NARCOLEPSY

aspects of the psychiatric phenotype

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NARCOLEPSY

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Chapter 1

Introduction and outline of the thesis

INTRODUCTION

Narcolepsy is a primairy sleep disorder, classified in the category of hypersomnias of central origin (ICSD-2, 2005) [1]. Narcolepsy is characterized by two main symptoms: excessive daytime sleepiness (EDS) and cataplexy. However, a rather broad spectrum of other symptoms is often present, including hypnagogic and hypnopompic hallucinations, sleep paralysis, nocturnal sleep disruption, as well as non-sleep symptoms such as obesity [2]. Disease onset varies from early childhood into the fifth decade of life, with a bimodal distribution with a large peak around 15 years of age and a small peak around 36 years [3]. The estimated prevalence in the western world (Europe and U.S.) is 0.02% to 0.07% [4,5] which would amount to 3500 – 10.000 patients in the Netherlands. In recent years, it was discovered that narcolepsy is caused by a deficiency in hypothalamic hypocretin (orexin) neurotransmission, which is reflected in a defiency of the hypocretin neuropeptide in the cerebrospinal fluid [6].

SEMIOLOGY

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) is usually the first symptom to appear and often the most disabling. The urge to fall asleep can be imperative and results in lapses into sleep at unusual times and occasions during the day. Naps typically have a refreshing effect, which is short lived however. Although patients can sometimes fall asleep during activities, sleep 'attacks' are most likely to occur during situations such as watching TV or sitting in the passenger seat of a car, when active participation is not required. When unmedicated the need to sleep is very hard to resist, and mostly uncontrollable [7]; moving around can on some occasions ward off a sleep attack. Maintaining daytime alertness is a major issue for patients, ever threatening their level of functioning. Patients can even become preoccupied with losing control of their alertness and falling asleep in public.

Cataplexy

Cataplexy, the second chief symptom of narcolepsy, is virtually pathognomonic for the disease. It is characterized by a sudden bilateral loss of muscle tone provoked by strong emotions, usually of the positive variety: laughter, startle, pride, elation, surprise and excitement in meeting someone [8]. Cataplexy can be generalized or partial, affecting the neck, mouth or limbs selectively. A head drop, facial sagging, slurred speech, buckling of the knees are all expressions of partial cataplexy. Cataplexy not only varies highly in distribution but also in

frequency. The duration of a cataplectic attack ranges from seconds to a few minutes at most. During cataplexy consciousness is maintained: patients hear and remember all what happens around them. A minority of patients reports multisensory hallucinations during cataplexy [8].

Hypnagogic hallucinations

Hypnagogic hallucinations occur at sleep- wake transitions, commonly experienced at sleep onset but incidentally during cataplectic attacks and sleep paralysis as well. They are called hypnopompic when occurring during waking up. These hallucinations can be extremely frightening and very realistic. They are claimed not to be unique for narcolepsy, occurring in other sleep disorders and in the general population as well [4,9]. This has been a reason for some authors to trivialize these symptoms, which is unfounded. Patients are often reluctant to report these hallucinations because of the fear of being viewed as mentally ill [10]. Indeed, hypnagogic hallucinations are sometimes mistaken for psychosis by psychiatrists [11-14] and can create misleading interpretations in the legal sphere [15]. Patients report an impressive loss of quality of life due to these sensory perceptions [10].

Sleep paralysis

Sleep paralysis occurs on sleep- wake transitions as well: patients wake up but cannot move or speak during a few minutes. Even lifting a finger is not possible at these periods. External stimuli such as noises or the touch of the bedpartner can sometimes end this state. This frightening experience is often accompanied by hypnagogic or hypnopompic hallucinations, which can push up the anxiety to an even higher level.

Disturbed nocturnal sleep

The sleep dysregulation in narcolepsy is also apparent in nocturnal sleep, which is often highly fragmented. Nocturnal sleep fragmentation is a common complaint, and often very troublesome to patients. The nighttime sleep disruption is not the cause of the daytime sleepiness however: treating nocturnal sleep fragmentation does not ameliorate the daytime sleepiness.. Over 24 hours patients do not sleep more than healthy controls [16].

Automatic behavior

Narcoleptic patients can show *automatic behavior*: inadequate behavior, most likely during periods with a decreased vigilance. A common example is during writing, when patients notice that they have written nonsense sentences, or illegible text. These automatisms are sometimes mistaken for dissociative behaviors.

Obesity

Narcolepsy patients have often been reported to be obese [17,18], with an an increased waist circumference as well, pointing to abdominal fat deposition [19]. The increased BMI can be a major psychological burden for patients, likely to contribute to the low self esteem that patients may report [10,20,21]. The increased BMI was classically attributed to a lifestyle of inactivity inherent to the tendency to fall asleep. However, nowadays metabolic changes, most probably due to the reduction in hypocretin signaling, are believed to be responsible for the increase in body weight [6,22].

DIAGNOSTIC CLASSIFICATION

The diagnosis of narcolepsy is based on a combination of reported symptoms, formal sleep recordings, and –in selected cases- measurement of hypocretin in the cerebrospinal fluid. The current diagnostic classification follows the International Classification of Sleep Disorders (ICSD-2), edited by the American Academy of Sleep Medicine (AASM), and these criteria are listed in Box 1 [1]. The DSM IV has a classification for narcolepsy as well [23]. These criteria are however less than satisfactory, leading to a clear overinclusion of narcolepsy patients. In the forthcoming DSM-V, new criteria are proposed that closely follow the ICSD-2.

NARCOLEPSY AND PSYCHIATRY

Narcolepsy misdiagnosed as psychiatric disease

Narcolepsy has been frequently misdiagnosed – especially by psychiatrists - as a psychiatric disorder. Psychiatrists have recognized a pattern of borderline personality disorder, psychosis, and do worse than other medical specialists in diagnosing narcolepsy [24]. This has lead to admissions of patients to psychiatric wards with diagnoses of schizophrenia or bipolar disorder [11,25]. What did deceive psychiatrists? The most conspicuous point of confusion are the hypnagogic hallucinations. These hallucinations can occur during daytime too, during moments that patients doze off to sleep. Psychiatrists may interpret this as a symptom of a psychotic disorder. Narcolepsy patients may suffer from mood swings, with irritated mood or even outbursts of anger when waking up, which may remind of mood swings in Borderline Personality Disorder. The distant impression that some patients make, and a certain indifference can remind of other personality disorders as well. Depression is diagnosed frequently: disturbed sleep can be a point of confusion here, as are loss of concentration, fatigue, loss

BOX 1 Diagnostic criteria for narcolepsy with cataplexy

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least three months.

B. A definite history of cataplexy defined as sudden and transient episodes of loss of muscle tone triggered by emotions, is present.
Note: To be labeled as cataplexy, these episodes must be triggered by strong emotions – most reliably laughing or joking – and must be generally bilateral and brief (less than 2 minutes). Consciousness is preserved, at least at the beginning of the episode. Observed cataplexy with transient reversible loss of deep tendon reflexes is a very strong, but rare, diagnostic finding.

C. The diagnosis of narcolepsy with cataplexy should, whenever possible, be confirmed by nocturnal polysomnography followed by an MSLT; the mean sleep latency on MSLT is less than or equal to eight minutes and tow or more SOREMP's are observed following sufficient nocturnal sleep (minimum six hours) during the night prior to the test. Alternatively, hypocretin 1 levels (less than or equal to 110 pg/mL or one third of mean normal control values.
Note: The presence of two or more SOREMP's during the MSLT is a very specific finding whereas a sleep latency of less than eight minutes can be found in up to 30% of the normal population. Low CSF hypocretin-1 levels (less than or equal to 110 pg/mL or one third of normal control values) are found in more than 90% of patients with narcolepsy with cataplexy and almost never in controls or in other patients with other pathologies.

D. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, medication use of substance use disorder.

of libido and the tendency to withdraw. Conversion disorder is another pitfall, and this diagnosis has been made frequently in the history of narcolepsy: sleep, cataplexy were seen as defense mechanisms, supposedly enabling patients to cover up more serious flaws in their personality.

The reasons for psychiatric misclassification

The intriguing question can be posed whether psychiatrists were just mistaken in diagnosing psychiatric disorders instead of narcolepsy, or that narcolepsy patients really do show psychiatric signs and symptoms, either secondary to narcolepsy symptoms or as a direct expression of the pathophysiological process. Although

the literature on narcolepsy is plentifully filled with references to psychiatric comorbidity, data as to prevalence or incidence of psychiatric disorders or frequency of symptoms are inconclusive. Most data come from case series, where psychiatric symptoms are often more illustrative than informative. Furthermore, most data come from self-report instruments such as the Beck Depression Inventory (BDI) as opposed to controlled studies with formal diagnostic instruments.

The psychiatric phenotype in narcolepsy is not well described
Currently, too few studies have tried to perform a detailed psychiatric assessment of narcolepsy patients, and the psychiatric phenotype of narcolepsy is only vaguely described. I sorely missed such psychiatric data as a reference, when I first encountered a narcoleptic patient, who is described in Box 2.

BOX 2 case vignette

Patient 1 is a 20-year-old physics student, who received the diagnosis of narcolepsy with cataplexy at age 14. Around the time he turned 18, hypnagogic hallucinations started to play an important role in his daily life. In a hypnagogic 'state' he sensed the presence of invisible beings which he called 'synteufles' that came from another 'dimension'. These 'synteufles' tried to possess him, throwing a yellow powder in his nose to bring him under their influence. They wanted to eat his brains, and kill him. After waking up, the reality of these hallucinatory world still existed. The patient developed the habit to 'wash them off', taking showers that sometimes took a whole night. In his dreams these beings could take the form of chewing gum. The dreams were threatening him, and he started feeling depressed. He began to eat more. At one point, he was not able to separate the 'dream world' from daytime reality for several weeks. He developed a way to 'defend' himself against the 'synteufli', fighting them by developing a glass plate in the frontal plane before him, that represented his mind. He always wanted to wipe this plate clean, for which he even created an extra extremity.

His neurologist prescribed antipsychotics which did not influence the symptoms. To get back to reality, it helped to start talking to someone or turning on the radio. He became obsessed with having fresh drinking water which he needed in his battle with the synteufles.

Only two years later, he gradually became able to put these experiences into perspective. Afterwards he started doing well in his studies, was able to get his MSc and now has a job as an information technology expert.

AIMS OF THIS THESIS

The main goal of this thesis is to investigate the psychiatric profile of narcolepsy in depth. We start from a systematic search of the older literature, looking for 'unexpurgated' psychiatric aspects in original descriptions of narcolepsy. Subsequently, the results of a detailed study are described in which the psychiatric symptoms of a large and well-defined cohort of narcolepsy patients is compared to population controls, mainly using a well-validated semi-structured diagnostic instrument, the Schedules for Assessment in Neuropsychiatry (SCAN) version 2.1 [26-29].

Chapter 2 contains a detailed historical analysis of primary papers on narcolepsy, with an emphasis on psychiatric features and involvement of psychiatrists working from different angles. Although a psychiatric approach was justified in many instances because of the psychological suffering, this all too often lead to stigmatization of patients, adding to a bad reputation that patients already had. Over the years, a reappraisal of psychiatric comorbidity took place, leading to a new synthesis of 'organic' and 'psychiatric' features of narcolepsy.

Chapter 3 focuses on psychotic symptoms in narcolepsy, because of the enduring discussion in the literature on the differential diagnosis of narcolepsy and schizophrenia. We studied psychotic symptoms in three groups: patients with narcolepsy, schizophrenic patients and a group of matched population controls. A detailed analysis of the pattern of hallucinations of narcolepsy patients and schizophrenic patients is given, to enable a clear differentiation between the two. Furthermore, we describe the actual experiences of hypnagogic hallucinations in detail, as reported by the narcolepsy patients.

Chapter 4 deals with symptoms of depression as well as anxiety in narcolepsy. Depression has received a lot of attention in the literature, which contrasts with the scarcity of information regarding anxiety symptoms. Many authors have suggested an overrepresentation of major depression, but few systematic diagnostic studies have been performed. Using the SCAN, symptom frequencies on depression and anxiety were assessed and compared with controls. A discussion is added on the significance of these symptoms; are they a primary disease expression, or secondary to the chronic symptoms of narcolepsy.

Chapter 5 describes the results of a study into eating disorders in narcolepsy, which was triggered by the overweight and obesity which are notorious associated features. A case- control study was performed, comparing symptoms of eating

disorders in patients with narcolepsy versus population controls. In addition, symptoms were compared to a separate control group which was matched for BMI as well.

In **Chapter 6,** a clinically relevant, but difficult topic is studied, namely the prevalence of fatigue in narcolepsy, and its differentiation from sleepiness. This subject has been neglected in the literature so far. To this end, a formal instrument to assess fatigue –the Checklist Individual Strength- was applied in a large cohort of narcolepsy patients. Determinants for the presence of severe fatigue were assessed, and clinical differences described between narcolepsy patients with and without fatigue.

Chapters 7 and 8 contain a summary of our results and a discussion of their relevance respectively. We elaborate on possible neurobiological mechanisms, but also on the patient's perspective and treatment options.

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Chapter 2

Narcolepsy and psychiatry: an evolving association

Based on:
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ABSTRACT

Gélineau originally described narcolepsy as a disease with an organic cause. However, the disorder had undeniable emotional triggers and psychiatric-like expressions, and soon a psychiatric etiology of narcolepsy became a seriously considered option. In fact, the psychiatric view dominated scientific thinking for a long time, not necessarily to the benefit of patients. When hypocretin (orexin) defects were proven to be the cause of narcolepsy Gélineau's original disease model was shown to be right. However, the psychiatric symptoms of the disease were not forgotten afterwards, but gained a different significance: as psychiatric expressions of a brain disease. These symptoms, such as anxiety and eating disorders, can be highly debilitating and warrant clinical attention. Here, we describe the role of psychiatry in the history of narcolepsy, showing their evolving association.

INTRODUCTION

Ever since its first description, narcolepsy has been associated with psychiatry in various ways (see Figure 1). While neurological explanations for narcolepsy prevailed at first, various alternative theories soon gained followers, suggesting underlying psychiatric disturbances as a cause of the disease (for an overview, see [1]). Psychosomatic mechanisms were pressed by psychiatrists treating narcolepsy patients, for example suggesting sexual deviations and psychopathic personality structures as underlying factors [2,3]. These views persisted for a long time, even far into the 20th century [4]. When defects in hypothalamic hypocretin (orexin) neurotransmission were pinpointed as the primary culprit at the end of the 1990s, narcolepsy was finally established as an organic brain disease [5]. Perhaps surprisingly, this paved the way for a thorough description *and* appreciation of the psychiatric comorbidity which affects many narcoleptic patients [6-14]. In this review we describe the role of psychiatry in the history of narcolepsy, showing the evolving association between the two (Figure 1).

A DISEASE, A SYMPTOM OR A SYNDROME?

Narcolepsy was described and named in the second half of the 19th century, by Westphal and Gélineau respectively [15-17]. Gélineau called narcolepsy a *'névrose rare'*, a rare form of neurosis, which term at that time was not solely used for psychiatric but also for neurological disorders [16,17]. This implicated that Gélineau regarded narcolepsy as a *'morbus sui generis'* ('disease of its own kind'), and although he did not use this term himself, the expression has been attributed to him ever since. The term 'disease' refers to a condition with a specific cause, and if possible a uniform treatment. But, although Gélineau suggested that narcolepsy was a disorder of the 'protuberance annulaire' (pons) he neither knew the cause of the disease nor had a treatment.

Gélineau's publication did not go unnoticed: he received reactions and case reports from many colleagues from France and abroad. However, many of these cases were patients with an underlying disease who merely had narcolepsy-like clinical symptoms. As a result, Gélineau described a *'narcolepsie secondaire'* due to various causes next to the original 'morbus sui generis' (*'narcolepsie essentielle'*) in his 1881 monograph [18]. In other words, narcolepsy was split up in a primary disease and a secondary syndrome due to hysteria, diabetes, heart disease and so on. Gélineau also proposed to fit narcolepsy due to hysteria in Charcot's classification of hysterical stages, even adding a subtype: *'état narcoleptique'* (Figure 2) [16].

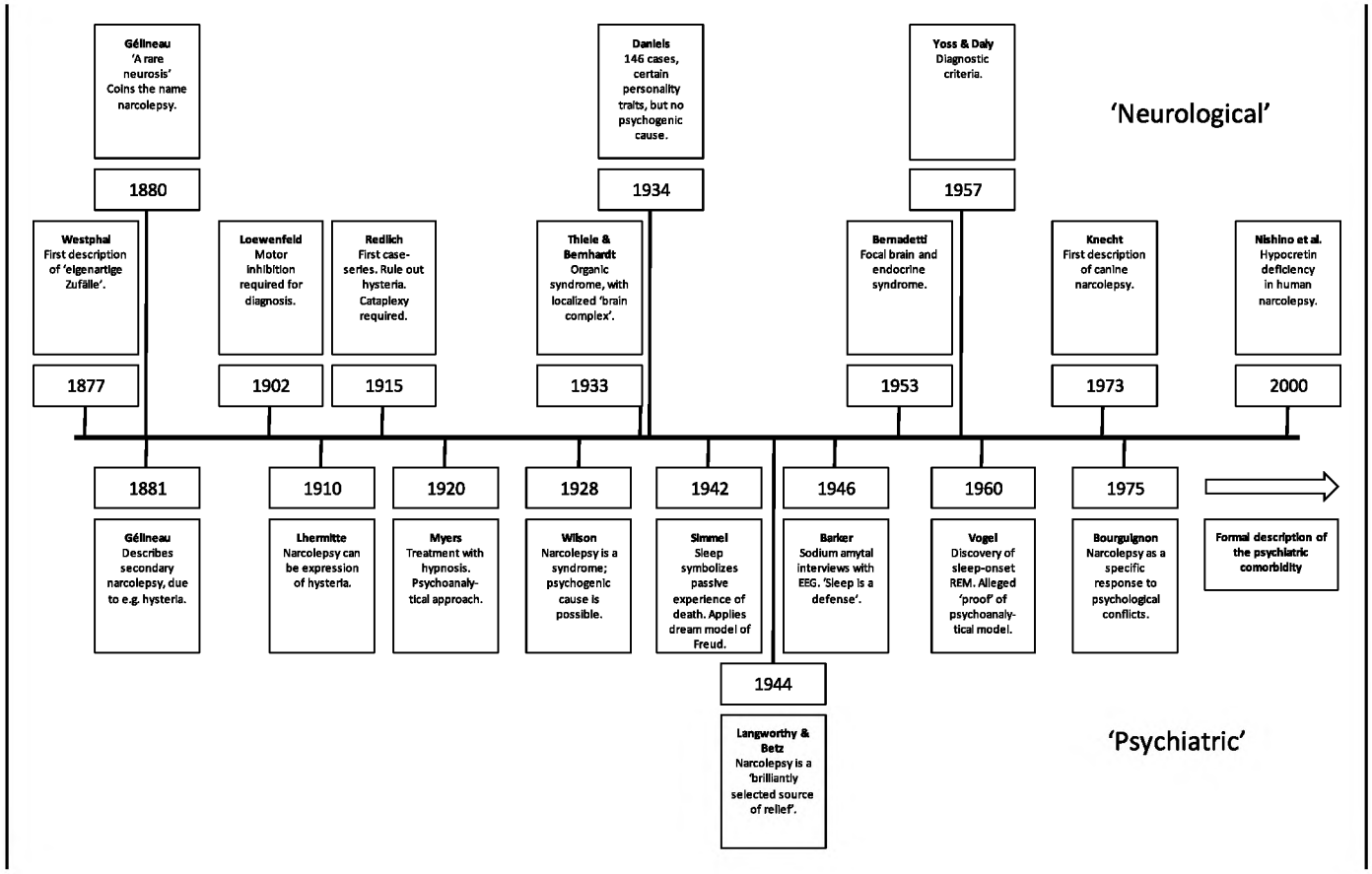
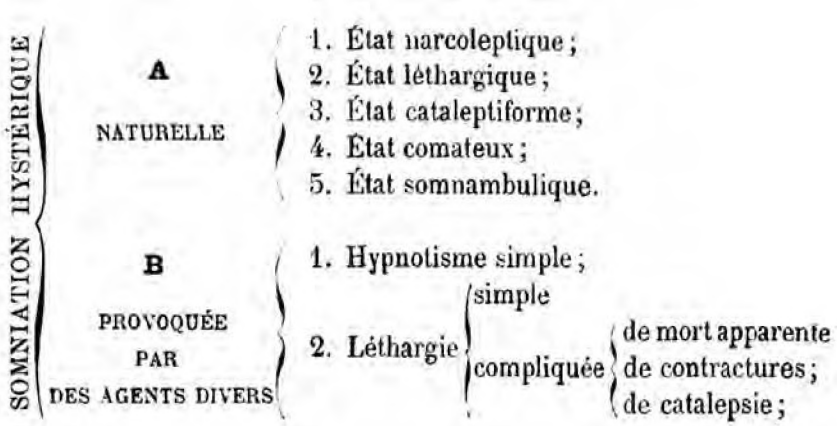


Figure 1 Timeline, illustrating both the neurological and psychiatric views on narcolepsy throughout time

Figure 2 Gélineau's proposal to fit narcolepsy secondary to hysteria into Charcot's classification of hysterical stages



The subdivision into essential and secondary types did not convince all however: the French neurologist Ballet stated in 1882: *'Narcolepsie n'est pas une affection définie, encore moins une maladie: c'est, nous le répétons, un symptôme qui a , nous le voulons bien, ces caractères propres, sa physionomie special'* [19] .

Parmentier (1891), a pupil of Charcot, advocated a slightly different classification, emphasizing that the 'hysterical patient' might mimic narcolepsy. He preferred: *'La forme narcoleptique de l´attaque de sommeil hysterique: pseudo-narcolepsie hysterique'* [20].
In France, Lhermitte (1910) wrote an article called 'les narcolepsies' in which he strongly positioned narcolepsy as a syndrome, with multiple etiologies, and not as a disease [21]. In contrast, the idea of narcolepsy as a disease remained still very much alive in Germany in the same period [22-25].

The controversies surrounding the question whether or not to consider narcolepsy as a primary disease, were partly fuelled by the fact that cataplexy was not yet sharply defined and was no requisite for the diagnosis.

CATAPLEXY, INCLUDED OR NOT?

In 1902, the German author Loewenfeld pointed to an important omission in the narcolepsy literature so far [22]. He discovered that Gélineau described 'astasia' as an important symptom that could be separated from the excessive daytime sleepiness in narcolepsy. He stipulated that these two symptoms -sleepiness and muscle weakness ('*kataleptische Starre*') triggered by laughing and other emotions - were the chief complaints in narcolepsy.

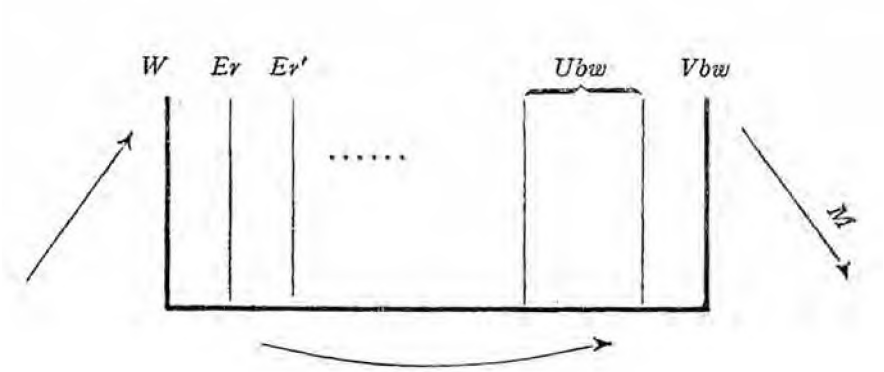
Although the term 'cataplexy' was introduced 14 years later by Henneberg, [26] Loewenfeld already emphasized that narcolepsy was an *'eigenartige Krankheits-zustand'* characterized not just by sleep episodes but also by attacks of motor inhibition. The discussion 'disease or syndrome' was now extended to the question: 'is cataplexy a requisite criterion to make a narcolepsy diagnosis or not? 'Many authors in Germany and Austria answered this question affirmative, implying a 'restricted definition' with exclusion of hysterical cases and the like [23-25,27-31]. In France, England and the USA most physicians defined narcolepsy in a much broader sense: by excessive daytime sleepiness and sleep attacks [21,32-35].

The 'syndrome versus disease' discussion, and the uncertainty about diagnostic criteria, allowed the emergence of alternative theories for the underlying cause of narcolepsy, and psychiatric explanations soon gained much more prominence.

INFLUENCE OF THE PSYCHO-ANALYTIC MOVEMENT

Starting around 1885, Freud started to study the dynamics of unconscious processes and their expression in psychological symptoms and behavioral changes. He published his opus 'Traumdeutung' ('on the interpretation of dreams') in 1900, in which he constructed his own model of sleep and dreaming [36]. He stated that during sleep neurons at the motor end were blocked and the mental processes were directed to the sensory end. In this regressive process, an intensification of internal perception took place while the ego was shut off from access to outward motor innervations (Figure 3). Freud attributed various 'functions' to sleep. In the first place, sleep provided a means to dream: hallucinatory gratification. Freud hypothesized that in dreams people would fulfill wishes -conscious as well as unconscious- that had arisen during daytime but were left unsatisfied. But second, Freud stated that sleep attacks could be a defense mechanism *against* sexual or aggressive impulses, at the same time shielding them from consciousness and gratifying them during sleep.

