Severe fatigue in narcolepsy with cataplexy

Citation for published version (APA):

DOI:
10.1111/j.1365-2869.2011.00943.x

Document status and date:
Published: 01/04/2012

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.

Download date: 18. Sep. 2020
Severe fatigue in narcolepsy with cataplexy

HAL A. DROOGLEEVER FORTUYN1, ROLF FRONCZEK2, MIRJAN SMITSHOEK2, SEBASTIAAN OVEREEM3,4, MARTIJN LAPPENSCHAAR1, JOKE KALKMAN5,6, WILLY RENIER3, JAN BUITELAAR1, GERT JAN LAMMERS2 and GIJS BLEIJENBERG6

1Departments of Psychiatry, Radboud University Nijmegen Medical Center, the Netherlands, 2Department of Neurology, Leiden University Medical Center, the Netherlands, 3Neurology, Radboud University Nijmegen Medical Center, the Netherlands, 4Sleep Medicine Center, ‘Kempenhaeghe’, the Netherlands, 5Medical Psychology, Radboud University Nijmegen Medical Center, the Netherlands and 6Expert Center Chronic Fatigue, Radboud University Nijmegen Medical Center, the Netherlands

Keywords
depression, fatigue, hypersomnia, narcolepsy, quality of life, sleep

Correspondence
H. A. Droogleever Fortuyn MD, Department of Psychiatry, Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, the Netherlands.
Tel.: 31-24-3613410; fax: 31-24-3540561; e-mail: H.Droogleever-Fortuyn@psy.umcn.nl

Accepted in revised form 14 May 2011; received 1 June 2010
DOI: 10.1111/j.1365-2869.2011.00943.x

SUMMARY
Excessive daytime sleepiness (EDS) is the core symptom of narcolepsy. However, there have been indications that fatigue – which should be separated from EDS – is also a frequent complaint. We determined the prevalence of severe fatigue in a group of narcolepsy patients and its relation with excessive daytime sleepiness, psychological distress, functional impairment and quality of life. We included 80 patients fulfilling the International Classification of Sleep Disorders (ICSD)-2 diagnostic criteria of narcolepsy with cataplexy. Fatigue was measured using the Checklist Individual Strength (CIS). In addition psychological distress, including symptoms of depression, functional impairment and quality of life, were assessed. Comparisons were made between patients with (CIS-fatigue score ≥ 35) and without severe experienced fatigue. Fifty patients (62.5%) reported severe fatigue. There were no sex or age differences between patients with and without severe fatigue. Both fatigued and non-fatigued patients had the same amount of daytime sleepiness (Epworth Sleepiness Score 14.3 ± 4.2 versus 13.1 ± 4.4, P = 0.22), confirming the separation between sleepiness and fatigue. Interestingly, fatigued patients more often used stimulant medication (64% versus 40%, P = 0.02). Severe fatigue was associated with a significantly increased functional impairment, increased depressive symptoms and a lowered general quality of life. In conclusion, a majority of patients with narcolepsy suffer from severe fatigue, which can be distinguished from daytime sleepiness, and results in severe functional impairment.

INTRODUCTION
Excessive daytime sleepiness and cataplexy form the core symptoms of narcolepsy, a primary sleep disorder with a prevalence of about five to six per 10 000 (Overeem et al., 2002). Fragmented night-time sleep, hypnagogic hallucinations and sleep paralysis are frequently reported additional symptoms. Many patients also complain about fatigue, a finding that was already reported in the older narcolepsy literature (Redlich, 1925). In a strict sense, fatigue should be defined as a subjective experience of mental or physical exhaustion that does not disappear after a period of sleep (Vercoulen et al., 1994). In contrast, daytime sleepiness is defined as the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness and/or sleep. However, patients may have trouble distinguishing between daytime sleepiness with sleep attacks and the physical feeling of fatigue. Medical doctors also have difficulty in differentiating between sleepiness and fatigue, often tending to equate them (Lichstein et al., 1997). In some languages, for example Finnish, sleepiness and exhaustion are even synonymous. However, although excessive daytime sleepiness and fatigue may have overlapping features, they are distinct symptoms that have been shown to co-occur independently in sleep-disordered patients (Lichstein et al., 1997).
Severe fatigue has been found in high percentages of patients with chronic neurological conditions such as Parkinson’s disease (Friedman et al., 2007), multiple sclerosis (van der Werf et al., 1998) and neuromuscular disorders (Kalkman et al., 2007). In these diseases, it was shown that severe fatigue has important clinical consequences, such as increased functional limitations and lowered general health status (Kalkman et al., 2005). Finally, there have been reports of patients diagnosed with ‘chronic fatigue syndrome’ who later turned out to have narcolepsy (Ambrogetti and Olson, 1994). The exact prevalence and the functional consequences of fatigue in narcolepsy remain unknown. Therefore, we performed a detailed questionnaire study on the presence, severity and consequences of fatigue in narcolepsy.

