

Health and Disability

Stress-related exhaustion disorder – clinical manifestation of burnout? A review of assessment methods, sleep impairments, cognitive disturbances, and neuro-biological and physiological changes in clinical burnout

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Grossi, G., Perski, A., Osika, W., Savic, I. (2015). Stress-related exhaustion disorder – clinical manifestation of burnout? A review of assessment methods, sleep impairments, cognitive disturbances, and neuro-biological and physiological changes in clinical burnout. *Scandinavian Journal of Psychology*.

The aim of this paper was to provide an overview of the literature on clinically significant burnout, focusing on its assessment, associations with sleep disturbances, cognitive impairments, as well as neurobiological and physiological correlates. Fifty-nine English language articles and six book chapters were included. The results indicate that exhaustion disorder (ED), as described in the Swedish version of the International Classification of Diseases, seems to be the most valid clinical equivalent of burnout. The data supports the notion that sleep impairments are causative and maintaining factors for this condition. Patients with clinical burnout/ED suffer from cognitive impairments in the areas of memory and executive functioning. The studies on neurobiological mechanisms have reported functional uncoupling of networks relating the limbic system to the pre-frontal cortex, and decreased volumes of structures within the basal ganglia. Although there is a growing body of literature on the physiological correlates of clinical burnout/ED, there is to date no biomarker for this condition. More studies on the role of sleep disturbances, cognitive impairments, and neurobiological and physiological correlates in clinical burnout/ED are warranted.

Key words: Clinical burnout, exhaustion disorder, stress, assessment, sleep, cognition, brain, physiology.

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INTRODUCTION

Beginning in the 1990s, Swedish sick leave rates due to stress-related psychological ill health have increased dramatically, particularly among women (e.g. Försäkringskassan, 2013a, 2013b, 2015; Lidwall, Marklund, Skogman & Thoursie, 2004; Persson, Danielsson, Rosen, Alexandersson & Lundberg, 2005). Similar patterns have been observed in other industrialized countries, for example, in the OECD countries, where psychological ill health has become the main cause of sickness absence (OECD, 2012, 2013). In everyday language, the word “burnout” is used as a generic term for stress-related psychological distress, due to its overlap with the burnout syndrome as described in social or work psychology (e.g. Freudenberger, 1989; Maslach & Leiter, 2008; Maslach, Schaufeli & Leiter, 2001). The most influential conceptualization of burnout was presented by Maslach and co-workers (Maslach *et al.*, 2001), who defined it as a syndrome of emotional exhaustion, depersonalization and reduced professional accomplishment, mainly afflicting highly motivated employees working in helping professions. While emotional exhaustion refers to the depletion of positive emotions towards the recipients of one's care, depersonalization implies an excessively callous, detached and cynical attitude towards them. The third component, reduced professional accomplishment, refers to an increase in self-appraisals as ineffective, incompetent and/or inadequate for the job. Another definition of burnout comes from Melamed, Kushnir and Shirom (1992) and Shirom (1989), who describe it in terms

of the chronic depletion of an individual's energetic resources as a consequence of chronic stress. In their conceptualization, burnout consists of the three dimensions: physical fatigue, emotional exhaustion and cognitive weariness, and these authors have been seminal in initiating a line of research examining the links between burnout and somatic disease (e.g. Melamed, Shirom, Toker, Berliner & Shapira 2006). In spite of some dissimilarities, all definitions of burnout emphasize the role of exhaustion as a key component of the construct (for a review, see: Schaufeli & Enzmann, 1998). Burnout is not solely work-related, and may ensue as a consequence of long-term exposure to any situation that is emotionally demanding (Gustafsson, 2007; Hallsten, Bellaagh & Gustafsson, 2002; Klaric, Franciskovic, Pernar *et al.*, 2010; Lindström, Aman & Norberg, 2011; Maslach & Leiter, 2008; Pines, 1987, 1994; Pines & Aronson, 1988).

Paine and Jones (1982) and Schaufeli, Bakker, Hoogduin, Schaap and Kladler (2001) have proposed a distinction between a milder form of burnout, that is, symptoms that are not sufficiently incapacitating to prevent the employee from working, and “clinical burnout,” namely, clinically significant exhaustion and impaired performance, which motivates seeking professional help. Typically, these patients report longstanding fatigue, sleep impairments, and problems with memory and concentration, as their chief complaints (Åsberg, Grape, Krakau *et al.*, 2010). Impaired sleep has been associated with high burnout scores in non-clinical populations (Brand, Beck, Hatzinger, Harbaugh, Ruch & Holsboer-Trachsler, 2010; Carter, Dyer & Mikan, 2013;

Melamed *et al.*, 2006; Papp, Stoller, Sage *et al.*, 2004; Rosen, Gimotty, Shea & Bellini, 2006; Saleh & Shapiro, 2008; Vela-Bueno, Moreno-Jiménez, Rodríguez-Muñoz *et al.*, 2008), and some longitudinal studies indicate that poor sleep may be a risk factor for subsequent exhaustion (e.g. Armon, Shirom, Shapira & Melamed, 2008; Söderström, Jeding, Ekstedt, Perski & Akerstedt, 2012). Difficulties with working memory, episodic memory and executive functions are among the most pronounced and incapacitating symptoms reported by patients seen in the clinic, and there is a growing body of literature confirming the associations between burnout and cognitive impairments in both clinical and non-clinical samples (e.g. Deligkaris, Panagopoulou, Montgomery & Masoura, 2014). Since burnout is a stress-related condition, associations with physiological parameters seem plausible. Also, burnout and other states of fatigue, such as vital exhaustion (Appels, Höppener & Mulder, 1987) have been linked to somatic morbidity (Appels & Mulder, 1988; Grossi *et al.*, 2009; Honkonen, Ahola, Pertovaara *et al.*, 2006; Melamed *et al.*, 2006; Shirom, 2009; Van Dienst & Appels, 2002). Studies have therefore sought to find the physiological mechanisms that may explain the symptomatology of burnout, as well as the links between burnout and bodily disease (Danhof-Pont, van Veen & Zitman, 2011; Melamed *et al.*, 2006). The majority of these studies have been conducted among working individuals scoring high or low on burnout questionnaires (e.g. Pruessner, Hellhammer & Kirschbaum, 1999; Melamed, Ugarten, Shirom, Kahana, Lerman & Froom, 1999), while only a minority have been performed among patients with diagnoses reflecting clinical burnout (e.g. De Vente *et al.*, 2003; Grossi *et al.*, 2005).