Figure 3 Freud's Ψ - model of the mental 'apparatus' : impulses to action at the motor end at the right (M) are blocked during sleep, and redirected to the sensory end (left). This leads to intensification of the internal perception: dreams. The preconscious (Vbw) disguises the 'dream material' in order not to disturb internal perception as well as sleep. In this way, 'hallucinatory wish fulfillment' is reached during the dream.



Ubw = unconscious, Er = memory.

As psychoanalysis gained ground as a modern scientific view, publications started to appear suggesting a relation between these unconscious processes and sleep attacks. One of the first exponents of this line of thinking was Oberndorf (1916), a psychoanalyst from New York, who wrote:

'...uncontrollable attacks of drowsiness were interpreted as an escape from intense shame attendant upon a masturbation conflict in which fantasies of incest with the mother played an important role. The drowsy spells at the same time provided a substitute for the autoerotic activity' [37].

The first psychoanalytically oriented publication on narcolepsy came from the British army psychologist Myers (1920) [38,39]. He reacted on a description of a placebo treatment of a narcoleptic patient that appeared in *the Lancet*: a piece of bone was removed from the skull of a narcoleptic patient and attached to a necklace for him to wear, turning out to be a cure [40,41]. Outraged about this 'indefensible treatment', Myers described his own 'treatment by exploration' for narcolepsy: *'Repression and dissociation are at the root of the disorder and reintegration alone*

can effect a true cure'. Worster-Drought (1923) a neurologist at the Queen's Square National Hospital in London, cited Myers and advised the following strategy for the treatment of narcolepsy in cases without evidence of organic disease:

'I believe the most satisfactory of the shorter methods of treatment to be (1) a preliminary modified 'psychoanalysis' with a detailed investigation into the history of the onset of the attacks, and of the individual, followed by (2) reconstruction of the origin of narcolepsy or the emotional experience giving rise to the condition, under light hypnosis' [33] .

Variations on this theme continued to appear in the literature. Willey (1924) described the escape mechanism that narcolepsy provided as *'temporary suicide' [42].* Missriegler (1924) portrayed narcolepsy as a way of gratifying murderous and sexual impulses during sleep: *'A criminal component will probably be found to exist in narcolepsy'* [43]. Furthermore, he described successful treatment of a patient with psychoanalysis.

Not only sleep attacks, but other symptoms of narcolepsy could be explained as neurotic symptoms as well. Coodley (1948) suggested for example that cataplexy might represent *'self castration, in which the entire body – equated with the penis – goes limp' [44].*
However, not all contemporary authors mentioned the publications on psychoanalysis in narcolepsy. For example, Adie (1926) in his famous thesis on narcolepsy did not cite one psychoanalyst. Neither did Redlich, the Austrian authority on narcolepsy, except in his very last paper in which he stated that he was not convinced of either the psychogenic causation of narcolepsy or an essential psychological influence on the disease:

'*Ich selbst habe mich, (...), von eine Psychogenese der Narkolepsie oder auch nur von einer wesentlichen psychologischen Beeinflussung der Narkolepsie nicht überzeugen können, ich kann also auch nichts von einer Psychotherapie berichten.'* [25,27-29,45,46].

INFLUENCE OF PAVLOV'S INHIBITION THEORY

A second approach to psychogenic mechanisms in narcolepsy was based on the work of Pavlov, one of the godfathers of behaviorism who received the Nobel Prize for his work on classic conditioning in 1904. Later on, Pavlov developed his own theory of sleep: the inhibition theory, based on experiments with dogs

[47,48]. He observed that dogs would fall asleep after withholding of a reward they were conditioned to. He reasoned that sleep was nothing but internal inhibition radiating over the cortex and involving lower brain centers as well. Brailovsky [49] and Adie [45]. applied this theory to narcolepsy, Adie using it to explain both sleep attacks *and* cataplexy:

'It seems then as if narcolepsy is an expression of fatigue in individuals with a kind of nervous activity that favors the spread of inhibitions and allows excessive emotional responses; further, that the local response to inhibitions, wherever they arise, is abnormal, and that the symptoms are due to a general alteration of nervous activity rather than to abnormal stimuli which affect normal structures at a distance'.

Levin, who started out as a neurologist in the military, extended this train of thought and suggested that narcolepsy was caused by a wave of inhibition, just as epilepsy was caused by a wave of excitation: *'the narcoleptic patient possesses a brain in which inhibition occurs with undue ease'.* Levin believed that the development of the 'machine age' caused the 'recent increase' in the incidence of narcolepsy: having to suppress reactions to stimuli, for instance when driving a car, would lead to inhibition and consequently to narcolepsy symptoms [50]. In his later work , he stressed the importance of guilt in cataplexy [51]. For example, hitting an adult in anger would not lead to cataplexy, while hitting one's own child would. Levin explained this by Pavlov's physiological concept of trained inhibition.

'The classic example is the angry father who raises his hand to punish his child and is at that moment stricken with weakness of the upraised arm. The weakness may spread to other limbs as well. This event must be viewed from two standpoints – the psychological and the physiological. Psychologically, the father is torn by a conflict; his aggressive impulse toward his child makes him feel guilty. Physiologically, he is the victim of what Pavlov called conditioned inhibition'.

Levin published on the subject repeatedly in high-ranking journals such as the American Journal of Psychiatry; his last publication (1961) fell in the same time frame as the last publications of psychoanalysts on narcolepsy [52]. However, in the 1950s, critical comments started to appear, for example from the British neurophysiologist Pond (1952): *'such terms have a deceptive simplicity and an appearance of explaining everything, but as Pavlov's later work shows, more and more ad hoc hypotheses have to be invented to cover the facts. Little is gained from his terminology, which does not completely bridge the gap between psychology and neurology' [53].*

A FURTHER BOOST FOR THE PSYCHODYNAMIC APPROACH

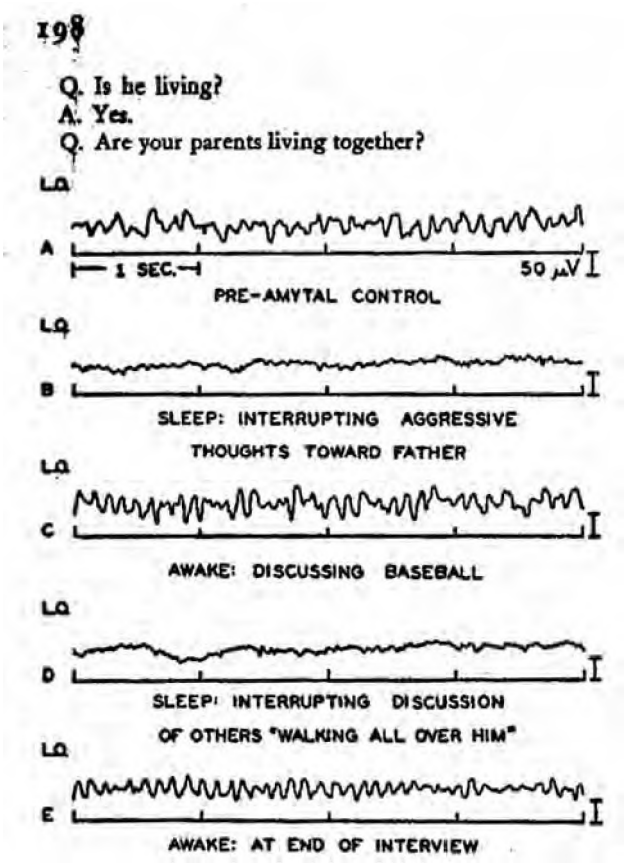
The psychoanalytic view on narcolepsy was strongly stimulated by the article in Brain by the famous British neurologist Kinnier Wilson in 1928 [34]. When analyzing the etiology of the narcoleptic syndrome, Wilson opened the door widely to psychiatry and psychoanalysis. Quoting articles of Carlill, Myers, Worster-Drought and the psychoanalyst Missriegler, he remarked about psychopathological causes; in a list of eight causal categories he placed 'the psychopathological group' second after the 'traumatic group' and before endocrinology, epilepsy and encephalitis. The consequence of Wilson's reasoning was that patients formerly called 'hysterical' could now fully be classified as having narcolepsy. Wilson's view meant recognition and a formidable breakthrough for psychiatrists with psychoanalytic orientation, and the paper was frequently cited in the later psychoanalytic literature on narcolepsy. Winnecot (1930), Jones (1935), Simmel (1942) and Schulte (1942) all reported their psychoanalytical work with narcoleptic patients, pointing to 'threatening sexual fantasies', 'escape from reality', 'reliving the death of a father in order to be with him', and 'homosexual inversion' as causing narcolepsy [54-57]. The psychodynamic descriptions of narcoleptic patients almost showed contempt, as the next citation from Langworthy and Betz (1944) shows:

'Narcoleptic and cataplectic reaction: a brilliantly selected source of relief. A non verbal admission of inadequacy, not incompatible with self- respect. (...) This condition is a personality reaction to emotional issues rather than an organic disease as has formerly been assumed. The symptoms of excessive diurnal sleep, cataplexy, sleep paralysis, somnambulism, [and] nocturnal hallucinations appear to be neurotic defenses with symbolic significance against primary anxieties associated with difficulties in realistic adjustments in personal relationships with others. The narcoleptic syndrome as a neurotic reaction seems similar in many respects to the hysterical reaction. They feel caught in a life-pattern to which they are expected to conform, but which they deeply resent' [58].

THERAPEUTIC CONSEQUENCES OF THE PSYCHODYNAMIC APPROACH

There was 'good news' for narcoleptic patients though: the psychodynamic approach provided a therapeutic option, namely psychoanalysis. Langworthy and Betz described six patients, two of whom proved responsive to their psychoanalytical approach with an amelioration of the narcoleptic symptoms.

Figure 4 Illustration from Barker's article on EEG registrations during a sodium amytal interview with a narcolepsy patient [60]. See main text for details.



The authors state that psychoanalytic psychotherapy provided *'a fundamental approach to their difficulty'*. Spiegel and Oberndorf (1944) described the contents of such a treatment: the breakthrough in therapy was a *'confessional catharsis'*, encouraged by the therapist [59]. In their case, a long standing sexual conflict supposedly was closely related to the patient's states of sleepiness and other physical symptoms. After an unsuspected element of her sexual life had been discussed with the therapist, she had fewer attacks of narcolepsy and her nocturnal insomnia diminished.

Barker (1948), a psychoanalyst from New York, used repeated interviews, free association, *and* intravenous sodium amytal in the search for information [60]. In an ambition to 'prove' the psychoanalytic approach, he recorded the EEG of two patients during such a sodium amytal interview (Figure 4). In the observations section of his paper, a candid description of the session was provided:

Three minutes after the patient had been given 0.3 grams of sodium amytal, the discussion which had dealt with early aggressive urges and his methods of handling them, proceeded as follows:

(...) did you ever have a fight with your father / No / What kind of a man was he? / He was a good guy / Is he living? / Yes / Are your parents living together? (...)
The patient did not respond to the question but turned his head to the right and went to sleep. The interview continued afterwards and Barkers final conclusion was:
'when the discussion was turned to incidents in which his aggressive urges conflicted with his guilt or fear of punishments, the patient went to sleep instead of discussing them and the EEG showed patterns as those of Fig. 1B and D [i.e. normal sleep]'.

THE TRIUMPH: FINAL 'PROOF' OF THE PSYCHOANALYTICAL VIEWS

In the post-war period, the psychoanalysts reached the peak of their influence on narcolepsy, much to the irritation of more biological thinking neurologists such as Daniels. In a letter to Kleitman, dated July 21, 1948, Daniels wrote: *'I (..) have been decidedly annoyed by recent attempts of the psychosomaticists to revive the old idea that narcolepsy is simply a form of escape' [61].*
However, psychoanalysis had a final word to say. In 1960, Vogel phrased the analytical views in the following hypothesis:

'Normal subjects dream to preserve sleep, narcoleptics sleep to dream. The narcoleptic attack provides hallucinatory gratification of forbidden fantasies by the specific mechanism of wish fulfillment through dreaming. In that case, the purpose of the pathological sleep is not only to defend, but also to provide the ego regression necessary for hallucinatory wish fulfillment through dreaming' [62].

Based on the recent discovery of REM sleep [63] and the finding that dreaming mostly occurred during this sleep stage [64], Vogel went on to test his hypothesis by performing EEG recordings in a narcoleptic patient in the afternoon in the sleep lab

[62]. He observed that his patient fall asleep only one minute after the start of the experimental procedure. Moreover, REM sleep recorded occurred within three minutes after sleep onset, much faster than normal. Vogel took these findings as proof of his theory: *'the purpose of some narcoleptic sleep is to obtain through a dream the hallucinatory gratification of an unacceptable fantasy'.*

Paradoxically, Vogel's findings marked the end of the psychoanalytic views on the pathophysiology of narcolepsy. He discovered Sleep Onset REM Periods (SOREMPs), which turned out to be a diagnostic hallmark of the disorder that is still in clinical use today. The occurrence of SOREMPs also formed a support for the sleep dissociation theory that was first suggested by Bonhoeffer in 1928 [65] and obtained neurobiological ground in 2001 [66]. Nevertheless, in those same 1970s, psychoanalysis for the treatment of narcolepsy was still advocated in the literature [4].

ALTERNATIVE VIEWS

In 1934 Daniels, neurologist at the Mayo clinic, wrote his landmark monograph in which he meticulously described 146 patients with narcolepsy [67]. As mentioned earlier, Daniels did not believe in a psychogenic origin of narcolepsy, and he addressed several psychoanalytical views directly. For example, Daniels made clear that even if Missriegler's reasoning that the libido may find expression in the dreams of some narcoleptics, this would not at all warrant general conclusions on the *etiology* of the syndrome. He also felt that narcoleptics did not have an altered personality, describing patients as stable, aside from a certain degree of irritability, *'likely to be manifested by any drowsy person'*.
Interestingly, exactly these possible personality changes were used as fitting with an *organic* cause by several authors. Thiele and Bernard (1933) were convinced that narcolepsy was a 'complex', localized in the brain, and pointed to the sleep center proposed by von Economo, tentatively including the hypothalamus [68,69]. Next to the sleep symptoms they also described psychological disturbances to be present in the *'genuine narcolepsy'* cases. Terms like *'phlegmatic, slow'* were used, but also *'Pomadigkeit' [indifferent, blasé]* and *'Dickfelligkeit' [thick skinned].* Importantly, personality symptoms were described to be 'organic' in nature and comparable to personality changes in post-encephalitis patients. Most patients were treated with medication (thyroxin in combination with caffeine or ephedrine).

The Swiss Benedetti (1953) followed Thiele and Bernard's line of reasoning and described the psychopathology of eight narcolepsy patients [70]. He regarded

narcolepsy as a focal brain and endocrine syndrome. After describing personality changes in the sense of apathy, lack of interest, indifference and mood lability, he linked these traits to endocrine dysfunction.

It is striking that Thiele, Bernard and Benedetti, being psychiatrists, totally disregarded all contemporary psychoanalytical publications, as their references show. In turn, psychoanalysts neglected the more 'organic' studies. This constituted a clear separation between 'organic' or 'phenomenological ' psychiatrists -at that time considered as more *traditional,* and 'psychogenic/ psychoanalytical' thinking psychiatrists, as the modern and revolutionary movement at that time.

THE NEUROBIOLOGICAL CAUSE OF NARCOLEPSY

In 1957, Yoss and Daly published a study of 241 patients they examined at the Mayo Clinic [71]. Based on these series, the formulated formal diagnostic criteria, and the classic 'tetrad' of narcolepsy was born: the combination of excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. Although recent insights show that the latter two are not true 'core' symptoms, Yoss and Daly's criteria constituted an important landmark, not only clinically, but also scientifically: the diagnostic criteria were pivotal for the systematic studies in the next decades.

The search for the neurobiological cause of narcolepsy was also stimulated tremendously, when in 1973 the canine model was described [72]. The narcoleptic dogs formed a perfect animal model for such a complex disease as narcolepsy, especially because the cataplexy phenotype was strikingly similar to cataplexy in humans. Research was further stimulated when it became clear that in a few breeds, narcolepsy was transmitted as a monogenetic trait in an autosomal dominant fashion [73]. The hunt for the narcolepsy gene had begun, coming to an end when it was identified in 1999: mutations in one of the receptors for the hypothalamic neuropeptide hypocretin (also known as orexin) were responsible for familial narcolepsy in both Dobermans and Labradors [5].

In an unusually fast string of discoveries, the hypocretin system was also pinpointed as the primary culprit in human narcolepsy. In early 2000 it was shown that the majority of patients with narcolepsy lack the hypocretin peptides in their cerebrospinal fluid [74]. With these discoveries, narcolepsy was finally and indisputably shown to be a primary neurological disorder.

The hypocretin system was found to have strong connections not only with sleep-wake systems in the brain, but also with a range of other brain regions, including the limbic system [75-77]. This notion opened up the way to address the psychiatric part of narcolepsy in a fundamental new way: as an essential part of the phenotype, and a direct consequence of the underlying pathophysiological mechanisms.

AN OPEN VIEW TOWARDS PSYCHIATRIC COMORBIDITY

In several case studies in the second half of the 20th century, several psychiatric symptoms were reported to be present in narcolepsy [78-83]. Depressive mood was most often described, next to personality and sexual disorders. In addition, the relation between narcolepsy and schizophrenia was discussed in several papers. Only recently, controlled studies into the psychiatric comorbidity of narcolepsy have been performed however.

In several controlled studies, a higher frequency of depressive symptoms was described in narcolepsy, using questionnaires such as the Beck Depression Inventory. However, the two studies which used a formal diagnostic instrument showed that the frequency of major depression or other affective disorders is not increased [6,11]. Anxiety disorders were recently shown to be of importance, with a high level of anxiety symptoms in more than half of the patients, and an increased prevalence of social phobia and panic attacks [11].

Daniels already showed that narcolepsy patients are often overweight, and population studies have now confirmed this view [67]. It remains unclear whether this overweight is related to the 'carbo craving' that patients often report. Indeed, eating disorders symptoms are frequently present in narcolepsy [8,13], although a higher presence of formal eating disorder diagnoses has been disputed [9].

CONCLUSIONS

The association between psychiatry and narcolepsy has shown many different faces in the past (Figure 1). Often, the psychiatric views on narcolepsy reflected the contemporary way of medical thinking. Unfortunately, some views were not favorable for the patients involved. Now that narcolepsy is firmly established as brain disorder, the time has come to carefully describe and understand the spectrum of psychiatric comorbidity in narcolepsy. Given that the psychiatric symptoms clearly affect quality of life in a negative way, it is of paramount importance that they are addressed in the clinical care. In addition, narcolepsy is an excellent 'model' to study the large number of different functions that the hypocretin system performs in the brain, and hopefully these insights will lead to new treatment options in the future.

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Chapter 3

Psychotic symptoms in narcolepsy

Phenomenology and a comparison with schizophrenia

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ABSTRACT

Objective: Patients with narcolepsy often experience pervasive hypnagogic hallucinations, sometimes even leading to confusion with schizophrenia. We aimed to provide a detailed qualitative description of hypnagogic hallucinations and other "psychotic" symptoms in patients with narcolepsy and contrast these with schizophrenia patients and healthy controls. We also compared the prevalence of formal psychotic disorders between narcolepsy patients and controls.

Methods: We used SCAN 2.1 interviews to compare psychotic symptoms between 60 patients with narcolepsy, 102 with schizophrenia, and 120 matched population controls. In addition, qualitative data was collected to enable a detailed description of hypnagogic hallucinations in narcolepsy.

Results: There were clear differences in the pattern of hallucinatory experiences in narcolepsy versus schizophrenia patients. Narcoleptics reported multisensory "holistic" hallucinations rather than the predominantly verbal- auditory sensory mode of schizophrenia patients. Other psychotic symptoms such as delusions were not more frequent in narcolepsy compared to population controls. In addition, the prevalence of formal psychotic disorders was not increased in patients with narcolepsy. Almost half of narcoleptics reported moderate interference with functioning due to hallucinations, mostly due to related anxiety.

Conclusions: Hypnagogic hallucinations in narcolepsy can be differentiated on a phenomenological basis from hallucinations in schizophrenia which is useful in differential diagnostic dilemmas.

INTRODUCTION

Narcolepsy is a central nervous system disorder with excessive daytime sleepiness, fragmented nighttime sleep and cataplexy as the core symptoms. In addition, patients often experience hypnagogic hallucinations, which are vivid hallucinations occurring when falling asleep. When hallucinations occur at awakening, they are called hypnopompic Overeem Narcolepsy is caused by a deficiency in hypothalamic hypocretin (orexin) signaling [1]. The hypocretin neurons are exclusively located in the lateral and perifornical hypothalamus, but project extensively through the rest of the brain, including the limbic system. Interestingly, recent data point to a possible role of the hypocretin system in psychiatric disorders, such as addiction [2,3] and schizophrenia [4]. These data in turn focus (renewed) attention to possible psychiatric symptoms in narcolepsy.

Hypnagogic hallucinations in narcolepsy patients can be very pervasive. In isolated cases this has been reported to create diagnostic confusion in physicians not familiar with narcolepsy [5-8] Narcolepsy patients have even been mistaken for having schizophrenia
[9-12] On the other hand, hypnagogic hallucinations have been reported to occur in the general population as well, which may question their pathological significance [13,14].

In the present study, we provide a detailed phenomenological study of "psychotic symptoms" such as (hypnagogic) hallucinations, other perceptual experiences as well as delusions in patients with narcolepsy, using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [15] The findings are contrasted with a cohort of schizophrenia patients and compared with a control group of matched population subjects. Furthermore, we assess differences between the prevalence of *DSM IV*-diagnosed psychotic disorders in narcolepsy patients and populations controls. Finally, we provide a qualitative description of the content of hypnagogic hallucinations in narcolepsy.

METHODS

We performed a cross-sectional study, comparing psychotic symptoms (hallucinations, other perceptual experiences and delusions) in three groups: 60 patients with narcolepsy-cataplexy, 102 patients with schizophrenia and 120 population controls.

Participants

Narcolepsy patients (n=60, group I), were recruited from the outpatient clinics of the Center for Sleep-Wake Disorders "Kempenhaeghe" (Heeze, The Netherlands) and the department of Neurology, Leiden University Medical Center (Leiden, The Netherlands). All patients fulfilled the ICSD-2 diagnostic criteria of narcolepsy with cataplexy [16]. In accordance, the Multiple Sleep Latency Test showed a mean sleep latency of less than 8 minutes as well as two or more sleep-onset REM periods. Other sleep disturbances, such as sleep-related breathing disorders, were excluded as a cause for the excessive daytime sleepiness.

Schizophrenia patients (n = 102, group II) were selected from the "MESIFOS" study which was designed to recruit patients with a first psychotic episode [17,18] We selected those subjects who fulfilled the DSM-IV A-criterion for schizophrenia. The majority (75%) had schizophrenia, 22% had schizophreniform and 3% schizoaffective disorder. Because of the primary aim of the MESIFOS study, the average age of the subjects was significantly lower compared to the narcolepsy cohort (see Table 1).

Table 1 Demographic and clinical variables

	Narcolepsy	Schizophrenia	Controls
N	60	102	120
Male	28 (47%)	68 (75%)[a]	56 (47%)
Age (years)	43 ± 16	26 ± 6[b]	43 ± 15
Symptom duration (years)	24 ± 16	1.1 ± 2.5	-
Medication			
Stimulants	28 (47%)	-	-
Antidepressants	26 (43%)	-	5 (4%)
Sodium oxybate	7 (12%)	-	-
Antipsychotics	2 (2%)	83 (81%)	-

[a]: $p < 0.001$ schizophrenia versus either narcolepsy or controls
[b]: $p < 0.001$ schizophrenia versus either narcolepsy or controls

Control subjects (n = 120, group III) were randomly selected from the cross-sectional population-based Nijmegen-Health-Area-2 study, in which psychiatric symptoms were assessed in 368 people from the Dutch population [19]. Controls were matched with the narcolepsy patients for age, gender and urban environment.

SCAN semi-structured interview

Symptoms of psychosis were assessed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1 [20]. All interviews were administered by trained and certified SCAN interviewers. The SCAN is a semi-structured interview that incorporates the Present State Examination, version 10 [21]. It is a valid and reliable diagnostic instrument that is widely endorsed [15,20,22]. DSM-IV diagnostic classifications were derived from the computerized version of the SCAN (Ishell, version 1.0.4.6). In addition to the formal SCAN analysis, qualitative descriptions of SCAN items referring to hallucinations were collected and described.

The SCAN chapters analyzed in this study cover "hallucinations" (chapter 17), "experiences of thought disorder and replacement of will" (chapter 18) and "delusions" (chapter 19). Although not used in the MESIFOS study, SCAN chapter 16 ("perceptual disorders other than hallucinations") was also completed by the narcolepsy patients and the control subjects.

Clinical judgment regarding the presence and the quality of the assessed symptoms was scored using rating scales with the following basic format: 0: a positive rating of absence; 1: symptom definitely occurred but uncommon or transitory; 2: symptom was definitely present, on multiple occasions or for part of the time; 3: symptom was present more or less continuously. According to the SCAN criteria, a symptom is 'present' when scored as 2 or 3.

In the SCAN, it is a formal prerequisite to score hallucinations in a state of clear consciousness. It may be that the hallucinations in narcolepsy, which are of hypnagogic or hypnopompic nature, occur in a state of lowered consciousness. Patients often describe hypnagogic hallucinations however as lively and clear, sometimes experienced in "wide awake condition" [23]. To make a systematic description possible of the *modality (visual, auditory, olfactory, tactile),* and *form (i.e. verbal, non- verbal, internal, external)* of the hallucinations, we scored the items for all hallucination types including the formal item of hypnagogic or hypnopompic character. It should further be noted that hypnagogic hallucinations in narcolepsy, although being described here as psychotic symptoms, are by itself no diagnostic criterion of a psychotic disorder.

