or poor effectiveness of work (Beck et al., 2014, Kessler et al., 1999, Lerner et al., 2004) and the fact that patients with depression often are not recognized by their general practitioner and therefore are not treated for depression (Cepoiu et al., 2008; Mitchell, Vaze, & Rao, 2009; Piek et al., 2012). Further, research on the treatment of depression indicates that only a small proportion of the

treated patients is able to recover completely from all its symptoms (Fava et al., 2014). Therefore, qualified recognition and appropriate treatment of depression is needed to minimize individual harm and financial and economic costs.

To achieve full remission, it is necessary to address all given (residual) symptoms of major depression during and after the therapy. Residual symptoms in major depressive disorder may be defined as symptoms that persist even after the patient has been determined as fully recovered, according to his/her clinical response to the given treatment (Fava et al., 2014; Karp et al., 2004). Several studies on residual symptoms of major depression illustrate that these can facilitate risk for relapse, recurrence, and chronicity of depression (Boulenger, 2004; Fava, Fabbri, & Sonino, 2002; Papakostas, 2009) and also psychosocial impairments like lack of private and social activity or motivation (Fried & Nesse, 2014; Judd et al., 2000a, 2000b). To the most common (residual) symptoms in major depression belong fatigue (extreme tiredness), sleepiness (hypersomnia) and tiredness (Arnold, 2008; Baldwin & Papakostas, 2006). Therefore, in the following these three related symptoms will be examined more in detail.

1.3 Fatigue, Sleepiness and Tiredness

Fatigue or related symptoms like sleepiness or tiredness belong to the most common human experiences. All of them are highly prevalent in the general population as well as in clinical patients. Prevalence rates of unexplained fatigue in the general and working population range around 20%. For example, a study by Bültmann, Kant, Kasl, Beurskens, & van den Brandt (2002) and Loge, Ekeberg, & Kaasa et al. (1998) reported a prevalence rate for unexplained fatigue of 22% in the Dutch working population and in a Norwegian sample. Another study found a prevalence rate of 18% in a UK sample (Pigeon, Sateia & Ferguson, 2003). Not surprisingly, studies considering clinical samples (patients in primary care) found similar high prevalence rates of (unexplained) fatigue. For example, studies by Kroenke, Wood, Mangelsdorff, Meier, & Powell (1988) and Hossain, Reinish, Kayumov, Bhuiya, &

Shapiro (2003) reported prevalence rates between 20% and 25% in primary care samples. Hereby, it should be noted that fatigue and related symptoms are often underreported by patients and therefore prevalence rates are probably higher than estimated (Shen, Barbera, & Shapiro, 2006). Not only have fatigue, tiredness, and sleepiness for themselves negative influence on the daily functioning of the individual but also they show a high co-morbidity with mental diseases, especially mood and anxiety disorders (Tkachenko et al., 2014), for example depression. In particular, fatigue and tiredness mostly affect between 94 – 97% of MDD patients (Baker, Dorzab, Winokur, & Cadoret, 1971; Maurice-Tison et al., 1998; Tylee, Gastpar, Lépine, & Mendlewicz., 1999). Further, several studies reported rates of sleepiness (hypersomnia) between 10-20% among patients with MDD (Horwath, Johnson, Weissman, & Hornig, 1992; Posternak & Zimmerman, 2002; Reynolds & Kupfer, 1987). However, it should be mentioned that fatigue, sleepiness, and tiredness are related but distinct phenomena (Shen et al., 2006). When it comes to the treatment and diagnosis of depression and related symptoms like fatigue, sleepiness and tiredness, it becomes necessary to differentiate between these symptoms to guarantee appropriate treatment. Therefore, short definitions of them will follow.

Firstly, Shen et al. (p. 2, 2006) define *sleepiness* as "a normal physiological state […] over any given 24 h period"; […] as "one's tendency to fall asleep, also referred as sleep propensity" […] which "is caused by an alteration or imbalance in sleep/wake mechanisms […]". This physiological state is driven by the interactional effect of "sleep homeostasis factors, which increase linearly throughout the day after waking, and circadian factors, which are especially responsible for increasing sleepiness in the early hours of the morning" (Phillips, 2015, p.52 from Borbély, 1982).

Secondly, *tiredness* is defined by Piper (1993, p. 279) as "a universal sensation that is expected to occur normally at certain times of the day or after certain types of activity or exertion that mostly is relieved after rest or sleep".

At last, *fatigue* is defined by Shen et al. (p.8, 2006) as "an overwhelming sense of tiredness, lack of energy and a feeling of exhaustion, associated with impaired physical and/or cognitive functioning […]" But, it needs to be mentioned that fatigue is a complex and multidimensional phenomenon that involves a number of psychosocial and behavioral factors like "rest and sleep history; circadian effects; […] work and home life; individual traits; diet; health, fitness and other individual states; and environmental conditions" (Phillips, 2015, p. 6) which can incorporate sleepiness, and tiredness as its sub-dimensions (Arnold, 2008). Further, Arnold (2008) describes this multidimensionality in terms of three different types of fatigue: physical, cognitive and emotional symptoms. Firstly, physical symptoms of fatigue include "reduced activity, low energy, *tiredness*, decreased physical endurance, increased effort with physical tasks and with overcoming inactivity, general weakness, heaviness, slowness or sluggishness, nonrestorative sleep, and *sleepiness*". Secondly, fatigue can also find expression on a cognitive level. In particular, during fatigue concentration, attention as well as mental endurance may be decreased and thinking processes can be slowed. Thirdly, the emotional dimension of fatigue can be described as a lack of motivation, initiative and interest, and feelings of boredom. These three different types of fatigue will be scrutinized with regard to fatigue-related symptoms in MDD.

1.4 Depression and Fatigue

When studied more closely it becomes obvious that fatigue (and its sub-types) and depression could be conceptual similar to each other. In detail, a study by Jacobsen, Donovan, & Weitzner (2003) states that fatigue can be, as can depression, described as a single symptom (unidimensional) as well as an accumulation of symptoms (multidimensional) or as a clinical syndrome (chronic fatigue syndrome or illness-related fatigue). Further, there is, at least to some extent, overlap in their symptomatology. In detail, the three different types of fatigue (physical, cognitive and emotional) can be found in the diagnosis criteria of MDD according to the DSM-IV (see also Table 1). For example, physical fatigue (e.g. "psycho-

motoric inhibition, tiredness or lack of energy"), mental fatigue (e.g. "diminishing ability to think or concentrate"), and emotional fatigue (e.g. "lack of interest in activities and lack of motivation"). Hence, the intersection in symptomatology makes it difficult to distinguish between both syndromes (Arnold, 2008). Hereby, we note that this review among others will study in how far and why fatigue and its sub-dimensions play a significant role in MDD and its symptoms.

Table 1

Three different types of fatigue (Arnold, 2008) related to the diagnosis criteria of MDD according to the DSM-IV (American Psychiatric Association, 2000)

	Physical fatigue	Mental fatigue	Emotional fatigue
Symptoms of MDD according to DSM IV	"psycho-motoric inhibition, tiredness or lack of energy"	"diminishing ability to think or concentrate"	"lack of interest in activities and lack of motivation"

Although fatigue is one of the main symptoms of MDD, only little research was conducted on the etiology of this symptom, maintaining factors, and its successful treatment. Growing public and scientific interest in (chronic) fatigue and in depressive symptoms beyond the core depressive symptomatology shifted the focus on fatigue in MDD (Demyttenaere, De Fruyt, & Stahl, 2005).

1.4.1 Etiology. Considering the etiology of fatigue and MDD, the results are equivocal and, yet, it is not clear what comes first, fatigue or depression (Leone, 2010). For example, several studies indicate that fatigue is predicted by MDD and belongs to its core symptoms (Kennedy, 2008; Nierenberg et al., 2010; Pae et al., 2007). Nevertheless, other studies also found that fatigue can be a risk for MDD. For instance, a study by Addington, Gallo, Ford, & Eaton (2001) found that the risk among patients with a history of unexplained fatigue for a new-onset MDD was notably increased. Further, a study by Moos & Cronkite (1999) revealed that fatigue is a strong predictor for the progression to a chronic course of depression. In addition, similar results were obtained in two studies regarding excessive sleepiness: Ford & Cooper-Patrick (2001) and Roberts, Shema, Kapla, & Strawbridge (2000) found that excessive sleepiness among non-depressed patients also predicts the subsequent onset of a major depressive episode. Fava, Grandi, & Sonino (1990) pose as an explanation that patients suffering excessive sleepiness or fatigue, particularly unexplained sleepiness or fatigue, may be experiencing prodromal symptoms of MDD and, therefore, are at risk of reoccurring MDD. Another explanation regarding the pathophysiology of fatigue and depression is stated by Gold & Chrousos (2002). They found that the hypo-activity of the core stress components that activate arousal could play a decisive part in developing fatigue symptoms that are characteristic of atypical depression (subtype of MDD). In contrast, a study by Hickie, Kirk, & Martin (1999a) suggests that fatigue seems to have genetic and environmental risk factors that are independent from psychiatric symptoms like depression. In detail, they found that prolonged fatigue states are etiologically distinct from other common presentations of psychological distress, for example depression. These findings go along with the results of a longitudinal study by Hickie, Koschera, Hadzi-Pavlovic, Bennett, & Lloyd (1999b). This study revealed that prolonged fatigue is a persistence diagnosis over time and there is no evidence for an etiological model considering longitudinal patterns of co-morbidity with psychological distress and fatigue as a risk factor. Comparably, with regard to results of

antidepressant treatment studies of MDD it seems that the occurrence of fatigue is associated with several neuronal circuits that may be different from those that influence depressed mood (Arnold, 2008). We go into details in the last section.

1.4.2 Maintenance of MDD by fatigue or related symptoms. In addition to etiological- also maintaining factors may play an essential role in the relation between fatigue and MDD. Factors maintaining depression could be more relevant for treating clinicians. Intriguingly, according to studies by Beekman et al. (2001) and Prince, Harwood, Thomas & Mann (1998) risk factors for the onset and persistence of depression are not necessarily associated. In addition, they argue that once patients developed depressive symptoms risk factors associated with incidence may become less relevant. For example, a study by Gallagher, Savva, Kenny, & Lawlor (2013) found that persistent insomnia, being a predictor of fatigue or tiredness, may serve to perpetuate MDD in elderly patients. Further, a study by Troxel et al. (2012) revealed that persistent insomnia is associated with depression non-remission, thus, maintaining depressive symptomology. Lastly, a hypothesis by Skapinakis, Lewis, & Mavreas (2004) states that "fatigue and depression could also be independent risk factors for each other in a manner that resembles an etiological vicious cycle" (p.334, see Figure 1 below). The authors suggest that the level of physical activity might be an important factor regarding the relation between fatigue and depression. Not only has physical activity preservative effect in depression (Strawbridge et al., 2002), it has also been suggested that physical deconditioning is positively associated with unexplained fatigue (De Lorenzo et al., 1998). Nevertheless, the complexity of this association requires further examination. Considering the results of the aforementioned studies, not only etiological (risk) factors may be relevant to describe the relation between fatigue and MDD, perpetuating factors of fatigue in MDD are needed to be taken into account, as well, especially regarding the treatment of fatigue-related symptoms in MDD.

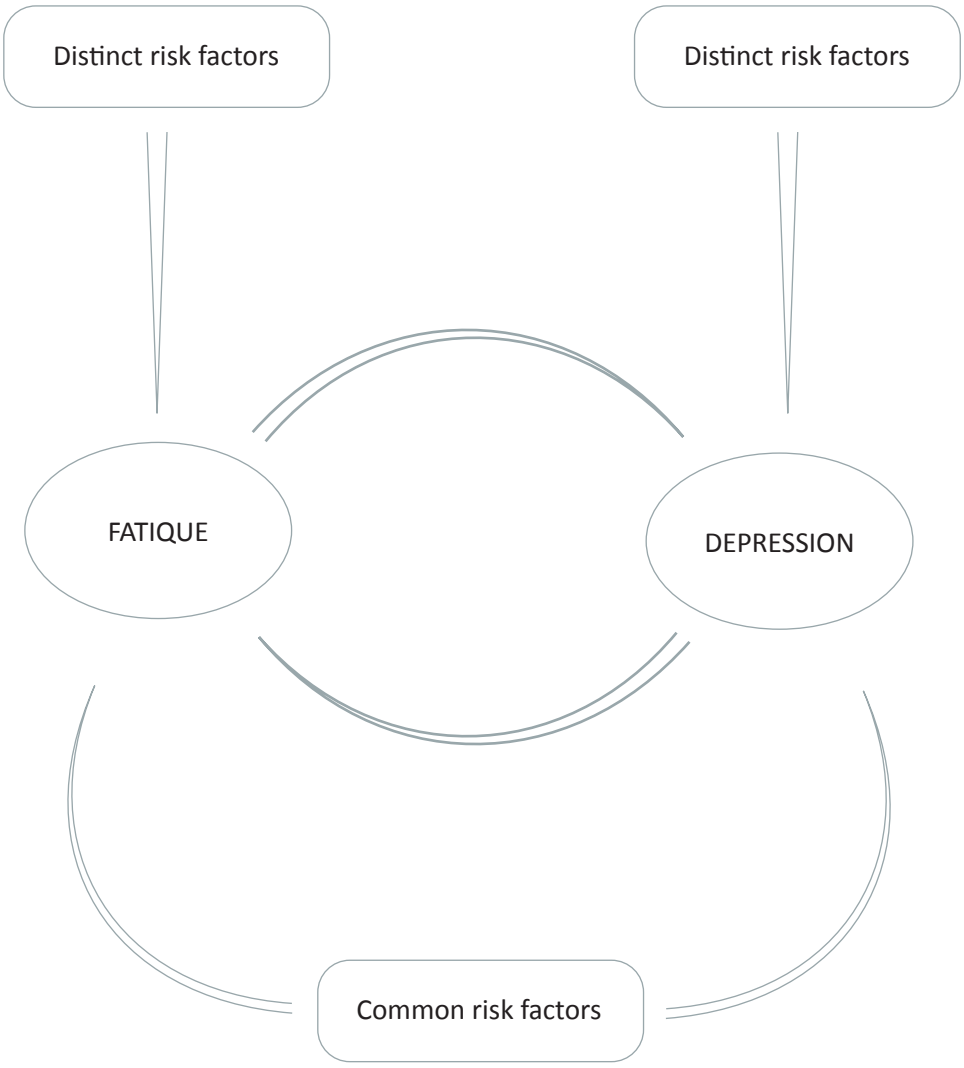

Figure 1. A vicious cycle model of depression and fatigue. In addition to common and distinct risk factors, unexplained fatigue and depression might also cause each other. Adapted from "Temporal relations between unexplained fatigue and depression: longitudinal data from an international study in primary care," by Skapinakis, P., Lewis, G., & Mavreas, V., 2004, *Psychosomatic Medicine*, *66*(3), 330-335.