Overall, clinical burnout has been inadequately investigated. One reason for this is that the Maslach Burnout Inventory (MBI; Maslach & Jackson, 1981, 1986; Schaufeli & Enzmann, 1998), the most widely used instrument for the assessment of burnout, was developed for non-clinical samples. Consequently, a large body of literature has examined the symptoms of burnout and their biological, psychological, and social aspects in people at work (e.g. Danhof-Pont *et al.*, 2011; Honkonen *et al.*, 2006; Lennartsson, Billing & Jonsdottir, 2014).

In view of the fact that stress related psychological ill health is one of the main causes of sick leave in Western societies, there is a great need for studies examining its manifestations, assessment methods, and the physiological and neuro-biological mechanisms underlying it. The aim of this paper was therefore to provide an overview of the literature on clinically significant burnout, focusing on methods for its assessment and on some of its most prominent features, namely sleep disturbances and cognitive impairments including their potential neuro-biological and physiological correlates.

SEARCH STRATEGY

Articles in English, published up until December 2014 were identified through searches on EBSCO Discovery Services (EDS), Psychinfo, Pubmed and Medline. The inclusion criteria were as follows: (1) published clinical trials and observational studies; (2) studies reporting on assessment methods for clinical burnout and stress related exhaustion; (3) studies reporting on the clinical picture of patients suffering from clinical burnout or stress related

exhaustion (studies were included if they comprised individuals who had received a diagnosis reflecting chronic psychosocial stress and/or were on sick leave for such disorders); (4) studies employing objective cognitive tests among patients with clinical burnout or stress related exhaustion; (5) studies examining neurobiological mechanisms in clinical burnout and stress related exhaustion; and (6) studies comparing biological markers between individuals suffering from clinical burnout or stress related exhaustion and healthy controls. We used the search terms “Clinical burnout” and “Exhaustion disorder” (anywhere in the text; the use of brackets denotes phrase search) alone, combined with each other and combined with the following: diagnostics, assessment, questionnaires, sleep, “cognitive impairments,” memory, “executive functions,” brain, “cerebral cortex,” amygdala, hippocampus, physiology, biomarkers, hormones, cortisol, prolactin, “immune system,” cardiovascular, metabolic. The full text of relevant articles was obtained and their reference lists were reviewed for additional studies.

RESULTS

In total, 168 papers were identified and screened by titles and abstracts. Of these, 131 were excluded because they were duplicates or did not fulfil the inclusion criteria, leaving 37 articles that were retrieved for detailed assessment. Additionally, 22 papers and six book chapters were retrieved after review of reference lists. Fifty-nine articles and six book chapters were included in this publication. Among these, 17 articles and six book chapters concerned assessment methods, six concerned sleep and sleep disturbances, 14 concerned cognitive impairments, seven concerned neurobiological mechanisms, and 22 concerned physiological markers. Seven papers (Olsson, Roth & Melin, 2010; Österberg, Karlson & Hansen, 2009, 2012; Rydmark, Wahlberg, Ghatan *et al.*, 2006; Sandström, Peterson, Sandström *et al.*, 2011; Sandström, Säll, Peterson *et al.*, 2012; Wahlberg, Ghatan, Modell, Nygren, Åsberg & Heilig, 2009) focused on two or more of the topics above.

ASSESSMENT OF CLINICAL BURNOUT

Neither burnout nor “Clinical burnout” are considered to be psychiatric disorders in their own right and are not included in the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013). In the International Classification of Diseases (ICD-10; WHO, 2010), burnout is classified as a “State of vital exhaustion” (Z73.0) under “Problems related to life-management difficulty” (Z73), but it is not considered a “disorder.” In studies among clinical samples, “clinical burnout” is usually assessed by a combination of burnout questionnaires and diagnostization based on other ICD or DSM criteria.

Among the burnout scales, the MBI (Maslach & Jackson, 1981, 1986), which has been used in approximately 90% of studies, is by far the most well-established (see also Kleijweg, Verbraak & Van Dijk, 2013; Roelofs *et al.*, 2005; Schaufeli *et al.*, 1996; Schutte, Toppinen, Kalimo & Schaufeli, 2000; Taris, Schreurs & Schaufeli, 1999; Worley *et al.*, 2008). Other scales include the Burnout Measure (BM; Enzmann, Schaufeli, Janssen & Rozeman, 1998; Pines & Aronson, 1988; Pines, Aronson &

Kafry, 1981), the Copenhagen Burnout Inventory (CBI; Kristensen, Borritz, Villadsen & Christensen, 2005), the Oldenburg Burnout Inventory (OLBI; Demerouti, Bakker, Vardakou & Kantas, 2002; Halbersleben & Demerouti, 2005), the Shirom-Melamed Burnout Questionnaire (SMBQ; Kushnir & Melamed, 1992; Lundgren-Nilsson, Jonsdottir, Pallant & Ahlberg, 2012; Melamed, Kushnir & Shirom, 1992), and its later development, the Shirom-Melamed Burnout Measure (SMBM; Shirom, 2003).