Statistics

Demographics are presented as frequency or as mean ± S.D. For each SCAN item, frequencies were determined by considering the first two categories as being a negative score and the other categories a positive score. Frequencies were

compared between the narcolepsy and schizophrenia group and between the narcolepsy and control group, using Fisher's test with a significance level of p=0.01. Fisher's exact test was also used to determine if there was any influence of medication and gender. Influence of age and duration of illness was tested by Spearman's rank correlation coefficient. These statistical analyses were performed using the SPSS package, version 14.0. In addition, the Mplus program was used to perform a latent class analysis, to test for the presence of patient subgroups that score high on a specific pattern of hallucinations. The Bayesian Information Criteria (BIC) and Lo-Mendell-Rubin (LMR) test were used as fit indexes [24].

RESULTS

Demographics and clinical variables

Demographic characteristics and medication use are listed in Table 1. Narcolepsy patients and population controls were well matched for gender, age and urban environment. About half of the narcolepsy patients used stimulant medication to suppress sleepiness; less than half used antidepressant medication for cataplexy or sodium oxybate (Table 1). Of the schizophrenia patients, a majority used antipsychotic medication. Four percent of the controls used antidepressant medication.

Hallucinations

In Table 2, characteristics of the hallucinations in the three groups are summarized (SCAN chapter 17). More than 80% of narcolepsy patients experienced hallucinations ever in life compared to 70% of schizophrenia patients and 2% of populations controls. In present state, 65% of narcolepsy patients reported hypnagogic or hypnopompic hallucinations. This contrasted strikingly with the schizophrenia group, who only reported hypnagogic/hypnopompic hallucinations in 4% of cases. None of the population controls scored 2 or higher on this type of hallucination, although sporadic hypnagogic hallucinations may thus be sometimes reported. In the narcolepsy patients, hypnagogic hallucinations occurred not only when going to sleep at night or waking up in the morning, but also in the context of daytime sleep episodes.

Modality and form

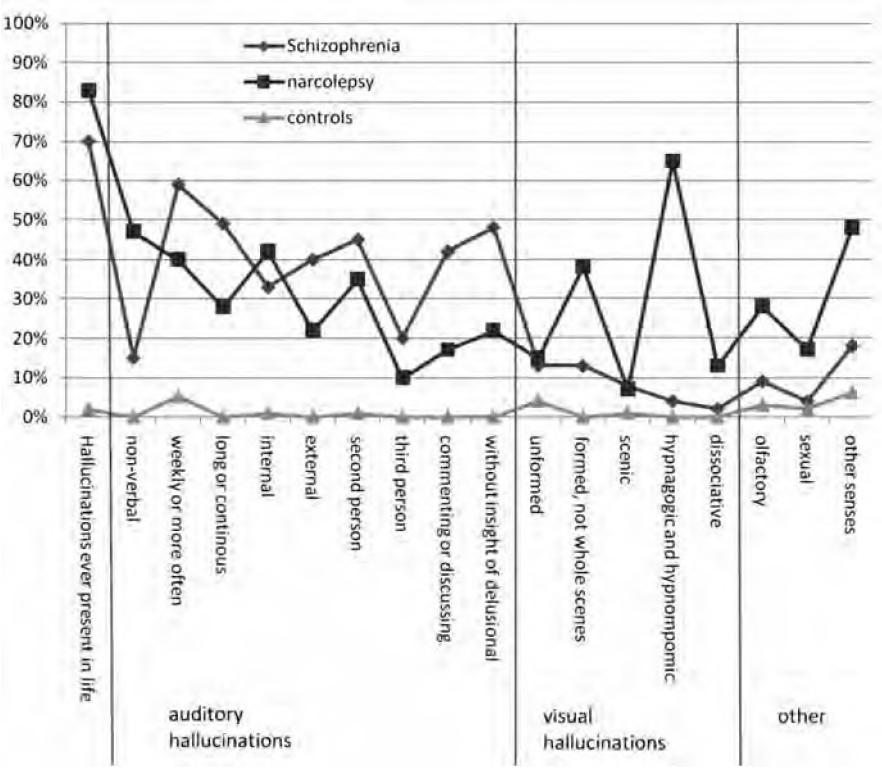
The analysis on modality and form was performed on all types of hallucinations, including hypnagogic or hypnopompic ones. Verbal auditory hallucinations were more prominently present in the schizophrenia patients than in the narcoleptics, with long duration, third person qualities and commenting voices as prominent

Table 2 Hallucinations

	Narcolepsy	Schizophrenia	Controls	p[a]	p[b]
Hallucinations ever present in life	48 (83%)	70 (70%)	2 (2%)	0.089	0.000 **
Hypnagogic and hypnopompic hallucinations	39 (65%)	4 (4%)	0 (0%)	0.000 **	0.000 **
Auditory hallucinations non-verbal	28 (47%)	15 (15%)	0 (0%)	0.000 **	0.000 **
Auditory hallucinations verbal					
Weekly or more often	24 (40%)	59 (59%)	0 (0%)	0.023	0.000 **
Long or continous auditory hallucinations	17 (28%)	49 (49%)	1 (1%)	0.012	0.000 **
Internal hallucinations	25 (42%)	34 (33%)	1 (1%)	0.313	0.000 **
External hallucinations	13 (22%)	41 (40%)	0 (0%)	0.017	0.000 **
Second person	21 (35%)	40 (45%)	1 (1%)	0.248	0.000 **
Third person	6 (10%)	19 (20%)	0 (0%)	0.179	0.001*
Voices commenting or discussing.	10 (17%)	41 (42%)	0 (0%)	0.001 *	0.000 **
Auditory hallucinations without insight or delusional	13 (22%)	47 (48%)	1 (1%)	0.001 *	0.000 **
Visual hallucinations					
Unformed	9 (15%)	13 (13%)	0 (0%)	0.813	0.000 **
Formed, not whole scenes	23 (38%)	13 (13%)	1 (1%)	0.000 **	0.000 **
Scenic visual hallucination	4 (7%)	8 (8%)	0 (0%)	1.000	0.012
Dissociative hallucinations	8 (13%)	2 (2%)	0 (0%)	0.006 *	0.000 **
Olfactory hallucinations					
Present	17 (28%)	9 (9%)	0 (0%)	0.002 *	0.000 **
Sexual hallucinations					
Present	10 (17%)	4 (4%)	1 (1%)	0.008 *	0.000 **
Hallucinations of other senses					
Temperature, pain, floating or like a crawling sensation under the skin	29 (48 %)	18 (18%)	1 (1%)	0.000 **	0.000 **

[a]: narcolepsy versus schizophrenia; [b]: narcolepsy versus controls; *: $p < 0.01$; **: $p<0.001$

Figure 1 Patterns of hallucinations based on latent class analysis for schizophrenic patients, narcolepsy patients and healthy controls.



features (Table 2). Auditory hallucinations in narcoleptics were more often of a non-verbal quality, examples including footsteps, music, doors opening or animal noises. Scenic and unformed visual hallucinations were equally present in both patients with narcolepsy and schizophrenia. Almost 40% of narcolepsy patients reported fragmentary formed visual hallucinations compared to only 13% of schizophrenia patients. In addition, other hallucinatory modalities, such as olfactory or tactile experiences were more often reported by the narcolepsy patients. Combining the above characteristics, 85% of the narcolepsy patients with hallucinations reported a combination of visual, auditory and tactile modalities, forming a multimodal, 'holistic' experience. This pattern of hallucinations is illustrated in Fig. 1. It differed from the schizophrenia patients,

as latent class analysis showed that a three group division (schizophrenia, narcolepsy and controls) is optimal (BIC=4390, p-value LMR = 0.01). Other solutions, either with more (e.g. different severities) or less (e.g., combining schizophrenia and narcolepsy) groups, had worse fit indexes.

Interference

About 40% of narcoleptics reported moderate interference with functioning due to hallucinations, mostly due to related anxiety. However, severe interference was significantly more often reported in the schizophrenia group (46% vs. 13%).

Experiences of disorder of thought and replacement of will

Experiences of disorder of thought or replacement of will was hardly ever experienced by narcolepsy patients, and the frequency of occurrence consequently did not differ from population controls (Table 3). These experiences were much more prevalent in the schizophrenia patients. Three narcolepsy patients described a fear of being taken over by an external force (i.e., the devil), but they did not keep this symptom while clearly awake.

Delusions

Only three (5%) of 60 narcolepsy patients reported delusions, yielding no differences with the population controls (Table 4). Again, these form a clear contrast with schizophrenia patients, where delusions were frequently present. However, narcolepsy patients were sometimes in doubt about the level of reality of experiences during hallucinations. Although this doubt at times persisted, narcolepsy patients kept enough insight to be rationally convinced that the experiences were not real. This was reflected in the fact that patients were often able to explicitly "check" the reality of the experiences.

Perceptual symptoms other than hallucinations

Interview of this chapter was not administered in the group of schizophrenia patients. As shown in Table 5 changed perception of time, déjà vu and jamais vu experiences were reported more frequently by the narcolepsy patients (25%) than by the population controls (1%). Feelings of derealization and de-personalization also were reported significantly more often in the narcolepsy group. Moderate interference of activities due to these perceptual disorders was considerable in the narcolepsy group (45%) compared to the population controls (1%).

Table 3 Experiences of disorder of thought and replacement of will

	Narcolepsy	Schizophrenia	Controls	p[a]	p[b]
Loud thoughts	1 (2%)	20 (20%)	0 (0%)	0.000 **	0.333
Thought echo	1 (2%)	13 (13%)	0 (0%)	0.010	0.333
Thought insertion	1 (2%)	28 (28%)	1 (1%)	0.000 **	0.557
Thought broadcast	0 (0%)	18 (18%)	0 (0%)	0.000 **	-
Thought block	2 (3%)	25 (25%)	0 (0%)	0.000 **	0.110
Thought withdrawal	1 (3%)	5 (5%)	0 (0%)	0.261	0.333
Other subjective disorder of thought	1 (3%)	5 (5%)	0 (0%)	0.269	0.333
Replacement of will by external force	0 (0%)	14 (14%)	0 (0%)	0.001 *	-
Replaced control of voice	1 (2%)	8 (8%)	0 (0%)	0.075	0.333
Replaced control of handwriting	1 (2%)	6 (6%)	0 (0%)	0.181	0.333
Replaced control of actions	1 (2%)	9 (9%)	0 (0%)	0.056	0.333
Replaced control of affect	0 (0%)	9 (9%)	0 (0%)	0.012	-
Other experiences of replaced control	0 (0%)	1 (1%)	0 (0%)	0.618	-

[a] : narcolepsy versus schizophrenia
[b] : narcolepsy versus controls
*: $p < 0.01$ **: $p<0.001$

Table 4 Delusions

	Narcolepsy	Schizophrenia	Controls	p[a]	p[b]
Delusions of being spied upon	1 (3%)	68 (67%)	0 (0%)	0.000 **	0.110
Delusions of reference	1 (2%)	54 (55%)	0 (0%)	0.000 **	0.333
Delusional misinterpretation	1 (2%)	21 (21%)	0 (0%)	0.000 **	0.333
Quotations of ideas	1 (2%)	23 (23%)	1 (1%)	0.000 **	0.557
Delusional misidentification	0 (0%)	16 (16%)	0 (0%)	0.000 **	-
Delusional perception	1 (2%)	24 (25%)	1 (1%)	0.000 **	0.557
Delusions of persecution	1 (2%)	68 (67%)	0 (0%)	0.000 **	0.333
Delusions of conspiracy	0 (0%)	58 (57%)	0 (0%)	0.000 **	-
Delusional memories and fantastic delusions	3 (5%)	9 (9%)	0 (0%)	0.279	0.036
Delusional paranormal explanations	1(2%)	23 (23%)	0 (0%)	0.000 **	0.333
Delusions of grandiose abilities	1 (2%)	15 (15%)	0 (0%)	0.004 *	0.333
Monothematic delusions	0 (0%)	26 (26%)	1 (1%)	0.000 **	0.667
Systematization of delusions	0 (0%)	68 (67%)	1 (1%)	0.000 **	0.667
Prominence of delusions	0 (0%)	65 (64%)	0 (0%)	0.000 **	-
Conviction about delusions or hallucinations	1 (2%)	67 (66%)	1 (1%)	0.000 **	0.557
Actions based on delusions or hallucinations	0 (0%)	36 (36%)	0 (0%)	0.000 **	-
Bizarreness of delusions	0 (0%)	45 (44%)	0 (0%)	0.000 **	-

[a] : narcolepsy versus schizophrenia
[b] : narcolepsy versus controls
*: $p < 0.01$ **: $p<0.001$

Table 5 Perceptual symptoms other than hallucinations

	Narcolepsy	Controls	p[a]
Unusual sensations	21 (35%)	1 (1%)	0.000 **
Changed perceptions	7 (12%)	1 (1%)	0.002 *
Dulled perceptions	2 (3%)	0 (0%)	0.110
Heightened perception	6 (10%)	0 (0%)	0.001 *
Changed perception of time, deja vu, jamais vue	15 (25%)	1 (1%)	0.000 **
Derealization (things)	8 (13%)	0 (0%)	0.000 **
Derealization (people)	9 (15%)	0 (0%)	0.000 **
Depersonalization	8 (13%)	1 (1%)	0.001 *
Depersonalized perception of self	4 (7%)	0 (0%)	0.012
Unfamiliarity (self)	4 (7%)	1 (1%)	0.043
Changed personal apprearance (dysmorphophobia)	0 (0%)	0 (0%)	-
Delusions concerning appearance	0 (0%)	0 (0%)	-
Delusion of depersonalization or derealization	1 (2%)	0 (0%)	0.333
Other perceptual abnormalities	9 (15%)	0 (0%)	0.000 **

[a] : narcolepsy versus controls
*: $p < 0.01$ **: $p<0.001$

Additional qualitative description of reported hypnagogic hallucinations

In the 39 patients reporting to have had hypnagogic hallucinations in the recent past, we collected descriptions of the content of the experiences. Patients described the multimodal hallucinations to be very hard to distinguish from real experiences. During the hallucination, typically a combination was present of the actual environment of the patient (such as the bedroom) superimposed with the hallucinated perceptions, for example a family member entering the room, while not actually being in the house. Tactile sensations (touching, pain) contributed to the impression of reality. The hallucinations, remembered in detail, were often very threatening and sometimes formed an impediment to go to bed. The content of the hallucinations had a typical pattern in which animals such as cats, dogs, mice, snakes, alligators or ants frequently played a role (n=17). The animals were often physically felt as if touching or crawling over the skin, in some cases strangulating the neck, stinging or biting. A patient described a hole in his bedroom from which a wave of mice poured out and ran over his body. "Realistic" hallucinations were reported such as footsteps on the stairs or on the roof (n=8), burglars in the house (n=7) or songs and music (n=5). One patient frequently heard her bedroom door opening in the night. She developed the habit of locking her door during the night to be sure that nobody could enter her room. One patient noticed the color of her lamp had changed during the hypnagogic hallucination (dyschromatopsia). There were more extravagant ones as well: feeling the presence of unseen, unheard visitors (n=10), touching of hands that strangulated, tore hair or extracted teeth (n=10). Contacts were reported with deceased family members, strangers or spirits from the dead (n=8). Patients further reported miscellaneous paranormal experiences (n=7) in which predictions such as future accidents or fatal illnesses were received. Contact with persons or messages from specific historic episodes (i.e., middle ages) were reported as well (n=5). In 17 cases "flying" was reported as frequent hypnagogic phenomenon, often felt as a pleasant experience. This type of hallucination has been called "kinetic hallucination" [25]. In order to check the reality level of the flying experience, one patient put a baseball cap on top of the bedroom cupboard: when he "flied" in the bedroom the missing cap on the cupboard would prove to him that the flying was not real. In 11 cases out-of-body experiences were reported. Sometimes there was a fear of not being able to return to the body. Three patients described witnessing a so called parallel universe. One of them could surf from one universe to another. Another had a small tunnel in the bedroom through which he could reach a "parallel world". Olfactory hallucinations (n=17) were mostly of bad odors as stool, burning material, and spoiled material. Ten patients reported sexual hallucinations that most often were unpleasant and threatening, such as being abused or raped.

Influencing factors

Gender, age and duration of illness did not show any effect on the frequency of the various SCAN items in either subject group. Furthermore, there were no differences between the frequency of items in narcolepsy patients without medication or using either stimulants, antidepressants or sodium oxybate.

Diagnosis according to DSM IV Classification

In the narcolepsy group, two patients reached the diagnostic criteria for a psychotic disorder according to DSM IV-TR. The third narcoleptic patient reporting delusions did not fulfill these criteria, because the delusions were not associated with distress or disability. One patient fulfilled the criteria of both "delusional disorder, persecutory type" and "psychotic disorder with delusions due to narcolepsy". The second patient received only the latter diagnosis. The first patient reported hypnagogic hallucinations in which demons played a dominating role: apart from this, she had the delusion of being watched by cameras. This delusion was not based on hypnagogic hallucinations or dreams and exclusively played a role in daytime, when awake. The second patient was bullied at night by spirits of deceased people that wanted to chase her out of her house. In daytime she believed these spirits were real. For this reason she eventually decided to move. Contact with spirits was not consonant with her social or cultural background. Two subjects from the population controls fulfilled the criteria for schizophrenia: one schizophrenia-paranoid type, and one schizophrenia-undifferentiated type. The prevalence of a diagnosed psychotic disorder did not differ between the narcolepsy patients and the population controls.

DISCUSSION

This study examined the prevalence and quality of hypnagogic hallucinations and other psychotic symptoms in patients with narcolepsy and addressed the question whether psychotic symptoms of narcolepsy can be distinguished from those of schizophrenia. We found, apart from their relation to sleep, two main differences: a qualitative difference in sensory modalities of hallucinations and a quantitative difference in the presence of concurrent delusions. In the narcolepsy group, there was no increased prevalence of formal psychotic disorders compared to the population controls.

Sensory modalities and concurrent delusions

Hallucinations of the visual modality were – in agreement with the literature [23,25] - much more frequent in narcolepsy patients than in schizophrenia, where

verbal-auditory was the most frequent sensory mode. Our data further showed that the hallucinations in narcolepsy are typically multimodal, combining visual, auditory (non-verbal and verbal) and tactile hallucinations. This "holistic" character of hallucinations in narcolepsy strongly contributed to a deceiving sense of reality of the experience. Patients could actually feel snakes crawling over their skin or blood dripping from a fresh wound. However, these "holistic" hallucinations hardly influenced reality testing: only three patients (5%) reported delusions, mostly based on hypnagogic experiences. Just one type of delusion was reported more frequently than in the population controls: delusional memories/ fantastic delusions, varying from memories of frightening encounters with ghosts to insistence on quite pleasurable flying expeditions. This scarcity of delusions is striking, given the high frequency and the realistic nature of the hallucinations, and points to relatively healthy insight in patients with narcolepsy. This combination of hallucinations with a low frequency of hallucination-congruent delusions is the second distinguishing feature between patients with narcolepsy and schizophrenia. Hallucinations can, however, influence interpretation of reality, creating confusion about the question whether an event really happened. Some patients claim to be clairvoyant on basis of hallucinated or dreamt messages. In other patients. the frequent déjà vue experiences help to create a multilayered sense of reality that even predisposes for paranormal interpretations. Psychiatric classification is complicated in these cases because of overlap with beliefs that are sanctioned in certain cultural and religious backgrounds.

Diagnostic classification

Although hypnagogic hallucinations are pervasive and influence daily functioning, they do not lead to a separate psychiatric classification in *DSM IV. DSM IV* places these perceptual symptoms within the range of normal experiences and includes them in the classification of narcolepsy. This is in keeping with our finding that the prevalence of a psychotic disorder according to *DSM-IV* in the narcolepsy group was very low and not different from the population controls.

Several authors discuss differentiation of psychotic disorders in narcolepsy -exceptional as they may be- in three possible subtypes: (a) as a psychotic form of narcolepsy, (b) as a chance coincidence with schizophrenia or (c) as stimulant induced psychosis [5,10,23,26,27]. In our study 2 patients were classified as having a psychotic disorder. One patient fell into Category (a): in this case, the delusions were completely consistent with the content of the hypnagogic hallucinations. The other patient fitted into Category (b): paranoid delusions were independent of content of hypnagogic hallucinations, and, clinically, there

was a mixture of the two disorders. Neither patient was using stimulants. In fact, we did not find any evidence for stimulant-induced psychotic symptoms in our study.

Differential diagnosis

While hypnagogic hallucinations in narcolepsy can usually be differentiated from schizophrenia, there remain a number of other differential diagnostic possibilities. Hallucinations in delirium are also accompanied by sleep disturbances. They are predominantly visual rather than auditory [28], often featuring animals, and are frequently accompanied by delusions [29]. In cocaine and amphetamine induced psychosis, hallucinations are more of the auditory sensory type and accompanied by thought disorders and delusions [30,31]. In Parkinson's disease, hallucinations often occur in combination with sleep disturbances, and are comparable to those in narcolepsy in having a visual and tactile character [32-34]. Hallucinations in Parkinson's disease are more frequently accompanied by delusions however. In focal epilepsy, hallucinations are brief and stereotyped. Symptoms are dependent of the localization of the epileptic focus and are associated with other epileptic manifestations [35].

Peduncular hallucinosis seems to be most similar to hypnagogic hallucinations [36]. Peduncular hallucinosis typically occurs in the evening, with an altered sleep pattern, and is seldom accompanied by delusions or paranoia [37]. The duration of episodes seems longer than hypnagogic hallucinations, however. The first description by Lhermitte in 1922 describes a patient that suffered from visual and tactile hallucinations [38]. In his summary he stated that peduncular hallucinations should be considered as expressions of sleep dysfunction and can be regarded as an equivalent of narcolepsy. Later reports described the visual, tactile and auditory modalities as well, although these modalities are less often occurring at the same time [36]. In this condition abnormally vivid dreams can occur too, and animals play a comparable role in the hallucinations. Usually, healthy insight into the nature of the hallucinations is preserved. Interestingly, lesions of pons and midbrain can cause both symptomatic narcolepsy and peduncular hallucinosis [39]. Lesions are often vascular [36] and may also occur as a complication of, e.g., neuroradiological interventions.

Previous studies

Goswami [40] studied hypnagogic hallucinations in 129 narcolepsy patients. In 79.4% of the patients hypnagogic hallucinations were present. Patients described visual, auditory, vestibular, somatic, olfactory and tactile hallucinations but frequencies of these sensory modalities were not given. Vourdas et al. [23] found

that 11 (24%) of 45 narcolepsy patients experienced hypnagogic hallucinations ever in their lifetime, according to the Present State Examination. Sensory modalities were not specified. Four patients (9%) met criteria for amphetamine-induced psychotic disorder. The difference in frequency of hypnagogic hallucinations compared to our results (65%, present state) is striking, and also much lower than in other studies. Dahmen et al. [25] compared hallucinations of 148 patients with narcolepsy to those of patients with schizophrenia and normal controls, using a telephone questionnaire. The percentage of hypnagogic hallucinations was 79.7%, using the Stanford Center for Narcolepsy Sleep Inventory. Unfortunately, no formal psychiatric diagnostic instrument was used. Additional analyses were carried out in a subgroup of 31 narcolepsy patients, showing that hallucinations were of the visual mode in 83%, kinetic in 71% and auditory in 45%. In the rare control subjects with hallucinatory experiences, the kinetic modality clearly dominated (53%, versus 19% visual and 9% auditory). This confirms a qualitative difference between narcoleptics and normal controls, as is also apparent in our data. The absence of formal hypnagogic hallucinations in our control subjects contrasts with other studies that found these present to some extent [13]. This difference may be explained by the rather stringent SCAN criteria, in which a phenomenon must be present on multiple occasions and not just incidentally.

Conclusion

In summary, this study adds to a more refined description of the psychopathological phenotype of narcolepsy. Hypnagogic hallucinations in narcolepsy can be differentiated on a phenomenological basis from hallucinations in schizophrenia which is useful in differential diagnostic dilemmas. The impact of hypnagogic hallucinations and their considerable interference with functioning calls for an active approach of patients inviting them to discuss these symptoms and fine tune treatment, in due balance with the other core symptoms of narcolepsy.

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Chapter 4

Anxiety and mood disorders in narcolepsy

Based on:
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ABSTRACT

Introduction

Narcolepsy is a primary sleeping disorder with excessive daytime sleepiness and cataplexy as core symptoms. There is increasing interest in the psychiatric phenotype of narcolepsy. Although many authors suggest an overrepresentation of mood disorders, few systematic studies have been performed, and conflicting results have been reported. Anxiety disorders in narcolepsy have only received little attention.

Methods

We performed a case-control study in 60 narcolepsy patients and 120 age- and sex-matched controls from a previous population study. The Schedules for Clinical Assessment in Neuropsychiatry were used to assess symptoms and diagnostic classifications of mood and anxiety disorders.

Results

Symptoms of mood disorders were reported by about one third of patients. However, the prevalence of formal mood disorder diagnoses – including major depression – was not increased. In contrast, more than half of the narcolepsy patients had anxiety or panic attacks. Thirty-five percent of patients could be diagnosed with anxiety disorder (odds ratio = 15.6), with social phobia being the most important diagnosis. There was no influence of age, sex, duration of illness or medication use on the prevalence of mood or anxiety symptoms and disorders.