1.4.3 Treatment of MDD. MDD is commonly treated with antidepressants, psychotherapeutic therapy (e.g. cognitive behavioral therapy, behavioral therapy, cognitive therapy or humanistic existential therapy), or a combination of both (van der Molen, 2007). Fatigue-related symptoms in MDD are mostly treated with selected antidepressants with behavioral activating or wake promoting effects (Doghramji, 2006). Nevertheless, a few studies on fatigue in depression show that patients who were successfully treated with antidepressants to relieve affective symptoms from MDD do not recover from lack of energy and other fatigue-related symptoms after remission (Arnold, 2008; Baldwin & Papakostas, 2006; Demyttenaere et al., 2005; Nierenberg et al., 2010). According to Demyttenaere et al. (2005) fatigue can persist as a residual symptom in MDD after treatment because the neurological effect of antidepressants relieving affective symptoms may have no implication on the neurological pathways related to fatigue. As a consequence, fatigue-related symptoms may persist even after treatment. Therefore, a better understanding of the pathophysiology of fatigue in depression and treatment effect of common used antidepressants on fatigue can give valuable insight in possible pharmacological medication to treat fatigue-related symptoms during depression and after remission.

Additionally, fatigue-related symptoms can also be treated with exercise training or movement therapy (Camacho, Roberts, Lazarus, Kaplan, & Cohen., 1991; Dunn, Trivedi, & O'Neal, 2001; Koch, Kunz, Lykou, & Cruz., 2014), in order to specifically focus on physical and mental fatigue and to encourage physical activity. For example, a study by Wang et al. (2016) found that meditative movement therapy reduces fatigue symptoms in depression by improving sleep quality. Furthermore, a study by Foley & Fleshner (2008) revealed that habitual exercise training improves central fatigue by prolonging the increase in dopamine transmission. Lastly, several studies showed that physical activity has positive influence on depressive symptoms in general, but among others fatigue (Babyak et al., 2000; Martinsen, 1994; McCann & Holmes, 1984).

Given the fact that only scattered information is available over the relation between MDD and fatigue, especially focusing on their mutual influence on etiology, persistence, diagnosis, and treatment of both syndromes, this explorative review seeks to collect and unify scientific knowledge to present a systematic overview over the relation between MDD and fatigue. The relation will be described by one research question subdivided in four sub-questions.

1.5 Research Questions

Accordingly, this study aims to answer the following research question: *How is fatigue related to MDD?* In order to fully answer this question, it will be subdivided in the following sub-questions:

1) In how far do fatigue and MDD influence each other's etiology?

2) In how far does fatigue influence the maintenance of MDD?

3) In how far is fatigue (and its sub-dimensions) relevant for the diagnosis (-criteria) of MDD according to the DSM IV?

4) In how far is fatigue (and its sub-dimensions) treated within common treatment concepts of MDD?

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. Methods

To explore scientific information about the relation between MDD and fatigue (and related terms) and to catalog these terms widespread and latest databases were used. Further, an evidence-based data collection was built by using systematic review methods to guarantee evidence-based research. Main objectives of this literature review were to assess the relationship between MDD and fatigue, and to analyze to what extent the relationship between MDD and fatigue has influence on the etiology, diagnosis criteria of fatigue in MDD and, finally, on the treatment of fatigue symptoms in MDD.

2.1 Literature Search

A comprehensive literature-search of recently published English, German and Dutch literature was conducted by the author, thereby using the following scientific electronic databases: Scopus, Science Direct, PsychInfo, PsychNet, ResearchGate and Google Scholar and PubMed. The search was conducted in the (early) summer period of 2016 (May 2016 – July 2016). The time period of publication was limited to the years 2006 – 2016, thus, including ten years of possibly relevant literature. Further, only scientific articles, systematic and explorative reviews and book chapters written in English, German or Dutch language were included in this study.

2.2 Search Terms

To bear reference to the fact that f*atigue* is a multidimensional phenomenon with several differentiated sub-dimensions the author used additional search terms like *sleepiness* and *tiredness* to gain a comprehensive overview of fatigue and its related sub-dimensions. The key-indexing term used by the author was *Major Depression Disorder* which was combined with search terms referring to fatigue and its multidimensionality like *tiredness* or *sleepiness.* In addition, the search terms *exhaustion* and *lack of energy* were used to cover diagnosis criteria of MDD related to fatigue according to the DSM-IV. Further, to specifically

answer the stated research questions the search terms *etiology* (RQ 1), *persistence* or *maintaining factors* (RQ 2), *diagnosis(-criteria)* (RQ 3), and, *pharmacological treatment*, *psychotherapeutic treatment* or *complementary and/or alternative therapy* (RQ 4) were used in combination with the key-indexing term *major depressive disorder* and the additional search terms *fatigue/tiredness/sleepiness* (see Table 2 in the appendix for specified search strings).

2.3 Literature Screening, Inclusion- and Exclusion-Criteria

The literature search was split up into three phases of screening. The first phase was conducted by searching the above mentioned electronic data bases using the in advance specified search terms, followed by a detailed screening of the titles and additional information (see exclusion criteria below) of possibly relevant studies for exclusion criteria.

The applied exclusion criteria were the following: case reports; literature published beyond the time period 2006 and 2016; literature written in other languages than English, German or Dutch; literature referring to fatigue in relation to somatic disorders; literature related to the chronic fatigue syndrome.

From all studies that were not excluded, the written abstracts were screened, again, for the aforementioned exclusion criteria (phase 2). From the selected studies full articles were obtained. In case that full articles could not be obtained, these studies were excluded from the data pool. Herewith, phase 2 of the screening was completed; followed by the third and last phase of screening. For this purpose, the following inclusion criteria were formulated: literature related to etiology or maintenance or diagnosis or treatment of MDD; literature related to etiology, maintenance or diagnosis or treatment of fatigue/tiredness/sleepiness in MDD; literature referring to the relation between MDD and fatigue and/or its sub-dimensions, studies including study populations and/or samples of patients that a) are diagnosed with MDD and/or b) report symptoms of fatigue and/or tiredness and/or sleepiness. Using the criteria, the in phase 2 obtained articles were screened in order to limit the data pool,

therefore, only containing literature related to the aforementioned subjects. Further, after the selection of relevant studies obtained in phase 2 and 3 their references were checked for trials and studies that the author did not identify through the first and second conduction of search. In addition, hand searches in major journals were conducted and key experts were contacted to gain more studies. Unfortunately, the number of gained studies through hand searches was low (n = 1) and the response rate of key experts was poor (n = 2) for the eligibility of full-texts (not included in data pool).

2.4 Data Extraction

After carefully studying the obtained studies, following data was extracted to identify relevant information: a) identification by name of the authors, publication date, location or institution, source of article as book title or journal and the digital object identifier (DOI) number; b) description of the study, design of the study including used theoretical models, sample characteristics of the population, and sample size and c) main results.

3. Results

All studies (abstracts) were screened on basis of the aforementioned inclusion- and exclusion criteria. Using the above mentioned search terms (and their combinations, see Table 1 in appendix) and inclusion criteria, in total 45 studies were obtained. For information regarding reasons for exclusion see below. To describe the selection process of studies a PRISMA flowchart (Moher, Liberati, Tetzlaff, & Altmann., 2009) was used (see Figure 2).

As presented in Figure 2, twenty-two studies were excluded before checking for full-text eligibility from the data pool based on title or abstract. Mostly, they approached case reports, were published beyond the time period (2006-2016), referred to different issues like the chronic fatigue syndrome or other somatic medical conditions (n = 22). These exclusion-criteria were unapparent while screening headlines or abstracts of the screened studies. Finally, two studies were excluded after full-texts have been obtained because they only approached specific kinds of major depression like atypical or melancholic depression.

The obtained studies differed in their study design. Of all 45 included studies that were included in the final sample, 8 studies were randomized controlled trials (RCTs) or similar, six studies used a cross-sectional design, four studies used a longitudinal design, two studies used a prospective design, four studies used a retrospective design, and one study used an open-label design. Further, one study was an un-blinded intervention study, thirteen studies were (editorial) reviews, four studies were meta-analyses, two studies were book chapters, and one study was journal article or other form of articles (editorial).

In addition, various study populations were used (see Figure 3), including MDD patients without comorbidity (n = 15), MDD patients with medical comorbidity (for differential diagnosis; n = 3), patients with an anxiety disorder without comorbidity (n = 1), psychiatric patients in general (n = 1), patients with a medical disorder (n = 3), and individuals of the general population (adolescents, employees; n = 8).

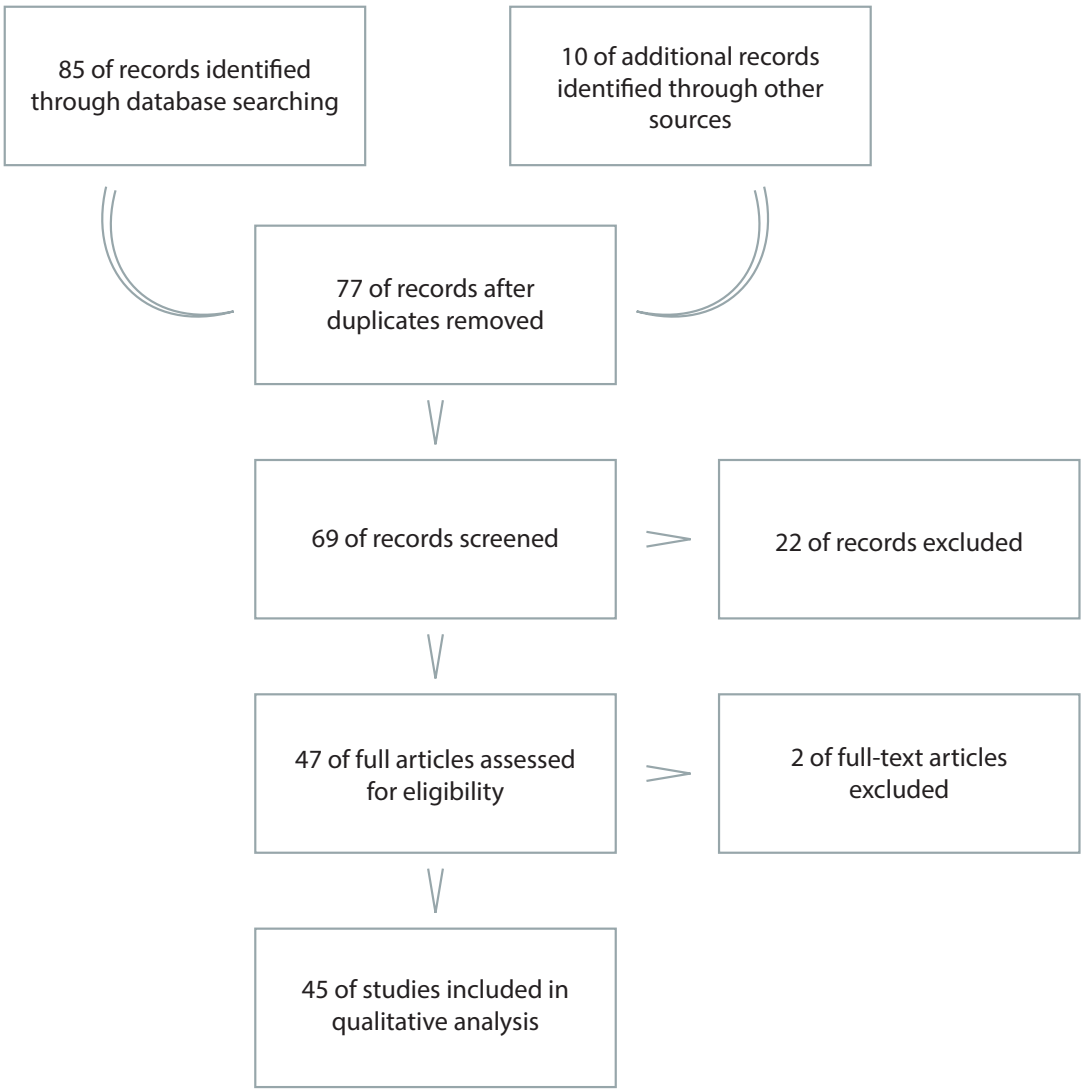

Figure 2. Selection process of studies using the PRISMA flowchart. Adapted from "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," by Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G.,2009, *Annals of internal medicine*, *151*(4), 264-269.

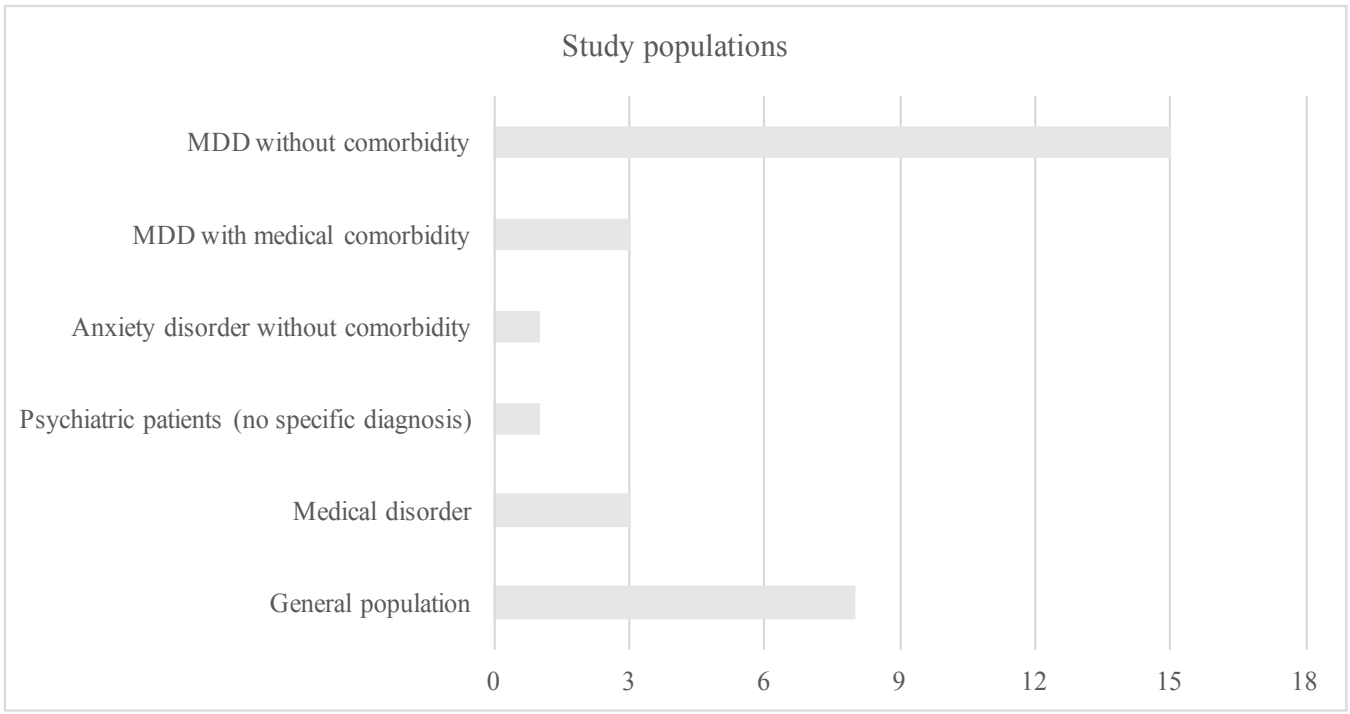

Figure 3. Total numbers of included study populations (n = 31) sorted by psychiatric/medical condition.

Further, the study populations differed in age: nineteen studies assessed an adult population (18 years and older), four studies concentrated on children or adolescents (under 13 or 13-18 years), and five studies examined an elderly population (60 years and older). Hereby, it should be noted that several studies using other age classifications were not outlined because the intersections in age ranges made a clear depiction not possible.