In a study investigating the clinical validity of the MBI, Schaufeli *et al.* (2001), found that “work related” neuroasthenia (ICD code F48.0) best fitted the symptoms presented by the participants with clinically significant burnout (see also Roelofs *et al.*, 2005; Sonnenschein, Sorbi, van Doornen, Schaufeli & Maas, 2007b; Sonnenschein, Mommersteeg & Houtveen 2007a; Sonnenschein, Sorbi, Verbraak, Schaufeli, Maas & van Doornen 2008; Sertoz, Binbay, Koylu, Noyan, Yildirim & Mete, 2008; Van Dam, KeijsersEling & Becker, 2011, 2012). Other diagnoses that have been used include undifferentiated somatoform disorder (DSM IV code: 300.82; ICD code F45.1; e.g. Kleijweg *et al.*, 2013; Mommersteeg, Heijnen, Verbraak & van Doornen, 2006b; Oosterholt, Maes, Van, Verbraak & Kompier 2015; Oosterholt, Van der Linden, Kompier, Maes & Verbraak, 2012; Oosterholt, Verbraak, Kompier, Maes & Van 2014), reactions to severe stress and adjustment disorder (DSM IV code: 309.9; ICD code: F43.20; e.g. Blix, Perski, Berglund & Savic, 2015; Golkar, Johansson, Kasahara, Osika, Perski & Savic, 2014; Grossi *et al.*, 2005; Jovanovic, Perski, Berglund & Savic, 2011; Mommersteeg *et al.*, 2006b; Österberg *et al.*, 2009, 2012; Saboonchi, Perski & Grossi, 2013; Savic, 2015), “other reaction to severe stress” (F.43.8; Lundgren-Nilsson *et al.*, 2012), and major depression (DSM IV code: 296.xx.; ICD code F32.xx; e.g. Rydmark *et al.*, 2006; Wahlberg *et al.*, 2009). In two studies by Sandström *et al.* (2011) and Österberg *et al.* (2014), clinically burned out participants were diagnosed with a range of axis I disorders – mainly anxiety and mood disorders – when assessed according to DSM criteria. In a study by Åsberg (2002), 80% of white-collar workers on sick leave due to stress-related disorders were found to have fulfilled the diagnostic criteria for major depression at sometime during the course of their illness. At the time of data collection their symptoms of low mood were in recession, but they were still unable to work due to fatigue, and problems with memory and concentration. Classic cases of major depression were rare within this group and the authors noted that exhaustion caused by chronic stress without restitution, together with neurocognitive problems and sleep impairments were the patients’ chief complaints.

Based on these and other clinical observations, the Swedish Board of Health and Welfare, introduced “exhaustion disorder” (ED; F43.8A) into the Swedish version of the 10th revision of the International Classification of Diseases (ICD-10-SE; Socialstyrelsen, 2010), in order to facilitate more accurate diagnostics of “clinical burnout.” An individual fulfils the criteria for ED if: (A) he or she has experienced psychological and physical exhaustion for at least two weeks; these symptoms must have developed as a consequence of clearly identified stressors, present for at least six months; (B) a significant lack of psychological energy or endurance dominates the clinical picture;

and (C) at least four of the following symptoms have been present virtually every day for the past two weeks: (1) problems with memory or concentration; (2) significantly decreased ability to handle demands or to perform under time pressure; or (3) emotional lability or irritability; (4) sleep disturbances; (5) significant physical fatigue and lack of endurance, (6) bodily symptoms such as muscular pain, chest pain, palpitations, gastrointestinal symptoms, dizziness, or hypersensitivity to sound. Besides causing significant distress and functional impairment, these symptoms must not be attributable to any other cause than stress at work or in the private sphere. If the patient fulfills the criteria for major depressive disorder (MDD), dysthymic disorder (DD), or generalized anxiety disorder (GAD), exhaustion disorder is to be used as a secondary diagnosis (Socialstyrelsen, 2010).

At least three questionnaires have been developed based on the diagnosis of ED. The Karolinska Exhaustion Scale (KES; Saboonchi, Perski & Grossi, 2012) consists of 26 items to be answered on a Likert-type scale ranging from 1 (not at all) to 5 (all the time), which are indexed in five interrelated dimensions. In line with the diagnostic criteria for ED, the respondent is asked if he/she has been exposed to significant stressors during the past six months. Further items are summed up into the subscales “Lack of recovery,” which taps the frequency of excessive fatigue and lack of restorative sleep, “Cognitive exhaustion,” which measures problems with memory and concentration and difficulties in coping with mental demands, “Somatic symptoms,” for example, palpitations, chest pain, muscular tension and pain, and “Emotional distress,” which covers symptoms of irritability, depression and anxiety. The psychometric properties of KES-26 indicate sound construct validity and the scale may also be used to provide information concerning possible different clinical profiles (Saboonchi *et al.*, 2012).

The Karolinska Exhaustion Disorder Scale (KEDS; Beser, Sorjonen, Wahlberg, Peterson, Nygren & Åsberg, 2014) consists of nine items (rated 0–6) with a scale range of 0–54. A cut-off score of 19 was shown to discriminate between healthy subjects and patients with exhaustion (Beser *et al.*, 2014). Finally, a short questionnaire for use in large groups of patients – the Stress-related Exhaustion Disorder (s-ED) scale – has been developed by Glise, Hadzibajramovic, Jonsdottir and Ahlberg (2010). This questionnaire has adequate validity and identifies individuals who are more likely to report sickness absence due to stress-related disorders at follow-up (Glise *et al.*, 2010).