Discussion

Anxiety disorders, especially panic attacks and social phobia's, often affect patients with narcolepsy. Although symptoms of mood disorders are present in many patients, the prevalence of major depression is not increased. Anxiety and mood symptoms could be secondary complications of the chronic symptoms of narcolepsy. Recent studies have shown that narcolepsy is caused by defective hypocretin signaling. As hypocretin neurotransmission is also involved in stress regulation and addiction, this raises the possibility that mood and anxiety symptoms are primary disease phenomena in narcolepsy.

INTRODUCTION

Sleep and psychiatric disorders often co-occur and influence each other mutually [1-3]. A case in point is narcolepsy, a prototypical primary sleep disorder with excessive daytime sleepiness and cataplexy –sudden attacks of muscle weakness triggered by emotions- as core symptoms [4,5]. Many patients also have hypnagogic hallucinations, sleep paralysis and nocturnal sleep fragmentation. However, psychiatric symptoms and disorders, including eating disorders and psychotic symptoms, have frequently been reported to affect narcoleptic patients [6,7]. The discovery that narcolepsy is caused by deficiencies in hypothalamic hypocretin (orexin) neurotransmission, has sparked a new interest in the psychiatric phenotype of the disorder. For example, recent data implicate the hypocretin system in the mediation of the stress response [8] and in a rat model of depression [9,10].

Depressive symptoms and mood disorders have been studied many times in narcolepsy, most often using self-report questionnaires such as the Beck Depression Inventory (BDI). In a large cross-sectional study using the BDI, Dauvilliers et al. found that 29% of narcoleptic patients had moderate to severe depressive symptoms [11]. An overrepresentation of depression is suggested by most authors, although others have questioned this thesis. Vourdas et al. did not find an increase in depressive disorders using a 'life-time approach' with a structured psychiatric interview [12]. Anxiety disorders have been studied less often in narcolepsy, although neurotic disorder is among the most frequent (mis) diagnosis given to patients before the diagnosis of narcolepsy is made [13].

The present study was undertaken to accurately examine the presence and severity of mood and anxiety disorders in narcolepsy. We used the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) as a validated formal diagnostic instrument in a large cohort of narcolepsy patients. Data were compared with those of a matched control group from a population study. Finally, we explored the influence of age, disease duration and medication use on symptoms of anxiety and depression.

METHODS

We performed a case-control study in 60 patients with narcolepsy-cataplexy and 120 matched population controls. Symptoms of depression and anxiety were assessed, as was the frequency of formal diagnoses of both anxiety and mood disorders, using a semistructured psychiatric interview.

Participants

Narcolepsy patients (n=60) were recruited from outpatient clinic of the Center for Sleep Medicine 'Kempenhaeghe' (Heeze, The Netherlands), and the Leiden University Medical Center Department of Neurology (Leiden, the Netherlands). All patients fulfilled the ICSD-2 diagnostic criteria of narcolepsy with cataplexy [14]. Sleep disordered breathing and other alternative causes for the excessive daytime sleepiness were excluded. Control subjects (n = 120) were selected from the cross-sectional population-based Nijmegen-Health-Area -2 study, in which psychiatric symptoms were assessed in 368 people from the Dutch population [15]. Controls were matched for age, sex and urban environment (living in a community with more or less than 100.000 inhabitants).

SCAN semi-structured interview

Symptoms of anxiety and depression were assessed using the Dutch edition of the SCAN, version 2.1 [16]. All interviews were performed by trained and certified SCAN interviewers. The SCAN consists of a semi-structured interview, developed from the Present State Examination, version 10 [17]. The SCAN is a reliable and valid diagnostic instrument that is widely endorsed [16,18,19]. DSM IV-TR diagnoses were generated with I-Shell, the analysis program developed for the SCAN.

For this study, we used SCAN chapters 3 (worrying and tension),Chaper 4 (panic, anxiety and phobias), Chapter 5 (obsessional symptoms),Chapter 6 (depressed mood and ideation) and Chapter 7 (thinking, concentration and energy) and Chapter 10 (expansive mood and ideation). We decided not to separately display individual symptom frequencies of Chapter 8 (bodily functions; e.g., sleep disturbances and weight changes) because of considerable overlap with the core symptoms of narcolepsy. However, bodily functions are included in the SCAN diagnostic algorithm. In this algorithm, weight loss and loss of concentration are taken into account, but sleep symptoms and fatigue are not, because these were typically scored as "due to an organic disorder" in narcolepsy.

Symptoms were recorded as "present state"(i.e., during the last month). The presence and the quality of the assessed symptoms were scored using the SCAN rating format: 0= a positive rating of absence; 1= symptom definitely present, but in a mild degree, considered below threshold for diagnosis; 2= symptom definitely present but of moderately severe intensity or, if severe, present for less than half of the time. 3= severe for more than half of the period. Ratings were then dichotomized as 'absent' (score 0 or 1) or 'present' (score 2 or 3). When patients spontaneously reported additional aspects of a certain symptom, these details were recorded and reported where appropriate.

Statistics

Demographics are presented as frequencies or as mean ± SD values. Assessed symptomps and diagnostic classifications are presented as the number of patients or controls who present the respective item. Patients and controls were then compared using logistic regression, showing odds ratios (ORs) together with 95%-confidence intervals (CIs). In cases in which ORs could not be computed (e.g., when the frequency of an item was zero in one of the groups), frequencies were compared using Fisher's exact test, with a significance level set at P=.01. Influence of sex and that of medication use on symptom frequency was tested with Fisher's exact test. Influence of age and duration of illness was tested using Spearman's rank correlation coefficient. All statistical analyses were performed using the SPSS package for Windows, Version 16.0.

RESULTS

Demographics and clinical variables

Demographic characteristics and medication use are listed in Table 1. Narcolepsy patients and population controls were well matched for gender and age. About half of the narcolepsy patients used stimulant medication to suppress sleepiness; 43% used antidepressant medication or sodium oxybate for cataplexy (Table 1). Less than one third of patients did not use medication. Average doses used for the most important medication classes are shown in Table 1.

Table 1 Demographic and clinical variables

	Narcolepsy	Controls
N	60	120
Male	28 (47%)	56 (47%)
Age (years)	43 ± 16	43 ± 15
Symptom duration (years)	24 ± 16	-
Medication		
Stimulants	28 (47%)	-
Antidepressants	26 (43%)	5 (4%)
Sodium oxybate	7 (12%)	-
Antipsychotics	2 (2%)	-
No medication	17(28%)	115 (96%)

Worrying and tension

In Table 2, the symptoms assessed in SCAN chapter 3 (worrying and tension) are summarized. As a whole, these symptoms were present significantly more in the narcolepsy patients. Two thirds of the patient scored positive on 'fatiguability and exhaustion'. Furthermore, 'irritability' was as a prominent symptom. A physical dimension of this category was reflected in 'localized tension pains' and 'increased general muscle tension'. Sixty percent of patients reported interference with daily activities due to symptoms of worrying and tension.

Table 2 Worrying and tension (SCAN chapter 3)

	Narcolepsy	Controls	Odds Ratio	C.I. / P*
Worrying	35 (58%)	11 (9%)	13.9	**6.20- 31.03**
Feeling of nervous tension	27 (45%)	10 (8%)	9.0	**3.96- 20.50**
General muscular tension	18 (30%)	12 (10%)	3,8	**1.69- 8.62**
Nervous in face of problems	14 (23%)	1 (1%)	35.3	**4.51- 276.25**
Localized tension pains	22 (37%)	7 (6%)	9.18	**3.63- 23.20**
Subjectively described restlessness	22 (37%)	8 (7%)	8.1	**3.33- 19.72**
Fatiguability and exhaustion	39 (65%)	6 (5%)	35.3	**13.28- 93.78**
Sensitivity to noise	18 (30%)	2 (2%)	25.1	**5.58- 112.68**
Irritability	26 (43%)	3 (3%)	29.8	**8.51- 104.58**
Simple ideas of reference	10 (17%)	0	-	**<0.001**
Suspiciousness	8 (13%)	2 (2%)	9.0	**1.85- 43.85**
Depersonalization and derealization	14 (23%)	0	-	**<0.001**
Non-delusional jealousy	4 (7%)	0	-	**<0.001**
Interference	36 (60%)	14 (12%)	11.4	**5.31- 24.28**

C.I. / P: This column shows the 95% confidence interval (C.I.) for the odds ratio comparing narcolepsy patients versus controls. When the odds ratio cannot be computed because the frequency of an item is zero in one of the groups, the P-value obtained by Fisher's exact test is given. All significant outcomes are printed in bold.

Panic, anxiety and phobias

Phobias and signs of panic and anxiety were often present in narcoleptic patients (Table 3). Anxiety or panic attacks were reported by 53% of patients. When the patients were questioned into more detail, panic attacks turned out to be frequently linked to frightening experiences during hypnagogic hallucinations, but could also be triggered in social situations, such as meeting strangers. The mean frequency of panic attacks was once a month. More than 25% of the patients reported considerable interference with activities due to panic attacks.

Phobias were often present in patients, with more than half of the patients describing some kind of phobia. Among the situational phobias, 'collapsing alone or with no help near' was the strongest (OR 23.8) and often related to a fear of getting a cataplexy attack. The most feared social situation was 'speaking in public to strangers' (OR= 51.0). Fear of heights was the most prevalent specific phobic symptom in patients. In some patients, phobic symptoms resulted from daytime associations with frightful previous experiences. For example, one patient answered to SCAN question 4.040 ('are you afraid in enclosed spaces'): 'yes, when I am lying in a coffin'. Only later did she realize that she had experienced this specific sensation in (recurring) hypnagogic hallucations; therefore, we scored this item negative.

Table 3 Panic, anxiety and phobias (SCAN chapter 4)

	Narcolepsy	Controls	Odds Ratio	C.I. / P*
Anxiety or panic attacks present	32 (53%)	10 (8%)	12.6	**5.52- 28.61**
Phobias present	33 (55%)	21 (18%)	5.8	**2.88- 11.52**
Panic	15 (25%)	9 (8%)	4.1	**1.68- 10.07**
Can't get breath	15 (25%)	9 (8%)	4.1	**1.68- 10.07**
Heart pounding	24 (40%)	9 (8%)	3.5	**1.72- 7.15**
Dizzy	21 (35%)	7 (6%)	8.6	**3.40- 21.83**
Tingling	8 (13%)	2 (2%)	9.1	**1.86- 44.22**
Chest pain	12 (20%)	11 (9%)	2.5	**1.02- 6.01**
Dry mouth	7 (12%)	12 (11%)	1.2	0.44- 3.16
Difficulty swallowing	5 (8%)	8 (7%)	1.2	0.40- 4.07
Sweating	28 (47%)	25 (21%)	3.3	**1.70- 6.51**
Trembling	8 (13%)	14 (12%)	1.15	0.46- 2.92
Hot or cold sweats	14 (23%)	8 (7%)	4.2	**1.66- 10.75**
Unreality	12 (20%)	5 (4%)	5.75	**1.92- 17.21**
Nausea	9 (15%)	9 (8%)	2.18	0.81- 5.81
Fear of dying	14 (23%)	3 (3%)	11.8	**3.26- 43.24**
Feeling of choking	14 (23%)	9 (8%)	3.75	**1.52- 9.28**
Fear of going crazy	17 (28%)	6 (5%)	7.5	**2.78- 20.31**
Apprehension	25 (42%)	19 (16%)	3.8	**1.87- 7.72**
Other	8 (13%)	6 (5%)	2.9	0.96- 8.78
Panic attacks	15 (25%)	3 (3%)	10.2	**2.76- 37.92**
Afraid for another panic attack	8 (13%)	1 (1%)	18.0	**2.19- 147.63**
Action to prevent or end panic attack	12 (20%)	2 (2%)	14.5	**3.12- 67.25**
Free-floating anxiety	7 (12%)	6 (5%)	2.5	0.82- 7.99

Table 3 Continued

Anxious foreboding with autonomic symptoms	11 (19%)	3 (3%)	8.9	**2.39- 33.46**
Depersonalization /derealizaton with anxiety	7 (12%)	3 (3%)	5.15	**1.28- 20.70**
Situational phobias				
Public place, open spaces	5 (8%)	2 (2%)	5.36	**1.01- 28.51**
Crowds, shops, theaters	10 (17%)	2 (2%)	11.8	**2.50- 55.81**
Going out or traveling alone	8 (13%)	2 (2%)	9.08	**1.86- 44.22**
Traveling away from home	7 (12%)	1 (1%)	15.7	**1.89- 130.96**
Collapsing alone or no help near	10 (17%)	1 (1%)	23.8	**2.97- 190.89**
Being alone at home	6 (10%)	1 (1%)	13.2	**1.56- 112.53**
Social phobias				
Eating, drinking, etc. in public	5 (8%)	2 (2%)	5.36	**1.01- 28.51**
Blushing, shaking, fear of vomiting, micturition or defecation	2 (3%)	1 (1%)	4.1	0.37- 46.19
Speaking in a small known group	6 (10%)	1 (1%)	13.2	**1.55- 112.53**
Speaking in public to strangers	18 (30%)	1 (1%)	51.0	**6.60- 393.86**
Specific (simple) phobias				
Storms, thunder, lightning	5 (8%)	2 (2%)	5.36	**1.01- 28.51**
Water – pool, lake, sea...	8 (13%)	3 (3 %)	6.0	**1.53- 23.53**
Animals – insects, birds, rats	13 (22%)	9 (8%)	3.4	**1.37- 8.52**
Enclosed spaces – lifts, tunnels	9 (15%)	5 (4%)	4.06	**9.39- 56.31**
Flying	4 (7%)	1 (1%)	8.5	0.93- 77.81
Heights – bridges, stairs	29 (48%)	7 (6%)	15.1	**6.04- 37.74**
Related to illness (hospitals, dentist, injections	9 (15%)	4 (3%)	5.12	**1.51- 17.39**
Fear of contracting illness (cancer, HIV)	8 (13%)	1 (1%)	18.3	**2.23- 150.14**
Other	4 (7%)	2 (2%)	4.2	0.75- 23.70
Interference with activities				
Due to situational phobias	17 (28%)	0	-	**<0.001**
Due to social phobias	17 (28%)	1 (1%)	45	**5.82- 349.07**
Due to specific phobias	8 (13%)	1 (1%)	18	**2.23- 150.14**
Due to panic and vegetative symptoms	16 (27%)	5 (4%)	8.4	**2.89- 24.20**

C.I. / P: This column shows the 95% confidence interval (C.I.) for the odds ratio comparing narcolepsy patients versus controls. When the odds ratio cannot be computed because the frequency of an item is zero in one of the groups, the P-value obtained by Fisher's exact test is given. All significant outcomes are printed in bold.

Obsessional symptoms

Patients reported the same frequency of symptoms related to obsession as did the population controls.

Depressed mood and ideation

A third of the patients reported a depressed mood (Table 4). The highest OR (21.5) among symptoms of depression was found for anhedonia. Loss of self esteem and self confidence was also reported significantly more in patients compared to controls. Interestingly, in contrast to depressive symptoms in other chronic diseases [20], pathological guilt (22%) and guilty ideas of reference (15%) were clearly part of the mood symptom profile in patients with narcolepsy. Suicidal thoughts or self harm were reported by 13% of the patients. Interference in daily activities by mood symptoms was present in 33% of patients.

Table 4 Depressed mood and ideation (SCAN chapter 6)

	Narcolepsy	Controls	Odds Ratio	C.I.
Depressed mood	18 (30%)	10 (8%)	4.71	**2.01- 11.04**
Masked depression	5 (8%)	3 (3%)	3.52	0.81- 15.24
Tearfulness and crying	15 (25%)	3 (3%)	12.8	**3.53- 46.26**
Anhedonia	16 (27%)	2 (2%)	21.5	**4.74- 97.14**
Loss of hope for the future	12 (20%)	4 (4%)	7.1	**2.16- 23.00**
Feeling loss of feeling	9 (15%)	4 (4%)	5.0	**1.48- 17.09**
Loss of reactivity	6 (10%)	7 (6%)	1.78	0.57- 5.55
Morning depression	3 (5%)	2 (2%)	3.08	0.50- 18.95
Preoccupation with death or catastrophe	3 (5%)	2 (2%)	3.05	0.50- 18.79
Suicide (thoughts) or selfharm	8 (13%)	2 (2%)	8.9	**1.83- 43.48**
Tedium vitae	10 (17%)	2 (2%)	11.5	**2.43- 54.40**
Pathological guilt	13 (22%)	2 (2%)	16.0	**3.48- 73.85**
Guilty ideas of reference	9 (15%)	1 (1%)	20.5	**2.53- 165.84**
Loss of self confidence	12 (20%)	3 (3%)	9.5	**2.57- 35.18**
Social withdrawal	13 (22%)	1 (1%)	22.1	**4.08- 252.24**
Loss of self esteem	8 (13%)	1 (1%)	18.0	**2.19- 147.63**
Interference	20 (33%)	8 (7%)	6.87	**2.81- 16.85**

Thinking, concentration and energy

Patients scored higher on many items of this category (Table 5). However, some of these items may be difficult to interpret. For example, 'loss of concentration', reported by 80% of patients, is inherent to the state of drowsiness and lowered consciousness that accompanies excessive daytime sleepiness, the hallmark of narcolepsy. The same may hold true for symptoms such as 'loss of energy'. This symptom category resulted in the most striking interference with daily activities, as reported by 90% of patients (OR= 89.2).

Table 5 Thinking, concentration, energy (SCAN chapter 7)

	Narcolepsy	Controls	Odds Ratio	C.I.
Loss of positive cognitive functioning	47 (78%)	6 (5%)	68.7	**24.64- 191.50**
Loss of concentration	48 (80%)	5 (4%)	91.2	**30.47- 273.00**
Subjectively inefficient thinking	25 (42%)	4 (3%)	20.5	**6.69- 63.02**
Loss of interest	12 (20%)	2 (2%)	14.6	**3.15- 67.82**
Subjective feeling of retardation	18 (30%)	2 (2%)	25.1	**5.58- 112.68**
Loss of energy (drive)	42 (72%)	5 (4%)	57.7	**20.04- 165.96**
Feeling of being overwhelmed by everyday tasks	35 (58%)	5 (4%)	31.9	**11.37- 89.61**
Interference	54 (90%)	11 (9%)	89.2	**31.31- 254.04**

Expansive mood and ideation

The frequency of (hypo)manic symptoms was low in the patient group, never affecting more than 10% of the subjects. However, four patients described hypomanic episodes, one of whom with a rapid cycling pattern. Three of these patients had been admitted with a manic episode in the past. Many patients (30%) reported an irritable mood compared to only 3% of controls (OR 16.7). However, this irritability was often reported to occur during moments of sleepiness and may therefore not necessarily be a symptom of a mood disorder.

Influence of demographic and clinical characteristics on symptom frequency

Women tended to score higher on many anxiety items compared to men. However, this only reached significance for a minority of symptoms, most notably phobic reactions to animals and avoidance of anxiety provoking social situations (both P <0.001). Age was unrelated to the symptom frequencies of any category. However, age was related to the degree of interference with activities in patients with depressive mood and ideation: higher age resulted in lower interference

(R^2 = -0.33, *P*=0.011). Longer disease duration was even a better predictor for lower interference (R^2= -0.37, p=0.004).
There were no differences in symptom frequency between patients with and those without medication. Furthermore, type of medication did not influence symptom profiles.
When patients with and those without medication were compared, there was no difference in (individual) symptoms frequencies. In addition, we performed comparisons between symptom frequencies and subgroups of medication. Only a few associations turned up in the analysis. Patients using SSRI's more often reported loss of libido (*P*=0.008). All three patients who were using venlafaxine described panic attacks (*P*=0.008 versus other patients). The items "depressed mood" and "tearfulness and crying" tended to occur more often in patients using methylphenidate (*P*=0.013 and *P*=.012, respectively).

Diagnostic Classification
Table 6 lists the frequency of DSM-IV diagnoses regarding mood disorders, panic attacks and anxiety disorders. Overall, there was no increase in the prevalence of mood disorders in narcolepsy patients. In contrast, anxiety disorders were strikingly more prevalent in narcolepsy patients (35%, OR= 15.6). The most important diagnosis in this category was social phobia, affecting 20% of patients (OR= 29.8). In addition, panic attacks were overrepresented in narcolepsy patients (22%, OR= 4.5).

DISCUSSION

Our study is the first one to show that anxiety - more than depression- dominates the psychiatric comorbidity of narcolepsy patients. We found an excess of panic attacks and social phobia in the patient group compared to the population controls. Furthermore, the frequency of mood- related symptoms in narcolepsy was significantly higher than that in controls. However, the prevalence of formal mood disorders – including major depression- was not increased.

The high prevalence of anxiety symptoms and that of formal anxiety disorders in narcolepsy are striking. In the past, anxiety disorders have not received the same amount of attention as mood disorders in narcolepsy. Older studies reported unspecified anxiety in 17% of patients [21] and 10% of narcoleptics having a history of anxiety disorder [22]. Personality studies reported higher levels of psychasthenia and hypochondria in patients with narcolepsy compared with patients with idiopathic hypersomnia [23], which may be associated with the increase in anxiety.

Table 6 Diagnostic classification according to the DSM-IV criteria

	Narcolepsy	Controls	Odds Ratio	C.I. / P*
Mood disorders	9 (15%)	6 (5%)	3.35	**1.13- 9.92**
Major depressive episode	4 (7%)	3 (3%)	2.79	0.60- 12.87
Dysthymic disorder	0 (0%)	3 (3%)	-	0.55
Bipolar I disorder	4 (7%)	0	-	0.012
Bipolar II disorder	1 (2%)	0	-	0.33
Anxiety disorders	21 (35%)	4 (3%)	15.62	**5.05- 48.30**
Panic attacks	13 (22%)	7 (6%)	4.47	**1.68- 11.90**
Panic disorder without agoraphobia	1 (2%)	1 (1%)	2.02	0.12- 32.82
Agoraphobia without panic disorder	1 (2%)	0	-	0.33
Specific phobia	1 (2%)	0	-	0.33
Social phobia	12 (20%)	1 (1%)	29.75	**3.76- 235.14**
Obsessive-compulsive disorder	0 (0%)	1 (1%)	-	1.00
Generalized anxiety disorder	1 (2%)	1 (1%)	2.02	0.12- 32.82
Adjustment disorder	1 (2%)	0	-	0.33
Anxiety disorder NOS	4 (7%)	0	-	0.012

C.I. / P: This column shows the 95% confidence interval (C.I.) for the odds ratio comparing narcolepsy patients versus controls. When the odds ratio cannot be computed because the frequency of an item is zero in one of the groups, the P-value obtained by Fisher's exact test is given. All significant outcomes are printed in bold.

The explanation for the frequent occurrence of anxiety symptoms and disorders in patients with narcolepsy may be twofold. On the one hand, anxiety may be secondary to having narcolepsy and being chronically exposed to anxiety-inducing situations or experiences. This mechanism has been described in other disorders – for example, Méniere's disease – in which paroxysmal dizziness may lead to phobic anxiety [24]. On the other hand, there may be a direct link between the primary pathophysiology of narcolepsy and that of anxiety.

Sensitivity to stress may be enhanced by the lack of control that narcoleptic patients experience during irregular sleep- wake states, cataplexy attacks, unpredictable automatic behaviour or bulimic attacks. These symptoms could all 'push up' the level of stress due to a more external locus of control. In addition,

social anxiety could be linked to shame from falling asleep or having cataplectic attacks in the company of others. The avoidance of social interaction can be seen as a strategy to gain control over these embarrassing situations. Specific phobias may also have a different source. Narcoleptic patients may have severe difficulty in discerning reality from experiences during hypnagogic hallucinations [7]. Associations between these 'two worlds' are frequently reported by patients, and frightening hallucinations can influence daytime reality. Specific phobic symptoms, such as a fear of certain animals or water, may well be related to frightful experiencies during hypnagogic hallucinations.

Regarding mood disorders, most previous studies in narcolepsy are case series that used self-report questionnaires such as the BDI, instead of formal diagnostic instruments. Many of these reported high frequencies of depression [11,21,25-27]. Quality-of-life instruments, such as the SF- 36, pointed to a high level of depressive symptoms in narcolepsy as well [28-30]. However, the controlled study by Vourdas et al [12], which used the Present State Examination, did not confirm an overrepresentation of depressive disorders in narcolepsy patients, which is comparable to our findings . One of the reasons for these discrepant results is the considerable overlap between the symptomatology of narcolepsy and the somatic features of depression, such as sleep disturbances, weight changes, and loss of concentration (see below). Using self- completed questionnaires with predefined cutoff scores may lead to high prevalence estimates.

Many individual mood symptoms, including depressed mood an anhedonia, were reported more often by the narcolepsy group. The question on whether these symptoms belong to the narcolepsy profile proper, reflect an adjustment reaction to the narcolepsy or are indicative of an independent psychiatric disorder, remains. This diagnostic dilemma complicates the psychiatric classification of depression in many chronic somatic illnesses and currently has not been adequately solved [31] . The cause of the dilemma lies in the "somatic symptoms "that are included in the *DSM-IV-TR* diagnostic criteria for depression (weight changes, disturbed sleep, fatigue and loss of concentration). Several solutions have been proposed, such as an "exclusive approach" in which symptoms overlapping with the somatic disorder are left out, and an "inclusive approach"in which all somatic symptoms count fully [32]. In our study, we followed the SCAN algorithm to obtain *DSM –IV* diagnoses that can be described as "partially inclusive", including weight changes and loss of concentration, but excluding sleep symptoms and fatigue [16]. Given the significant impairments that depressive symptoms can pose on patients, it is still prudent to apply a rather inclusive approach in clinical practice, in order not to withhold treatment.