To get an overview over all included studies with additional information like the title of the study, name/s of the author/s, year of publication, location, objectives of the study, study population, sample size, study design, and database from where the study was obtained, see Table 2 in the Appendix.

3.1 Etiology

The first research question was: “In how far do fatigue and MDD influence each other’s etiology?” To answer this first research question, we found 10 studies that examined the reciprocal influence of fatigue and MDD on their etiology. Those results are shortly described in the following section (see also Table 2).

3.1.1 Prediction of fatigue in MDD. There is high agreement amongst researchers that fatigue is one of the core symptoms of MDD (Kennedy, 2008; Nierenberg et al., 2010; Pae et al., 2007) and both are interrelated to some extent (Leone, 2010;). The prediction of fatigue in MDD was examined by three studies.

For example, a study by Chinese researcher (Yu & Lee, 2012) found that elderly Chinese people diagnosed with MDD had a two-times higher risk of experiencing fatigue or fatigue-related symptoms than non-depressed individuals. In this sample more than 70% of the depressed patients were affected by fatigue. Similar results were obtained in studies by Ter Wolbeek, van Doornen, Kavelaars, & Heijnen (2008) and Viner et al. (2008): These studies revealed that (new-onset) fatigue was predicted by depression or depressive symptoms and that persistently fatigued participants had also higher levels of depression. Specifically, the study by Viner et al. (2008) showed that prior symptoms of depression in adolescents predicted 1-year persistence of fatigue and development of new fatigue-related symptoms. Further, ter Wolbeek et al. (2008) found that persistently fatigued participants had higher levels of depression, were less physically active, and slept shorter.

3.1.2 Neurobiology of fatigue in MDD. Next to predicting and persisting factors of fatigue in MDD, neurobiological processes may influence the etiology of fatigue in MDD and vice versa. The underlying neurobiological processes were examined by six studies.

For example, two studies considering the neurobiology of fatigue found that pro-inflammatory, post-inflammatory, and immunological processes could be essential regarding the etiology of fatigue in MDD (Hegerl et al., 2013; Himmerich et al., 2008;). These studies

indicate that fatigue often comes along with bacterial or viral infections and is triggered by pro-inflammatory cytokines such as interleukin (IL)-I α and β, IL-6, and tumour necrosis factor α (TNF-α). Further, it has been shown that vagal afferents, macrophage-like cells in circumventricular organs, and endothelial cells of brain vessels are essential in immune-to-brain communications and in inducing sickness behavior like fatigue. These immunological processes could also play an important role with regard to fatigue-related symptoms in depression because elevated levels of circulating pro-inflammatory cytokines such as TNF-α were also found in depression (Himmerich et al., 2008; Krishnadas & Cavanagh, 2012). These results are supported by systematic review from Fava et al. (2014) considering the clinical relevance of residual fatigue in MDD. They found that residual fatigue may reflect downstream effects of neurotransmitter and cytokine dysregulation that was associated with depression. Supporting a possible relation between depression-related fatigue and immunological processes, a study by Müller & Schwarz (2007) found that pro-inflammatory cytokines (TNF-α, interferon-gamma) reduce the bioavailability of tryptophan, which again is antecedent of serotonin. Two studies by Cowen & Browning (2015) and Krishnadas & Cavanagh (2012) revealed that depletion of tryptophan can induce depression among individuals at risk for depression.

3.1.3 Summary. The conducted literature review revealed diverse results considering the interdependent relationship between fatigue and MDD and their reciprocal influence on their etiology and persistence. Firstly, considering the examined studies, there is no doubt that fatigue and MDD are strongly related and that the risk of comorbidity is high. We found high comorbidity rates of fatigue and MDD in several samples. Secondly, the results revealed that that fatigue is predicted by depression or depressive symptoms, and, that persistent fatigue in MDD affects the level of MDD negatively. Thirdly, the etiology of MDD and fatigue may be traced back to neurobiological processes. We found that the same or related inflammatory and

immunological processes play an essential role in, both, fatigue and MDD resulting in the co-occurrence of them.

Table 2

Etiology of Major Depressive Disorder and fatigue

Authors	Objective	Outcome
Cowen & Browning (2015)	To examine of the serotonin hypothesis and the role of diminished tryptophan availability in triggering depression	Simple biochemical theories that link low levels of serotonin with depressed mood are no longer tenable. Further, depletion of tryptophan may induce depression among patients with risk for MDD
Fava et al. (2014)	To review the clinical relevance of residual fatigue in MDD	Residual fatigue my also reflect downstream effects of neurotransmitter and cytokine dysregulation that is associated with depression
Hegerl et al. (2013)	To conceptualize the neurobiology of fatigue	Inflammatory and immunological processes can induce sickness behavior like fatigue and cause fatigue-related symptoms in MDD
Himmerich et al. (2008)	To investigate associations between a medical history of depression, its comorbidities and cytokine plasma levels	Elevated levels of pro-inflammatory cytokines such as TNF-α (tumor necrosis factor alpha) were found in depression
Huibers et al. (2007)	To investigate how unexplained fatigue and depression are associated over time	Fatigue and depression are strongly associated in time and might become more intertwined as time persists
Krishnadas & Cavanagh (2012)	To examine the links between MDD and inflammation	Inflammation seems to be associated with MDD and may play a role in the etiology and persistence of MDD
Müller & Schwarz (2007)	To examine the importance of the immune system, the serotonergic system and the glutamatergic neurotransmission in depression	Strong evidence that these factors play a key role in depression because they contribute to the overweight of NMDA (N-methyl-D-aspartate) agonists in depression
Viner et al. (2008)	To examine whether sedentary behavior, obesity, smoking, and depression are risk factors for persistent fatigue in adolescents	Being highly sedentary or highly active independently increased the risk of persistent fatigue. Mental health is important in the etiology of persistent fatigue.

Wolbek et al. (2008)	To investigate the stability of fatigue in adolescents and whether psychological, somatic, and lifestyle factors are involved in the onset and persistence of fatigue	Persistently fatigued participants had higher levels of depression, were less physically active, and slept shorter.
Yu & Lee (2012)	To identify the pattern of somatic presentation of depression among older Chinese by examining the association between medically unexplained somatic symptoms and depression	Older Chinese with depression were more likely to have multiple medically unexplained somatic symptoms, particularly fatigue and insomnia.

3.2. Maintenance of MDD and Fatigue

The second research question was formulated as follows: "In how far does fatigue influence the maintenance of MDD?" To fully answer this research question, we found six studies that examined the two-way relationship between fatigue and MDD and the influence of fatigue on the maintenance of MDD and associated perpetuating factors (see also Table 3).

3.2.1 Maintaining factors of fatigue in MDD. For example, a study by Huibers et al. (2007) found that the maintaining impact of depression on fatigue even increased as time persisted. A similar increase was not observed when the impact of fatigue on depression was scrutinized. The authors supposed that this association between depression and fatigue becomes more interwoven as time persists because depression reinforces fatigue, which is again enhanced by subsequent factors such as physical deconditioning and social isolation. In detail, they presume that fatigue and MDD reinforce each other by building an etiological vicious cycle: Fatigue, being a symptom of MDD, enhances physical deconditioning and social isolation, which reinforce severity of MDD which again intensifies fatigue. In addition, three studies examined side effects of antidepressant therapy related to fatigue (Block & Nemeroff, 2014; Doghramji, 2006; Saltiel & Silvershein, 2015). They found that pharmacotherapy with SSRIs, TCAs, MAOIs, NDRIs, or atypical antidepressants may cause unwanted side effects like insomnia, fatigue, or other fatigue-related symptoms because of their sedative effects. Lastly, Pigeon et al. (2008) and Chan et al. (2014) examined insomnia and sleep disturbances being predictors of fatigue and tiredness in MDD patients. Pigeon et al. (2008) found that in addition to being a risk factor for a depressive episode, long-lasting insomnia may perpetuate MDD in elderly patients especially when they receive standard care for depression in primary care. Similar results were obtained in the study by Chan et al. (2014). This study examined independent risk factors for non-remission in MDD patients. They found that sleep latency, short sleep duration, and insomnia were independent risk factors in contributing to non-remission of MDD.

3.2.2. Summary. In conclusion, the conducted literature review regarding maintenance of fatigue and MDD revealed that three different kinds of perpetuating factors may be essential in this reciprocal relationship. At first, fatigue and MDD may reinforce each other by building on an etiological vicious cycle and being enhanced by subsequent factors such as physical deconditioning and social isolation. Secondly, fatigue-related symptoms may occur due to side-effects of pharmacological AD (antidepressant) therapy and, hereby, perpetuate the illness itself. Lastly, insomnia, sleep latency, and short sleep duration being highly associated with fatigue or tiredness may perpetuate MDD and prevent patient's remission of MDD.

Table 3

Maintaining and perpetuating factors of fatigue in Major Depressive Disorder

Authors	Objective	Outcome
Block & Nemeroff (2014)	To summarize latest treatment modalities for MDD including pharmacotherapy, ECT*, RTMS** and psychotherapy	Fatigue and fatigue-related symptoms in MDD can occur due to sedative side effects of several antidepressants
Chan et al. (2014)	To examine the degree to which insomnia, objective sleep disturbances, or their combination predicts depression remission following pharmacotherapy and /or psychotherapy treatment	Prolonged sleep latency or in combination with insomnia predicted increased risk of non-remission. In addition, insomnia and sleep duration individually and in combination were associated with significantly increased risk for non-remission
Doghramji (2006)	To review the longitudinal course, manifestation, and treatment of sleepiness and fatigue in depression	Excessive sleepiness, hypersomnia and fatigue are highly prevalent symptoms in depression and may precede the onset of depressive episodes. A variety of pharmacological options are available (incl. single AD pharmacotherapy, and adjunctive use of AD, stimulants, wake promoting agents)
Huibers et al. (2007)	To investigate how unexplained fatigue and depression are associated over time	Fatigue and depression may reinforce each other by building on an etiological vicious cycle and being enhanced by subsequent factors like physical deconditioning and social isolation
Pigeon et al. (2008)	To examine the relationship of insomnia to the continuation of depression in the context of an intervention study in elderly subjects	Insomnia being a risk factor for a depressive episode may also serve to perpetuate MDD in elderly patients receiving standard care in a primary care setting
Saltiel & Silvershein (2015)	To provide an evidence-based framework within clinicians may tailor pharmacotherapy to symptomatology for improved treatment outcome	Fatigue or fatigue-related symptoms may occur due to sedative side effects of particular AD therapy

*electric convulsive therapy

**repetitive transcranial magnetic stimulation

3.3 Diagnosis

The third research question was worded as follows: “In how far is fatigue (and its sub-dimensions) relevant for the diagnosis (-criteria) of MDD according to the DSM IV?”. The conducted literature review considering in how far fatigue or fatigue-related symptoms like sleepiness or tiredness are incorporated in and are relevant for the diagnosis criteria of MDD in the DSM-IV included 13 studies which contained information about this sub-question (see also Table 5). To get an overview of the diagnosis criteria for MDD according to the DSM-IV see Table 4.

Table 4

DSM-IV Symptom Criteria for Major Depressive Disorder (American Psychiatric Association, 2000)

A. Five (or more) of the following symptoms have been present during the same 2-wk period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest in pleasure

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children consider failure to male expected weight gains.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

In the next section the diagnosis-criteria for MDD related to and the overlaps between fatigue and MDD fatigue are shortly described and then presented in Figure 4.

3.3.1 Fatigue-related symptoms in MDD and overlaps between fatigue and MDD.

Several studies indicate that fatigue and its related subtypes (sleepiness and tiredness) are incorporated in the diagnosis criteria for MDD in the DSM-IV and often are reported by patients diagnosed with MDD as core symptoms or residual symptoms (Arnold, 2008; Baldwin & Papakostas, 2006; Carney, Moss, Lachowski, & Atwood, 2014; Fava et al., 2014; Leone, 2008; Lessov-Schlaggar, Bliwise, Krasnow, Swan, & Reed, 2008; Moore et al., 2009; Nierenberg et al., 2010; Zimmerman, McGlinchey, Young, & Chelminski, 2006). Hereby, it should be noted that for the diagnosis of MDD at least five or more of the above mentioned characteristic features are required, at least one of which is depressed mood or anhedonia (Zimmerman et al., 2006).

Further, a study by Arnold (2008) revealed that according to the author's definition of fatigue with its three subtypes (emotional, physical and mental) the relation to MDD is far more intertwined. According to Arnold (2008) fatigue-related symptoms in MDD are manifested in three out of nine diagnosis criteria for MDD in the DSM-IV. The author describes fatigue by means of three subtypes: Emotional fatigue, physical fatigue, and mental fatigue. Emotional fatigue occurs as "decreased motivation or initiative, decreased interest, feeling overwhelmed, feeling bored, aversion to effort and feeling low." (Arnold, 2008, p. 2) and is, according to the author, related to the second diagnosis-criterion of MDD according to the DSM-IV "Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)." (American Psychiatric Association, 2000). Further, physical fatigue is described as "reduced activity, low energy, tiredness, decreased physical endurance, increased effort with physical tasks and with overcoming inactivity, general weakness, heaviness, slowness or sluggishness, nonrestorative sleep, and sleepiness" (Arnold, 2008, p.2) which related the author to the fifth diagnosis criterion of MDD according to the DSM-IV "Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings

of restlessness or being slowed down) (American Psychiatric Association, 2000). Lastly, the author defines mental fatigue as "decreased concentration, decreased attention, decreased mental endurance, and slowed thinking" (Arnold, 2008, p.2) and related it to the eighth diagnosis criterion of MDD according to the DSM-IV "Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)." (American Psychiatric Association, 2000). To gain an overview over all fatigue-related symptoms in MDD according to Arnold (2008) see also Figure 3 below.