**METHODS**

**Patients**

Patients were recruited from the outpatient clinic of the department of Neurology, Leiden University Medical Center (Leiden, the Netherlands). The local medical ethical committee approved the study. All patients signed informed consent to participate in the study.

A total of 127 patients under active treatment were approached by mail to participate. We did not approach patients with comorbid sleep apnoea (defined by an apnoea–hypopnoea index of more than 15 per hour on the original diagnostic polysomnography) and those not proficient in Dutch. All patients were clinically assessed by G.J.L. and fulfilled the International Classification of Sleep Disorders (ICSD)-2 clinical diagnostic criteria of narcolepsy with cataplexy (International Classification of Sleep Disorders (ICSD), 2005). A total of 80 (63%) patients returned a completed questionnaire. Cerebrospinal fluid (CSF) hypocretin-1 measurements were performed in 25 of these patients: hypocretin-1 was undetectable in 23, and within normal limits in two patients. Diagnostic polysomnographic and Multiple Sleep Latency Test registrations were performed on average more than 6 years before data collection, so these data were not used in the present study.

**Questionnaires**

**Fatigue severity**

Fatigue severity was assessed using the Fatigue Severity Scale (eight items, score range 8–56) of the validated Dutch version of the Checklist Individual Strength (CIS-fatigue) (Vercoulen et al., 1999). Each item was rated on a seven-point Likert scale, with higher scores representing a higher severity of fatigue. Healthy subjects also score fatigue symptoms. In other words: ‘fatigue’ should be regarded as a continuum. Previous studies showed a population mean of around 16 on the CIS-fatigue. The cut-off for ‘severe fatigue’ was defined as two standard deviations above this value, i.e. at 35 points (Vercoulen et al., 1994). The CIS is a validated measure with good internal consistency and international recognition (Dittner et al., 2004). This scale has been used in studies on the presence of fatigue in several neurological disorders (Kalkman et al., 2007; Tieleman et al., 2010).

**Depression and psychological distress**

Depression was assessed using the Beck Depression Inventory for Primary Care (BDI-PC) (Beck et al., 1997). The primary care version was used because the complete BDI contains somatic symptoms of depression which overlap with the physical aspects of fatigue. A score of 4 or higher indicates the presence of clinical depression. The Symptom Checklist-90 (SCL-90) was used to assess psychological distress (Derogatis et al., 1973).

**Functional impairment and quality of life**

Functional impairment was described and quantified with the Sickness Impact Profile (SIP) (Bergner et al., 1981), containing the eight categories: sleep and rest, home management,
mobility, social interaction, ambulation, alertness behaviour, work and recreation and pastimes. A higher score on the SIP indicates more impairment. The following subscales of the RAND Short Form-36 (SF-36) were used to assess overall quality of life: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, mental health, bodily pain and general health perception (McHorney et al., 1994). The transformed scores for all SF-36 scales range from 0 to 100, with a higher score indicating better functioning or less pain.

Daytime sleepiness

The Epworth Sleepiness Scale (ESS) is a validated scale to measure the presence and severity of excessive daytime sleepiness (Johns, 1991). Subjects rate the chance of falling asleep on eight different circumstances often encountered in daily life.

Data analysis and statistics

All data analyses were performed using SPSS for Windows (version 14; SPSS, Inc., Chicago, IL, USA). Overall data were analysed using descriptive statistics. We divided our sample into patients with and without severe experienced fatigue (cut-off value of ≥35 on the CIS-fatigue, see above). Afterwards, differences between groups were assessed using Student’s t- or chi-square tests on continuous and categorical variables, respectively. Levene’s test was used to assess equality of variances and P-values adjusted when appropriate. In addition to the above analyses, correlations between CIS-fatigue scores and psychological distress, depression, functional impairment and quality of life were calculated using Spearman’s coefficients. All data are shown as mean ± SD, unless otherwise indicated.

RESULTS

Prevalence of severe fatigue

Severe fatigue was present in 50 patients (62.5%) (Table 1). There were no age or sex differences between patients with and without severe fatigue. Patients with severe fatigue more often used stimulant medication (64% versus 40%, Table 1). This latter relation was stronger for patients using methylphenidate [eight of nine patients severely fatigued; likelihood ratio (LR) 3.5, \( P = 0.028 \)] than for patients using modafinil (21 of 31 severely fatigued, LR 2.8, \( P = 0.078 \)). There were no other differences in medication use between the groups.