Recent data raise the interesting possiblity that anxiety and mood symptoms in narcolepsy may be a direct consequence of the neuropathophysiology of the disease. It is now firmly established that narcolepsy is caused by deficiencies in hypothalamic hypocretin (orexin) signaling [4,5], with more than 90% of patients with clear-cut cataplexy being deficient in hypocretin. Studies suggest a role for the hypocretin system in the mediation of the stress response [8]. Changes in hypocretin levels have been reported in a rat model for depression [9,10]. Brundin et al. [33] reported significantly lower hypocretin concentrations in the cerebrospinal fluid (CSF) of patients with major depressive disorder who attempted suicide, compared to control suicide attempters with dysthymia or adjustment disorder. In a follow-up sample of suicide attempters with miscellaneous diagnoses, cerebrospinal hypocretin concentrations were negatively correlated with symptoms of lassitude and slowness of movement [33]. Hypocretin neurons are part of the central reward circuit- for example, by influencing dopaminergic neurons in the ventral tegmental area [34,35]. Animal data show that hypocretin defects indeed lead to abnormal reward processing [36]. Interestingly, changes in reward processing are also found in patients with social anxiety disorder, in whom positive and reinforcing aspects of social interactions are muted [37-39]. Although we do not have data on the hypocretin status of our patients, a direct connection between the hypocretin deficiency in narcolepsy and anxiety and mood disorders a likely possibility. Studies in hypocretin- deficient animal models for narcolepsy may shed further light on this mechanism.

Our findings have consequences for the care for patients with narcolepsy. Anxiety symptoms are often not spontaneously reported, and should be actively asked for. Recognition and discussion of these symptoms can provide important relief for patients. Many patients reported a clear impairment in daily functioning due to anxiety and mood problems. Interference with activities due to mood symptoms diminished with longer disease duration, indicating better adjustment in time possibly by acquiring effective coping strategies. However, by paying attention to these complaints, physicians can help patients become less isolated and gain more control over these symptoms. It is crucial for doctors to realize that patients with narcolepsy display a highly complex phenotype, that is not just limited to sleep symptoms.

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Chapter 5

High prevalence of eating disorders in narcolepsy

Based on:
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ABSTRACT

Objectives. To study the prevalence of (symptoms of) eating disorders in patients with narcolepsy.

Design. We performed a case-control study comparing symptoms of eating disorder in patients with narcolepsy versus healthy population controls, using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1). To study whether an increased body mass index (BMI) could be responsible for symptoms of eating disorder, we also compared patients to BMI-matched controls, using the SCAN as well as the Eating Disorder Examination-Questionnaire.

Patients and participants. Patients with narcolepsy/cataplexy (n=60) were recruited from specialized sleep centers. Healthy controls (n=120) were drawn from a population study previously performed in the Netherlands. Separately, 32 BMI-matched controls were recruited.

Measurements and Results. In total, 23.3% of the patients fulfilled the criteria for a clinical eating disorder, as opposed to none of the control subjects. Most of these were classified as Eating Disorder – Not Otherwise Specified, with an incomplete form of binge eating disorder. On the symptom level, half of the patients reported a persisting craving for food, as well as binge eating. Twenty-five percent of patients even reported binging twice a week or more often. When compared to BMI-matched controls, the significant increases persisted in symptoms of eating disorders among patients with narcolepsy. Except for a higher level of interference in daily activities due to eating problems in patients using antidepressants, medication use did not influence our findings.

Conclusions. The majority of patients with narcolepsy experience a number symptoms of eating disorders, with an irresistible craving for food and binge eating as the most prominent features. Eating disorder symptomatology interfered with daily activities. These findings justify more attention for eating disorders in the treatment of patients with narcolepsy.

INTRODUCTION

Narcolepsy is a clinically heterogeneous condition [1,2]. Next to the core features of excessive daytime sleepiness and cataplexy, there is a varying number of additional symptoms. Besides sleep related symptoms, such as sleep paralysis, hypnagogic hallucinations and fragmented nocturnal sleep, non-sleep symptoms are often encountered. One of the more prominent of those is the increase in body weight in many patients. Already in the 1930s, Daniels reported that 57% of his patients with narcolepsy were overweight or obese [3]. Recently, a number of epidemiological studies showed a clear increase in Body Mass Index (BMI) in narcoleptic patients compared to the general population[4-6], with a preferential storage of fat in the abdominal compartment. Several explanations for the weight gain have been put forward. Although the psychoanalytic theory of weight gain due to 'substitutive oral activity' held for a while [7], recent discoveries into the biological basis of narcolepsy provided more founded mechanisms.

Most cases of narcolepsy with cataplexy are caused by a deficiency in hypocretin (orexin) neurotransmission [8,9]. The hypocretin neurons are located in the perifornical area of the lateral hypothalamus and are involved not only in the regulation of sleep, but in endocrine and autonomic regulation as well [10]. The weight gain in narcolepsy could be caused by changes in energy expenditure due to excessive sleepiness, changes in basal metabolic rate [11,12] or endocrine disturbances [13,14]. Excessive daytime sleepiness is not likely to be a major factor, as patients with narcolepsy have a significantly higher BMI than do patients with idiopathic hypersomnia [6]. Interestingly, recent studies showed that the hypocretin system may also be active in the psychiatric domain [15,16]. This, in combination with the known stimulatory effect of hypocretin on food intake [17] raises the possibility that eating disorders may be present in narcolepsy.

Although a controlled diary study showed no differences in total caloric intake between patients with narcolepsy and controls [18], there have been some reports on symptoms of eating disorders. Kotagal et al found a history of binge eating in 5 out of 31 children with narcolepsy [19]. Recently, Chabas et al reported a mild eating disorder, classified as Eating Disorder Not Otherwise Specified (EDNOS), in 6 patients with narcolepsy-cataplexy [12]. Besides this study, no systematic studies on the prevalence of (symptoms of) eating disorders have been carried out. Furthermore, the influence of an increased body weight per se on such symptoms remains unknown in narcolepsy.

To determine whether eating disorders (at the diagnostic as well as the symptom level) are indeed more prevalent in narcolepsy, we performed a large cross-sectional case control study comparing 60 patients with narcolepsy-cataplexy with healthy controls from the general population. In addition, to study the influence of overweight, we performed a separate study in which 32 patients with narcolepsy were compared with 32 controls, who were also matched for BMI.

METHODS

General study design

We conducted two separate cross-sectional case-control studies. In study I, we compared symptoms of eating disorder in 60 narcolepsy-cataplexy cases with 120 age- and sex-matched controls taken from a large population based study. In study II, 32 patients with narcolepsy were compared (using an additional diagnostic instrument) with 32 specifically recruited controls, matched not only for age and sex, but also for BMI. This study was conducted according to the guidelines of the medical ethical committee of the Radboud University Nijmegen Medical Center. All subjects gave informed consent prior to entering the study.

Participants

Narcoleptic patients were recruited from the outpatient clinics of Sleep-Wake Center 'Kempenhaeghe' (Heeze, The Netherlands) and the department of Neurology, Leiden University Medical Center (Leiden, The Netherlands). All patients fulfilled the ICSD-2 diagnostic criteria of narcolepsy with cataplexy [20]. All were HLA-DQB1*0602 positive, and Multiple Sleep Latency Testing showed a mean sleep latency of less than 8 minutes as well as 2 or more sleep-onset rapid eye movement periods. In only a minority of patients, CSF hypocretin-1 measurements were performed [9]. Other sleep disturbances, such as sleep-related breathing disorders were excluded as the cause for the excessive daytime sleepiness.

In study I, 60 narcoleptic patients were compared with 120 control subjects. Controls were randomly taken from the cross-sectional population-based Nijmegen-Health-Area-2 study, in which psychiatric symptoms were assessed in 368 people from the Dutch population [21]. Controls were matched for age, sex and urban environment (living in residential area with less or more than 100.000 inhabitants).

In study II, 32 narcoleptic patients were compared with 32 controls, recruited by advertisement in a local newspaper. Here, subjects were also matched for BMI, as BMI has been shown to influence eating attitudes and behavior [22-24].

Measurements

Symptoms of eating disorders were assessed using chapter 8 and 9 of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1. The SCAN consists of a semi-structured interview that incorporates the Present State Examination, version 10 [25]. The SCAN is a validated diagnostic instrument that is widely endorsed [25-28]. Both the patients and the population controls were interviewed by trained and certified SCAN investigators. From the SCAN data, symptoms of eating disorders can be assessed on the item level. In addition, it is possible to classify symptoms into the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic classification for eating disorders: anorexia nervosa, bulimia nervosa, and EDNOS [29]. EDNOS contains incomplete forms of anorexia nervosa or bulimia nervosa, as well as Binge Eating Disorder. To enable classification as binge eating disorder with more certainty, we added 1 question from the Structured Clinical Interview for DSM-IV to our SCAN interview. Section 8 of the SCAN assesses physical functions such as changes in BMI over time. Section 9 assesses various symptoms of eating disorders, as well as the interference with daily activities due to these symptoms. We added section 6 and 7 from the SCAN, which cover depressive symptomatology, in order to assess the influence of mood symptoms on eating behavior.

In study II, besides the SCAN, subjects completed the Eating Disorders Examination-Questionnaire (EDE-Q 4th edition) [30]. The EDE-Q is a self report version of the Eating Disorder Examination[31]. It is a 36-item scale that assesses features of eating disorders, generating 4 subscale scores: dietary restraint, eating concern, weight concern and shape concern. Respondents rate the items on a 7-points scale, indicating the number of days out of the previous 28 in which specific behaviors and attitudes occurred. The EDE-Q has received psychometric support, including adequate test- retest reliability[32,33] and a good convergence with the EDE-interview [30,34,35]. Disordered eating was defined when subjects scored 4 or greater on either the weight concern or the shape concern subscale, had a mean global score of 4 or greater, or had more than 1 episode of self-induced vomiting, binging with loss of control or diuretic or laxative use over the last 4 weeks [24,36].

Statistical analysis

All data are presented as mean ± standard deviation. Mean item scores and item frequencies were compared between groups using Students t-test and Fisher

exact test respectively. To obtain DSM IV diagnostic classifications from the SCAN interview, we used the software algorithm written by C.R. in SAS version 8, in consultation with and after approval of the World Health Organization SCAN workgroup. All other statistical comparisons were done using SPSS version 14. Significance level was set at p= 0.05.

RESULTS

Demographic and clinical variables

In table 1, the demographic characteristics of the participants are listed. In both studies, patients and controls were well matched for sex and age. On average, patients had narcolepsy symptoms for around 20 years at the time of study. Fifty-two percent of patients used stimulant medication (modafinil or methylphenidate), 12% used sodium oxybate, and 43% antidepressants for cataplexy.

Table 1 Demographic and clinical characteristics

	Study I			**Study II**		
	Patients	*Controls*	*p*	*Patients*	*Controls*	*p*
N	60	120		32	32	
Age	43.5 ± 15.6	43.5 ± 15.4	0.97	40.4 ± 15.1	42.2 ± 11.7	0.079
Males	28 (47%)	56 (47%)	1.00	11 (34%)	11 (34%)	1.00
BMI	27.8 ± 5.7	24.6 ± 3.3	0.001	27.6 ± 7.1	27.6 ± 5.0	0.43
Age at onset	20.1 ± 9.2			19.7 ± 7.6		
Age at diagnosis	30.6 ± 11.6			28.2 ± 10.8		
Duration of symptoms	23.9 ± 15.8			20.4 ± 13.0		
Duration since diagnosis	10.5 ± 11.0			11.10 ± 9.4		

In study I we again confirmed that patients with narcolepsy are overweight: there was a significant difference in BMI between patients (27.8 ± 5.7) and controls (24.6 ± 3.3, p= 0.001). BMI was not influenced by sex. In study II, patients and controls were well matched for BMI.

Symptoms of eating disorders

The percentages of participants scoring positive on the various items of the SCAN are listed in table 2. In study I, patients with narcolepsy scored significantly higher on all items, except for 'actions to loose weight through purgation'. About half of

Table 2 SCAN Section 9 (item level symptoms of eating disorders)

	Study I			**Study II**		
	Patients	*Controls*	*p*	*Patients*	*Controls*	*p*
N	60	120		32	32	
Dread of becoming fat	62%	8%	<0.001	78%	31%	<0.001
Earlier episode of undereating	13%	5%	0.074	22%	16%	0.75
Irresistible and persistent craving for food	67%	5%	<0.001	66%	13%	<0.001
Earlier episode of overeating	42%	5%	<0.001	50%	22%	0.036
Self perception of fatness w/ intrusive dread of becoming too fat	33%	1%	<0.001	38%	22%	0.274
Imposes low weight threshold	5%	0%	0.036	13%	3%	0.355
Avoidance of fattening foods	45%	3 %	<0.001	53%	34 %	0.207
Actions to lose weight through self restriction	42%	2%	<0.001	43%	13%	0.011
Actions to lose weight through purgation	3%	1%	0.258	9%	0%	0.24
Binge eating w/ sense of lack of control						
None	45%	99%	<0.001*	31%	78%	0.002*
Binges but retains control	12%	0%		13%	13%	
Binges infrequently w/ feeling of loss of control	18%	1%		28%	9%	
Binges twice a week, w/ a feeling of lack of control	20%	0%		16%	0%	
Binges more frequently w/ a feeling of loss of control	5%	0%		9%	0%	
Dread of getting too fat in spite of craving	30%	0%	<0.001	28%	0%	0.002
Actions to correct binging through purgation	7%	0%	0.012	6%	3%	1.000
Restrictive actions to correct binging	18%	0%	<0.001	25%	0%	0.005

*: Chi-square test

the patients reported a persisting craving for food, experienced an earlier episode of overeating, and experienced binge eating. Twenty-five percent of patients even reported binging twice a week or more. The majority of patients reported a dread of becoming fat, a self-perception of fatness or both. Patients also took more measures for weight control, such as the avoidance of fattening foods or trying to lose weight through self-restriction. No endocrine disturbances were reported, such as delayed onset of puberty or amenorrhea.

Female patients showed significantly higher scores than males on the following items: dread of becoming fat (78 vs 43%, P =0.001) and dread of getting too fat in spite of craving (44 vs 15%, P=0.02). Furthermore, women more often reported a certain level of interference of symptoms of eating disorder in daily life (72% vs 43%, P=0.013).

In study II, BMI-matched controls also reported symptoms of eating disorders, such as a self-perception of fatness and measures for weight control (table 2). However, even when compared to BMI matched controls, patients with narcolepsy had a significantly increased frequency of episodes of overeating, binge eating and a persistent craving for food. Furthermore, within the patient group, there was no difference in BMI between subjects who reported binge eating and those who did not. There were also no significant correlations between BMI and the EDE-Q subscales on objective and subjective bulimic episodes.

Symptoms of eating disorder posed a clear interference with daytime activities in patients. Over 30% of patients reported moderate to severe (and incapacitating) interference with activities, compared to 1% of controls in the general population and 6% in BMI-matched controls (P< 0.001).

DSM IV classification of eating disorders

Using the SCAN data, subjects were classified in the DSM-IV eating disorders diagnoses (table 3). In total, 23.3% of the patients fulfilled the criteria for a clinical eating disorder, against none of the control subjects. Only 1 patient was classified as having anorexia nervosa. Four patients (6.7%) fulfilled the criteria of bulimia nervosa. Nine patients (15%) were classified as EDNOS. Within this category, 2 patients were subthreshold anorexia nervosa cases (having all criteria except amenorrhea), 1 patient subthreshold bulimia nervosa (having all criteria, but binge frequency was less than twice a week). Six patients met the criteria for binge eating disorder, 5 of whom were subthreshold because of missing the DSM IV criterion of 'marked distress regarding binge eating'. In study II, the results regarding DSM-IV eating disorders diagnoses were essentially the same as in study I.

Table 3 DSM IV eating disorders classification

	Study I			Study II		
	Patients	*Controls*	*p*	*Patients*	*Controls*	*p*
N	60	120		32	32	
Anorexia	1 (1,7%)	0 (0%)	0.33	1 (3%)	0 (0%)	1.00
Bulimia	4 (6.7%)	0 (0%)	0.012	2 (6.3%)	0 (0%)	0.49
Eating Disorder NOS	9 (15%)	0 (0%)	<0.001	8 (25%)	0 (0%)	0.005

At the time of study, 17 out of 60 patients (28.3%) did not receive treatment for their narcolepsy, with stimulants, sodium oxybate, or antidepressants. Only 6 control subjects (5%) used antidepressant drugs. We compared BMI, eating disorders diagnoses and the most salient eating disorders symptoms between treated and untreated patients and, separately, between patients with or without the use of antidepressants or stimulants. The results are shown in table 4. Interestingly, medication use did not increase BMI. Treated patients even tended towards a lower BMI. Furthermore, medication use did not influence the prevalence of eating disorders symptoms and diagnoses, except for a trend towards more irresistible craving in the patients using antidepressants. Furthermore, the patients who received treatment reported a significantly higher level of interference with activities due to eating problems.

Mood disorders may interact with the presence of eating disorders diagnoses and symptoms of eating disorders. The number of patients fulfilling the criteria for depression or bipolar disorder was too small to make any comparisons. We therefore compared patients with and without the SCAN-symptom 'depressive mood' and 'anhedonia' on BMI, key symptoms of eating disorders and diagnoses of eating disorders. We found no effect of these mood symptoms, except for a higher prevalence of binge eating with lack of control (with depressed mood: 67% vs 33%, P=0.024, P= 0.024; with anhedonia 75% vs 7% P = 0.008) and a higher number of EDNOS diagnoses (39% vs. 5%, P=0.002). So, especially for the diagnosis EDNOS there seems to be a relation with the presence of depressed mood and anhedonia.

EDE-Q results

Results from the EDE-Q auto-questionnaire are presented in tables 5 and 6. Several measures of attitudes in eating behavior (dietary restraint, eating and weight concern) were significantly higher in patients compared to BMI-matched controls. Objective bulimic episodes showed a trend to occur more often in

Table 4 Influence of medication on BMI, key eating disorders symptoms and eating disorders diagnoses

	Med	No med	p	AD	no AD	p	Stim	No Stim	p
N	43	17		26	34		28	32	
BMI	26.8	30.2	0.09	26.9	28.4	0.31	26.6	28.8	0.13
Dread of becoming fat	61%	65%	1.0	62%	62%	1.0	61%	63%	1.0
Irresistible and persistent craving for food	72%	53%	0.23	81%	56%	0.06	71%	63%	0.59
Earlier episode of overeating	37%	53%	0.38	35%	47%	0.43	39%	44%	0.80
Actions to lose weight through purgation	2%	6%	0.49	4%	3%	1.0	0%	6%	0.49
Binge eating w/ sense of lack of control	40%	53%	0.40	42%	44%	1.0	39%	47%	0.61
Interference with activities due to eating problems	33%	24%	0.55	46%	18%	0.02	29%	31%	1.0
Diagnosis Anorexia Nervosa	2%	0%	1.0	4%	0%	0.4	4%	0%	.047
Diagnosis Bulimia Nervosa	7%	6%	1.0	4%	9%	0.63	7%	6%	1.0
Diagnosis EDNOS	9%	29%	0.1	12%	18%	0.72	11%	19%	0.48

Med: medication
AD: antidepressants
Stim: stimulants

Table 5 EDE-Q subscale scores in patients versus BMI-matched controls

	Patients	Controls	p
N	32	32	
Dietary Restraint	8.0 ± 7.3	2.6 ± 3.6	<0.001
Eating Concern	5.2 ± 7.8	1.1 ± 2.5	0.009
Weight Concern	9.3 ± 7.1	5.8 ± 5.6	0.031
Shape Concern	17.0 ± 13.1	11.1 ± 11.8	0.067
Objective Bulimic Episodes	2.0 ± 5.0	0.2 ± 0.8	0.057
Subjective Bulimic episodes	1.1 ± 4.5	0.4 ± 1.8	0.40

patients than in controls. However, the frequency of subjective bulimic episodes was not significantly higher.

Female patients scored significantly higher than males on the dietary restraint (9.5 ± 8.4 vs 5.2 ± 3.1, p = 0.046) and eating concern (7.3 ± 9.1 vs 1.5 ± 1.5, P = 0.011) subscales. Weight and shape concern showed a trend towards a higher score in women (11.0 ± 7.4 vs 6.2 ± 5.5, P = 0.068; 20.1 ± 12.8 vs 11.1 ± 12.2, P = 0.064 respectively). There were no differences in the frequency of objective and subjective binges between men and women.

Disordered eating behavior can be assessed using cut-off criteria for the various EDE-Q subscales (table 6) [24,36]. Disordered eating is a measure of pathogenic eating behavior, at risk for developing an eating disorder. Our analysis yielded a high degree of disordered eating in narcoleptic patients, even when compared to BMI-matched controls, corroborating the results from the SCAN.

DISCUSSION

In this study, we showed that a considerable number of patients with narcolepsy-cataplexy display various symptoms of eating disorders, with an emphasis on a craving for food and binge eating behavior. In almost a quarter of patients, it was even possible to make a formal DSM-IV eating disorder classification. Many patients reported a dread of becoming fat, and the eating problems posed a clear interference with daily activities in more than one third of our cohort. Eating disorders seem to be an integral part of the narcolepsy phenotype and not only due to the increase in BMI, as narcoleptic patients scored significantly higher on

Table 6 Disordered eating behaviors in patients versus BMI-matched controls

	Patients	Controls	p
N	32	32	
Score ≥ 4 dietary restraint	62.5%	21.9%	0.002
Score ≥ 4 eating concern	29%	9.7%	0.11
Score ≥ 4 weight concern	78.1%	51.6%	0.036
Score ≥ 4 shape concern	90.6%	64.5%	0.016
Mean global score ≥ 4	82.8%	50%	0.012
> 1 episode of self induced vomiting	3.2%	0%	0.49
> 1 episode of self induced binging with lack of control	29%	6.3%	0.022
>1 episode of diuretic use	0%	0%	*
>1 episode of laxative use	0%	0%	*

* no statistics computed because both patients and controls = 0

various items of both the SCAN and EDE-Q when compared to BMI-matched healthy controls.

On the symptom level, narcoleptics reported irresistible and persistent craving for food, binge eating with lack of control, and restrictive actions to correct binging. However, there was no single specific eating disorder classification within the patient group: bulimia nervosa (4/60), anorexia nervosa (1/60) and EDNOS (9/60) were all present. Within the EDNOS group however, 6 out of 9 patients could indeed be categorized into binge eating disorder, while the others had subthreshold bulimia or anorexia. These prevalence numbers are clearly higher than those in the overall population. In our control cohort, no formal eating disorders could be diagnosed, and this is in line with previous studies who found very low prevalences, even in selected populations that would be at higher risk, such as young females (in the range of 0.7% for anorexia nervosa to 1-2% for bulimia nervosa) [37]. The prevalence for EDNOS has been established less extensively; a recent study of 2018 Portuguese young females found a prevalence of not more than 2.4% [38].

Interestingly, the effect of the various medications used for narcolepsy had no clear influence on the prevalence of diagnoses and symptoms of eating disorders, nor on BMI. In fact, medication use tended to be associated with a lower BMI. There was as slight trend towards more craving in patients using antidepressants,

and these patients also report more interference in activities due to eating problems. Regarding the influence of symptoms of mood disorders, patients with depressive mood and/or anhedonia had a higher number of EDNOS diagnoses as well as binge eating with lack of control. However, in our cross-sectional study design, it is not possible to decipher the 'direction' of this correlation. Further (longitudinal) studies may shed light on this issue.

The few other reports on eating disorder symptomatology in narcolepsy also found an emphasis on binge eating [3,12]. Recently, Chabas et al. reported that half of 6 typical and 7 atypical patients with narcolepsy could be classified as EDNOS, with features of bulimia nervosa [12]. Diagnosis of EDNOS seems to have been made on a rough exclusion of anorexia and bulimia nervosa without precise criteria however [12]. Because of the small sample size, the influence of sex on eating behavior could not be assessed. In our study, we did not find a difference in binging behavior between men and women. However, women more often reported a dread of becoming fat and a higher level of interference activities. So, despite binging to the same extent, women are more worried about their eating behavior.

Previous studies into Binge Eating Disorder have shown a positive correlation between binge eating and obesity [39]. Chabas et al also showed a trend towards more pronounced symptoms in the narcoleptics who were overweight compared to those with a normal BMI [12]. However, in our study, we could not establish a relation between BMI and binge eating. In fact, the relationship between symptoms of eating disorder and BMI may be the other way: a higher BMI has been shown to influence eating attitudes and behaviors [22,23]. The controls subjects in study II (matched with the patients for BMI) indeed showed an increase in symptoms, compared with the general population controls in study I. However, even when compared to BMI-matched controls, patients had significantly more eating disorder symptomatology. This suggests that the eating disorder is an integral part of the narcolepsy phenotype and not a pure consequence of the obesity per se. We propose that the eating disorder could be a direct consequence of the hypocretin deficiency. This is not in contradiction with the fact that Chabas et al found that both 'typical' and 'atypical' patients displayed symptoms of eating disorders; in that study hypocretin levels were not measured, and even in patients with normal hypocretin levels, it remains possible that the hypocretin system is dysfunctional, for example through postsynaptic mechanisms.

Although the hypocretin system was initially proposed to be mainly *stimulating* feeding [40], it is now clear that it subserves a broad range of functions, including

metabolic and endocrine regulation [10,41]. One tantalizing link between hypocretin defects and binge eating forms the melanocortin system. Binge eating has been reported as a major phenotype of mutations in the melanocortin-4 receptor (MC4-R) [42]. The hypocretin system has connections with cells in the arcuate nucleus that produce pro-opiomelanocortin (POMC), the precursor of melanocortin [43]. So, hypocretin deficiency may directly influence melanocortin signaling, which in turn may cause eating disorders.