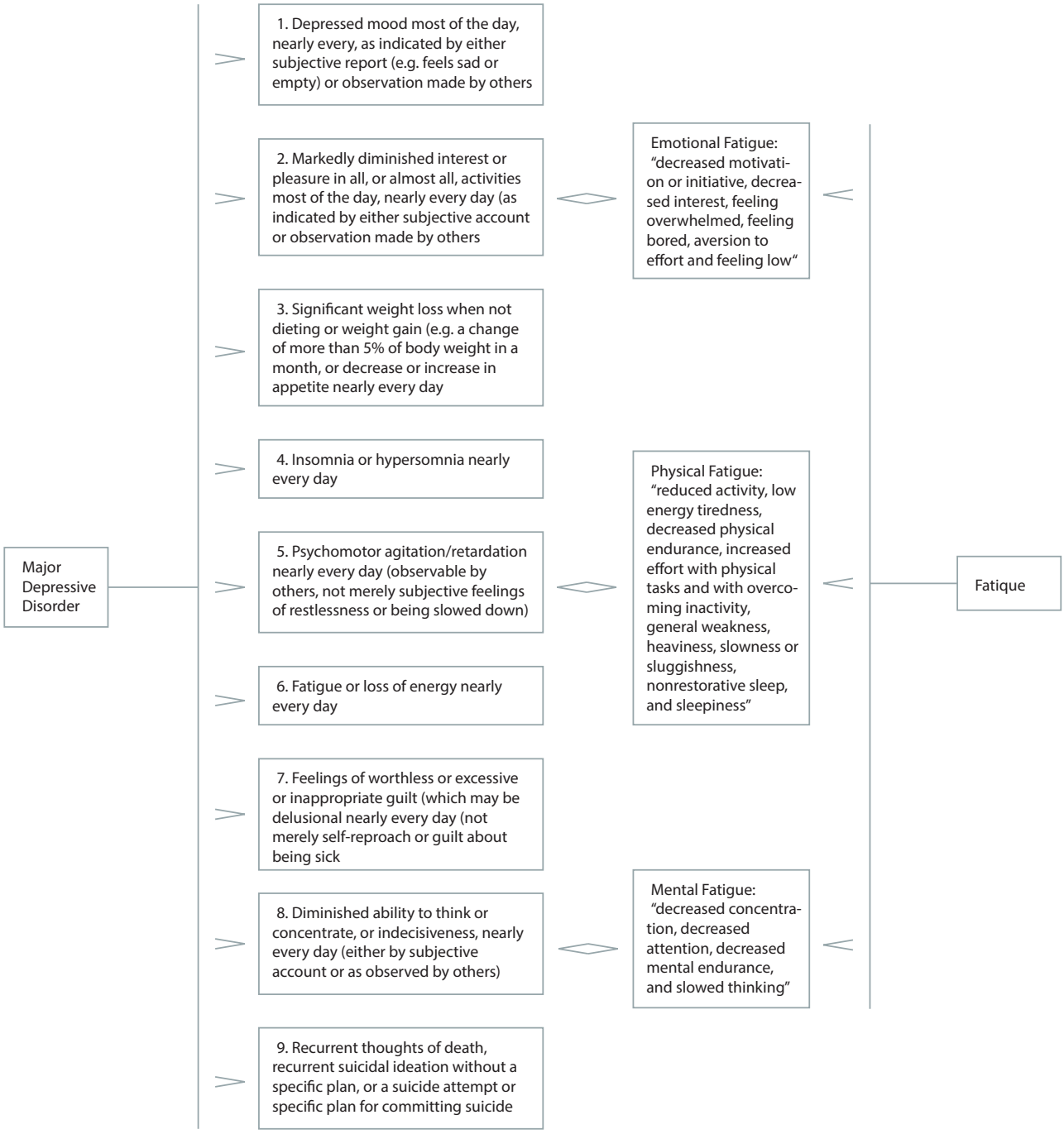

Figure 4. Overlap and differences of symptoms of MDD (according to DSM-IV) related to three different types of fatigue according to Arnold (2008). Adapted from "Diagnostic and statistical manual of mental disorders by American Psychiatric Association., 2000, (4th ed., text rev)", p. 356. and "Understanding fatigue in major depressive disorder and other medical disorders," by Arnold, L. M., 2008, *Psychosomatics*, *49*(3), 185–90.

3.3.2 Differential diagnosis of MDD and fatigue: the problem of comorbidity.

According to one study by Kapfhammer (2006), there are difficulties to distinguish between fatigue and MDD because of the similarity and the overlapping of their symptoms. In detail, several somatic symptoms such as fatigue, sleep disturbances, or changes of appetite could characterize both the pathophysiological process of a discrete medical condition and a depressive disorder as well (Kapfhammer, 2006), making a differential diagnosis far more difficult. Moreover, among researchers the possible insufficiency of the DSM-IV criteria for MDD is discussed regarding medical comorbidities such as other fatigue-related syndromes (chronic fatigue syndrome) or other medical conditions like cancer or chronic pain (Jones et al., 2015; Knaster, Estalnder, Karlsson, Kaprio, & Kalso, 2016; Simon & Von Korff, 2006;).

3.3.3 Summary. The results of the obtained studies regarding the relevance of fatigue or fatigue-related symptoms in the diagnosis-criteria of the DSM-IV reveal that, indeed, fatigue or fatigue-related symptoms like tiredness, exhaustion or lack of energy are incorporated within the DSM-IV diagnosis of MDD. Nevertheless, to make a diagnosis of MDD at least five of the aforementioned criteria need to be fulfilled, at least one of them is depressed mood or anhedonia, independently of fatigue or fatigue-related symptoms appear as symptoms. Therefore, the relevance of fatigue-related symptoms in the DSM-IV diagnosis criteria and their positioning next to other diagnostic criteria needs further discussion. However, several studies indicated that there is a considerably overlap of symptoms between fatigue and depression rising the question how to differentiate between or to classify both syndromes.

Table 5

Diagnosis criteria of fatigue in Major Depressive Disorder

Authors	Objective	Outcome
Arnold (2008)	To assess the of state of knowledge about fatigue in depression and other disorders	An approach that emphasizes the similarities between fatigue and depression may improve the understanding of these complex syndromes
Baldwin & Papakostas (2006)	To examine three different (antidepressant treatment) approaches addressing fatigue- and sleepiness-related symptoms in depression	It remains unclear whether any of the available AD classes are particularly effective. There is some evidence that bupropion and modafinil are more effective than SSRIs
Carney et al. (2014)	To examine predictors of mental and physical fatigue among patients with comorbid insomnia and depression	Activity may be less influential to daytime symptoms of both mental and physical fatigue than cognitive factors such as dysfunctional believes
Fava et al. (2014)	To review the clinical relevance of residual fatigue in MDD	High prevalence of fatigue as residual symptom in MDD, response to treatment is relatively poor or delayed; residual fatigue is highly predictive of inability to achieve remission
Jones et al. (2015)	To examine what effect somatic symptoms may have on the measurement of depressive symptoms in people with cancer using item response theory and differential item function	Somatic symptoms of depression can continue to be administered to people with cancer although sleep disturbance and fatigue are not the strongest markers of depression
Kapfhammer et al. (2006)	To review somatic symptoms in MDD with regard to diagnosis-criteria, their neurobiology and treatment	A reasonable combination of pharmacological and psychotherapeutic approaches can improve the treatment results regarding psychopathologic/somatic symptoms in depressed patients
Knaster et al. 2016)	To assess the relationship of the somatic and cognitive-emotional items of BDI with diagnosis of depression, pain intensity, and disability	Somatic symptoms of depression are common in chronic pain and should not be excluded when diagnosing depression in pain patients

Leone et al. (2008)	To provide information over issues relating to fatigue and its relationship to depression	The concept fatigue and its relationship with depression and functional impairment are complex. Focusing on nature, identification and treatment of functional impairment at different stages in course of fatigue could reduce impact on fatigue
Lessov-Schlaggar et al. (2008)	To examine whether daytime sleepiness and depressive symptoms are genetically related	Often reported phenotypic correlation between daytime sleepiness and depressive symptoms due to modest overlap in genetic factors. Individual variation in daytime sleepiness/depressive symptoms attributable to individual-specific environmental factors
Moore et al. (2009)	To examine associations among adolescent sleepiness, (variability in) sleep duration, and psychological functioning	Sleepiness was associated with higher scores of MDD; findings highlight the potential importance of addressing sleepiness in health/psychological evaluations of adolescents
Nierenberg et al. (2009)	To describe types/frequency of residual depressive symptoms and their relation to subsequent depressive relapse after treatment with citalopram (STAR*D trial)**	Patients with remission of MDD after treatment with citalopram continue to experience selected residual depressive symptoms, which increase the risk of relapse
Simon & Von Korff (2006)	To assess medical co-morbidity and validity of DSM-IV depression criteria	DSM-IV criteria for diagnosis of depression do not require significant modification for patients with medical co-morbidity
Zimmerman et al. (2006)	To examine whether diagnostic criteria such as insomnia, fatigue and impaired concentration that are also diagnostic criteria for other disorders are less specific than the other DSM-IV MDD symptom criteria	Symptom-criteria such as insomnia, fatigue, and impaired concentration generally performed diagnosis criteria as well as criteria that are unique to depression such as suicidality, worthlessness, and guilt.

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3.4 Treatment

The fourth research question was worded as follows:" In how far is fatigue (and its sub-dimensions) treated within common treatment concepts of MDD?" In total, we found 25 studies containing information over common treatment concepts for fatigue or fatigue-related concepts in MDD (see Table 6). However, we firstly describe results considering pharmacological and psychotherapeutic treatment of MDD in general to give an overview of common treatment concepts for MDD. Hereafter, we focus specifically on the treatment of fatigue and fatigue-related symptoms in MDD.

According to several studies, MDD is in general pharmacological treated with currently used antidepressants like *tricyclic antidepressants (TCAs), norepinephrine-dopamine reuptake inhibitors, (NDRIs) monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonine norepinephrine reuptake inhibitors (SNRIs),* or atypical antidepressants like *bupropion, mirtazapine, nefazodone* and *trazodone* (Block & Nemeroff, 2014; Candy, Jones, Williams, Tookman, & King, 2008; Kennedy, 2008; Lin & Stevens, 2014; Montgomery, 2006). Further, other included studies considering psychotherapeutic strategies revealed that MDD is also commonly treated with cognitive behavioral therapy (CBT), mindfulness-based cognitive therapy (MBCT), eclectic psychotherapy (EP), interpersonal psychotherapy (IPT), and psychodynamic psychotherapy (PP) (Craighead, Sheets, Brosse, & Ilardi, 2007; Cuijpers, van Straten, Andersson, & van Oppen, 2008; McCarty & Weisz, 2007; Pinquart, Duberstein, & Lyness, 2006). In the following results regarding pharmacological, psychotherapeutic treatments, and complementary treatment strategies, especially for fatigue-related symptoms in MDD during the illness and after remission, are presented.

3.4.1 Pharmacological treatment of fatigue-related symptoms in MDD. According to 9 studies, fatigue-related symptoms in MDD and after remission are mainly treated with antidepressants like *bupropion* or *atomoxetine* (NDRIs), which may increase noradrenergic and dopaminergic activity, *citalopram* (SSRI), *levomilnacipran* (SNRI), *atypical antipsychotics,* or *modafinil* (psychostimulant), which may increase hypothalamic histaminergic activity (Arnold, 2008; Doghramji, 2006; Fava et al., 2014; Ferguson, Dennehy, Marangell, Martinez, & Wisniewski, 2014; Konuk, Atasoy, Atik, & Akay, 2006; Papakostas et al., 2006; Saltiel & Silvershein, 2015; Thase et al., 2006). As mentioned above MDD is usually treated with *SSRIs, TCAs, MAOIs, NDRIs* or *atypical antidepressants,* which may cause unwanted side effects like insomnia, fatigue, or other fatigue-related symptoms because of their sedative effects (Block & Nemeroff, 2014; Doghramji, 2006; Saltiel & Silvershein, 2015). Therefore, pharmacological treatment involving medication without sedative effects is advised. However, according to a study by Ferguson et al. (2014) lower baseline fatigue and remission of fatigue during antidepressant treatment in MDD patients was associated with higher rates of remission of depressive symptoms, better function, and quality of life.

The effectiveness of specific drugs to treat fatigue-related symptoms was assessed by 7 studies. A study by Papakostas et al. (2006) assessed 6 randomized clinical trials comparing bupropion (NDRI) treatment and SSRI treatment. The results indicate that bupropion treatment was more effective and resulted in greater resolution of sleepiness and fatigue than SSRIs treatment. Two studies by Thase et al. (2006) and Konuk et al. (2006) examined an augmentation therapy with the psychostimulant modafinil in combination with SSRI treatment. They found that this combination treatment was especially effective for patients who continue to experience fatigue and excessive daytime sleepiness as residual symptoms. In addition, a study by Freeman et al. (2016) scrutinized the effects of levomilnacipran extended-release (ER) on depression-related fatigue. The results indicate that levomilnacipran ER treatment was effective in reducing depression-related fatigue in adult patients with MDD.

Further, a study by Hardy (2009) reviewed 19 clinical trials of methylphenidate in medically-ill older adults or patients in palliative care and found that methylphenidate (MPH) may have positive effect on fatigue-related symptoms in MDD. In contrast, a study by Iovieno, van Nieuwenhuizen, Clain, Baer, & Nierenberg (2011) indicated that after a 12-week treatment with fluoxetine (SSRI) patients with remission of MDD still showed residual symptoms like fatigue and daytime sleepiness and other residual symptoms. Similar results were obtained in study by Nierenberg et. al (2010) which examined the treatment of citalopram (SSRI) in primary care and psychiatric patients with MDD.

3.4.2 Psychotherapeutic and complementary treatment of fatigue-related symptoms in MDD. Next to pharmacological treatment, there are also psychotherapeutic treatments and complementary strategies to reduce fatigue or fatigue-related symptoms in MDD.

For example, Ashworth et al. (2015) examined whether cognitive-behavioral therapy for insomnia (CBT-I) delivered by a therapist compared with CBT-I self-help reduces insomnia and depression severity. They found that CBT-I significantly reduced, among symptoms of insomnia and depression, fatigue and fatigue-related symptoms compared to the control condition (CBT-I self-help). Similar results were obtained by a study by Manber et al. (2008) but here CBT-I in combination with pharmacotherapy. They evaluated cognitive behavioral therapy for insomnia (CBTI) as augmenting therapy to antidepressant medication escitalopram (EsCIT) in individuals with MDD and insomnia. The results showed that CBT-I combined with escitalopram therapy was effective in reducing both depression and insomnia, hereby reducing fatigue and fatigue-related symptoms as well.

Next to psychotherapeutic interventions several studies examined the effect of yoga and physical activity on fatigue and fatigue-relate symptoms in MDD (Chen et al, 2008; Puetz, O'Connor, & Dishman., 2006, Shapiro et al., 2007). For example, Shapiro et al. (2007) examined yoga as complementary treatment for MDD. They found that yoga had significantly

positive effect on energy-arousal (attentive, fatigued, alert, energetic, sleepy) in MDD patients, and, in addition to it, reduced depressive symptoms in general in these patients. Further, a study by Chen et al. (2008) scrutinized the effectiveness of yoga on sleep disturbances and sleep quality in MDD patients. The results revealed that sleep disturbances were reduced and sleep quality was improved in these patients after 3 months of the intervention. Moreover, the positive effects were maintained throughout 6 months of the study. At last, a review from Puetz et al. (2006) examined the effects of chronic exercise on feelings of energy and fatigue. They found that chronic exercise increased feelings of energy and reduced feeling of fatigue compared with the control group. The authors suppose that these findings also may help patients with psychological distress, for example depression.

3.4.3 Summary. The examination of the obtained studies regarding common treatment concepts for fatigue and fatigue-related symptoms in MDD revealed various results.

At first, fatigue and fatigue-related symptoms are commonly treated with antidepressant therapy (NDRIs, SSRIs, SNRIs or psychostimulants), psychotherapeutic therapy by means of cognitive behavioral therapy, and with complementary therapy strategies like yoga or aerobic exercises.

Secondly, there are differences in effectiveness to treat fatigue or fatigue-related symptoms in pharmacotherapy. According to several studies the treatment with SNRIs (levoescitalopram), NDRIs (bupropion or atomexatine) and psychostimulants like modafinil is more effective than treatment with SSRIs (e.g. fluoxetine or citalopram).

Thirdly, fatigue and fatigue-related symptoms in MDD can occur due to side effect of AD therapy with sedative agents.

Fourthly, according to several studies CBT-I may be effective in the treatment of fatigue and fatigue-related symptoms in MD by reducing sleep disturbances and insomnia.

Lastly, three studies revealed that complementary treatment strategies like yoga or aerobic exercise may have positive effect on fatigue or fatigue-related symptoms in MDD.

In conclusion, the conducted literature-review showed that there are effective and various treatment concepts for fatigue and fatigue-related symptoms in MDD.