Fatigue and sleepiness

There was only a weak correlation between scores on the ESS and the CIS-fatigue subscale (\( r = 0.274, P = 0.014 \)). ESS scores did not differ between the severely and not severely fatigued patients (see Table 2).

Fatigue and depression, psychological distress, quality of life and impairment

In Table 2, levels of psychological distress, depression, impairment in daily life as well as quality of life are compared between the patient subgroups. For the different scales, a direct correlation with CIS-fatigue scores was also computed. Both the correlation analysis and the comparison between groups, with different levels of fatigue, showed converging results.

Beck Depression Inventory for Primary Care scores were higher in the severely fatigued patients compared to the not severely fatigued patients (\( P < 0.01 \), Table 2). Although the presence of clinical depression (i.e. a BDI-PC >4) was not significantly different between groups (Table 2), depression was correlated with fatigue (\( r = 0.324, P = 0.002 \)). Severely fatigued patients showed high levels of psychological distress, on almost all SCL-subscales (Table 2 and Fig. 1a). The SCL-sleep subscale, which probes disturbed nocturnal sleep, was significantly higher in the severely fatigued patients as well.

Severe fatigue was related significantly to more functional impairment, as the total SIP score was almost doubled in the severely fatigued group (1051.2 ± 664.0 versus 527.5 ± 449.1, \( P < 0.001 \)). However, even the not severely fatigued narcoleptics had scores that were higher than reported in a reference group of 450 patients treated by general practitioners for mild somatic complaints (mean total score of 211) (Vercoulen et al., 1994). SIP subscores on various categories of activities are shown in Table 2 and Fig. 1b. Severely fatigued patients were most impaired in the domains of mobility, ambulation, social interaction and recreation and pastimes. However, the SIP score ‘work’ was not significantly different between the two subgroups, suggesting that impairment of the severely fatigued subgroup was felt mainly in the private domain. There was a significant decrease in all dimensions of quality of life as measured in the SF-36 in the severely fatigued group (Fig. 1c).

DISCUSSION

In this study we show that severe fatigue is highly prevalent in narcolepsy with cataplexy. On average, ESS scores did not differ between patients with and without severe fatigue, with only a weak correlation between individual fatigue and sleepiness scores. Severe fatigue was, however, associated with global psychological distress including depressive symptoms, functional impairment and a loss of quality of life.

Severe fatigue is more prevalent in narcolepsy than, for example, epilepsy, in which group 48% of the patients scored mild/moderate or severe on the Fatigue Severity Scale (FSS) (Senol et al., 2007). The high prevalence of severe fatigue in narcolepsy (62%) is comparable to prevalence
Table 2 Levels of psychological distress, depression, quality of life and impairment in daily life, as possible determinants of fatigue