SLEEP DISTURBANCES

Among the six studies about sleep disturbances, two were cross-sectional investigations (Ekstedt, Söderström & Åkerstedt, 2009; Grossi *et al.*, 2015), while four had longitudinal designs (Ekstedt, Söderström, Åkerstedt, Nilsson & Sondegaard, 2006; Sonnenschein, 2007b, 2008; Söderström *et al.*, 2012). The n’s ranged from 24 (Ekstedt *et al.*, 2015) to 420 (Grossi *et al.*, 2015). Ekstedt *et al.* (2006) found profound sleep disturbances in a study comprising 12 white-collar workers on sick leave due to ED and 12 healthy control subjects, who underwent polysomnographic recordings in the home. The patients’ sleep was characterized by more micro-arousals and sleep fragmentation, more awake time and stage 1 sleep, poorer sleep efficiency, less slow wave sleep

and rapid eye movement sleep and lower delta power density in non-rapid eye movement sleep. Sonnenschein *et al.* (2007b) found that ED patients had poorer sleep quality and derived less recovery from sleep than healthy controls, irrespective of depression. In another study, Sonnenschein *et al.* (2008) followed 59 ED patients using electronic diaries for two weeks and again after six months. At follow-up, 37% of the patients returned to work and their symptom levels were similar to the healthy group. Patients who had trouble falling asleep and complained about non-refreshing sleep at baseline had higher exhaustion levels at follow-up and were less likely to return to work.

In a study by Ekstedt *et al.* (2009), 23 white-collar workers on long-term sick leave and 16 control subjects were studied using polysomnographic recordings at baseline and at 6–12-months follow-up. The symptoms in the ED group improved considerably, but did not reach the levels of healthy controls. The patients' recovery was accompanied by improved sleep continuity. Recovery from fatigue was related to a reduction of the micro-arousals from sleep and was the best predictor of return to work. In a prospective questionnaire study, Söderström *et al.* (2012) noted that insufficient sleep (less than six hours), thoughts of work during leisure time and high work demands predicted ED at two-years follow-up.

Insomnia-type sleep disturbances are the most prevalent in ED, but 15% of patients report sleep lengths ≥ 9 hours per day "mostly or always" (Grossi *et al.*, 2015). These patients were found to have better sleep quality than other ED patients, but were also more often on sick leave, reported more depression, fatigue, and daytime sleepiness, and consumed more antidepressants than the other patients. The association between excessive sleep and fatigue was independent of sick leave, depression, antidepressants, and quality of sleep.

COGNITIVE IMPAIRMENTS

Among the 14 reviewed studies, 11 employed a cross-sectional case control design (Jonsdottir, Nordlund, Ellbin *et al.*, 2013; Olsson *et al.*, 2010; Öhman, Nordin, Bergdahl, Slunga Birgander, Stigsdotter Neely, 2007; Oosterholt *et al.*, 2014; Österberg, Karlson & Hansen, 2009; Rydmark *et al.*, 2006; Sandström *et al.*, 2005, 2011, 2012; Wahlberg *et al.*, 2009; Van Dam *et al.*, 2011), while three (Österberg *et al.*, 2012; Oosterholt *et al.*, 2012; Van Dam *et al.*, 2012) used longitudinal designs. The n's ranged from 30 (Sandström *et al.*, 2012) to 130 (Österberg, Karlson & Hansen, 2009).

Sandström *et al.* (2005) found that female patients and controls performed equally well on measures of general cognitive ability and verbal memory. Patients performed significantly poorer in terms of immediate and delayed recall on tests of non-verbal memory, as well as auditory and visual attention. In contrast, Öhman *et al.* (2007) found no group differences in the domains of non-verbal memory, or auditory and visual attention, but observed inferior performance among patients on tests of letter fluency, trail making, digit symbol and prospective memory. The authors argue that these findings suggest the presence of deficits related to executive control functioning and the prefrontal cortex. Rydmark and co-authors (2006), found that female patients performed less well than controls on tests of working memory and reaction time. Österberg *et al.* (2009) found that patients had

significantly more subjective complaints of cognitive impairments relative to controls but performed comparably well on objective tests, with the exception of a small impairment on a cognitive speed test. In line with this, Olsson *et al.*, (2010), noted that patients responded more quickly but with more errors to a task involving vigilance and signal detection.

In a more recent study, Sandström *et al.* (2011) found that patients performed significantly poorer on measures of attention and response control, as well as visuo-spatial memory ability.

Similarly, Jonsdottir *et al.* (2013) compared patients and controls on tests of speed, attention, working memory, learning and episodic memory, executive functions, visuospatial memory and language. The patients had significantly poorer executive functions, in terms of speed, control and working memory. They also performed less well on tests of attention span, learning and episodic memory, the latter operationalized in terms of delayed recall and the difference between immediate and delayed recall. The severity of burnout symptoms was related to delayed recall, indicating that decreased cognitive sustainability is an important feature in clinical burnout. In a study comprising patients, and participants scoring high (non-clinical burnout) and low on a burnout questionnaire, Oosterholt *et al.* (2014) found that patients had slower reaction times but did not have decreased executive functions compared to the other groups. The patients did, however, report higher energy expenditure in completing the tests, as indexed by higher levels of fatigue from pre to post test.