Table 6

Pharmacological and psychotherapeutic/complementary treatment of MDD and fatigue-related symptoms in MDD

Authors	Objective	Outcome
Arnold (2008)	To assess the of state of knowledge about fatigue in depression and other disorders	An approach that emphasizes the similarities between fatigue and depression may improve the understanding of these complex syndromes
Ashworth et al. (2015)	To examine whether CBT for insomnia delivered by a therapist compared with self-help CBT reduces insomnia and depression severity	CBT therapy reduced significantly insomnia and depression severity compared to the control condition (self-help CBT)
Block & Nemeroff (2014)	To summarize latest treatment modalities for MDD including pharmacotherapy, ECT*, RTMS** and psychotherapy	There are many effective treatments for depression but still patients continue to suffer with unrelenting severe depressive symptoms. Therefore, a patient-centered protocol tailored to each individual is needed to optimize treatment
Candy et al. (2008)	To determine the effectiveness of psychostimulants (PS) in the treatment of depression and to assess adverse events associated with PS	There is some evidence that PS reduce significantly symptoms of depression, but the clinically significance is less clear.
Chen et al. (2008)	To test the effect of 6 months of silver yoga exercise in promoting mental health of older adults	Most of the mental health indicators of the participants in experimental group had significantly improved after silver yoga intervention and were all better than the participants in the control group
Craighead et al. (2007)	To examine the effect of Behavioral Therapy (BT), Cognitive Behavioral Therapy (CBT) and Interpersonal Psychotherapy (IPT) in depressed outpatients	Behavioral therapy, cognitive behavioral therapy and interpersonal psychotherapy are efficacious interventions for depressed outpatients
Cuipers et al. (2008)	To examine the efficacy of seven major types of psychological treatment for mild to moderate adult depression	There are no large differences in efficacy between the major psychotherapies for mild to moderate depression

Doghramji (2006)	To review the longitudinal course, manifestation, and treatment of sleepiness and fatigue in depression	Excessive sleepiness, hypersomnia and fatigue are highly prevalent (residual) symptoms in depression and may precede the onset of depressive episodes. A variety of pharmacological options are available (incl. single AD pharmacotherapy, and adjunctive use of AD, stimulants, wake promoting agents)
Fava et al. (2014)	To review the clinical relevance of residual fatigue in MDD with respect to treatment implications	Recognition of the significant consequences of residual fatigue should reinforce the need for further therapeutic interventions that specifically include the impact of therapy on residual fatigue.
Ferguson et al. (2014)	To explore relationships between baseline and changes in fatigue during treatment (monotherapy citalopram) with outcomes in patients with MDD	Lower baseline fatigue and remission of fatigue during antidepressant treatment in patients with MDD are associated with higher rates of remission of depressive symptoms and better function and quality of life.
Freeman et al. (2016)	To evaluate the effects of levomilnacipran extended release (ER) on depression-related fatigue in adults with MDD	Levomilnacipran ER treatment was effective in reducing depression-related fatigue in adults with MDD and was associated with remission of fatigue symptoms
Hardy (2009)	To review the efficacy and tolerability of methylphenidate in the treatment of depressive symptoms, fatigue and apathy in medically ill older adults	Trials of low-dose methylphenidate in medically ill adults with depression, fatigue, or apathy, with monitoring for response and adverse effects, are appropriate.
Iovieno et al. (2010)	To assess the type and frequency of residual symptoms and their relationship to subsequent depressive relapses after remission of MDD with fluoxetine	Great majority of patients with remission of MDD after treatment with fluoxetine continue to experience selected residual symptoms

Konuk et al. (2006)	To investigate the efficacy of modafinil in augmenting SSRIs in depressed patients with residual fatigue or excessive daytime sleepiness	Modafinil may be effective in augmenting ongoing SSRI treatment for a portion of patients with MDD who have residual fatigue and sleepiness
Lin & Stevens (2014)	To present the theory and evidence for an individualized, patient-centered treatment model for MDD designed around a targeted symptom cluster-based approach to AD selection	AD treatment should be guided by the presence of 1 of 4 common symptom clusters: anxiety, fatigue, insomnia, and pain
McCarty & Weisz (2007)	To determine the effect size of youth psychotherapy for depression (meta-analysis)	Cognitive treatments fared no better than non-cognitive approaches. Youth depression treatments appear to produce significant modest effects in strength, breadth, and durability
Montogomery (2006)	To examine the efficacy of agomelatine treatment for MDD	Favorable tolerability of agomelatine which is associated with less sexual side effects. Agomelatine improves sleep quality without associated daytime drowsiness
Nierenberg et al. (2009)	To describe types and frequency of residual depressive symptoms and their relationship to subsequent depressive relapse after treatment with citalopram (STAR*D trial)**	Patients with remission of MDD after treatment with citalopram continue to experience selected residual depressive symptoms, which increase the risk of relapse
Papakostas et al. (2006)	To examine whether the treatment of MDD with bupropion results in greater resolution of sleepiness and fatigue than with SSRIs	Treatment of MDD with bupropion resulted in a greater solution of sleepiness and fatigue than SSRIs
Pinquart et al. (2006)	To improve interventions for depressed adults, data are needed on the comparative effect of pharmacotherapy vs psychotherapy	Available treatments for depression work, with effect sizes moderate to large (fatigue was not directly measured)
Puetz et al. (2006)	To investigate the effect of chronic exercise on feelings of energy and fatigue using meta-analytic techniques	Chronic exercised increased feelings of energy and lessened feelings of fatigue compared with control conditions

Saltiel & Silvershein (2015)	To provide an evidence-based framework within clinicians may tailor pharmacotherapy to patient symptomatology for improved treatment outcomes	Mechanism-based pharmacotherapy is the crucial for personalized treatment, and provides a rational basis for clinicians to make initial therapeutic choices for newly diagnosed patients, and those struggling with unremitting symptoms
Shapiro et al. (2007)	To examine the effect of yoga as complementary treatment of depression	Yoga had significantly positive effect on energy-arousal (attentive, fatigued, alert, energetic, sleepy) in MDD patients
Thase et al. (2006)	To evaluate modafinil in patients with MDD who were partial responders to adequate SSRI therapy and excessive sleepiness and fatigue	Modafinil is an effective well-tolerated augmentation therapy for partial responders to SSRI therapy, particularly when patients continue to experience fatigue and excessive sleepiness

*electroconvulsive therapy
**repetitive transcranial magnetic stimulation

4. Discussion

4.1. Main Findings

The current review focused on the interdependent relationship between fatigue and major depressive disorder (MDD). Specifically, we examined the reciprocal influence on their etiology, maintaining factors, the relevance of fatigue-related symptoms in MDD for a clinical diagnosis of MDD, and common treatment concepts for fatigue and fatigue-related symptoms in MDD. Main objective of this systematic literature review was to deliver a comprehensive overview and to illustrate specific characteristics of this relationship between fatigue and MDD regarding the aforementioned factors. We shortly describe the main findings of this study in the next section.

Firstly, with regard to the etiology we found a strong relationship between fatigue (and fatigue-related symptoms) and MDD. Several studies indicate that not only the risk of co-morbidity is high, but also that MDD predicts fatigue and fatigue-related symptoms and enhances their persistence in MDD. Further, the same or related pro-inflammatory and immunological processes may influence the co-occurrence of MDD and fatigue.

Secondly, fatigue (and fatigue-related symptoms) may reinforce each other's maintenance by building on a vicious cycle and being enhanced by subsequent factors (physical deconditioning, social isolation), due to side effects of antidepressant therapy or because of common sleep disturbances in MDD.

Thirdly, according to diagnosis-criteria of the DSM-IV for MDD, fatigue-related symptoms do not solely fulfill the requirements for an MDD diagnosis. However, there is considerate overlap in symptoms between fatigue and MDD which are incorporated in the diagnosis-criteria for MDD according to the DSM-IV.

Fourthly, fatigue and fatigue-related symptoms in MDD are commonly treated with pharmacological treatment (SSRIs, NDRIS, SNRIs or psychostimulants), and/or psychotherapeutic strategies (CBT), and/or complementary treatment (yoga, physical

activity), achieving positive results. However, according to several studies SSRIs may be the least effective pharmacological strategy to treat fatigue or fatigue-related symptoms in MDD.

4.2 Comparison with Other Studies

In accordance with results from prior studies studying fatigue as a risk factor for and in major depression and vice versa, we found that not only MDD patients have a higher risk experiencing fatigue but also that persistently fatigued participants have higher levels of depression (Yu & Lee, 2012; ter Wolbeek et al., 2008; Viner et al., 2008). These findings go along with other studies considering the etiological relationship between fatigue and MDD. For example, a study by Kennedy (2008) scrutinized core symptoms of MDD and their relevance to diagnosis and treatment. They found that fatigue itself and fatigue-related symptoms such as sleep disturbances, insomnia or hypersomnia, and exhaustion were associated with and predicted by MDD in several samples. However, the relationship seems to be interdependent. For example, a study by Moos & Cronkite (1999) examined risk factors for a chronic course of depression over a 10-year interval in sample of 424 depressed patients. Their results revealed fatigue itself or fatigue-related symptoms in MDD such as loss of energy, trouble sleeping, or sleeping too much as being considerable risk factors which were associated with the likelihood of a chronic course of depression. In contrast, a twin study by Hickie & Martin (1999a) reported genetic and environmental risk factors of fatigue that are different from psychiatric symptoms. In addition, a cohort study by Harvey, Wessely, Kuh, &Hotopf (2009) found different and specific risk factors for fatigue with psychiatric comorbidity (e.g. family history of psychiatric disorder) and fatigue without psychiatric comorbidity (e.g. having excessive energy as a child). Evidently, there are contradicting results considering risk factors in the mutual relationship between fatigue and MDD.

To broaden the view on etiological processes of fatigue in MDD, also studies considering the pathophysiology of both syndromes were taken into account. Prior studies such as Gold et al. (2002) mainly focused on a dysregulation of the stress response system or

the corticotropin releasing hormone (CRH) system. They suppose that a downregulated hypothalamic-pituitary adrenal axis triggers arousal in, for example, atypical depression (subtype of MDD) which again may induce neuro-vegetative symptoms such as fatigue or excessive sleepiness. Hereby, we note that this study examined these neurological processes, specifically in (melancholic and) atypical depression. Therefore, patients with major depression may have a combination of cognitive, affective, and physiologic characteristics that do not match with the classifications of (melancholic and) atypical depression. Still, these results might be relevant in the etiology of MDD as well.

The included studies did not examine a dysregulation of the CRH system as a possible explanation for the etiology of fatigue and MDD. Rather, they assessed immunological and inflammatory processes in fatigue and MDD. Nevertheless, our findings may deliver alternative explanations regarding etiological processes and may give new valuable insight in the neurobiology of fatigue and MDD. In addition, our results can give additional information and enrich existing knowledge on the etiological relationship between fatigue and MDD.

For example, we found that immunological and pro- and post-inflammatory processes such as interleukin (IL)-I α and β, IL-6, and tumor necrosis factor α may play an essential role in the etiology of fatigue and MDD (Hegerl et al., 2013; Himmerich et al., 2008, Krishnadas & Cavanagh, 2012). Similar results were obtained in a study by Miller, Maletic, & Raison (2009). In this review they found associations between inflammatory markers and individual depressive symptoms such as fatigue, cognitive dysfunction, and impaired sleep. In detail, the results indicated that both sleep deprivation and dysregulated sleep in depressed patients were associated with increased interleukin (IL)-6, as well as activation of nuclear factor kappa B (NF-κB), a primary transcription factor in the initiation of the inflammatory response. Further, they found that cytokines mediate this innate immune response, including IL-1, tumor necrosis factor (TNF)-α , and IL-6, which seems to be one of the most reliable peripheral biomarkers in MDD. The overlap of these findings emphasizes the significance of pro-and

post-inflammatory processes in the etiology of fatigue and fatigue-related symptoms in MDD and MDD itself. In addition to it, the resemblance in etiology of fatigue and MDD indicates that the separation between both syndromes seems to be far more difficult than anticipated. A perspective from Arnold (2008), which was included in the data pool, scrutinized this elusiveness of segregation. The findings of this study were earlier described in the result section. However, we want to single out this perspective because the author not only highlights the conceptual similarities of fatigue and MDD for clinical relevance, he also approached the overlap in neurobiological processes in the etiology of fatigue and MDD, and illustrated fatigue as residual symptom in MDD and its proper treatment. According to the author, the strong emphasis on distinguishing fatigue associated with depressive disorders from fatigue related to other medical disorders may have impeded the development of a new approach that enhances the similarities between fatigue and depression which again may open up new avenues for research in these complicated syndromes. Contingently, only looking for differences in neurobiological processes between fatigue related to MDD and fatigue related to other medical disorders may have obscured the investigation of the similarity of both syndromes. Following this perspective, learning more about the pathophysiology of the heterogeneous syndrome depression may enrich our knowledge about the etiology of symptom domains, including fatigue, sleepiness or tiredness, that are associated with depression.

Considering maintaining factors in fatigue and depression our results emphasize among others that fatigue and MDD preserve each other by building on a vicious cycle (Huibers et al., 2007). This model connects to a proposal from Skapinakis et al. (2004). According to the authors fatigue can trigger feelings of psychological distress in a person because he or she suffers from the fatigued condition and its physical, social, and mental limitations. However, the opposite remains difficult to explain, notwithstanding that decreased energy and motivation, and feelings of fatigue or tiredness belong to the diagnostic

criteria of MDD. Therefore, the authors proposed a cyclic model to explain the interdependent relationship between fatigue and MDD. We shortly introduced this model before (see Figure 1). In detail, the authors suppose that the level of physical activity might be a key factor in this relationship because physical activity not only has a protective effect in depression (Strawbridge, Deleger, Roberts, & Kaplan, 2002), but is has also been suggested that physical deconditioning might be associated with the occurrence of unexplained fatigue (De Lorenzo et al., 1998). Huibers et al. (2007) presumed an additional explanation for the intertwined relation between fatigue and MDD. They supposed that lack of interest/motivation and the social isolation in MDD may account for the inactivity of the individual and could eventually lead to physical deconditioning and increased fatigue. In addition to both presumptions, Moorey (2010) proposed a cyclic model to explain the maintenance of depression, the *Six Cycles of Maintenance Model*. Among five other cycles which may contribute to the maintenance of depression, we want to single out one subpart, *motivation and physical symptoms*. According to the author, common symptoms in MDD such as insomnia, tiredness, and psychomotor retardation isolate the depressed person into the depression mode and may perpetuate the illness by building reinforcing cycles between physical symptoms and negative thoughts. For example, tiredness may be associated with less physical activity, which generates negative thoughts with regard to the physical inactivity ("I'm lazy") of the individual and worsens depression, which again leads to more fatigue or fatigue-related symptoms. However, by adding the cognitive component as supposed by Moorey (2010) to the vicious model by Skapinakis (2004) and the findings from Huibers et al. (2007) regarding physical deconditioning respectively social isolation, the maintenance of fatigue in MDD and of MDD itself becomes a multivariate construct with the aforementioned processes involved.