The increased scores on weight and eating concern in the EDE-Q data reflect the impact that the symptoms of eating disorder have on the lives of patients. This was further corroborated with the high levels of interference with activities as assessed in the SCAN. Clearly, symptoms of eating disorder pose a great burden on the patients. Now that obesity has become a social and even political issue, the pressure to correct the increase in body weight may even add to the suffering and concern of patients. It is not improbable that shame around this theme suppresses communication, partly explaining that eating disorders in narcolepsy are a relatively unknown issue to physicians. It is important that doctors treating patients with narcolepsy discuss these symptoms, and give proper information and guidance. In patients with prominent symptoms of eating disorders, referral to a specialized psychiatrist may be indicated. Cognitive behavior therapy can be useful in certain eating disorders, such as bulimia, binge eating disorder, and other EDNOS subtypes [44]. Guided weight-reduction programs may also be used. Although we did not have information on formal diagnoses of the metabolic syndrome in our cohort, patients with a BMI greater tan 30 more often used cardiovascular and antidiabetic medication than did those with a BMI less than 30 (6/7 vs 4/43, P = 0.004). An increased BMI is thus suggested to predispose narcoleptic patients to complications such as the metabolic syndrome, which warrants medical intervention.

This is the first epidemiological study assessing eating disorder symptomatology in narcolepsy with cataplexy, using a cross-sectional case-control design in a large number of subjects. Furthermore, we not only used auto-questionnaires, but also a semi-structured interview to assess symptoms. We used both a general population control group, as well as controls matched for BMI. All patients fulfilled the ICSD-2 criteria[20] for narcolepsy with cataplexy. Hypocretin-1 levels were known in only a small number of patients, so we were not able to assess the influence of hypocretin-deficiency. However, it is known that in patients with sporadic and clear-cut cataplexy, over 90% of subjects is hypocretin-1 deficient [9]. Although we used validated instruments to assess symptoms, we did not systematically collect data to measure the timing of binges and craving for food.

We were thus unable to assess the presence of the night eating syndrome. Six out of 32 patients in study II spontaneously mentioned binging at night; other patients reported that, with a build-up of sleep pressure throughout the day, the resistance against binging diminished. Future studies should include a formal assessment of the night eating syndrome and address circadian, sleep homeostatic and mood influences on the frequency and severity of binging. Furthermore, the prevalence of the metabolic syndrome and other (cardio)vascular and endocrine complications should be assessed in narcolepsy.

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Chapter 6

Severe fatigue in narcolepsy

Based on:
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ABSTRACT

Excessive daytime sleepiness (EDS) is the core symptom of narcolepsy. However, there have been indications that fatigue -that should be separated from EDS- is a frequent complaint as well. 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 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 vs. 13.1 ± 4.4, p=0.22), confirming the separation between sleepiness and fatigue. Interestingly, fatigued patients more often used stimulant medication (64% vs. 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 5-6 per 10,000 [1]. Fragmented nighttime 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 [2]. 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 [3]. 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. Patients however may have trouble distinguishing between daytime sleepiness with sleep attacks and the physical feeling of fatigue. Medical doctors have difficulty to differentiate between sleepiness and fatigue as well, often tending to equate them [4]. 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 [4].

Severe fatigue has been found in high percentages of patients with chronic neurological conditions such as Parkinson's disease [5], multiple sclerosis [6] and neuromuscular disorders [7]. In these diseases, it was shown that severe fatigue has important clinical consequences, such as increased functional limitations and lowered general health status [8]. Finally, there have been reports of patients diagnosed with chronic fatigue syndrome, who later turned out to have narcolepsy [9]. 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.

A total of 127 patients under active treatment were approached by mail to participate. We did not approach patients with comorbid sleep apnea (defined by an apnea-hypopnea index of more than 15 per hour on the original diagnostic

polysomnography) and those not proficient in Dutch. All patients were clinically assessed by GJL and fulfilled the ICSD-2 clinical diagnostic criteria of narcolepsy with cataplexy [10]. A total of 80 (63%) patients returned a completed questionnaire. 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 six years before data collection, so these data were not used in the present study.

The demographic characteristics are summarized in Table 1. Some form of narcolepsy medication was used by 62 patients (77.5%), including stimulants, anti-depressants for cataplexy, or sodium oxybate at night.

Questionnaires

Fatigue Severity

Fatigue severity was assessed using the Fatigue Severity Scale (8 items, score range 8- 56) of the validated Dutch version of the Checklist Individual Strength (CIS)-fatigue [11]. Each item was rated on a 7 point Likert scale, with higher scores representing a higher severity of fatigue. Healthy subjects do score fatigue symptoms as well. 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 [3]. The CIS is a validated measure with good internal consistency and international recognition [12]. This scale has been used in studies on chronic fatigue syndrome (CFS), but also on the presence of fatigue in several neurological disorders [7,13].

Depression and Psychological Distress

Depression was assessed using the Beck Depression Inventory for Primary Care (BDI-PC) [14]. 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 [15].

Functional impairment and quality of life

Functional impairment was described and quantified with the Sickness Impact Profile (SIP) [16], containing the eight categories: sleep and rest, home management, mobility, social interaction, ambulation, alertness behavior, work, and recreation and pastimes. A higher score on the SIP indicates more impairment. The following subscales of the 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 [17]. The transformed scores for all SF-36 scales range from 0 – 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 [18]. Subjects rate the chance of falling asleep on eight 8 different circumstances often encountered in daily life.

Data analysis and statistics

All data analyses were performed using SPSS for Windows (version 14) Overall data were analyzed using descriptive statistics. We divided our sample in 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 ± standard deviation, 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% vs 40%, Table 1). This latter relation was stronger for patients using methylphenidate (8 out of 9 patients severely fatigued; likelihood ratio 3.5, p = 0.028), than for patients using modafinil (21 out 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 computed as well. Both the correlation analysis and the comparison between groups with different level of fatigue, showed converging results.

BDI-PC 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 to fatigue ($r= 0.324$, $p= 0.002$). Severely fatigued patients showed high levels of psychological distress, on almost all SCL-subscales (Table 2 and figure 1A). The SCL-sleep subscale which probes disturbed nocturnal sleep, was significantly higher in the severely fatigued patients as well.

Severe fatigue was significantly related to more functional impairment, as the total SIP score was almost doubled in the severely fatigued group (1051.2± 664.0 vs 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) [3]. SIP subscores on various categories of activities are shown in Table 2 and figure 1B. Severely fatigued patients were most impaired in the domains of mobility, ambulation, social interaction and recreation & pastimes. However, the SIP score 'work' was not significantly different between the two subgroups,

Table 1 Demographic variables and medication use

	Total	Severely fatigued (CIS-fatigue ≥ 35)	Not severely fatigued (CIS-fatigue < 35)	*p*
N	80	50 (62.5 %)	30 (37.5 %)	
Age	48.3 ± 14.7	47.3 ± 13.2	49.8 ± 17.2	0.47
Males (%)	46 (57.5%)	28 (56%)	18 (60%)	0.73
Working	50 (62,5 %)	32 (64%)	18 (40%)	0.451
Medication total	62 (77.5%)	42 (84%)	20 (66.7%)	0.07
Stimulants	44 (55%)	32 (64%)	12 (40%)	*0.02*
Antidepressants	19 (23.8%)	10 (20%)	9 (30%)	0.37
Sodium oxybate	26 (32.5%)	16 (32%)	10 (33.3%)	0.98

Data as mean ± SD. Medication total: number of patients using any (combination of) narcolepsy medication; Stimulants: modafinil, methylphenidate and/or mazindol; Antidepressants: tricyclics or SSRI's.

suggesting that impairment of the severely fatigued subgroup was mostly felt 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 (figure 1C).

Table 2 Levels psychological distress, depression, quality of life and impairment in daily life, as possible determinants of fatigue

	Comparison between subgroups			Correlation analysis	
Subscale	**Severely fatigued**	**Not severely fatigued**	***p***	**Spearman**	***p***
SCL anxiety	16.3 ± 6.1	11.9 ± 2.7	*0.000*	0.492	*0.000*
SCL agoraphobia	10.4 ± 4.8	7.9 ± 1.8	*0.002*	0.468	*0.000*
SCL depression	31.4 ± 13.5	21.4 ± 4.6	*0.000*	0.525	*0.000*
SCL somatization	23.1 ± 7.3	16.6 ± 3.6	*0.000*	0.638	*0.000*
SCL insufficiency	21.9 ± 7.2	15.0 ± 4.8	*0.000*	0.638	*0.000*
SCL sensitivity	30.3 ± 13.2	21.8 ± 4.7	*0.000*	0.436	*0.000*
SCL hostility	8.5 ± 2.6	6.8 ± 1.3	*0.000*	0.405	*0.000*
SCL sleep	8.6 ± 3.2	6.3 ± 2.7	*0.001*	0.370	*0.001*
BDI primary care	3.6 ± 3.51	1.00 ± 1.62	*0.000*	0.495	*0.000*
BDI total	13.7 ± 8.4	5.8 ± 5.3	*0.000*	0.588	*0.000*
BDI- PC > 4	13 (26%)	3 (10%)	0.083	0.324	0.002
RAND physical functioning	65.5 ± 28.5	89.3 ± 13.6	*0.000*	0.673	*0.000*
RAND social functioning	54.5 ± 26.3	75.8 ± 20.7	*0.000*	0.571	*0.000*
RAND role limitations – physical	40.5 ± 40.1	60.0 ± 39.1	0.037	0.431	*0.000*
RAND role limitations – social	59.3 ± 46.3	87.8 ± 28.3	*0.001*	0.345	0.002
RAND mental health	64.8 ± 20.9	80.53 ± 12.1	*0.000*	0.429	*0.000*
RAND vitality	36.1 ± 17.9	61.5 ± 16.1	*0.000*	0.746	*0.000*
RAND bodily pain	69.8 ± 29.7	84.5 ± 20.1	*0.010*	0.405	*0.000*
RAND general health perception	49.3 ± 23.0	64.8 ± 20.6	*0.003*	0.459	*0.000*
RAND change in health (1 year)	41.5 ± 17.2	50.0 ± 13.1	0.015	0.236	0.035

SIP sleep & rest	146.7 ± 92.8	87.6 ± 90.3	*0.007*	0.370	0.001
SIP home management	89.1 ± 92.7	48.7 ± 61.9	0.022	0.379	*0.000*
SIP mobility	60.9 ± 84.5	16.3 ± 34.4	*0.001*	0.489	*0.000*
SIP social interaction	235.1 ± 213.1	102 ± 122.5	*0.001*	0.399	*0.000*
SIP ambulation	45.7 ± 83.6	3.9 ± 12.1	*0.001*	0.462	*0.000*
SIP alertness behavior	251.7 ± 214.2	133.7 ± 166.5	*0.008*	0.430	*0.000*
SIP work	101.16 ± 132.3	75.4 ± 122.0	0.388	0.238	0.034
SIP recreation & pastimes	120.9 ± 80.2	60.0 ± 72.9	*0.001*	0.431	*0.000*
SIP total	1051.2 ± 664.2	527.5 ± 449.0	*0.000*	0.548	*0.000*
ESS total	14.3±4.2	13.1 ± 4.4	0.215	0.274	0.014

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).

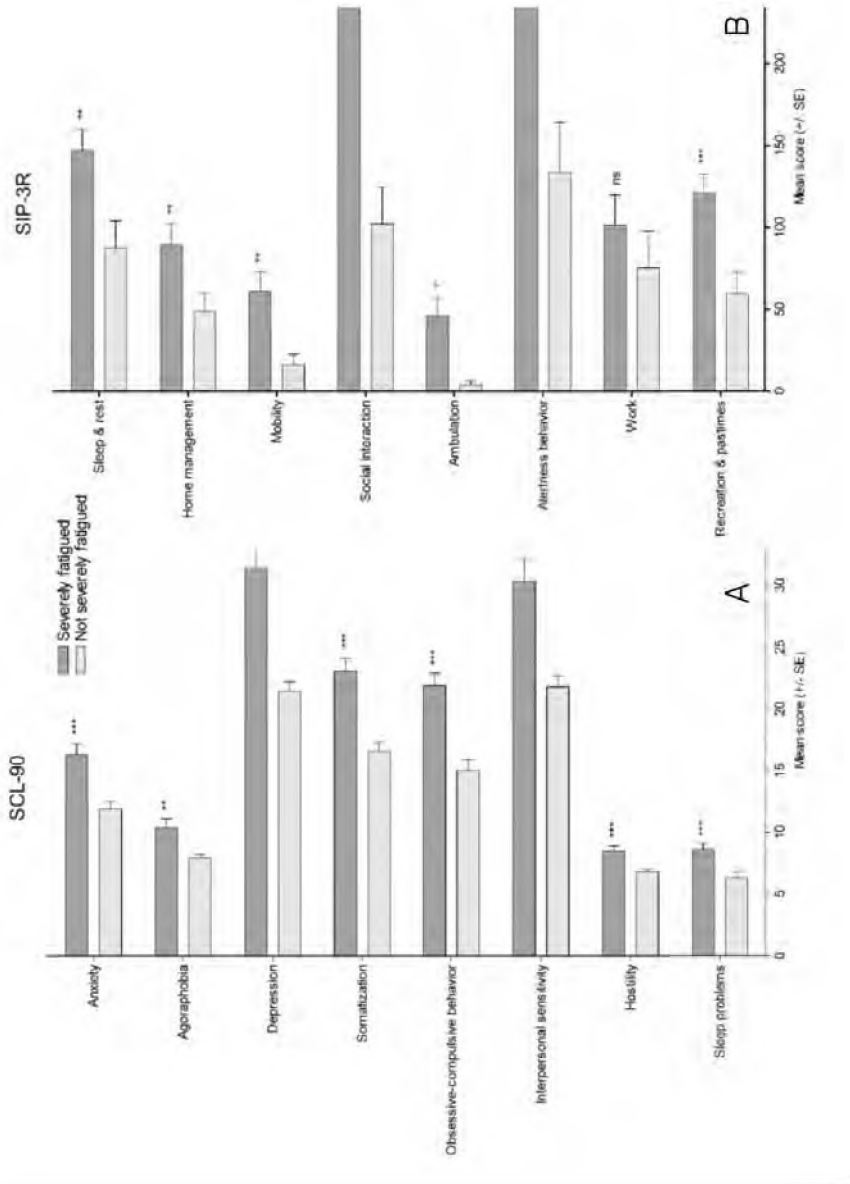
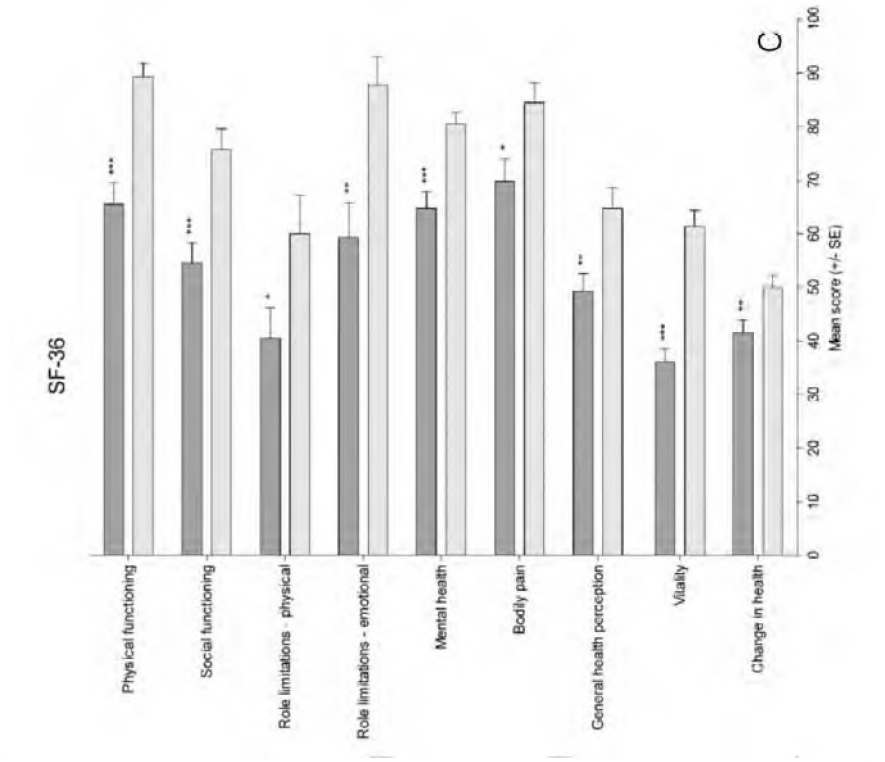


Figure 1 C) Subscores on the Short Form-36 to assess quality of life



DISCUSSION

Here 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) [19]. The high prevalence of severe fatigue in narcolepsy (62%) is comparable to prevalence indicators in neuromuscular disorders such as

facioscapulohumoral dystrophy (60% severely fatigued), myotonic dystrophy (74%), and HMSN-1 (64%) [8]. In a recent validation study of the FSS in a Swiss cohort of 429 sleep-wake disordered patients, Valko et al. showed that the small subgroup (n=22) of narcolepsy patients had the highest fatigue scores, together with insomnia group [20]. In contrast to our results, these authors did find a significant correlation in the narcoleptics between sleepiness as measured with the ESS, and the FSS (r=0.71).

Daytime sleepiness and nocturnal sleep disturbances

In this study, there was a clear separation between sleepiness and fatigue. This relative independency of fatigue and sleepiness has been described in other populations as well. In a recent study, daytime sleepiness and fatigue were measured in patients with chronic fatigue syndrome (CFS), sleep apnea and healthy controls [21]. Sleepiness was not only measured subjectively by the ESS, but also assessed with the Multiple Sleep Latency Test (MSLT). The distinction between fatigue and sleepiness was confirmed: CFS patients turned out to be less sleepy than both healthy controls and sleep apnea patients.

The positive relation between disturbed nocturnal sleep and fatigue has previously been described in healthy subjects [22] and in various neurological disorders [7]. 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, as was suggested by studies of sleep quality in patients with chronic fatigue syndrome [23].

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 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 [24] but alse in patients with chronic fatigue syndrome [25]. The direction of the association remains unclear however, as longitudinal studies have been inconclusive so far [24]. Interventional studies of fatigue using antidepressants show discouraging results, influencing depression and anxiety but not severe fatigue [25-27]. 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 [28]. Therefore, although there is a clear overlap of symptoms

of fatigue and symptoms of depression, severe fatigue is not adequately explained 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 before [29]. 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 [7]. 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 [26], although e.g. modafinil showed only limited results for this indication [30]. Could stimulants negatively affect nocturnal sleep quality, resulting in daytime fatigue? A study of modafinil in narcolepsy patients did not show adverse effects on sleep quality [31]. A recent study of methylphenidate in adult ADHD patients [32] 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 nonetheless. 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 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 [33]. They commented that treatment apparently was not sufficiently effective to restore health status to normal.

Limitations of this study

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 six 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 apnea between the diagnostic PSG 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 actively inquire 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.

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Chapter 7

Summary

SUMMARY

CHAPTER 2
NARCOLEPSY AND PSYCHIATRY IN HISTORICAL PERSPECTIVE

Chapter 2 illustrates the fascinating and instructive historical relation between narcolepsy and psychiatry. Gélineau (1880) originally defined narcolepsy as a neurosis, which was in that period believed to be an organic disease. Soon thereafter he suggested the existence of a secondary type of narcolepsy as an expression of hysteria. Psychoanalysts later diagnosed narcolepsy as a conversion disorder and accordingly offered psychoanalysis as treatment. Another group of psychiatrists stayed however faithful to the more traditional 'organic' model of narcolepsy. The two directions in psychiatry hardly referred to each other, and during half a century made their progress in isolation, immunized to chances of correction. As a consequence of the rapid development of neuroscience in the second half of the 20th century the cellular and molecular base of narcolepsy was discovered. Narcolepsy was finally established as a brain disease, as originally suggested by Gélineau. At the same time, this also provided the basis for an open view towards the psychiatric phenotype of narcolepsy, and on this topic formal studies started to appear in the beginning of the 21st century studies. Soon it became clear that narcolepsy is not just a sleep disorder, but a highly complex behavior disorder as well.

The involvement of psychiatry with narcolepsy over the course of more than a century made a complete turn around: the original 'organic' model first shifted to a psychodynamic model of conversion hysteria and then again moved back to the 'organic' point of departure. Patients often have been passive watchers of these historical trends, and sometimes even victims, not always being able to benefit from the change of scientific scenery.

CHAPTER 3
EATING DISORDERS

Narcolepsy patients are known to have a high body mass index (BMI). In addition, reports of so-called 'carbo-craving' are often provided by patients. These facts sparked interest in the exact nature of eating habits and disorders in narcolepsy. We compared our cohort of narcolepsy patients (n=60) with age- and sex-matched population controls (n=120). Additional comparisons were made between a

subgroup of patients (n=32) and a group of controls that were also matched for BMI (n=32). Eating disorders were assessed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), as well as the Eating Disorder Examination-Questionnaire (EDE-Q). Criteria for a clinical eating disorder were fulfilled in 23% of patients, as opposed to none of the control subjects. Most of these were classified as Eating Disorder Not Otherwise Specified (EDNOS), with an incomplete form of binge eating disorder. Half of the patients reported a persistent craving for food as well as binge eating. A quarter of the patients reported binge eating twice a week or more often. Binge eating was not correlated with an increased BMI. When compared to BMI matched controls, the pattern of disordered eating behavior was again confirmed. Medication use did not influence the findings, except for a higher interference in daily activities due to eating disorders in patients using antidepressants.

In the narcolepsy group a quarter of patients have an eating disorder, classified as EDNOS, which is significantly more than population controls. Most patients had an incomplete form of binge eating disorder, with irresistible craving and binge eating as most prominent features. Disordered eating clearly interfered with daily activities.

CHAPTER 4
PSYCHOTIC SYMPTOMS OF NARCOLEPSY

Patients with narcolepsy often experience pervasive hypnagogic hallucinations that even can lead to diagnostic confusion with schizophrenia. This may result in mismanagement of narcoleptic patients, as treatment with antipsychotics is ineffective. We aimed to provide a detailed qualitative description of hypnagogic hallucinations and other 'psychotic' symptoms in patients with narcolepsy and contrast these with schizophrenia patients and healthy controls. We also compared the prevalence of formal psychotic disorders between narcolepsy patients and controls. We used the SCAN interview to compare psychotic symptoms between patients with narcolepsy (n=60), with schizophrenia (n= 102) and matched population controls (n=120). In addition, qualitative data was collected to enable a detailed description of hypnagogic hallucinations in narcolepsy. We found clear differences in the pattern of hallucinatory experiences in narcolepsy versus schizophrenia. Narcoleptics reported multisensory 'holistic' hallucinations rather than the predominantly verbal auditory sensory mode of schizophrenia patients. Delusions were not more frequent in narcolepsy compared to population controls. Just a few patients reported delusional

memories or fantastic delusions. Memories of hallucinations or dreams were sometimes hard to separate from real life memories. This caused confusion in some patients. In spite of the 'psychotic symptoms', the prevalence of formal psychotic disorders was not increased in patients with narcolepsy, mainly because of preserved insight. Almost half of the narcoleptics reported moderate interference with functioning due to hypnagogic hallucinations, mostly due to related anxiety.

Multisensory, 'holistic' hallucinations of narcolepsy patients can clearly be differentiated from predominantly 'verbal auditory' hallucinations in schizophrenia patients. Narcolepsy patients did not fulfill DSM-IV criteria for psychotic disorders more frequently than population controls. Reality testing was compromised in some patients by memories from vivid hallucinations and dreams that can be hard to separate from memories from real life experiences.

CHAPTER 5
ANXIETY AND MOOD DISORDERS

A high frequency of depression has since long been reported in narcolepsy patients. Usually this was measured with self-report scales such as the Beck Depression Inventory (BDI). However, the only controlled study with a diagnostic instrument (Present State Examination) did not show a higher prevalence of major depression or other mood disorder classification in the narcolepsy group. We therefore aimed to answer this pending question of prevalence of mood and anxiety disorder in narcolepsy. We performed a case control study in 60 narcolepsy patients and 120 age- and sex-matched controls from the Nijmegen Health Area 2 population study, using the SCAN. We assessed symptom frequency as well as DSM-IV diagnostic classification of mood and anxiety disorders. Up to a third of patients had symptoms of a mood disorder. There was considerable overlap between regular symptoms of narcolepsy and symptoms of depression, complicating the diagnostic process. Importantly, major depression or any other mood disorder was not overrepresented in the narcolepsy group. Interestingly, we found that more than half of the patients had anxiety or panic attacks. A third of the patients could be diagnosed with anxiety disorder. Social phobia was the most important diagnosis. There was no influence of age, sex, duration of illness, or medication use on the prevalence or mood or anxiety symptoms and disorders.

Narcolepsy patients did not suffer from major depression or other mood disorders more frequently than controls. However, the frequency of depressive symptoms was significantly higher in the narcolepsy patient group. There was a considerable overlap between the symptom of narcolepsy and the somatic symptoms of depression, which complicated the diagnostic process. Although largely ignored in the past literature, anxiety symptoms and disorders, especially panic attacks and social phobias, were strikingly increased in narcolepsy.