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Comparison between subgroups</th>
<th>Correlation analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe fatigue</td>
<td>Not severe fatigue</td>
</tr>
<tr>
<td>SCL anxiety</td>
<td>16.3 ± 6.1</td>
<td>11.9 ± 2.7</td>
</tr>
<tr>
<td>SCL agoraphobia</td>
<td>10.4 ± 4.8</td>
<td>7.9 ± 1.8</td>
</tr>
<tr>
<td>SCL depression</td>
<td>31.4 ± 13.5</td>
<td>21.4 ± 4.6</td>
</tr>
<tr>
<td>SCL somatization</td>
<td>23.1 ± 7.3</td>
<td>16.6 ± 3.6</td>
</tr>
<tr>
<td>SCL insufficiency</td>
<td>21.9 ± 7.2</td>
<td>15.0 ± 4.8</td>
</tr>
<tr>
<td>SCL sensitivity</td>
<td>30.3 ± 13.2</td>
<td>21.8 ± 4.7</td>
</tr>
<tr>
<td>SCL hostility</td>
<td>8.5 ± 2.6</td>
<td>6.8 ± 1.3</td>
</tr>
<tr>
<td>SCL sleep</td>
<td>8.6 ± 3.2</td>
<td>6.3 ± 2.7</td>
</tr>
<tr>
<td>BDI primary care</td>
<td>3.6 ± 3.51</td>
<td>1.00 ± 1.62</td>
</tr>
<tr>
<td>BDI total</td>
<td>13.7 ± 8.4</td>
<td>5.8 ± 5.3</td>
</tr>
<tr>
<td>BDI-PC &gt;4</td>
<td>13 (26%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>RAND physical functioning</td>
<td>65.5 ± 28.5</td>
<td>89.3 ± 13.6</td>
</tr>
<tr>
<td>RAND social functioning</td>
<td>54.5 ± 26.3</td>
<td>75.8 ± 20.7</td>
</tr>
<tr>
<td>RAND role limitations – physical</td>
<td>40.5 ± 40.1</td>
<td>60.0 ± 39.1</td>
</tr>
<tr>
<td>RAND role limitations – social</td>
<td>59.3 ± 46.3</td>
<td>87.8 ± 28.3</td>
</tr>
<tr>
<td>RAND mental health</td>
<td>64.8 ± 20.9</td>
<td>80.53 ± 12.1</td>
</tr>
<tr>
<td>RAND vitality</td>
<td>36.1 ± 17.9</td>
<td>61.5 ± 16.1</td>
</tr>
<tr>
<td>RAND bodily pain</td>
<td>69.8 ± 29.7</td>
<td>84.5 ± 20.1</td>
</tr>
<tr>
<td>RAND general health perception</td>
<td>49.3 ± 23.0</td>
<td>64.8 ± 20.6</td>
</tr>
<tr>
<td>RAND change in health (1 year)</td>
<td>41.5 ± 17.2</td>
<td>50.0 ± 13.1</td>
</tr>
<tr>
<td>SIP sleep and rest</td>
<td>146.7 ± 92.8</td>
<td>87.6 ± 90.3</td>
</tr>
<tr>
<td>SIP home management</td>
<td>89.1 ± 92.7</td>
<td>48.7 ± 61.9</td>
</tr>
<tr>
<td>SIP mobility</td>
<td>60.9 ± 84.5</td>
<td>16.3 ± 34.4</td>
</tr>
<tr>
<td>SIP social interaction</td>
<td>235.1 ± 213.1</td>
<td>102 ± 122.5</td>
</tr>
<tr>
<td>SIP ambulation</td>
<td>45.7 ± 83.6</td>
<td>3.9 ± 12.1</td>
</tr>
<tr>
<td>SIP alertness behaviour</td>
<td>251.7 ± 214.2</td>
<td>133.7 ± 166.5</td>
</tr>
<tr>
<td>SIP work</td>
<td>101.16 ± 132.3</td>
<td>75.4 ± 122.0</td>
</tr>
<tr>
<td>SIP recreation and pastimes</td>
<td>120.9 ± 80.2</td>
<td>60.0 ± 72.9</td>
</tr>
<tr>
<td>SIP total</td>
<td>1051.2 ± 664.2</td>
<td>527.5 ± 449.0</td>
</tr>
<tr>
<td>ESS total</td>
<td>14.3 ± 4.2</td>
<td>13.1 ± 4.4</td>
</tr>
</tbody>
</table>

BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; RAND, RAND Short Form-36; SCL, Symptom Checklist-90; SIP, Sickness Impact Profile; Data are mean ± SD.

Figure 1. (a) Group scores on the various items of the Symptom Checklist-90, measuring general psychopathology. (b) Functional impairment, reflected in changes of conduct in everyday activities due to sickness (Sickness Impact Profile). (c) Subscores on the Short Form-36 to assess quality of life. NS: not significant; * P < 0.05; ** P < 0.01; *** P < 0.001.
showed that the small subgroup ($n = 22$) of narcolepsy patients had the highest fatigue scores, together with insomnia group. In contrast to our results, these authors found a significant correlation in the narcoleptics between sleepiness as measured with the ESS and the FSS ($r = 0.71$). In part, this discrepancy may be found in the differences between the fatigue scales. The FSS measures the impact of fatigue on specific types of functioning, rather than ‘pure’ perceived fatigue severity (Dittner et al., 2004). The CIS-F focuses more on perceived fatigue and (lack of) fitness. Conversely, the relative independency of fatigue and sleepiness that we found in our study has also been described by other authors. In a recent study (Neu et al., 2008), daytime sleepiness and fatigue were measured in patients diagnosed with ‘chronic fatigue syndrome’ or sleep apnoea and healthy controls. Sleepiness was measured by the Multiple Sleep Latency Test (MSLT) as well as by the ESS. The distinction between fatigue and sleepiness was confirmed: patients with chronic fatigue turned out to be less sleepy than both healthy and sleep apnoea controls. In another study with mainly sleep apnoea patients, daytime sleepiness was objectified using the MSLT, and no relation with fatigue was found (Lichstein et al., 1997).