One relevant question is whether burnout patients' poorer cognitive test performance is due to physiological changes or reflects a temporary lack of motivation to engage in effortful mental activity. In a study employing functional magnetic resonance imaging (fMRI), Sandström *et al.* (2012) found that clinically burned out patients tended to under-recruit pre-frontal cortical areas while performing tasks involving memory and executive functions. The authors found this frontal hypoactivation in the presence of apparently intact functional networks. In a study testing whether patients' performance could be increased through a motivational intervention, Van Dam and co-authors (2011) noted that patients' inferior performance on tests of attention and reaction time, could not be enhanced by false positive feedback or by monetary incentives. In a two-year follow-up study, Van Dam *et al.* (2012) found substantial decreases in self-reported symptoms, an increase in cognitive performance and a normalization of motivational responses among the patients who had undergone CBT-treatment. Although 85% of the patient group no longer fulfilled the diagnostic criteria for any psychiatric disorder, they still reported more subjective symptoms of burnout and performed less well on cognitive tasks than controls. Both symptoms and cognitive performance were significantly more improved in those patients (74% of the sample) who had resumed work. In an intervention study by Oosterholt *et al.* (2012), patients reported more cognitive impairments and performed less well than controls on tests of executive functions. After 10 weeks of psychological treatment, the patients' self-rated cognitive symptoms had improved, but they still performed less well on standardized test batteries.

In a study by Wahlberg *et al.* (2009), the initial differences in cognitive performance between patients and controls were no longer evident at one-year follow-up, apparently due to decreased

performance among the controls. Oosterholt *et al.* (2014) found significant decreases in subjective cognitive impairments, but no improvements in performance on neuropsychological tests in a patient sample that had undergone ten weeks of CBT-treatment. Österberg *et al.* (2012), on the other hand, found that patients had improved significantly on both subjective and objective cognitive performance measured at approximately 18 months follow-up. The absence of a comparison group made it impossible to draw conclusions about whether these improvements reflected a complete or only partial recovery. In order to address the issue, Österberg and colleagues (2012) performed a cross-sectional study in which former patients were compared with healthy controls on subjective and objective neuropsychological tests 14 to 30 months after participation in an intervention aimed at work-resumption. The results showed that former patients rated their memory, attention and concentration as poorer than controls, and performed less well on tests of sustained attention and reaction time. Surprisingly, they performed slightly better on some memory tests and a test of simultaneous capacity. The authors conclude that the cognitive improvements seen in former ED patients are partial and that the group continues to manifest slight attention deficits, in spite of a significant general recovery.

NEURO-BIOLOGICAL MECHANISMS

All the identified studies employed a cross-sectional case-control design and sample sizes ranged from 30 (Sandström *et al.*, 2012) to 110 (Golkar *et al.*, 2014). Rydmark *et al.* (2006) and Sandström *et al.* (2011) found no differences in prefrontal or hippocampal volumes between burnout patients and controls. In a later study, Sandström *et al.* (2012) noted an under-recruitment of pre-frontal cortical areas in burnout patients processing cognitive tasks, in the presence of seemingly intact functional networks. In a study using Positron Emission Tomography (PET), Jovanovic *et al.* (2011) reported a functional disconnection between the amygdala and the medial prefrontal cortex in patients, indicating that they lose the ability to inhibit stress responses of the limbic system from the higher cortical centres. The same authors (Jovanovic *et al.*, 2011) also showed significant reductions in the serotonin (5-HT_{1A}) receptor binding in the hippocampus, the anterior insular cortex and anterior cingulate cortex. There was a positive correlation between the magnitude of this reduction and scores for the SMBM. In an fMRI study (Blix *et al.*, 2013), significant reductions were found in the relative volume of the caudate nucleus and putamen in subjects reporting cognitive impairment attributed to chronic occupational stress. To further investigate whether chronic stress could be associated with a functional uncoupling of the limbic networks and an impaired modulation of emotional stress, Savic's group investigated 40 subjects suffering from ED and 70 healthy controls using resting state functional MRI (Golkar *et al.* 2014). The participants' ability to regulate emotion was evaluated by recording their acoustic startle response while viewing neutral and negatively loaded images. ED subjects were less capable of down-regulating negative emotion, but had normal responses when asked to up-regulate or maintain emotion and when no regulation was required. When analysing functional connectivity of amygdala to the anterior cingulate cortex, a significant correlation was found

with the ability to down-regulate negative emotion. This connectivity was significantly weaker in the ED group, as was the amygdala connectivity with the dorsolateral prefrontal cortex and the motor cortex. In subjects with ED, the functional couplings within the emotion- and stress-processing limbic networks seem to be altered and associated with a reduced ability to down-regulate the response to emotional stress, which in turn may contribute to a further facilitation of stress responses.

PHYSIOLOGICAL ASPECTS

We found 22 studies of physiological mechanisms among patients with clinical burnout. Eighteen focused on the hypothalamic-pituitary-adrenocortical axis (HPA-axis; De Vente *et al.*, 2003; Grossi *et al.*, 2005; Moch, Panz, Joffe, Havlik & Moch, 2003; Olsson *et al.*, 2009; Olsson *et al.*, 2010; Oosterholt *et al.*, 2015; Österberg *et al.*, 2009, 2012; Mommersteeg *et al.*, 2006b, 2006c; Mommersteeg, Keijsers, Heijnen, Verbraak & van Doornen, 2006d; Rydmark *et al.*, 2006; Sertoz *et al.*, 2008; Sonnenschein *et al.*, 2007a; Wahlberg *et al.*, 2009; Sandström *et al.*, 2011, 2012; Sjörs, Ljung & Jonsdottir, 2013), and 11 on other systems (Åsberg, Nygren, Leopardi *et al.*, 2009; Bäckström, Bixo, Nyberg & Savic, 2015; De Vente *et al.*, 2003; Grossi & Santell, 2009; Moch *et al.*, 2003; Mommersteeg *et al.*, 2006a; Olsson *et al.*, 2010; Sandström *et al.*, 2011; Sertoz *et al.*, 2008; Sonnenschein *et al.*, 2007a; Sjörs *et al.*, 2013). Fifteen studies employed a cross-sectional case-control design (Åsberg *et al.*, 2009; Bäckström *et al.*, 2013; De Vente *et al.*, 2003; Grossi *et al.*, 2005; Mommersteeg *et al.*, 2006b, 2006a; Olsson *et al.*, 2010; Oosterholt *et al.*, 2015; Österberg *et al.*, 2009; Rydmark *et al.*, 2006; Sertoz *et al.*, 2008; Sandström *et al.*, 2011, 2012; Sjörs *et al.*, 2013), while seven had longitudinal designs (Grossi and Santell, 2009; Moch *et al.*, 2003; Mommersteeg *et al.*, 2006d, 2006c; Olsson *et al.* 2009; Österberg *et al.*, 2012; Sonnenschein *et al.*, 2007a). Sample sizes varied between 22 (Bäckström *et al.*, 2013) and 324 (Åsberg *et al.*, 2009).