CHAPTER 6
FATIGUE

Excessive daytime sleepiness is the predominant symptom of narcolepsy. However, patients often complain of fatigue as well. This symptom has been erroneously equated to sleepiness by doctors as well as patients. We examined the prevalence of severe fatigue in narcolepsy patients and its relation to excessive daytime sleepiness. Furthermore, we assessed the relation of fatigue to depression, psychological distress, functional impairment, and quality of life. Using the Checklist Individual Strength- Fatigue (CIS-F), fatigue was measured in 80 narcolepsy-cataplexy patients. Sleepiness was assessed with the Epworth Sleepiness Scale (ESS). Psychological distress, depression, functional impairment and quality of life were assessed with appropriate and validated scales. We compared patients with severe fatigue (CIS-F score $\geq$ 35) with patients without severe fatigue (CIS-F score < 35). Fifty patients (62.5%) reported severe fatigue. Both groups had the same level of daytime sleepiness, confirming the separation between sleepiness and fatigue. There were no sex or age diffences between patients with and without severe fatigue. Interestingly, fatigued patients more often used stimulant medication. Severe fatigue was associated with a significantly increased functional impairment, a lowered general quality of life, more depressive symptoms as well as psychological distress. The degree of fatigue was comparable to other chronic neurological disorders as Multiple Sclerosis. We have the impression that fatigue reflects the way patients adjust to the disease rather than being a measure of disease severity.

A majority of narcolepsy-cataplexy patients suffered from severe fatigue which could be distinguished from daytime sleepiness. Severe fatigue was associated with significantly more functional impairment. Severe fatigue correlated with psychological distress and lower quality of life, and thus possibly reflected a poorer adjustment to the narcolepsy.

Chapter 8

Discussion & Perspectives

DISCUSSION & PERSPECTIVES

The studies described in this thesis indicate that patients with narcolepsy present with a complex behavioral or psychiatric phenotype, in addition to the key defining characteristics of hypersomnia and cataplexy. This narcolepsy behavioral phenotype includes symptoms of eating disorders, psychotic signs and symptoms, anxiety and depressive symptoms and complaints about fatigue.

Two aspects of this behavioral phenotype merit attention. First, these symptoms span several domains of psychic functioning and are not confined to just one area. Second, though these symptoms can be categorized within more classic psychiatric categories as eating disorder, psychotic disorders and affective disorders, they do not wholly fit the full diagnostic criteria of these classic categories. For example, the eating problems are best described as an atypical eating disorder or eating disorder NOS, and the psychotic features do not reach the threshold of classification of a psychotic disorder. Although there is a high frequency of depressive symptoms in patients with narcolepsy, major depression is not overrepresented. Panic attacks are seldom accompanied by agoraphobia. How is it possible that psychopathology expresses itself systematically in such an atypical way? Further research is needed into whether this complex behavioral phenotype of narcolepy is replicated in other unselected groups of patients with narcolepsy, and whether these various symptoms of eating problems, psychosis, anxiety and fatigue co-occur more often than by chance in the same patient. The special and complex behavioral phenotype does suggest a particular etiology, pointing to an essential role for the hypothalamic hypocretin system.

NEUROBIOLOGICAL UNDERPINNINGS: THE HYPOCRETIN SYSTEM

The hypocretin system

Over the last decade, narcolepsy has firmly been established as a hypocretin deficiency syndrome. The hypocretin (also known as orexin) peptides were discovered in 1998 [1-4].

There are two known hypocretin peptides, known as hypocretin 1 and hypocretin 2 which are ligands for two receptors: the hypocretin receptor-1 and 2. Hypocretin-1 has a greater affinity for the hypocretin receptor-1, while both peptides have the same affinity for the hypocretin receptor-2.

The hypocretin receptor-1 is expressed in the locus coeruleus (LC), dorsal raphe (DR), ventral tegmental area (VTA), the prefrontal and infralimbic cortex, hippocampus, amygdala, , laterodorsal tegmental nucleus (LDT) as well as the pediculopontine nucleus (PPT). The hypocretin receptor-2 is richly expressed in the arcuate nucleus (Arc), tuberomamillary nucleus (TMN), dorsomedial hypothalamic nucleus (DMH), paraventricular nucleus, hippocampus, and the medial septal nucleus.

The hypocretin system not only is crucial in sleep- wake control; the intense connections to the limbic system for example show a function in stress regulation, reward related behavior, eating behavior, as well as memory. Deficiency of hypocretin, as is the case in narcolepsy, not only influences sleep- wake behavior but also emotional balance, adjustment to stress, addiction and motivational behavior. The role of the hypocretin system in sleep/wake regulation has been extensively reviewed elsewhere. Below we describe some considerations on 'psychiatry-related ' functions.

Hypocretin and stress: animal studies

Arousal during fear and stress is accompanied by heightened sympathetic activity. An intracerebroventricular injection with hypocretin in rats resulted in an increase of sympathetic tone with an increase in corticosterone level [5]. This suggests that hypocretin has a role in enhancing wakefulness during emotional and stressful states. In a 'fight or flight' type experiment this response was demonstrated. Mice, tested in a resident- intruder paradigm, showed locomotor and cardiovascular responses to this stressor, while in prepro- hypocretin knockout mice these responses were attenuated [6]. Furthermore air-jet stress induced elevations in heart rate and blood pressure were diminished in hypocretin neurons ablated mice [7]. Sympathetic responses during emotional events seem to be conveyed by hypocretin activity. The stress axis has important connections with the hypocretin system. One of these links is the input of corticotrophin-releasing factor (CRF) neurons in the amygdala [8], where they directly innervate hypocretin neurons via the CRF-R1 receptor. Frequent signaling of hypocretin neurons during foot shock stress is severely impaired in CRF-R1 receptor deficient mice [9]. This suggests that the activation of hypocretin neurons is mediated by CRF. This is further demonstrated by the fact that production of pre-prohypocretin mRNA is enhanced by CRF administration [10]. The link between the CRH and the hypocretin system is functional in maintaining arousal during stressful events.

Hypocretin and the reward system in addiction

Hypocretin neurons, located in the most lateral part of the hypothalamus (LH), are involved in the modulation of reward. Hypocretin neurons in the more medially located perifornical/ dorsomedial area of the hypothalamus (PFA- DMH) are functional in sleep- wake regulation and arousal [11]. In the reward circuit the mesolimbic dopamine pathways have an essential role. Central in this circuit is the ventral tegmental area (VTA). Neurons in the VTA send axons to the nucleus accumbens, striatum and frontal cortex, structures thought to be involved in motivation. The dopamine neurons in the VTA carry Hcrt-1-R's so as to make a direct influence of the Hcrt system on the VTA possible. Hypocretin knockout mice are less susceptible than wild type mice to develop morphine dependence as measured by the withdrawal response [12]. Furthermore animals were studied by Harris et al in a two- chamber conditioned place preference model, in which one chamber was associated with drug or food reward whereas the other chamber was associated with no reward [13]. The conditioned animals had greater place preference and dramatically higher Fos activation in hypocretin neurons in LH than non conditioned ones. Reinstatement of an extinguished preference for a drug- paired environment, a drug seeking model, was tested and demonstrated. This reinstatement was blocked by a hypocretin 1 antagonist. These experiments show how hypocretin neurons are involved in reward processing and drug seeking behavior. This processing is effectuated by the connections between hypocretin neurons and the reward circuit. These are reciprocal between hypocretin neurons and the VTA, while hypocretin neurons receive projections from the nucleus accumbens and the lateral septum [14]. In vivo administration of a hypocretin 1 antagonist blocks locomotor sensitization to cocaine and stops cocaine- induced potentiation of VTA dopamine neurons [15]. Drug craving is suggested to be a consequence of the hyperarousal and excitement due to increased activity of hypocretin neurons [16].

A special role for the amygdala: opposed reactions to reward and aversive stimuli

The fact that narcolepsy patients react with cataplexy on strong positive emotions constitutes a clear change in emotional behavior. The change entails more than cataplexy alone: patients handle aversive and rewarding stimuli differently from controls. Ponz et al. [17] found a striking difference on aversive conditioning in an experimental study, using as stimulus a brief painful electrical stimulation, delivered on one finger. Subjects had to focus on a computer screen. A colored triangle signaled a possible upcoming unconditioned stimulus. In the acquisition phase this figure was learned to be the conditioned stimulus (CS+). Controls reacted to the conditioned stimulus with increased amygdala activation and

increase in functional coupling between the amygdala and the medial prefrontal cortex. Although narcolepsy patients showed the same reaction in the pain circuit as controls to the CS+ followed by an actual electrical stimulation, no reaction was seen after presentation of CS+ alone: there was no enhancement of the amygdala response and no functional coupling with the medial prefrontal cortex or any other area in the brain. This constituted an impaired aversive conditioning in human narcolepsy. In a previous experiment [18] amygdala dysfunction was demonstrated in a blunted startle eye blink response to unpleasant (aversive) stimuli in human narcolepsy but also in patients with amygdala lesions. The failure of aversive conditioning in patients is in stark contrast with exaggerated amygdala response to pleasant stimuli [19] and reward [20]. In an experiment, in which expectancy and the experience of winning money was measured in fMRI, patients showed abnormal activity *increases* in the amygdala and dorsal striatum. However at the same time patients did not, like controls, show increased activation of the dopaminergic VTA, during high reward expectancy and showed, unlike controls, reduced activation of the ventral striatum during actual winning. This indicates a functional unbalance of the reward circuit in narcolepsy, apparently due to hypocretin deficiency. The dysfunctional reward circuit offers an explanation for the fact that narcolepsy patients hardly ever abuse the stimulants that they are prescribed, contrary to for instance ADHD patients.

The atypical reactions to reward and positive stimuli with enhanced amygdala signal on one side and reduced amygdala signal to aversive stimuli on the other side reveal an emotional unbalance in narcolepsy. The absent reaction to the conditioned fear stimulus could be linked to a dysfunctional 'alarm system 'that is reported by family members of narcolepsy patients: reactions to impendent harm seem to be dampened. This way the terms that were used to describe personality traits in the older German literature 'dickfelligkeit ' and 'pommadigkeit ' could fall into place.

THE HYPOCRETIN SYSTEM IN PSYCHIATRIC DISORDERS

A role for hypocretin in human psychopathology has been suggested in depression, schizophrenia treatment and addiction, although its contribution is relatively minor, and conclusive evidence is still scarce.

Depression

Brundin [21] studied a group of suicide attempters diagnosed with major depression, dysthymia and adjustment disorder. The patients with depression had a significantly

lower hypocretin level than the dysthymic and adjustment disordered suicide attempters. This finding has not been replicated yet, and the significance of this finding is unclear. In another study by Brundin [22] of suicide attempters with miscellaneous diagnoses, she found a negative correlation between hypocretin levels and slowness of movement and lassitude (difficulty to initiate activities). A low hypocretin level in CSF was related to inertia and reduced motor activity in suicidal patients. This finding has not been replicated either, and awaits further study.

Panic

Johnson et al. (2010) [23] found that patients with panic have elevated levels of hypocretin in CSF. Testing the panic model in animal studies, he found that rats with silenced hypocretin gene product, or treated with hypocretin antagonists showed a blocked panic response as opposed to wild type rats. He concluded that the hypocretin system has an important role in the pathophysiology of panic anxiety in the rat model. He suggested that hypocretin antagonists could be usesful as a novel treatment strategy for panic disorder in humans. Our findings of increased panic in narcolepsy patients seem to contradict these findings.

Schizophrenia treatment

Fadel (2002) [24], reported that antipsychotic drugs that have excessive weight gain as adverse event, activate hypocretin neurons in the lateral hypothalamus. The degree of activation correlated with the weight gain. This finding suggests that the metabolic syndrome as adverse event in antipsychotic drug treatment is possibly related to hypocretin. In a recent study of olanzapine in rats this hypothesis of drug induced metabolic syndrome due to increased hypo cretin signaling was not confirmed [25]. Dalal (2003) [26] found that patients with schizophrenia who were treated with haloperidol had lower hypocretine levels than unmedicated subjects. This could be explained by the changed inhibitory influence of dopamine on hypocretin neurons in the haloperidol treated group. Animal research revealed yet another association of an antipsychotic drug adverse event and the hypocretin system: a hypocretin-1 antagonist blocked catalepsy, caused by neuroleptics in rats. Catalepsy is thought to be a reliable predictor of extrapyramidal symptoms in humans [27]. This suggests that hypocretin antagonists could be used as drug for extrapyramidal adverse events in antipsychotic drug treatment.

Addiction

Addiction researchers foresee a possibility to use hypocretin antagonists as drug to cut craving or to prevent relapse [28], based on animal research of addiction

(see above). Of course the cure could be just as bad as the addiction itself, because of predictable adverse events of a hypocretin antagonist which could mimic narcolepsy.

IMPLICATIONS FOR THE DAILY CARE FOR NARCOLEPSY PATIENTS

Informing the patient

Therapeutic advice starts with assessment of the psychological burden. This first step has therapeutic implications by itself because it gives the patient an opportunity to communicate experiences that he hesitates to share. The doctor could start by taking time to ask about the content of hypnagogic hallucinations, eating habits, anxieties, phobia's, mood symptoms and fatigue. Alternatively a short list with psychiatric signs and symptoms that are frequently seen in narcolepsy could be filled out in advance of the appointment. This would facilitate discussion of the most disabling complaints and could spare time for both patient and doctor. In time it is not enough to just inform the patient: the family should be informed about narcolepsy and its main psychiatric features as well.

Consultation, psychopharmacology, and other treatment is teamwork

Therapeutic consultation is best performed by a joint effort of a neurologist or sleep specialist and a psychiatrist with experience in narcolepsy. Changes in psychotropic medication can have consequences for the treatment of narcolepsy per se. Standard evidence based treatments for psychiatric disorders according to protocol do not always apply to the narcolepsy patient. There have been no psychiatric treatment studies of the patient population. Treatment of hypnagogic hallucinations is atypical for a psychiatrist: neuroleptics are not effective while tricyclic antidepressants and SSRIs are. Interestingly, anxiety symptoms are also reported by patients that use antidepressant medication in a dose that is usually effective in anxiety and panic attacks (Chapter 5): this makes effectiveness of this medication doubtful. There is even an indication that venlafaxine might induce panic attacks as adverse event (Chapter 5). This raises the question if pathophysiology is different in narcolepsy patients due to differences in anxiety pathways. There are indications that narcolepsy patients do have different fear pathways from controls [29]. Antidepressant treatment for affective disorders in narcolepsy has not been studied. In my own experience regular treatment of depression with antidepressants can be effective. High dose stimulants are not indicated to cure depression in narcolepsy, because this strategy is not effective and can lead to serious adverse events as psychosis [30,31]. Mood swings can

occur as adverse event in methylphenidate or modafinil treatment, especially when used in 'pro re nata (PRN)' fashion.

Non pharmacological treatments

Cognitive behavioral treatment by a psychologist with enough experience in narcolepsy can be effective in overcoming social phobias and in treating depression. Patients that are turning into recluse need stimulation in order to overcome the thresholds of social fear. A psychologist or specialized social worker can help to pave the way. In severe cases the patient does not dare to leave home any more, and patients have to be visited at home. Regular exercises, if needed accompanied by the therapist, can accomplish a breakthrough of this social fear so that the action radius can be extended. In extremely socially phobic patients a social dog can be a facilitating step in building up more interaction with the outside world. Exercises to fill in leisure time, perhaps a visit or a small holiday can be part of a behavioral program. Introduction of more physical movement by an adapted program (e.g. 'running therapy ' or regular fitness) as some patients have experienced, can be helpful too for alleviating depressive states. Special attention in counseling should be paid to regular topics as shame for being overweight or fat, about falling asleep in public and having cataplexy attacks. Guilt feelings about dependency, disappointing significant others, and failing to accomplish tasks are other important foci. Patients are valuable as experience specialists. Group sessions, combining 'experienced' patients with patients that just recently acquired the disease, can be very valuable [32]. A big issue is accepting narcolepsy.

Accepting narcolepsy

A very difficult, but crucial step in treatment is the topic of accepting narcolepsy. This does not just mean accepting to live with the burden of the disease per se, it also involves accepting the social consequences. The disease itself brings not only sleep- wake regulation disturbance, but also problems with weight, sexuality, memory and psychological functioning. The social consequences are numerous: reactions from others give rise to shame and trigger avoidant behavior. Functioning at work as well as in intimate relations is often affected. Patients can have different reaction styles. One of these attitudes that we encountered is denial: 'narcolepsy is not an illness '. Another reaction can be severe anger at and resistance to the diagnosis itself. The anger can change into sadness when diagnosis is slowly admitted. Coping with narcolepsy can refer to skills in handling symptoms and in capacity to deal with the emotional reactions that are raised by the disease. Examples of skills developed by patients are self-pinching when getting sleepy, countering cataplexy by emotional control, and tricks to assess the reality of experiences in hypnagogic hallucinations (see Appendix for further

details). In order to increase the capacity to deal with the emotional consequences patients can extend their social network, be active in the narcolepsy patient association, and can try to increase control over their life by changing their attitude, setting goals, investing in time management and preparing for stressful situations. Therapeutic work can include patient groups focusing on bottlenecks in daily situations and exchanging practical solutions.

In the process of accepting narcolepsy, the disease is at first often externalized, i.e. placed outside of the person. When acceptation starts to be successful, narcolepsy can become an integral part of the personality. Responsibility can be taken for the disease and finally a shift in identity can be reached. Next to the negative consequences some positive aspects can be seen: narcolepsy can bring about a deeper contact with the unconscious, psychic awareness and personal growth: narcolepsy patients hardly ever lead superficial lives.

Advice for the neurologist and sleep specialist: assess these psychological symptoms!

Psychiatric comorbidity, panic attacks, phobia's and fatigue are features that are frequently seen in narcolepsy patients, but patients may be reluctant to report impairment in their functioning due to these symptoms. Therefore psychiatric assessment is no luxury and should be a standard part of a comprehensive diagnostic work-up. This assessment could take the form of a self-report questionnaire, to be filled out in advance of the appointment with the doctor. A face-to-face interview is most informative. After consulting a psychiatrist or psychologist, a treatment plan can be proposed. This strategy would help overcome undue anxiety of the patient to report these 'notorious mental symptoms 'and open the way to consider psychotherapeutic treatment.

Advice for the psychiatrist

Psychiatrists, working in consultation and in psychosomatic psychiatry, should be informed of the psychiatric phenotype of narcolepsy and of the psycho-pharmacological pitfalls. Hypnagogic hallucinations should not be treated with antipsychotics. Psychiatric admission of narcoleptic patients should only be considered in crisis situations. More generally speaking, in the training of psychiatrists' implementation of education in sleep physiology and sleep disorders should be considered. Sleep disorders are in the majority of cases a psychological problem and if they persist for longer periods can act as a trigger for mood disorder, suicidal behavior, psychosis and substance abuse. Having a sleep specialist on the educational board who is able to diagnose and treat sleep disorders would benefit the training of psychiatrists.

SUGGESTIONS FOR FURTHER RESEARCH

Narcolepsy is a disease that can be described as a hypocretin deficiency syndrome. It demonstrates a functional impairment of a neurotransmitter system with many behavioral functions. The functions of hypocretin for motivational behavior, addiction, stress responses, emotional coordination, are being studied as shown above. Drugs are being tested that act as hypocretin agonists, possibly effective as (co)medication in depression, or as hypocretin antagonists, that can treat craving for drugs [33] or as functional in prevention of relapse into drug abuse. The role of narcolepsy in personality disorder is still unknown: emotional dysregulation, as presented in mood swings of borderline personality disorder, could be related to hypocretin abnormalities. A study of maternal deprivation in rats showed changes in the hypocretin system [34] that might also be relevant for personality development. Studying hypocretin and its role in the limbic system will enhance our understanding of the regulation of behavior in humans as well as animals and might one day result in a cure not just for narcolepsy but also for modulation of expression of different psychiatric disorders.

Our study of psychiatric morbidity in narcolepsy is far from complete: there are disorders that we did not assess but have been suggested to be overrepresented in narcolepsy. Among these there are disorders that are mentioned in the classic literature as being more frequent: personality disorders and disorders of sexual functioning. The changed reactions to stressors as measured in animals and the reactions to aversive as opposed to rewarding stimuli in humans would predict changed adjustment reactions in patients, which have not been studied so far. Another important topic that needs to be studied is the reality testing of patients: interference of reality testing by experiences of hallucinations and dreams that are recorded in memory. With the SCAN methodology we could not assess this in detail. Longitudinal studies are needed to answer questions about the course of the psychiatric expression of narcolepsy over time. An intriguing question is why positive emotions and anger lead to cataplexy, rather than anxiety and sadness. The answers to these questions will enrich not only the treatment of narcolepsy but also enhance insight in the functioning of the limbic system and related networks and as such the understanding of pathophysiology of psychiatric disorders in general.

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Chapter 9

Appendix

Additional Clinical Notes

ADDITIONAL CLINICAL NOTES

In this appendix, some further notes on the clinical psychiatric presentation of narcolepsy patients are provided based on my clinical experience in the previous years. This information may complement the more empirical chapters in this thesis.

The SCAN 2.1 is a semi-structured interview, in which relevant data are quite strictly categorized. However, the original 'analogue' description as reported by patients is lost in this process. Here we describe a few of such 'lost' features, as reported by the patients in our studies. One must realize that, as narcolepsy has a highly heterogeneous expression, not all patients report all of these features.

COPING AND ADJUSTING TO STRESS: 'OBLOMOV STYLE'

We have seen several patients who react in an atypical style to stress, and demonstrate a striking lack of urgency in reacting to stressors. Some typical examples are described in Box 1.

In these examples, the patients do not seem to 'hear the alarm bell' and do not take action to prevent unfavorable consequences. Their partners were surprised by this indifferent reaction style. The same indifferent style seems to be present in dealing with 'to do lists'. Patients are reported to be notoriously slow and inefficient in translating plans into actions. We encountered this in our research, when getting slow and incomplete responses to questionnaires handed out by treating physicians. Although patients enthusiastically agreed to participate in the study, they had a lower response rate than expected compared to studies in other patient groups.

BOX 1 'Oblomov style' reactions

Patient A is a 45-year-old accounting officer in a nonprofit governmental organization. He had trouble meeting with his deadlines. His boss warned him repeatedly and finally told him that he would be laid off in case he would not meet the term for a next assignment. To the surprise of his wife, he reacted very relaxed to this warning, showing no distress whatsoever. He did not change his style of working and did not seem to be alarmed about the possible loss of his job at all.

Patient B is a 43-year-old married painter who has a wife and 3 boys. Especially at the end of the day, he often had fits of anger. Not only did he shout and slam doors, but every now and then he hit his 7 year old son. The son talked about this at school and the school officials undertook an official investigation. They reported the case of child molestation to the authorities. The family was approached and a report was to be made up about the home situation. As the investigating organization has the authority to place children out of the home, the wife was very upset, but not the patient himself. When seeing his doctor, he grinned and stated that he never seriously touched the kid. He showed no concern about possible measures that could be taken. His wife described his typical reaction style as 'hard to come through', and 'as if covered by a grey veil'.

This coping style of narcolepsy patients reminds of the novel figure 'Oblomov', the gentleman described by the Russian author Gonsjarov. Oblomov passed his days in a semi slumber, dreaming about many actions, but systematically postponing them, insensitive to the consequences. Whether this 'Oblomov' style is just a paroxysmal coping problem or part of a more permanent narcolepsy personality profile, is still unclear and awaits further study. Patients have been shown to have impairments in executive function [1,2], which may play a role.

DID IT HAPPEN OR NOT? A DOUBLE REALITY

Because memories of hallucinations and dreams are remembered and stored into memory better in patients than in controls [3], patients can be left with the question whether an event really took place, or just happened in a hallucination or dream. We described this in Chapter 3. These difficulties in reality testing may have striking social consequences, as illustrated in Box 2.

BOX 2 'Double reality' examples

Patient C, a 28-year-old female doctor's assistant, had a crush on a man working in the same hospital. There had been no physical erotic exchange between the two. Probably after dreaming that they had kissed each other, she was not sure whether the occasion had occurred in reality or not. This created confusion and an uneasy feeling that could not easily be settled.

Patient D, a 26 year old female patient, living with her parents, frequently heard and saw family members entering her room at night. However the next day they denied having visited her. In order to stop this confusion she decided to lock her door before going to bed. This way she could be sure that the family members entering her room at night had been hallucinated.

Patient E, was a 46 year old woman who, on a journey abroad, took a massage. On the table she experienced sleep paralysis. She then felt as if the massage therapist started to touch her private parts, but she was unable to react. After the treatment she went to the police to complain and make a declaration of assault. She discarded the possibility that she had been experiencing haptic hallucinations during sleep paralysis, which not unusual in narcolepsy. Afterwards it remained unclear whether the assault really took place.

This type of confusion can have painful consequences because in some instances, patients are convinced of the fact that the event really happened although it can be proven that it did not [4]. As illustrated in Box 2, some patients use tricks in order to differentiate real events from hallucinated ones. Many patients report paranormal experiences in which contact with deceased persons played an important role. This type of experiences had a strong influence on reality perception and its 'story line'. Note, that many patients do not speak overtly about such extraordinary experiences, and these may represent a 'dark side' of patients.

SOME POSITIVELY LABELED FEATURES: PSYCHIC AWARENESS

Patients report paranormal experiences and contacts with the world of death, as discussed above. This is experienced by some patients as an extra dimension and a few patients do work as a professional medium. Patients sometimes claim to have enhanced insight into the character of others: 'I knew a lot about this person as soon as I first saw him'. These psychic features can have an additional, personal meaning for some patients, as they may be perceived as additional 'special qualities' that others do not possess. Other patients do not appreciate this faculty because of the great responsibility that accompanies this uninvited knowledge: the message that someone in the street is going to be killed by a car incident can make patients feel conscience-stricken.