In addition to the cognitive, physical and behavioral processes which may perpetuate fatigue in MDD and MDD itself, we found that fatigue or fatigue-related symptoms in MDD may occur due to (sedative) side effects of antidepressant (AD) therapy (Block & Nemeroff,

2014; Doghramji, 2006; Saltiel & Silvershain, 2015). These results were also confirmed in other studies examining side effects of AD therapy. For example, a study by Thase et al. (2005) indicated prevalence rates of somnolence and fatigue during treatment with SSRIs around 12% vs. 5% with placebo treatment. Similar results were gained in a study by Papakostas (2007) reviewing side effects of pharmacological treatment with agents including moclobemide, nefazodone, venlafaxine, and duloxetine. Moreover, in a study by Hu et al. (2004) patients were asked to rank which side effects they suffered most from during AD treatment: drowsiness/fatigue were rated 16.5% after sexual dysfunction (16.7%), and insomnia 11.2% after weight gain (11.5%). Considering our results and findings from other studies the selection of AD therapy and possibly occurring side effects require careful consideration and consultation by the responsible practitioner. More specifically, AD therapy with sedative side effects should be avoided in case that fatigue or fatigue-related symptoms in MDD continue to occur in the patient.

Lastly, we found that common sleep disturbances in MDD such as (long-lasting) insomnia, sleep latency or short sleep duration may perpetuate MDD and may be risk factors in contributing to non-remission of the disorder (Pigeon et al., 2008; Chan et al., 2014). Results from a study by Riemann, Berger, & Voderholzer (2001) support the bidirectional linkage between sleep disturbances and MDD. The authors present two possible explanations for this reciprocal relationship. On the one hand, sleep disturbances like insomnia might be a prodromal symptom or predictor of a later occurring depression. On the other hand, insomnia itself might be an important factor that facilitate depression. Patients suffering from (chronic) insomnia may experience feelings of helplessness and despair because their efforts to fight insomnia remain unsuccessful. According to the theory of 'learned helplessness' by Seligmann (1975), which is still considered as a valid model, fruitless attempts to initiate sleep may lead to the induction of depression. Further, studies by Buysse (2004) and Riemann & Voderholzer (2003) also identified (primary) insomnia as risk factor for developing of

MDD. Apparently, our results seem to be consistent with findings from other studies.

The relevance of fatigue or fatigue-related symptoms for the diagnosis of MDD still remains unclear. On the one hand, symptoms such as fatigue, tiredness, lack of energy, and exhaustion are incorporated within the diagnosis criteria of MDD according to the DSM IV (4^{th} ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000). Nevertheless, showing a majority of fatigue-related symptoms still is not sufficient to get a MDD diagnosis because at least five of the aforementioned criteria (see Table 4) need to be fulfilled, at least one of them is depressed mood or anhedonia. The question arises why fatigue or fatigue-related symptoms solely do not live up to the requirements for a MDD diagnosis according to the authors of the DSM-IV. However, the authors of this review did not expect that fatigue-related symptoms alone fulfil these premises but the similarity between fatigue and MDD with regard to symptomatology supports this question. Interestingly, the overlapping of symptoms was demonstrated by Arnold (2008). Based on scientific research he proposed a definition of fatigue by delivering three different subtypes of fatigue (emotional, physical and mental) with detailed descriptions. The resemblance of these subtypes to at least three of the aforementioned diagnosis criteria according to the DSM-IV (fatigue or loss of energy or insomnia or hypersomnia not included) cannot be ignored (see Figure 4). In addition, the findings of a study by Ferguson et al. (2014) support the relevance of fatigue-related symptoms in MDD. They found that lower baseline fatigue and remission of fatigue during antidepressant therapy in MDD patients is associated with higher rates of remission of depressive symptoms and better function and quality of life. Hereby, underlining the importance of these symptoms for the progress of the disease. Notwithstanding, there are still diagnosis criteria in the DSM-IV for MDD that describe unique symptoms of a depression such as depressed mood or anhedonia, significant weight loss or gain, feelings of worthlessness or excessive or inappropriate guilt, and recurrent thoughts of death or suicidal ideation (without plan), or suicide attempts. The majority of these symptoms are not directly

related to fatigue or tiredness or sleepiness and still distinguish MDD from fatigue. However, in our opinion the overlapping and similarity of symptoms encourages the discussion to reconsider the required diagnosis criteria for MDD. We do not say that fatigue or fatigue-related symptoms by themselves are sufficient to give a MDD diagnosis and do not deny the relevance of the other symptoms for the diagnosis. Rather, we presume to reconceive the weighting of criteria in the light of the fact that MDD and fatigue (and its subtypes) share considerable characteristics, not only in their symptoms but also in their pathophysiology that we described before. One might suppose that fatigue as a symptom, including mental, physical and emotional fatigue, should be classified as one of the required main criteria of MDD such as depressed mood and anhedonia or, at least, stand next to them. This proposal might become more debatable when considering the similarity between emotional fatigue according to Arnold (2008) and anhedonia according to the DSM-IV that was specifically illustrated in the results section of this review (see also Figure 4). Hereby, we note that this proposal is solely based on interpretations of the included scientific literature and not on experiences in clinical practice. Anyways, reconsidering and weighing the diagnosis criteria of MDD according to the DSM-IV is not part of this study and requires further scientific research and discussion among clinical practitioners and researchers. But yet, this review may have the potential to initiate further discussion on that matter.

When it comes to the treatment of fatigue or fatigue-related symptoms this review gained various results. We concentrated on pharmacological- as well as psychotherapeutic- and complementary treatment strategies.

Considering pharmacological treatment we found that common used antidepressants to treat fatigue or fatigue-related symptoms in MDD (bupropion or atomextine, citalopram, levomilnacipran, atypical antipsychotics, and psychostimulants) not only differ in effectivity (Papakostas et al., 2006; Thase et al., 2006; Konuk et al., 2006, Freeman et al., 2016, Hardy et al., 2009; Iovieno et al., 2011; Nierenberg et al., 2010), but also that certain antidepressants to

treat MDD in general (SSRIs, TCAs, MAOIs, NDRIs or atypical antidepressants) may perpetuate the illness itself due to serious side effects that worsen fatigue or fatigue-related symptoms in MDD (Block & Nemeroff, 2014; Doghramji, 2006; Saltiel & Silvershein, 2015).

A study by Cooper, Tucker, & Papakostas (2014) confirmed the findings of a study by Papakostas et al. (2006), included in this review. They found as well that SSRIs might be less effective in relieving residual tiredness or fatigue in MDD patients by comparing bupropion-with SSRI treatment (sertraline, paroxetine or escitalopram) on data pooled from six double-blind, randomized trials. Their results indicate that MDD patients treated with bupropion showed greater remission and greater improvement in sleepiness and fatigue complaints than patients treated with the aforementioned SSRIs. Further, studies by Thase et al. (2005) and Papakostas (2007) examined side effects of pharmacotherapy for depression. They found high prevalence rates ranging around 12% of somnolence and fatigue among MDD patients treated with SSRIs. Nevertheless, according to a study by Becker & Sattar (2009) therapy for mild to moderate depression with comorbid insomnia should begin with bedtime dosing of sedating antidepressants such as mirtazapine, nefazodone or TCAs, because of their sedative effects. These findings seem to be contrary to the results from studies by Block & Nemeroff (2014), Doghramji (2006), and Saltiel & Silverstein (2015). Hence, treating fatigue or fatigue-related symptoms in MDD demands meticulous consideration. According to data from Physicians' Desk Reference (Thomson, 2007) antidepressants such as mirtazapine or nefazodone may have unwanted side effects, for example somnolence (54% resp. 25%), while having positive treatment effects on insomnia in the patient. The physician or practitioner needs to be aware of the symptom he or she wants to treat and of possible negative side effects on related symptoms which may be worsened due to these side effects. In conclusion, these findings require more consideration and may have far-reaching implications for the clinical practice that will be discussed in one of the following sections.

The effectiveness of additional treatment strategies such as CBT (Becker & Sattar,

2009; Jacobs, Pace-Schott, Stickgold, & Otto, 2004; Rybarczyk et al., 2005) or physical activity/yoga (Dritsa, Da Costa, Dupuis, Lowensteyn, & Khalifé, 2008; McKercher et al., 2013; Weinstein, Deuster, Francis, Beadling, & Kop, 2010), or both in combination to relieve patients from fatigue or related symptoms in depression were also demonstrated in other studies not included in this review. Nevertheless, treatment concepts with CBT mostly focus on insomniac symptoms in MDD patients while they supplementary relieve the patient from fatigue and related symptoms. This is due to the fact that insomnia predicts, and, is associated with fatigue, tiredness, or sleepiness (Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin; 2010). Lastly, we want to emphasize the findings from a study by Carney et al. (2011). They found that daily activities may be less influential to daytime symptoms of both mental and physical fatigue than cognitive factors such as dysfunctional believes about sleep and a tendency to ruminate. These findings suggest the importance of CBT treatment on fatigue and fatigue-related symptoms in MDD.

Summarizing our results and the findings of other studies considering fatigue and related symptoms in MDD, the importance of these symptoms cannot be denied. The similarity in etiology, their reciprocal influence on the maintenance of MDD, and the considerable overlap in symptoms (incorporated in the diagnosis criteria in the DSM-IV) shed light on this complex relationship between fatigue and MDD. The complexity of this interdependent relationship becomes extremely clear when contemplating the pharmacological treatment of both syndromes.

4.3 Fatigue or Related Symptoms in Mood and Anxiety Disorders

Symptoms of fatigue, tiredness, or sleepiness are not only common in MDD but also in other psychiatric disorders (Tkachenko, 2014), especially in mood and anxiety disorders (Soehner & Harvey, 2012). Similar to the results found in this review, the relation between fatigue or related symptoms and anxiety disorders seems to be complicated as well (Mellman; 2008; Papadimitriou & Linkowski, 2005; Ramsawh, Stein, Belik, Jacobi, & Sareen, 2009).

For example, a study by Taylor et al. (2005) indicated that sleep disturbance seems to worsen psychopathological symptoms, with higher frequencies of insomnia correlating with greater severity of anxiety and depression. In addition, this link was also found in a study by Cox & Olatunji (2016) studying obsessive-compulsive symptoms. According to Neckelmann, Mykletun, & Dahl (2007) sleep disturbances such as sleep disruption may not only be a symptom of psychopathology, but rather this symptom may represent a risk factor itself for developing an affective disorder such as Generalized Anxiety Disorder leading to more fatigue or related symptoms. These perspective may also hold true for the relationship between fatigue and MDD as we found in several studies included in this review (Pigeon et al., 2008; Chan et al., 2014). Unfortunately, until now there are no studies known to the authors examining sleep disturbances such as insomnia as a risk factor for obsessive-compulsive disorder. However, the available evidence suggest that fatigue and related symptoms play an essential role in other affective disorders as well by being a risk factor and exacerbating their symptoms.

4.4 Integrated Model of Results

To illustrate this vicious cycle and the particular processes involved in the maintenance of fatigue and MDD, we integrated the model by Skapinakis et al. (2004) with the findings from Huibers et al. (2007) and the subpart (motivation and physical symptoms) from the 6 Cycles Maintenance Model by Moorey (2010) (see Figure 4 below) and developed a new one. Hereby, we note that our model is based on our interpretation of the aforementioned findings. We shortly describe distinct and common risk factors for depression respectively fatigue, and the processes involved in the maintenance of both.

On the one hand, according to Rimes, Goodman, Hotopf, et al. (2007) female gender, conduct disorder, older age, or depression are distinct risk factors for developing fatigue or related symptoms. On the other hand, the risk for developing a MDD is considerably increased by factors such as adverse life events, previous depressive symptoms, substance abuse, unemployment (Batterham, Christensen, & Mackinnon, (2009), and a history of unexplained fatigue (Addington et al., 2001). However, both syndromes share also common risk factors such as comorbidity with other psychiatric disorders or medical conditions (Arnold, 2008) and pro- and post-inflammatory processes in their neurobiology (Hegerl et al., 2013). The aforementioned factors, next to fatigue and depression themselves, might considerable increase the risk of developing a MDD or fatigue.

Considering the maintaining processes of fatigue in MDD a vicious cycle is built between MDD and fatigue. According to our model a MDD patient shows symptoms such as lack of interest and lack of motivation which leads to social isolation and less physical/social activity in the patient. Subsequently, the patient becomes more physically deconditioned and may develop fatigue-related symptoms which again decreases the level of physical activity. Due to his/her depressive condition, the patient might develop more quickly negative thoughts about his/her low level of physical activity (“I’m lazy”) which again worsens depressive symptoms. Hereafter, the vicious cycle starts again perpetuating the illness itself.

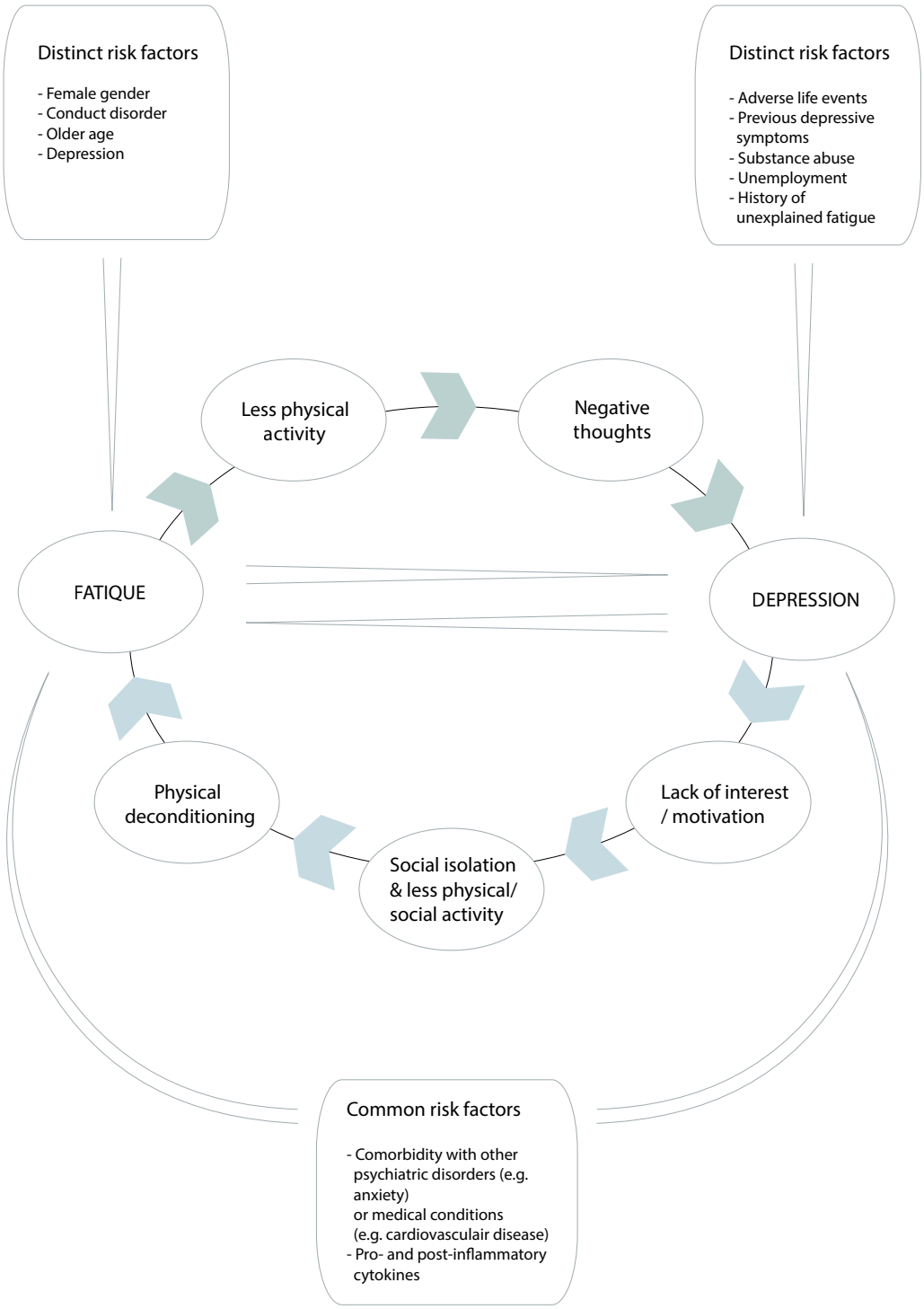

Figure 5. Integrated model of results. Adapted from "Associations of fatigue and depression among fatigued employees over time: A 4-year follow-up study," by Huibers, M. J., Leone, S. S., van Amelsvoort, L. G., Kant, I., & Knottnerus, J. A., 2007, *Journal of psychosomatic research*, *63*(2), 137-142. and "The six cycles maintenance model: Growing a "vicious flower" for depression," by Moorey, S., 2010, *Behavioural and cognitive psychotherapy*, *38*(02), 173-184. and "Temporal relations between unexplained fatigue and depression: longitudinal data from an international study in primary care," by Skapinakis, P., Lewis, G., & Mavreas, V., 2004, *Psychosomatic Medicine*, *66*(3), 330-335.