The majority of the studies concerning HPA-activity relied on saliva sampling (De Vente *et al.*, 2003; Grossi *et al.*, 2005; Olsson *et al.*, 2009, 2010; Oosterholt *et al.*, 2015; Österberg *et al.*, 2009, 2012; Mommersteeg *et al.*, 2006b, 2006d, 2006c; Rydmark *et al.*, 2006; Sandström *et al.*, 2011, 2012; Sonnenschein *et al.*, 2007a), and four employed blood or urine samples (Moch *et al.*, 2003; Sandström *et al.*, 2011; Sertoz *et al.*, 2008; Sjörs *et al.*, 2013). In addition to measuring the circulating levels of hormones, some studies assessed HPA-axis feedback sensitivity through the administration of dexamethasone (e.g., Mommersteeg *et al.*, 2006c; Sertoz *et al.*, 2008; Sonnenschein *et al.*, 2007a) or the combined dexamethasone/corticotropin-releasing hormone challenge (DEX-CRH; Rydmark *et al.*, 2006; Wahlberg *et al.*, 2009). The published results show both positive (De Vente *et al.*, 2003; Grossi *et al.*, 2005; Olsson *et al.*, 2010), and negative (Mommersteeg *et al.*, 2006d; Oosterholt *et al.*, 2015; Rydmark *et al.*, 2006; Sandström *et al.*, 2011, 2012; Sonnenschein, 2007a; Wahlberg *et al.*, 2009) and non-significant (Mommersteeg *et al.*, 2006b) associations between burnout and saliva cortisol.

Moch *et al.* (2003) found lower serum cortisol levels among patients than controls, four months after therapy. No group differences were seen at baseline or after one or two months.

Sertoz *et al.* (2008) and Sjörs *et al.* (2013) found no differences in serum cortisol between patients and controls. Moch *et al.* (2003), observed a reduction of urine free-cortisol excretion in their sample of patients, while Sandström *et al.* (2011) found no differences in total diurnal output between patients and controls.

Longitudinal changes in HPA-axis activity

In one of the studies by Mommersteeg *et al.* (2006d), 22 patients who had undergone 14 sessions of psychotherapy manifested an increase in their initially lower morning cortisol levels. In another study, Mommersteeg *et al.* (2006c) followed 74 patients, at pre- and post-treatment, and at eight months follow-up, and found a small decrease in daytime cortisol levels, but no changes in morning cortisol levels after awakening and after dexamethasone administration. Similar results were obtained by Österberg *et al.* (2012), who examined changes in salivary cortisol levels among 45 patients who were followed for a period of 18 months. In line with Mommersteeg *et al.* (2006c), they found no significant changes in cortisol levels at awakening, 30 minutes thereafter or in the evening, from baseline to follow-up. However, they could observe a slightly more pronounced suppression of cortisol following dexamethasone administration. In contrast, Olsson *et al.* (2009), observed a normalization of the patients' initially greater AUC, following treatment with *Rhodiola rosea*.

Other hormones

We found eleven studies of the associations between clinical burnout and hormones other than cortisol. Clinical burnout has been related to higher salivary dehydroepiandrosterone sulphate (DHEAs) (Mommersteeg *et al.*, 2006a, Sonnenschein *et al.*, 2007a), although no differences between patients and controls were seen in the study employing blood samples (Moch *et al.*, 2003).

Åsberg and co-workers (2009) found lower prolactin, thyroid stimulating hormone (TSH) and total triiodothyronine (T3), and higher testosterone in female patients and working females with elevated burnout scores, compared to healthy controls. Sandström *et al.* (2011) reported lower TSH and higher thyroxine (T4) among patients.

In a study by Bäckström *et al.* (2013), female patients demonstrated an increased sensitivity to the progesterone metabolite and gamma-aminobutyric-acid-A (GABA-A) receptor modulator allopregnanolone, as indexed by saccadic eye movement velocity (SEV), indicating a greater sedative effect of this compound. Administration of flumazenil led to an unexpected agonistic rather than antagonistic effect on allopregnanolone among patients, but not among controls. The authors hypothesize that changes in the alpha4 and delta-subunits of the GABA-A receptors take place in women exposed to chronic stress.

Cardiovascular and metabolic measures

De Vente *et al.* (2003) found slight elevations in heart rate among patients compared to controls, both at rest and following a stress provocation. The authors found no associations between burnout and blood pressure or vagal activity. Olsson *et al.* (2010) observed

that women on long-term sick leave due to stress-related fatigue had significantly lower heart rate variability (HRV) together with other signs of autonomic arousal than healthy controls.

In the study by Grossi and Santell (2009), glycated haemoglobin (HbA1c) was used as an independent variable in the longitudinal data collection. Participation in a stress management programme was related to decreased symptoms of depression and burnout, but contrary to expectations, also to a significant increase in HbA1C, that was also evident in the control condition. In contrast to these findings, Sjörs *et al.* (2013), found no significant differences in HbA1C between ED patients and controls, but lower plasma glucose and higher insulin levels, principally among male patients.