**Daytime sleepiness and nocturnal sleep disturbances**

The positive relation between disturbed nocturnal sleep and fatigue has been described previously in healthy subjects (Haack and Mullington, 2005) and in various neurological disorders (Kalkman et al., 2007). In narcolepsy, fatigue could also be linked to disturbed nocturnal sleep, which is an important part of the narcolepsy phenotype. The direction of the association between nocturnal sleep disturbances and daytime fatigue remains unclear, however: disturbed sleep may both be a cause or a consequence of fatigue (Kishi et al., 2008).

**The role of depression and physical activity**

There was an association between severe fatigue and a high level of depressive symptoms. The question can thus be raised as to whether severe fatigue is just an equivalent of depression in the narcolepsy population. The association of fatigue with depressive symptoms is often found in studies of somatically ill patients (Brown and Kroenke, 2009) but also in patients with ‘chronic fatigue syndrome’ (Prins et al., 2005). The direction of the association remains unclear, however, as longitudinal studies have been inconclusive so far (Brown and Kroenke, 2009). Intervventional studies of fatigue using antidepressants show discouraging results, influencing depression and anxiety but not severe fatigue (Minton et al., 2010; Prins et al., 2005; Van et al., 2010). In the present study, antidepressant use was not associated with fatigue severity either. Several studies have shown an increase in depressive symptoms in narcolepsy, but without an increase in major depression according to DSM-IV criteria (Vourdas et al., 2002). Therefore, although there is a clear overlap of symptoms of fatigue and symptoms of depression, severe fatigue is not explained adequately by the presence of major depression in narcolepsy.

In our sample, decreased physical activity correlated with severe fatigue. Decreased daytime physical activity has been reported in narcolepsy previously (Bruck et al., 2005). In a predictive model of fatigue in neuromuscular disorder patients, both sleep disturbances and decreased physical activities were found to be perpetuating factors of experienced fatigue (Kalkman et al., 2007). Whether a similar mechanism is also present in narcolepsy requires further study.

**Stimulant medication**

A striking result was the association of severe fatigue and the use of stimulant medication. This seems paradoxical, because stimulants are frequently prescribed to treat fatigue in many patient categories (Minton et al., 2010), although modafinil, for example, showed only limited results for this indication (Kumar, 2008). Could stimulants affect nocturnal sleep quality negatively, resulting in daytime fatigue? A study of modafinil in narcolepsy patients did not show adverse effects on sleep quality (US Modafinil in Narcolepsy Multi-center Study Group, 1998). A recent study of methylphenidate in adult attention deficit hyperactive disorder (ADHD) patients (Bejerot et al., 2010) reported initial insomnia and increased need for sleep as adverse events, more than half a year after the start of the study. In this view, methylphenidate-induced insomnia may be a factor leading to an increase in fatigue. However, another explanation could be that more severely affected patients need more stimulants in order to stay awake, but remain fatigued none the less. A final explanation may be that fatigue represents a suboptimal adjustment to the burden of narcolepsy in daily life. The SIP results showed a considerable impairment in daytime functioning of narcolepsy patients, which was by far the most striking in the patients with severe fatigue. Interestingly, in a quality of life study, Daniels et al. (2001) found lower scores on the physical and social subscales of the SF-36 as well as higher depression scores, in patients taking stimulants combined with anticataplectic medication. They commented that treatment was apparently not sufficiently effective to restore health status to normal.

**Study limitations**

Possible relations between objective measures of nocturnal sleep quality and severe fatigue could not be assessed in this...
study, as the mean interval between data collection and diagnostic sleep studies was more than 6 years. During this period, a variety of life-style changes may have taken place, and — perhaps more importantly — treatment was initiated. We cannot exclude that a few patients developed comorbid sleep apnoea between the diagnostic polysomography and fatigue assessment, although there were no clear symptoms indicating this. To further our understanding of the mechanisms leading to severe fatigue in narcolepsy, future studies, preferably in a controlled design, should add objective sleep assessment in combination with fatigue measurements.

CONCLUSIONS
There is a high prevalence of severe fatigue in patients with narcolepsy, which is associated with important psychological distress. These findings have consequences for the clinical care of narcolepsy patients. Doctors should inquire actively not only after the classical sleepiness, but also after the presence of fatigue. Just the recognition of severe fatigue by the physician will already be valuable for the patient, although the most effective treatment strategy still needs to be defined.

ACKNOWLEDGEMENTS
We thank Claire Donjacour, Wendy van der Zande and Mojca van Schie for help in maintaining the patient database. Sebastiaan Overeem was supported by a Vidi grant from the Netherlands Organization for Scientific Research (grant no. 016.116.371).

CONFLICTING OF INTERESTS
None.

REFERENCES