4.5 Implications for (Future) Clinical Research and Practice

Our findings confirmed already existing knowledge but also enriched this knowledge by adding additional information regarding the link between fatigue and MDD. Moreover, we delivered a comprehensive overview about this interdependent relationship by gathering literature that examined etiology, maintenance, relevance for diagnosis criteria, and treatment concepts. Our (new) findings may have important implications for clinical research and practice which are outlined in the following two sections.

4.5.1 Clinical research. The findings of the current review may have implications for future research on the relationship between fatigue and related symptoms and MDD. First of all, our findings suggest that an accurate definition of the three concepts, fatigue, tiredness, and sleepiness, is needed to guarantee that studies examine the same constructs making comparisons with other studies as well as conclusions based on clear conceptualizations possible. Otherwise, there is still the risk that authors using different definitions draw conclusions on that matter while measuring different constructs. For example, it needs to be questioned whether the tiredness or sleepiness occurring due to antidepressant therapy is distinguishable from tiredness or sleepiness arising from circadian effects (or fatigue as a result of physical or mental exertion). As a consequence, the required measurement instrument should be able to differentiate between various concepts. Similarly, there is the need for using identical measurement methods to assess fatigue or at least using instruments that measure the same constructs (or concepts) by definition making a direct comparison and conclusion possible. This matter is also discussed in the limitations of the current review.

Lastly, when it comes to research on the relationship between fatigue and related symptoms and MDD studies are needed that solely focus on this specific relationship and do not include medical or other psychiatric conditions. We do not say that fatigue and related symptoms in other conditions do not influence this relationship. Rather, we presume that other factors may mediate the relation between fatigue and MDD, for example, General

Anxiety disorder or Chronic Fatigue Syndrome. Nevertheless, the problem of comorbidity makes a valid conclusion solely on the relationship between fatigue and MDD hardly possible. Therefore, we suggest to concentrate in first instance on fatigue and MDD alone. Following this, looking for similarities and overlaps in etiological and pathophysiological processes in other medical or psychiatric conditions may add useful information and enrich our knowledge on symptom domains, such as fatigue, that are associated with depression.

4.5.2 Clinical practice. In addition to implications for future research the current review brought out findings that may have consequences for the clinical practice. Firstly, treating fatigue and fatigue-related symptoms such as tiredness or sleepiness in MDD requires an accurate diagnosis of MDD whereby the responsible practitioner needs to account for other diagnoses on comorbid conditions. This becomes especially important for the pharmacological treatment with antidepressants. As we showed before certain antidepressants, such as SSRIs (sertraline, paroxetine or escitalopram, moclobemide, nefazodone, venlafaxine, duloxetine or fluoxetine), do have sedative side effects or may worsen fatigue or related symptoms in depression (Block & Nemeroff, 2014; Cooper et al., 2014; Doghramji, 2006; Papakostas, 2007; Saltiel & Silvershain, 2015). Further, our findings suggest that pharmacological treatment with SSRIs (fluoxetine, citalopram) is less effective in relieving the patient from fatigue (Iovenio et., 2011; Nierenberg et al., 2010). Hence, treatment using agents that worsen fatigue or related symptoms or do not relieve the patient from them should be avoided when these symptoms continue to occur in the patient; or at least require the careful consideration of the practitioner when they are needed for treatment on other symptoms, for example, insomnia.

Further, according to our findings psychotherapeutic treatment strategies such as Cognitive Behavioral Therapy (CBT) solely focusing on fatigue and fatigue-related symptoms in MDD are still rare. Rather, we found that CBT for related symptoms like insomnia, hereby, having positive effect on fatigue, tiredness or sleepiness in MDD (Ashworth et al., 2015).

Hence, there is considerable demand for the usage of CBT focusing directly on fatigue or similar symptoms. Unfortunately, the current review did not include any studies concentrating on that matter. However, in our opinion, CBT might be a useful and effective treatment on these symptoms because we found that negative thoughts may perpetuate the illness itself by building on a vicious cycle reinforcing physical symptoms, promoting social isolation, and physical decondition (Huibers et al., 2007; Skapinakis, 2004; Moorey, 2010). Moreover, CBT strategies on fatigue are applied in other medical conditions such as Chronic Fatigue Syndrome with positive treatment effects (Knoop, Bleijenberg, Glielissen, van der Meer, & White, 2007) or in Generalized Anxiety Disorder by significantly decreasing fatigue or fatigue-related symptoms (Bélanger, Morin, Langlois & Ladouceur, 2004).

At last, complementary strategies to treat fatigue in MDD or other medical conditions such as yoga or aerobic become more popular but are rarely implemented by practitioners. However, we advise the usage of these strategies because by activating the patient and enhancing physical activity positive results with regard to fatigue symptoms and health behavior can be achieved (Dritsa, Da Costa, Dupuis, Lowensteyn, & Khalifé, 2008; McKercher et al., 2013; Weinstein, Deuster, Francis, Beadling, & Kop, 2010). Moreover, patients becoming more physically fit might become more self-confident about their body and denying negative thoughts they had before, hereby, interrupting the reciprocal influence between negative thoughts and physical activity. Moreover, using yoga or aerobic to enhance physical activity might promote social behavior because these exercises often are trained in groups with patients suffering the same problem, and are also easily implemented. This might counteract the vicious cycle building on social isolation and physical deconditioning we have mentioned before. For these reasons, more usage of these complementary strategies is recommended.

4.6 Limitations

The limitations of the current review are discussed in the following section.

4.6.1 Definition and conceptualization of fatigue and its subtypes. Firstly, for the use of this scientific literature review we introduced three distinct definitions of the terms fatigue, tiredness and sleepiness, which, according to the authors, accounted for an accurate description of these three concepts. Unfortunately, there was still no consensus regarding a defined conceptualization among other authors in general, and an absolute definition and conceptualization of the terms *fatigue* and its subtypes *tiredness* and *sleepiness* was still missing. This might have had implications for the examination of the relation between fatigue (and tiredness and sleepiness) and Major Depressive Disorder. In the first instance, there was a risk that authors of literature included in this review made use of different definitions and conceptualizations of the aforementioned terms which solely met their own personal imagination and understanding of these terms. As a consequence, the included studies might have studied and assessed distinct concepts of the fatigue, tiredness, or sleepiness in relation to MDD in different contexts. This heterogeneity of the terms would make three distinct and absolute conclusions about the relation between fatigue (resp. tiredness and sleepiness) and MDD hardly possible. For future research on fatigue and MDD there is a need for an absolute definition and conceptualization that bears reference to the multidimensionality of fatigue. At this point, we want to point out to Phillips (2015) and Arnold (2008). Phillips (2015) reviewed different definitions of the concept fatigue and introduced a new definition that accounts for the multidimensionality of fatigue. The authors incorporated the subjectivity of experience of fatigue, psychosocial and physiological processes during fatigue and performance decrement at physical and cognitive level due to fatigue in their definition. Further, Arnold (2008) proposed a definition in direct relation to Major Depressive Disorder describing fatigue on a cognitive, mental and emotional level. The use of these

aforementioned definitions apart or in combination might be useful when studying the complicated relation between fatigue (tiredness, sleepiness) and MDD.

4.6.2 Measurement instruments of fatigue and MDD. Secondly, an overview of used measurement instruments in the included studies is missing. Knowledge about used measurement methods, their validity and reliability, and measured constructs, shall make a comparison between the studies easier and conclusions based on this comparison more valid. Unfortunately, reviewing all used measurement instruments in the included studies exceeded the scope of this thesis.

4.6.3 The problem of co-morbidity. Thirdly, there is a high comorbidity of fatigue and MDD with other medical conditions such as cancer, rheumatoid arthritis, fibromyalgia, anemia, multiple sclerosis, or chronic fatigue syndrome (Aaronson et al., 1999; Agnihotri et al., 2007; Shapiro, 1998; Zautra et al., 2007), and psychiatric disorders such as anxiety disorders (Gillin, 1998; Shen et al., 2006). However, the used exclusion criteria (see Methods sections) implied that literature with regard to somatic disorders or other medical conditions were not included in this review. Still, symptoms such as fatigue, tiredness or sleepiness in MDD showed considerable overlap with symptoms of General Anxiety Disorder (GAD) or others or might occur due to other factors that were not assessed in the included studies. As a consequence, there was a risk that several studies did not examine fatigue purely related to MDD and the used samples might not be representative for a clear diagnosis of MDD alone. In addition, comorbid psychiatric or medical disorder that have not been assessed might have mediated the relationship between fatigue and MDD leading to a distorted depiction of this relationship in the current review. Therefore, for future research on fatigue and MDD, reporting used measurement methods is advised in order to rule out the assessment of different constructs and to avoid possible comorbidities.

4.6.4 Heterogeneity of included samples. Thirdly, the current review included studies with various study designs, population samples, and sample sizes. This implies that

particular conclusions by the authors were based on the given conditions and context in the study. The heterogeneity of study designs, population samples, and sample sizes might not have resulted in a representative representation of the relation between fatigue and MDD. In addition, the included studies used different measurement methods and instruments to assess fatigue (and its subtypes) and MDD. As a consequence, no conclusion could be drawn about the validity and the reliability of the used measurement instruments in general because they were not directly compared. Further, the use of different measurement methods intended to assess one concept fatigue respectively MDD came with the risk that particular instruments emphasize specific symptoms above others making a comparison far more difficult. Hence, conclusions on the relationship between fatigue and MDD need to be drawn with caution.

4.6.5 Study publication bias and selective reporting bias. Fourthly, the findings of the current review might be distorted due to bias. Two of types of bias could have been relevant when discussing the findings of this review and are discussed in the following.

According to Dwan, Gamble, Williamson, & Kirkham (2013) bias from missing outcome data may affect a literature review on two levels. Firstly, non-publication due to submission or rejection of study reports (publication bias, study level problem) and, secondly, selective non-reporting of outcomes within published studies on the basis of the findings (outcome reporting bias, outcome level problem).

The publication bias refers to the issue that not all studies that are conducted in a particular domain are actually published (Cuijpers, 2016). This is because authors, editors and journals but also companies tend to prefer publication of studies which show significant and large effects of interventions. Studies with no or small effect often are not published or at least only positive outcomes are reported. Hence, reviewing numerous studies may have led to an overestimation of the true effect of an intervention, especially with regard to treatment outcomes in pharmacological studies, because negative studies are not or less published. As a consequence, bias in the included studies will automatically lead to bias in the current review.

However, the researchers reduced the chance of bias by weighing randomized control trials more than studies with an experimental study design. Yet, no qualitative research catalogue was used. Further, the current review only included published studies by time period 2006 to 2016. For that reason, including studies conducted but not published in this time period might have led to other conclusions. Still, the probability of results deviant from ours is estimated to be low.

In addition to publication bias, the current review might also be susceptible to within-study selective reporting bias, an outcome reporting bias, which refers to the selective reporting of findings based on a subgroup of the original variables recorded for inclusion in a publication (Dwan et al., 2013). Hence, the likely bias from selective outcome reporting is to overestimate the effect of an experimental treatment because planned experiments such as randomized controlled trials are deemed as the gold standard of study design to evaluate the effectiveness of a treatment (Kane, Wang, & Garrard; 2007). To counteract outcome reporting bias all studied in this study were carefully read and investigated, and all outcomes were fully reported. However, the chance of bias could not be ruled out completely.

4.7 Conclusion

In conclusion, there is only scattered information about the relationship between fatigue (and its subtypes) and Major Depressive Disorder. By means of the current review we tried to deliver a comprehensive overview of the available information and summed it up to make a detailed depiction of this relation as good as possible.

Fatigue and its subtypes in Major Depressive Disorder is often reported but there is still uncertainty with regard to etiology, maintenance and the relevance of diagnosis criteria of fatigue in MDD. According to our findings particular neurobiological and cognitive processes are involved in the development and maintenance of fatigue and related symptoms in MDD. Notwithstanding, there is moderate agreement among researchers which processes are involved and, moreover, how they influence the origin and preservation of fatigue. In addition

to this, according to authors of the current review the relevance of fatigue or related symptoms for a diagnosis of MDD needs further discussion. The overlapping and similarity of symptoms of both syndromes cannot be ignored; therefore, the diagnostic criteria of MDD related to fatigue deserve a reconsideration and perhaps a new weighing. However, regarding common treatment concepts for fatigue in depression there are lots of strategies in pharmacological, psychotherapeutic and complementary treatments available with positive treatment results. Nevertheless, the choice of appropriate antidepressant therapy must be made with caution and with consideration of potential (sedative) drug side effects. Further, psychotherapeutic interventions have to focus on breaking through the vicious cycle between fatigue and MDD by reorganizing negative thinking constructs. Hereby, complementary strategies to encourage physical activity and social interaction might be helpful as well.

4.8 Acknowledgments

Hereby I would like to express my gratitude to my attentands Dr. Peter Meulenbeek and Dr. Christina Bode from the University of Twente, Enschede, The Netherlands, for their detailed and useful feedback and comments on my master thesis, their engagement and inspiration, and, especially, for their helpful guidance through the writing process of this literature review. Moreover, I would like to thank my family and closest friends for their emotional and mental support, for holding me, and, especially, for tolerating my mood swings.