Immune system, growth factors and trophic factors

Mommersteeg *et al.* (2006a) found no differences between patients and controls in T cells, B cells or NK cells or circulating levels of tumor necrosis factor alpha (TNF-alpha) or gamma interferon. They did, however, observe increased production of the anti-inflammatory cytokine interleukin 10 (IL-10) by lipopolysaccharide (LPS) stimulated monocytes among patients. Sertoz *et al.*, (2008) found decreased serum levels of brain derived neurotrophic factor (BDNF) among hospital staff diagnosed with work related neurasthenia. Åsberg *et al.* (2009) observed group differences in monocyte chemotactic protein 1 (MCP1), which was more than twice as high among participants on sick leave compared to the healthy controls. The same group found a dose-response relationship between levels of emotional distress and epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF), but no group differences in pro-inflammatory and anti-inflammatory cytokines. Sandström *et al.* (2011), found no differences in interleukin 6 (IL-6) or TNF-alpha between patients and controls, but noted that significantly more patients than controls had detectable levels of interleukin 1-beta (IL-1-beta).

DISCUSSION

The aim of this paper was to provide an overview of the literature on clinical burnout, focusing on its manifestations, assessment, associations with sleep disturbances, cognitive impairments, as well as neurobiological and physiological correlates.

Assessment

Since burnout is not included in the DSM or ICD, professionals choose diagnoses that have the greatest concordance with the symptoms reported by the patients. The present review indicates that a wide selection of Axis I mood and anxiety disorders have been employed to this end. Clinical observations indicate that the established diagnoses for mood and anxiety disorders are not fully adequate for the assessment of clinical burnout. Major depression and clinical burnout have partially overlapping symptoms and are frequently co-morbid, but are not redundant concepts (Glass & McKnight, 1996; Schaufeli & Enzmann, 1998). While concentration difficulties, fatigue, loss of energy, and sleep impairments, are prevalent in both conditions, ED characteristically

lacks the persistently low mood, anhedonia, self-blame, and/or suicidal ideations that are hallmarks of MDD. The sleep impairments seen in ED are more frequently characterized by difficulties in falling asleep, while individuals with MDD report more frequent early awakenings. Patients with ED typically perceive a reduction of symptoms in the morning while depressed patients, experience an amelioration in the evening. ED develops gradually, often over a period of many years, and its symptoms' onset is frequently experienced as fulminant and very dramatic. The recovery period is prolonged, often requiring several years. The onset of depression is not experienced as dramatically and its course is episodic, with a high risk of relapse. Between depressive episodes, the individual may experience significant improvements in symptoms (Åsberg *et al.*, 2010, 2011, 2013). The diagnosis of ED, as described in the Swedish version of the ICD-10 (Swedish Board of Health and Welfare, 2010) may thus be a more viable way of operationalizing "clinical burnout."

Sleep

The associations between impaired sleep and burnout are rather well established in non-clinical populations (e.g. Armon *et al.*, 2008; Ekstedt *et al.*, 2004; Jansson-Fröjmark and Lindblom, 2010; Söderström, Ekstedt, Åkerstedt, Nilsson & Axelsson, 2004) and our review indicates that disturbed sleep is one of the best predictors of ED. As postulated by Söderström *et al.* (2012), stress – related to worry and ruminations in the evening – may lead to difficulties falling asleep, to a more superficial sleep, and a higher frequency of arousals. Unrefreshing sleep contributes to a chronic lack of restitution, which results in a state of profound exhaustion. Chronic insomnia-like sleep disturbances thus seem to be the mechanism mediating the associations between stress and ED. The findings from the review also indicate that a minority of patients sleep excessively. Improved sleep is related to work resumption.

Cognitive impairments and neurobiology

The available studies show that patients with clinical burnout manifest deficiencies in executive functions, attention and episodic and working memory. These dysfunctions could be ascribed to impairments in one or more of the four components of working memory, i.e. the central executive, the phonological loop, the visuo-spatial sketchpad and/or the episodic buffer (Baddeley, 2000; Deligkaris *et al.*, 2014). The central executive – which is mainly located in the prefrontal brain regions – could be the component that is most vulnerable to chronic stress, since its higher order attentional control functions are more demanding and complex than those performed by the other subcomponents (Deligkaris *et al.*, 2014). To our knowledge there are only seven studies investigating the neuro-biological underpinnings of such dysfunctions in clinical burnout. No evidence for structural hippocampal and pre-frontal alterations have been observed in three of them (Rydmark *et al.*, 2006; Sandström *et al.*, 2011, 2012), while the remaining four have reported functional uncoupling of networks relating the limbic system to the pre-frontal cortex (Golkar *et al.*, 2014; Jovanovic *et al.*, 2011; Savic,

2015), and decreased volumes of structures within the basal ganglia – the caudate nucleus and putamen – which are not only involved in voluntary movement, but also in goal-directed behaviour and working memory (Blix *et al.*, 2013).

Studies indicate that cognitive impairments seen in clinical burnout are partially reversible through treatment, but patients are still cognitively impaired at follow-up.

The studies concerning cognitive impairments show some inconsistencies in findings, which may be ascribed to heterogeneity in sample compositions, differences in burnout assessment, poor control for co-morbidity, and/or to differences in assessment tools.