CHANGES AROUND THE LIFE CYCLE

The first years of having narcolepsy are notoriously difficult for patients. In many cases there is a long delay in diagnosis, leaving patients in limbo about what is happening to them. Next to the vigilance problems that influence the level of functioning, and the unexpected cataplexy attacks, hypnagogic hallucinations make patients fear that they are getting insane. Usually it takes some time before patients start to report this to parents or significant others. There are indications that disease duration has a positive influence on quality of life. The most influential independent factor predicting loss of quality of life over time is presence of depressive symptoms [5,6].

Childhood

Although adolescence is the modal age of disease onset, 30% of patients develop narcolepsy under the age of 15. Children with narcolepsy are more frequently introverted [7], and hesitant to discuss their dreams and hallucinations with their parents. Hallucinations may have a broad content in children, including monsters and dinosaurs, big spiders, 'seeing a screaming and bleeding eye', zombies and other strange figures. Depression scores are raised and general mental health scores are lowered [8]. Anxiety in general, and more specifically, social anxiety, is frequently underestimated in children. Emotional outbursts of patients can surprise parents and teachers [9].

Adolescence

In adolescence, peer group behavior is often impaired. Patients participate less in after school activities, and we witnessed how patients had to drop out of team sports such as soccer. Patients often have difficulty sustaining close friendships and meeting potential partners. When growing up, the first sexual experiences can be influenced by narcolepsy: cataplexy attacks just before the most exciting moments can spoil the date [10]. At school, patients report to function below their true level and do not reach their full potential. We have seen several young patients who had to change to a lower level of education after disease onset.

Adulthood

Patients have difficulties in interpersonal relations, with women reporting this more frequently than men. Narcoleptics can have difficulty listening to their partners 'story of the day', when concentration diminishes and sleep takes over. Divorce rates are increased [11]. Women with narcolepsy are living alone more frequently than men [12], and living without a partner is associated with a decrease in quality of life. Patients complain about leisure activities even more

than about work activities: taking holidays, visiting movies or the theatre, a pub or nightclub, attending sport events and playing sports can pose serious problems [13]. Not just the fear of falling asleep in a passive situation, but also the tendency towards social phobia can play a key role here (see Chapter 5). Patients report more accidents at home, for example smoking accidents resulting in serious fires, falls, burns, cuts and fractures [14].

In work situations, patients may feel they are unable to use their qualifications fully and are more frequently unemployed. Furthermore motor vehicle accidents, accidental injuries, poor job performance, job loss, loss of promotion are reported, which is troublesome, as patients consider the possibility of having a job particularly desirable. One of our patients had to quit his career in a family business: his father had always seen him as his successor, and his academic success qualified him for the job as director of the firm. After disease onset he could not live up to the expectations any more due to his lack of concentration and vigilance.

Old age

As patients grow older, quality of life may get somewhat better, as some studies have shown [15]: patients report an increase in quality of life after retirement, although sleepiness is not clearly improved. As mentioned in Chapter 5, depressive symptoms tend to abate with older age.

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List of Publications

LIST OF PUBLICATIONS

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Abbreviations

ABBREVIATIONS

5- HT	5 Hydroxy Tryptamine (serotonin)
AASM	American Association of Sleep Medicine
ADHD	Attention Defecit Hyperactive Disorder
APD	Anti Psychotic Drug
Arc	Arcuate Nucleus
BDI	Beck Depression Inventory
BDI- PC	Beck Depression Inventory- Primary Care
BIC	Bayesian Information Criteria
BMI	Body Mass Index
BST	Bed Nucleus of the Stria Terminalis
CFS	Chronic Fatigue Syndrome
CI	Confidence Interval
CIS	Checklist Individual Strength
CRP	Corticotropin Releasing Factor
CS+	Conditioned Stimulus
CSF	Cerebrospinal Fluid
DR	Dorsal Raphe
DSM	Diagnostic and Statistical Manual of Mental Disorders
EDE-Q	Eating Disorders Examination-Questionnaire
EDNOS	Eating Disorder Not Otherwise Specified
EDS	Excessive Daytime Sleepiness
EEG	Electro Encephalogram
ESS	Epworth Sleepiness Scale
fMRI	Functional Magnetic Resonance Imaging
Hcrt	Hypocretin
HH	Hypnagogic Hallucinations
HLA	Human Leucocyt Antigen
ICSD	International Classification of Sleep Disorders
LC	Locus Ceruleus
LDT	Laterodorsal Tegmental Nucleus
LHA	Lateral Hypothalamic Area
MDD	Major Depressive Disorder
MSLT	Multiple Sleep Latency Test
Nac	Nucleus Accumbens
NE	Norepinephrine
OR	Odds Ratio
PFH	Perifornical Hypothalamus
POMS	Profile of Moods States
PPT	Pediculo Pontine Nucleus
PSE	Present State Examinaion
RCT	Randomied Controlled Trial
REM	Rapid Eye Movements
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCL-90	Symptom Check List- 90
SF -36	Short Form Health Survey Scale 36
SIP	Sickness Impact Profile
SOREMP	Sleep Onset REM Period
SSRI	Serotonergic System Reuptake Inhibitor
TMN	Tuberomamillary nucleus
VPLA	Ventrolateral Preoptic Area
VTA	Ventral Tegmental Area

Summary in Dutch
Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Narcolepsie is een slaapziekte met als kernsymptomen overmatige slaperigheid overdag en kataplexie, een plotselinge verslapping van de skeletspieren die na een emotionele prikkel (bijvoorbeeld zoals bij lachen, woede, opwinding) kan optreden. Verder is er vaak sprake van een verstoorde nachtelijke slaap, hypnagoge hallucinaties en van slaapparalyse. Na het begin van de klachten duurt het vaak lang totdat de diagnose narcolepsie wordt gesteld. In die "latente periode" stellen artsen vaak tal van psychiatrische diagnoses, zoals neurotische stoornis, depressie, persoonlijkheidsstoornis en aanpassingsstoornis. Dit proefschrift doet verslag van een inventarisatie van psychiatrische symptomen en stoornissen die gepaard gaan met deze aandoening: het psychiatrische phenotype van narcolepsie. Per hoofdstuk volgt nu een korte samenvatting van de inhoud.

HOOFDSTUK 2
NARCOLEPSIE EN PSYCHIATRIE IN HISTORISCH PERSPECTIEF

Hoofdstuk 2 bevat de fascinerende en instructieve geschiedenis van de relatie tussen de narcolepsie en de psychiatrie. Gélineau (1880), die de term narcolepsie heeft bedacht, noemde deze ziekte een "névrose". Indertijd werd een neurose gezien als een organische, neurologische aandoening. Niet lang daarna (1881) stelde hij voor dat "secundaire narcolepsie" ook een uitingsvorm van hysterie kon zijn. Psychoanalytici zagen vanaf het begin van de 20ste eeuw narcolepsie als een conversiestoornis, en boden de psychoanalyse aan als behandeling daarvoor. Een andere groep psychiaters en neurologen bleef trouw aan een meer traditioneel "organisch" model van narcolepsie. De twee stromingen hadden weinig wederzijds contact en negeerden elkaar, zoals blijkt uit de literatuurreferenties. Bijna een halve eeuw lang gingen deze twee stromingen hun eigen weg, min of meer immuun voor kritische geluiden van buitenaf. In het kader van de snelle ontwikkelingen van de neurowetenschappen in de tweede helft van de 20ste eeuw werd stapsgewijs de cellulaire en moleculaire achtergrond van narcolepsie ontdekt, met als uiteindelijke doorbraak de ontdekking van het ontbreken van hypocretine in het lumbale vocht van narcolepsie patiënten. Narcolepsie bleek toch een "organische" ziekte te zijn, zoals oorspronkelijk gesuggereerd door Gélineau. Nu kon met open vizier gekeken worden naar het psychiatrische phenotype van narcolepsie en over precies dit onderwerp begonnen studies te verschijnen na het begin van de 21ste eeuw. Het werd snel duidelijk dat narcolepsie niet alleen een slaapziekte is, maar eveneens een bijzonder complexe gedragsstoornis.

De psychiatrische visie op narcolepsie heeft over het beloop van meer dan een eeuw een bijna volledige cyclus gemaakt: het oorspronkelijke "organische model" maakte plaats voor het psychodynamische model van de conversie hysterie en kwam uiteindelijk weer terug op het "organische" vertrekpunt. Patiënten zijn in die periode onderworpen geweest aan deze historische ontwikkelingen en werden hiervan soms zelfs het slachtoffer, zoals achteraf kan worden vastgesteld.

HOOFDSTUK 3
EETSTOORNISSEN

Het is bekend dat narcolepsie patiënten een verhoogde "body mass index (BMI)" hebben. Bovendien melden patiënten vaak dat ze buien hebben waarin ze behoefte hebben aan koolhydraten: het zogenaamde "carbo- craving". Hierdoor werd de nieuwsgierigheid gewekt naar de eetgewoontes of misschien zelfs eetstoornissen bij narcolepsie. We hebben een groep narcolepsie patiënten (n=60) vergeleken met een groep personen uit de algemene bevolking met dezelfde leeftijd en hetzelfde geslacht (n-120). Deze controlegroep was gerekruteerd in het kader van de "Nijmegen Health Area-2 population study". Een tweede vergelijking maakten we tussen een subgroep van patiënten (n=32) en een controlegroep (n= 32) die niet alleen gematched was op leeftijd en geslacht, maar ook op BMI. Het voorkomen van eetstoornissen werd gemeten met behulp van een diagnostisch onderzoeksinstrument: "vragenschema's voor de klinische beoordeling in de neuropsychiatrie" (SCAN 2.1) en met een ander onderzoeksinstrument dat alleen eetstoornissen meet: de EDE-Q. Van de patiënten voldeed 23% aan de criteria voor een eetstoornis volgens DSM IV, terwijl geen van de personen in de controlegroep hieraan voldeed. De diagnose die het vaakst werd gesteld, was "eetstoornis niet anders omschreven (N.A.O.)" , vaak een onvolledige variant van een "vreetbuistoornis". De helft van de patiënten gaf aan vreetbuien te hebben en een onweerstaanbare en aanhoudende zucht naar voedsel. Een kwart van de patiënten rapporteerde tweemaal per week of vaker een vreetbui te hebben. Vreetbuien waren niet gecorreleerd aan een hoger BMI. Dit patroon werd bevestigd toen de patiënten werden vergeleken met een groep controlepersonen met een gematched BMI. Het gebruik van antidepressiva was geassocieerd met een hogere belemmering van de activiteiten in de dagelijkse bezigheden ten gevolge van eetproblemen.

In de narcolepsie groep had een kwart van de patiënten een "eetstoornis niet anders omschreven", significant meer dan gevonden werd bij de controlegroep die geselecteerd werd uit de algemene bevolking. De meeste patiënten hadden een onvolledige variant van een "vreetbuistoornis", met vreetbuien en een onweerstaanbare, aanhoudende zucht naar voedsel als belangrijkste symptomen. De eetproblemen veroorzaakten een belemmering van activiteiten in de dagelijkse bezigheden.

HOOFSTUK 4
PSYCHOTISCHE SYMPTOMEN BIJ NARCOLEPSIE

Patiënten met narcolepsie ervaren vaak indringende hypnagoge hallucinaties waardoor diagnostisch verwarring kan ontstaan met psychiatrische stoornissen als schizofrenie. Dit kan leiden tot een behandeling van narcolepsie patiënten met antipsychotica. Deze behandeling is echter onjuist, want antipsychotica zijn ineffectief voor deze indicatie. Ons doel was om tot een gedetailleerde kwalitatieve beschrijving te komen van hypnagoge hallucinaties en andere "psychotische symptomen" bij narcolepsie patiënten en deze te vergelijken met die van een groep patiënten die lijdt aan schizofrenie en van een controlegroep met personen uit de algemene bevolking. We wilden ook het vóórkomen van diagnoses van psychotische stoornissen vergelijken tussen narcolepsie patiënten en de controle personen. Ter vergelijking van psychotische symptomen bij narcolepsie patiënten (n=60), schizofrenie patiënten (n=102) en controlepersonen uit de algemene bevolking (n= 120) gebruikten we de SCAN vragenschema's. Bovendien verzamelden we kwalitatieve gegevens om te komen tot een gedetailleerde beschrijving van hypnagoge hallucinaties bij de narcolepsie patiënten. We hebben gevonden dat het patroon van hallucinatoire ervaringen bij narcolepsie patiënten duidelijk verschilde van het patroon dat aanwezig was bij patiënten die lijden aan schizofrenie. Narcolepsie patiënten bleken multisensorische "holistische" hallucinaties te hebben, terwijl schizofrenie patiënten voornamelijk verbaal akoestische hallucinaties rapporteerden. Wanen kwamen niet vaker bij narcolepsie patiënten voor dan bij personen uit de algemene bevolking. Slechts enkele patiënten hadden waanherinneringen / fantastische wanen. Herinneringen van hallucinaties of dromen bleken soms moeilijk te onderscheiden van herinneringen van in werkelijkheid meegemaakte situaties. Hierdoor kon bij sommige patiënten onzekerheid of verwarring ontstaan. Ondanks de "psychotische symptomen" kwamen psychotische stoornissen niet vaker voor bij de patiënten met narcolepsie dan in de groep controlepersonen uit de algemene bevolking, mede dankzij het feit dat het inzicht met betrekking tot de

hallucinatoire ervaringen behouden bleef. Bijna de helft van de narcoleptici rapporteerde een matige belemmering in de activiteiten ten gevolge van de hypnagoge hallucinaties, vooral door de angst waarmee dezen gepaard kon den gaan.

De multi sensorische "holistische" hallucinaties van narcolepsie patiënten kunnen goed gedifferentieerd worden van de voornamelijk verbaal akoestische hallucinaties van patiënten met schizofrenie. In de groep narcolepsie patiënten kwamen psychotische stoornissen, geclassificeerd volgens het DSM IV-TR systeem, niet vaker voor dan in de controlegroep uit de algemene bevolking. De werkelijkheids toetsing was bij een aantal patiënten gecompromitteerd vanwege het feit dat de herinneringen aan levendige hallucinaties en dromen soms moeilijk te onderscheiden bleken te zijn van werkelijk meegemaakte ervaringen.

HOOFDSTUK 5
ANGST- EN STEMMINGSSTOORNISSEN

Het in verhoogde mate voorkomen van symptomen van depressie is al sinds geruime tijd beschreven bij patiënten met narcolepsie. Dit bleek bijvoorbeeld uit metingen met instrumenten waarmee de ernst van depressie kan worden vastgesteld, zoals de Beck Depressie Schaal. De diagnose depressie of stemmingsstoornis werd echter niet vaker bij narcolepsie patiënten gesteld dan bij gezonde controle personen in het enige onderzoek waarbij gebruik werd gemaakt van een gevalideerd en diagnostisch onderzoeksinstrument (Present State Examination).
Vanwege deze nog prangende discrepantie stelden we ons ten doel angst- en stemmingsstoornissen in kaart te brengen bij narcolepsie patiënten. We hebben met behulp van de vragenschema's voor de klinische beoordeling in de neuropsychiatrie (SCAN 2.1) een "case- control" studie uitgevoerd bij 60 patiënten met narcolepsie en 120 controlepersonen uit de algemene bevolking. We hebben zowel symptoomfrequenties als diagnostische classificaties volgens DSM IV gemeten en vergeleken. Symptomen van stemmingsstoornissen bleken bij maximaal een derde van de patiënten aanwezig te zijn. Een complicerende factor was de overlap die bestond tussen de gebruikelijke symptomen behorend bij narcolepsie en de symptomen van depressie, waardoor het diagnostisch proces werd bemoeilijkt. Hiermee rekening houdend, kon de diagnose "depressieve episode" of een andere diagnose uit de groep van stemmingsstoornissen niet vaker worden gesteld bij narcolepsie patiënten. Wel hebben we gevonden dat

angstsymptomen of paniekaanvallen bij meer dan de helft van de patiënten voorkwamen. Een derde van de narcolepsie patiënten kreeg de diagnose "angststoornis", hetgeen significant vaker dan in de controle groep het geval was. Sociale fobie was de meest voorkomende diagnose. Leeftijd, geslacht, ziekteduur, of medicatiegebruik hadden geen invloed op de prevalentie van stemmings- of angststoornissen.

Depressieve episodes of andere stemmingsstoornissen komen niet vaker bij narcolepsie patiënten voor dan in de algemene bevolking. De frequentie van depressieve symptomen is echter wel significant hoger in de patiëntengroep. De symptomen van narcolepsie en de "somatische" symptomen van depressie overlappen elkaar in aanzienlijke mate, waardoor het diagnostisch proces wordt bemoeilijkt. Angststoornissen en symptomen daarvan zijn echter wel duidelijk in verhoogde mate aanwezig bij narcolepsie patiënten: met name paniekaanvallen en sociale fobie komen vaker voor.

HOOFDSTUK 6
VERMOEIDHEID

Buitensporige slaperigheid overdag is het belangrijkste symptoom van narcolepsie. Patiënten klagen echter ook regelmatig over vermoeidheid. Dit symptoom is door behandelaars vaak ten onrechte gelijkgesteld aan de klassieke slaperigheid. We hebben het vóórkomen van ernstige vermoeidheid onderzocht alsmede de relatie tussen vermoeidheid en slaperigheid. Daarnaast onderzochten we de relatie met depressie, psychologisch onwelbevinden, functionele beperking en kwaliteit van leven. Met de "Checklist Individual Strength- Fatigue (CIS-F)" hebben we vermoeidheid gemeten bij 80 narcolepsie patiënten. De slaperigheid werd gemeten met de "Epsworth Sleepiness Scale". Psychologisch onwelbevinden, depressie, functionele beperking en kwaliteit van leven hebben we gemeten met de daarvoor geschikte gevalideerde onderzoeksinstrumenten. We hebben de subgroep patiënten met ernstige vermoeidheid (CIS-F score > 35) vergeleken met patiënten zonder ernstige vermoeidheid (CIS-F score < 35). Vijftig (62.5%) van de 80 patiënten waren ernstig vermoeid. Patiënten in de beide subgroepen hadden dezelfde mate van slaperigheid, waardoor het onderscheid tussen vermoeidheid en slaperigheid werd bevestigd. Er waren geen verschillen in leeftijd of geslacht tussen de beide subgroepen. De patiënten in de "ernstig vermoeide" groep gebruikten vaker medicatie met stimulerende werking. Ernstige vermoeidheid was geassocieerd met een hogere mate van functionele beperking, een lagere

kwaliteit van leven, een hoger psychologisch onwelbevinden en meer depressieve symptomen. De mate van vermoeidheid was vergelijkbaar met die bij andere chronische neurologische aandoeningen zoals Multiple Sclerose. Onze indruk was dat ernstige vermoeidheid eerder te maken had met de wijze waarop patiënten zich aan de ziekte aanpasten, dan dat het een uitdrukking was van de ernst van deze ziekte.

Een meerderheid van de narcolepsie patiënten lijdt aan ernstige vermoeidheid, die los gezien dient te worden van slaperigheid overdag. Terwijl narcolepsie al een aanzienlijke functionele beperking met zich meebrengt, is er bij de ernstig vermoeide groep sprake van een verdubbeling van deze beperking. Ernstige vermoeidheid is verder gerelateerd aan depressieve gevoelens, psychologisch onwelbevinden, het gebruik van stimulantia en een lagere kwaliteit van leven

Dankwoord

DANKWOORD

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de artikelen was gaan bezig houden. Ik heb van deze jonge senior onderzoeker heel veel geleerd: hij heeft mij onder meer leren ordenen, tot aan het inrichten van niet allen mijn memory stick, maar ook van mijn rugzak aan toe. De ruimte in dit dankwoord is te beperkt om een volledige inventarisatie te geven van wat ik heb mee gekregen. Zijn stijl van coachen was onverbloemd en soms confronterend. Ook van zijn creatieve kanten ("Is this Sebastian?" vroeg een verbaasde Amerikaanse senior onderzoeker bij zijn popzang optreden in de wandelgangen van een internationaal congres) heb ik getuige kunnen zijn. Ik gun elke promovendus een dergelijke coach. Veel dank ben ik ook verschuldigd aan de Leidse specialist op het gebied van narcolepsie, dr. Gert Jan Lammers en zijn onderzoeksteam. Hij was onvermoeibaar in zijn bijdrage aan het vermoeidheids-onderzoek, dat vanuit Leiden werd uitgevoerd. Hij was actief co auteur van enkele artikelen. Zijn stijl van informeel en persoonlijk communiceren stelde ik bijzonder op prijs. Van de Leidse groep noem ik ook graag dr. Rolf Fronczek , Clair Donjacour, Mirjan Smitshoek en Mojca van Schie. Het samenwerken met hen was inspirerend en plezierig. Ik kwam hen op allerlei plaatsen in de wereld tegen als "flying dutchmen".

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Dr. Sophie Swinkels hielp mij vlot en met volle aandacht met de methodologie en statistiek van het eetstoornissen artikel. Martijn Lappenschaar, wiskundige en arts, stond me statistisch terzijde bij achtereenvolgens drie artikelen. Ik heb hem op ongebruikelijke tijden en soms tijdens zijn vakantie gebeld met prangende vragen; hij reageerde of het allemaal doodgewoon was.

Door de cursus van psycholoog Fokko Nienhuis (UMCG) kon ik gecertificeerd worden voor het afnemen van de SCAN. Wij werkten vervolgens vruchtbaar samen bij het "psychose project".

Prof. Dr. Gijs Bleijenberg (Hoofd Kenniscentrum Chronische Vermoeidheid) hielp me op positieve wijze en zonder terughoudendheid met het instrumentarium, de methodologie en de formuleringen van het vermoeidheidsonderzoek. Uit zijn omgeving noem ik graag Carel Kruip, dr. Hans Knoop en – nadrukkelijk - dr. Joke Kalkman: ze wezen me de weg bij het duiden van de betekenis van de verschillende onderzoeksinstrumenten.

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Rachel Fraanje- Fikse deden bij mij hun student onderzoeksstages en hielpen met de data verzameling. Anouk's echtgenoot, dr. Paul Dechering, deed pionierswerk in de automatisering.
De publicaties die voortvloeiden uit het functie onderzoek bij narcolepsie patiënten, dat plaatsvond bij het Nijmegen Institute for Cognition and Information (NICI) onder leiding van Prof. Dr. A. Coenen, zijn niet meegenomen in dit proefschrift ter wille van de handhaving van de homogeniteit van het onderwerp. Ik bedank Dr. Annika Smit, Dr. Paul Eling en Prof. Ton Coenen voor de goede en royale samenwerking.
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Lieve Marijke, dochters Keetie, Lara, Sabine en Brigitte, schoonzoons Chris, Ricardo en Martijn, kleinkinderen Bowi en Marilú: als echtgenoot, vader, schoonvader en grootvader geniet ik van jullie en ben ik met jullie verbonden. Dat gaat veel verder dan dankbaarheid: onze uitwisselingen zijn van een geheel andere orde. Wat niet wegneemt dat narcolepsie een dankbaar gespreksonderwerp is geworden.

Curriculum Vitae

CURRICULUM VITAE

Hal Droogleever Fortuyn werd op 14 november 1944 geboren in Amsterdam. In 1963 behaalde hij zijn eindexamen Gymnasium bèta aan het Praediniusgymnasium te Groningen. Hierna studeerde hij geneeskunde bij de Universiteit van Amsterdam. Hij vervulde zijn coassistentschap gynaecologie/ obstetrie in Paramaribo, Suriname. Na het behalen van zijn artsexamen nam hij gedurende een jaar als huisarts waar in diverse praktijken. Van 1974-1977 verbleef hij in Californie, USA. Hij leerde daar "Primal Therapy" in het Center for Primal Therapy, geleid door David Rosen, psychiater. Hij werkte als arts in de "Height- Ashbury Free Clinic", San Francisco. In 1975 behaalde hij zijn Educational Commisschion for Foreighn Medical Graduates (ECFMG) diploma dat toegang gaf tot het instromen binnen internships en residency programma's in de Verenigde Staten. In 1977 keerde hij terug naar Nederland waar hij ging werken in dagkliniek "Welgelegen" te Velp, destijds onderdeel van psychiatrisch ziekenhuis Wolfheze. Hij vervulde zijn inrichtingsstage op het Socio Therapeutisch Centrum in Wolfheze onder supervisie van dr. H. van der Drift. Van 1978-1981 specialiseerde hij zich tot psychiater in het Universitair Medisch Centrum Groningen. Prof. Dr. W.K. van Dijk was zijn opleider. Van 1981 tot 1986 werkte hij als psychiater in Wolfheze. Hij zette samen met collega's een Hiërarchische Therapeutische Gemeenschap op, gecombineerd met een 'detox', ter behandeling van verslavingsproblematiek. Van 1986 tot 1995 werkte hij als psychiater op de PAAZ van het Zaans Medisch Centrum. Hij was daar B- opleider psychiatrie en eerste geneeskundige. Gedurende enige tijd was hij lid van het stafbestuur van dit ziekenhuis. In deze periode was hij tevens consulent voor de Reclassering Alkmaar. Van 1995 tot zijn pensioen in 2009 werkte hij in het UMC St. Radboud als universitair docent. Hij was hoofd van de consultatiedienst psychiatrie. Gedurende enkele jaren maakte hij deel uit van het bestuur van de sectie Consutatieve en Liaisonpsychiatrie van de Nederlandse Vereniging voor Psychiatrie. Hij fungeerde als opleider voor de assistenten in opleiding tot specialist (AIOS) in forensische rapportages. In 2009 kreeg hij van de AIOS "de Pluim", een onderscheiding voor zijn werk als supervisor. Hij huwde in 1978 Marijke Toes. Zij kregen vier dochters: Keetie, Lara, Sabine en Brigitte. Ze hebben bij het verschijnen van dit proefschrift twee kleinkinderen: Bowi en Marilú.