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Appendix

Table 1. Key-indexing term, search terms and additional search for research questions

Key-indexing term	*Search terms*	*Additional search terms*	*Combination research question (AND): key-indexing term + specified search term*
Major Depression Disorder	Fatigue		Major Depression Disorder AND Fatigue
Major Depression Disorder	Tiredness		Major Depression Disorder AND tiredness
Major Depression Disorder	Sleepiness		Major Depression Disorder AND Sleepiness
Major Depression Disorder	Exhaustion		Major Depression Disorder AND Exhaustion
Major Depression Disorder	Lack of Energy		Major Depression Disorder AND Lack of Energy
Major Depression Disorder	Etiology	Fatigue/Tiredness/Sleepiness	Major Depression Disorder AND Etiology AND Fatigue/Tiredness/Sleepiness
Major Depression Disorder	Persistence	Fatigue/Tiredness/Sleepiness	Major Depression Disorder AND Persistence AND Fatigue/Tiredness/Sleepiness
Major Depression Disorder	Maintaining factors	Fatigue/Tiredness/Sleepiness	Major Depression Disorder AND Maintaining factors AND Fatigue/Tiredness/Sleepiness
Major Depression Disorder	Diagnosis(-criteria)	Fatigue/Tiredness/Sleepiness	Major Depression Disorder AND Diagnosis(-criteria) AND Fatigue/Tiredness/Sleepiness
Major Depression Disorder	Pharmacological treatment	Fatigue/Tiredness/Sleepiness	Major Depression Disorder AND Pharmacological treatment AND Fatigue/Tiredness/Sleepiness
Major Depression Disorder	Psychotherapeutic treatment	Fatigue/Tiredness/Sleepiness	Major Depression Disorder AND Psychotherapeutic treatment AND Fatigue/Tiredness/Sleepiness
Major Depression Disorder	Complementary and/or alternative therapy	Fatigue/Tiredness/Sleepiness	Major Depression Disorder AND Complementary and alternative therapy AND Fatigue/Tiredness/Sleepiness

Tabel 2. Overview over all included studies with additional information

Authors	Year of publication	Location	Objectives	Study population	Sample size	Study design	Database
Arnold	2008	Cincinnati	To assess the of state of knowledge about fatigue in depression and other disorders	---	---	Review	Scopus
Ashworth, Sletten, Simpson, Clarke, Junge Cunnincton & Rajaratnam	2015	Monash	To examine whether cognitive behavioral therapy for insomnia (CBT-I) delivered by a therapist compared with self-help CBT reduces insomnia and depression severity	Patients with comorbid depression and insomnia aged 18-64 years	N = 41	Analytic: RCT of CBT-I vs. self-help intervention, mixed model analysis of covariance to assess impact of CBT-I and self-help intervention	Pubmed
Baldwin & Papakostas	2006	Southampton	To examine three different (antidepressant treatment) approaches addressing fatigue- and sleepiness-related symptoms in depression	---	---	Review	Scopus
Block & Nemeroff	2014	Miami	To summarize latest treatment modalities for MDD including pharmacotherapy, electrical convulsive therapy, repetitive transcranial magnetic stimulation and psychotherapy	---	---	Review	Scopus

Candy, Williams & King	2008	London	To determine the effectiveness of psychostimulants (PS) in the treatment of depression and to assess adverse events associated with PS	---	---	Review	Scopus
Carney, Moss, Lachowski & Atwood	2014	Toronto	To examine predictors of mental and physical fatigue among patients with comorbid insomnia and depression	treatment-seeking individuals with MDD and insomnia aged 20-62 years	N = 62	Analytic: retrospective study, hierarchical linear multiple regression analysis on variables of interest	Scopus
Chan, Lam, Li, Yu, Chan, Zhang & Wing	2014	Hong Kong	To examine the degree to which insomnia, objective sleep disturbances, or their combination predicts depression remission following pharmacotherapy and /or psychotherapy treatment	MDD patients aged 18 years or older	N = 253 (previous sample N = 371)	Analytic: prospective cohort study, logistic regression model with non-remission depression as DV with eveningness as IV	Pubmed
Chen, Chen, Chao, Hung, Lin & Li	2009	Taiwan	To test the effect of 6 months of silver yoga exercise in promoting mental health of older adults	MDD patients aged 60 or older	N = 139	Analytic: follow up study (3-, 6-months) RCT with experimental (silver yoga intervention) vs CG (attendance at selected senior activities), statistical analyses	Google Scholar

Cowen & Browning	2015	Oxford	To examine of the serotonin hypothesis and the role of diminished tryptophan availability in triggering depression	---	---	Review	Scopus
Craighead, Sheets, Brosse & Ilardi	2007	Illinois	To examine the effect of Behavioral Therapy (BT), Cognitive Behavioral Therapy (CBT) and Interpersonal Psychotherapy (IPT) in depressed outpatients	---	---	Book chapter	Google Scholar
Cuipers, van Straten, Andersson & van Oppen	2008	Amsterdam	To examine the efficacy of seven major types of psychological treatment for mild to moderate adult depression	Articles on psychological treat of depression in general	N = 832 (articles)	Meta-analysis	Google Scholar
Doghramji	2006	Philadelphia	To review the longitudinal course, manifestation, and treatment of sleepiness and fatigue in depression	---	---	Book chapter	Google Scholar
Fava, Ball, Nelson, Sparks, Konechnik, Classi & Thase	2014	Boston	To review the clinical relevance of residual fatigue in MDD	---	---	Review	Scopus

Ferguson, Dennehy, Marangell, Martinez & Wisniewski	2014	Toronto	To explore relationships between baseline and changes in fatigue during treatment (monotherapy citalopram) with outcomes in patients with MDD	Outpatients with nonpsychotic MDD	N = 2868	Analytic: prospective design, secondary analyses of STAR*D data: to assess the association of fatigue status on outcome variable treatment	Scopus
Freeman, Fava, Gommoll, Chen, Greenberg & Ruth	2016	Boston	To evaluate the effects of levomilnacipran extended release (ER) on depression-related fatigue in adults with MDD	MDD patients aged 18-80 years	N = 2598	Analytic: 5 randomized, double-blind, placebo-controlled studies of levomilnacipran ER for the treatment of MDD, statistical analyses	Scopus
Hardy	2009	Pittsburgh	To review the efficacy and tolerability of methylphenidate in the treatment of depressive symptoms, fatigue and apathy in medically ill older adults	---	---	Review	Pubmed
Hegerl, Lam, Malhi, McIntyre, Demyttenaere, Mergl & Gorwood	2013	Leipzig	To conceptualize the neurobiology of fatigue	---	---	Review	Scopus

Himmerich Fulda, Linseisen, Seiler, Wolfram, Himmerich, Gedrich, Kloiber, Lucae, Ising, Uhr, Holsboer & Pollmächer	2008	München	To investigate associations between a medical history of depression, its comorbidities and cytokine plasma levels	Bavarian population aged 13-80 years	N = 1050	Analytic: cross-sectional study, random route sampling, computerized face-to-face interview to assess medical history, blood sampling, and standardized anthropometric measurements	Scopus
Huibers Leone, van Amelsvoort, Kant & Knottnerus	2007	Maastricht	To investigate how unexplained fatigue and depression are associated over time	Employees	N = 151	Analytic: follow-up study (over 4 years), prospective, RCT of CBT vs. natural course, repeated-measures analysis	Scopus
Iovieno, van Nieuwenhuizen, Clain, Baer & Nierenberg	2011	Boston	To assess the type and frequency of residual symptoms and their relationship to subsequent depressive relapses after remission of MDD with fluoxetine	Patients with MDD aged 18-65 years	N = 627	Analytic: after 1-week medication-free wash-out 12-week course of open-label treatment with fluoxetine, then randomized double-blind study fluoxetine vs. placebo (52 weeks); statistical analyses	Scopus

Jones, Ludman, McCorkle, Reid, Bowles, Penfold & Wagner	2015	Seattle	To examine what effect somatic symptoms may have on the measurement of depressive symptoms in people with cancer using item response theory and differential item function	Patients diagnosed with breast, lung or colorectal cancer	N = 251	Analytic: longitudinal study, differential item function (DIF) using item response theory models (IRT), 4-month assessment	Scopus
Kapfhammer	2006	Graz	To review somatic symptoms in MDD with regard to diagnosis-criteria, their neurobiology and treatment	---	---	Review	Google Scholar
Knaster, Estlander, Karlsson, Kaprio & Kalso	2016	Helsinki	To assess the relationship of the somatic and cognitive-emotional items of BDI with diagnosis of depression, pain intensity, and disability	Chronic pain patients	N = 100	Analytic: cross-sectional study, regression analysis to assess the association of BDI scores and pain-related variables with diagnosis of MDD	Scopus
Konuk, Atasoy, Atik & Akay	2006	Kozlu/Zonguldak	To investigate the efficacy of modafinil in augmenting SSRIs in depressed patients with residual fatigue or excessive daytime sleepiness	Turkish psychiatric outpatients with MDD aged 18-64 years	N = 25	Open-label study, modafinil was added to SSRI treatment; analytic: 1 way within-subject analysis of variance	Scopus
Krishnadas & Cavanagh	2012	Glasgow	To examine the links between MDD and inflammation	---	---	Review	Google Scholar

Leone	2010	Amsterdam	To provide information over issues relating to fatigue and its relationship to depression	---	---	Editorial review	Pubmed
Lessov-Schlaggar, Bliwise, Krasnow, Swan & Reed	2008	Saint Louis	To examine whether daytime sleepiness and depressive symptoms are genetically related	Elderly male twins aged 69-82	N=15.924	Analytic: bivariate genetic analysis, descriptive: cross-sectional design	Scopus
Lin & Stevens	2014	Stanford	To present the theory and evidence for an individualized, patient-centered treatment model for MDD designed around a targeted symptom cluster-based approach to AD selection	---	---	Journal Article	Scopus
McCarty & Weisz	2007	Boston	To determine the effect size of youth psychotherapy for depression (meta-analysis)	American children (under 13) and adolescents (13 or older)	N = 35 (studies)	Meta-analysis	Google Scholar
Montogomery	2006	London	To examine the efficacy of agomelatine treatment for MDD	MDD patients	N = 212	Analytic: randomized, double-blind, placebo-controlled study agomelatine vs. placebo (over 6 weeks), statistical analyses	Scopus

Moore, Kirchner, Drotar, Johnson, Rosen, Ancoli-Israel & Redline	2009	Pennsylvania	To examine associations among adolescent sleepiness, (variability in) sleep duration, and psychological functioning	Adolescents aged 13-16 years	N = 247	Analytic: bivariate correlation analysis between sleep variable and psychological variables, descriptive: cross-sectional analysis from a community based cohort study	Scopus
Müller & Schwarz	2007	München	To examine the importance of the immune system, the serotonergic system and the glutamatergic neurotransmission in depression	---	---	Review	Scopus
Nierenberg, Husain, Trivedi, Fava, Warden, Wisniewski, Miyahara & Rush	2010	Boston	To describe types and frequency of residual depressive symptoms and their relationship to subsequent depressive relapse after treatment with citalopram (STAR*D trial, Sequenced Treatment Alternatives to Relieve Depression)	MDD (out)-patients (in primary and psychiatric care) aged 18-75 years	N = 4041 (n= 18 primary care, n=23 psychiatric care, n = 4000 outpatients)	Descriptive: retrospective follow-up study, based on data of STAR*D trial, statistical analysis for characteristics of remitters, analytic: Kaplan-Meier curves and log-rank statistic to compare the cumulative probability of relapse in follow-up over 1 year	Scopus

Papakostas, Nutt, Hallett, Tucker, Krishen & Fava	2006	Boston	To examine whether the treatment of MDD with bupropion results in greater resolution of sleepiness and fatigue than with SSRIs	MDD patients	N = 1.317 (n = 662 bupropion, n = 655 SSRI)	Analytic: 6 double-blind, randomized clinical trials comparing bupropion with SSRI for treatment of MDD; statistical analyses	Scopus
Pigeon, Hegel, Unützer, Fan, Sateia, Lyness, Phillips & Perlis	2008	New York	To examine the relationship of insomnia to the continuation of depression in the context of an intervention study in elderly subjects	MDD patients aged 60 or older	N = 1801 (data from Project IMPACT)	Analytic: retrospective study, data from multisite intervention (randomized assignment to intervention program) logistic regression analysis to determine whether persistent insomnia was prospectively associated with increased risk of remaining depressed	Pubmed
Pinquart, Duberstein & Lyness	2006	Jena	To improve interventions for depressed adults, data are needed on the comparative effect of pharmacotherapy vs psychotherapy	Depressed older adults (age, mean: 71 years)	N = 89 (controlled studies), N= 5.328 patients	Meta-analysis	Pubmed

Puetz, O'Connor & Dishman	2006	Georgia	To investigate the effect of chronic exercise on feelings of energy and fatigue using meta-analytic techniques	Subjects with no medical condition, cancer, chronic fatigue, fibromyalgia, cardiac rehabilitation, anxiety and depression (age, mean: 50 years)	N = 6807 (70 studies)	Meta-analysis	Google Scholar
Saltiel & Silvershein	2015	New York	To provide an evidence-based framework within clinicians may tailor pharmacotherapy to patient symptomatology for improved treatment outcomes	---	---	Review	Scopus
Shapiro, Cook, Davydov, Ottaviani, Leuchter & Abrams	2007	Los Angeles	To examine the effect of yoga as complementary treatment of depression	MDD patients (age, mean: 45 years)	N = 37	Unblinded intervention study (yoga classes), pre- and post-intervention for data assessment, analytic: random regression model to analyze mood ratings and general linear model to assess effect of IV (remission or not)	Pubmed

Simon & Von Korff	2006	Seattle	To assess medical co-morbidity and validity of DSM-IV depression criteria	American in- and outpatients with Ischemic Heart Disease, Diabetes, COLD aged (age, mean: 55 years comorbidity, 45 years general)	N = 439 (n = 235 Comorbidity, n = 204 General)	Analytic: longitudinal study, item response analysis to examine significance of specific depressive symptoms among patients with and without chronic medical illness	Pubmed
Thase, Fava, Debattista, Doghramji, Arora & Hughes	2006	Pittburgh	To evaluate modafinil in patients with MDD who were partial responders to adequate SSRI therapy and excessive sleepiness and fatigue	MDD patients with several residual symptoms	N = 348	Analytic: 2 randomized, double-blind, place-controlled studies of modafinil (6-week) + SSRI therapy	Scopus
Viner, Clark, taylor, Bhui, Klineberg, Head, Booy & Stansfeld	2008	London	To examine whether sedentary behavior, obesity, smoking, and depression are risk factors for persistent fatigue in adolescents	Adolescents aged 11 to 12 and 13 to 14 years	N = 1880 (49% male, 81% nonwhite British)	Analytic: Longitudinal population-based survey, 28 randomly selected schools	Scopus

Ter Wolbek, van Doornen, Kavelaars & Heijnen	2008	Utrecht	To investigate the stability of fatigue in adolescents and whether psychological, somatic, and lifestyle factors are involved in the onset and persistence of fatigue	Dutch adolescent girls (age, mean: 14.4 years)	N = 653 (previous sample N=1747)	Analytic: longitudinal survey study, logistic/multiple regression analysis	Author
Yu & Lee	2012	Hong Kong	To identify the pattern of somatic presentation of depression among older Chinese by examining the association between medically unexplained somatic symptoms and depression	MDD patients aged 65 years or older	N = 1433	Analytic: cross-sectional correlational study, binary logistic regression analysis for association of non-specific somatic symptoms with depression as well as socio-demographic and medical profile	Scopus
Zimmerman, McGlinchey, Young & Chelminski	2006	Rhode Island	To examine whether diagnostic criteria such as insomnia, fatigue and impaired concentration that are also diagnostic criteria for other disorders are less specific than the other DSM-IV depressive symptom criteria	Psychiatric outpatients (age, mean: 38 years)	N = 1800 (to date)	Analytic: retrospective, conducting SCID-I interview, logistic regression analysis to examine which MDD symptoms significantly, and independently, are associated with the diagnosis of MDD	Scopus