Physiological aspects

The results concerning HPA-activity remain contradictory, with studies showing both higher (De Vente *et al.*, 2003; Grossi *et al.*, 2005; Olsson *et al.*, 2010), and lower (Mommersteeg *et al.*, 2006d; Oosterholt *et al.*, 2015; Rydmark *et al.*, 2006; Sandström *et al.*, 2011, 2012; Sonnenschein, 2007b; Wahlberg *et al.*, 2009), or comparable (Mommersteeg *et al.*, 2006b) levels of salivary cortisol among patients compared to controls. The studies on longitudinal changes in HPA-activity also yield an inconclusive picture, with some showing increased (Mommersteeg *et al.*, 2006d) and some decreased (Mommersteeg *et al.*, 2006c; Olsson *et al.*, 2009) cortisol levels after treatment. As is the case in the studies of cognitive impairments, the way clinical burnout was defined in the different studies may contribute to the contrasting findings. While Rydmark *et al.* (2006) and Wahlberg *et al.* (2009) used a diagnosis of "work stress induced depression" to define their sample, Mommersteeg and co-workers (2006b, 2006d, 2006c, 2006a) and Grossi *et al.*, (2005) used reactions to severe stress and adjustment disorder. This may indicate the presence of differences between the studies in the variety and severity of participants' symptoms, co-morbidity, use of medications, phase in the burnout process and degree of sick leave. Other variables that may have differed between the groups are the use of oral contraceptives and hormonal replacement, alcohol consumption, other life-style factors, and phase in the menstrual cycle. Hypothetically, there may be heterogeneity in subsamples within the population of individuals with clinical burnout, some of which may manifest hypercortisolism and others the opposite. Also, the assessment methods varied between the studies included in the present review, with some employing challenges (e.g. Rydmark *et al.*, 2006; Wahlberg *et al.*, 2009) and others not (e.g. Grossi *et al.*, 2005). In the majority of studies, the researchers sought associations between questionnaire scores and indices of HPA-activity. According to Sonnenschein *et al.* (2007a), the retrospective memory bias that is associated with questionnaires may be one possible explanation for inconsistent findings concerning HPA-axis activity. Supporting this notion, the Sonnenschein *et al.* (2007a) study revealed associations between cortisol and burnout symptoms measured moment to moment by means of electronic diaries, but not between cortisol and regular questionnaires. The use of electronic diaries may, thus, be a more viable approach when it comes to analysing the associations between psychological symptoms and physiological variables.

Besides the studies on HPA-axis activity, eleven studies examined differences between patients and controls in a great variety of endocrine, cardiovascular, metabolic, and immune variables. Some of these variables were measured in more than one study, and the results are contrasting. Levels of DHEAs, for instance, were found to be elevated among patients in the studies employing salivary samples (Mommersteeg *et al.*, 2006a; Sonnenschein *et al.*, 2007a) while there were no differences in the study employing blood samples (Moch *et al.*, 2003). DHEAs is an adrenocortical hormone with immunomodulatory effects opposite to those of cortisol (Chen & Parker, 2004) and the biological meaning of these findings remains to be elucidated.

Prolactin was analysed in one study (Åsberg *et al.*, 2009) showing lower levels among patients compared to controls. The pituitary hormone prolactin increases in response to various stressors (e.g. Theorell, 1992), possibly in order to protect against their noxious effects (Dorshkind & Horseman, 2001; Drago, D'Agata, Iacona *et al.*, 1989). Elevated levels of prolactin would thus be expected in clinical burnout, and this topic deserves further investigation. Åsberg *et al.* (2009) and Sandström *et al.* (2011) observed lower TSH levels among patients compared with controls. In the study by Åsberg and co-authors (2009), T3 levels were somewhat lower among patients, while in the Sandström *et al.* (2011) investigation patients had higher T4 levels. The findings are in line with those from studies showing changes in thyroid functioning in psychiatric disorders (Wysokinski & Kloszewska, 2014).

In spite of the observed associations between burnout and cardiovascular morbidity (e.g., Melamed, Shirom, Toker, Berliner & Shapira, 2006), we only found five studies on cardiovascular/metabolic variables comparing patients and controls. Although the general picture indicates a state of autonomic hyperarousal and a somewhat higher cardiovascular risk among patients, the results are far from conclusive. Stress is known to affect the immune function (e.g. Kiecolt-Glaser *et al.*, 2002), and inflammatory processes may account for the symptoms of fatigue reported by individuals with burnout (Vollmer-Conna, Fazou, Cameron *et al.*, 2004). In the studies that we found on this subject, a great variety of variables related to immune and inflammatory functioning were assessed. Taken together, these studies indicate both inflammatory (Sandström *et al.*, 2011) and anti-inflammatory responses (Mommersteeg *et al.*, 2006a) in clinical burnout, but more research is needed (see also Åsberg *et al.*, 2009).

The results concerning neurosteroid sensitivity (Bäckström *et al.*, 2013), testosterone, and trophic and growth factors (Sertoz *et al.*, 2008; Åsberg *et al.*, 2009) indicate promising new directions for studies of physiology in clinical burnout, but are in need of replication.

Although the findings relating burnout to low cortisol are in accord with a meta-analysis by Chida and Steptoe (2009), indicating that the cortisol awakening response is positively related to work stress and general life stress and negatively to burnout and other states of fatigue, we agree with Danhof-Pont and colleagues (2011) in saying that there is, to date, no potential biomarker for burnout.

One shortcoming of the present paper is that the data are only presented in a qualitative way and no quantitative measures are included. In spite of this limitation, this review

article on the manifestations, assessment methods, sleep, cognitive, neurobiological and physiological correlates of "clinical burnout" indicates that a diagnosis of exhaustion disorder seems to be the clinical manifestation of burnout. Although there is a lack of studies on sleep physiology in ED, the available data supports the notion that sleep impairments are important causative and maintaining factors for this condition. Patients with ED suffer from cognitive impairments in the areas of memory and executive functioning. The available studies on neuro-biological mechanisms indicate the presence of structural changes that may account for these impairments. There is to date no biomarker for clinical burnout/exhaustion disorder.

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Received 11 March 2015, accepted 20 July 2015