Depression in narcolepsy–

A comparative analysis of depression severity and daytime sleepiness in patients with narcolepsy and idiopathic hypersomnia

Inaugural-Dissertation zur Erlangung der Doktorwürde

der Philosophischen Fakultät II

(Psychologie, Pädagogik und Sportwissenschaft)

der Universität Regensburg

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Regensburg 2011

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1. GENERAL INTRODUCTION

Sleep and mood disorders often occur simultaneously. The connection between sleep disorders and specifically major depressive disorder is a relation that has been called “the chicken and egg situation” because there is such a close connection between disrupted sleep and mental disorders. It is difficult to determine which came first: “the chicken or the egg” (Van Moffaert, 1994). This metaphor has mostly been used to describe patients with insomnia and to a lesser extent, patients with hypersomnia. Indeed, insomnia is recognized as a core symptom across mood disorders but less is known about the relationship between hypersomnia and mood disorders (Kaplan & Harvey, 2009).

Depression is frequently reported in narcolepsy and idiopathic hypersomnia, although an overrepresentation of the symptoms is argued by some authors. In fact, several authors reported depressive symptoms in 6% to 56% of the narcolepsy patients (Dauvilliers et al., 2009; Rovere, Rossini & Reimao, 2008; Vignatelli et al., 2004; Vandeputte & de Weerd, 2003; Billiard & Dauvilliers, 2001; Daniels, King, Smith & Shneerson, 2001; Broughton et al., 1981). In idiopathic hypersomnia, patients’ depressive symptoms are reported in a range from 14 to 26% (Roth & Nevsimalova, 1975).

The difference in the prevalence of depression reported by authors, which in some cases was huge, was something worthy of consideration. The variation in these studies could reflect varying measurements, the use of different research instruments and varying cut-off scores. Even so, it could be influenced by specific questions in the psychometric tests related to sleep and the overlap between symptoms of depression and the clinical spectrum of narcolepsy. Furthermore, the prevalence of depression after the division of narcolepsy with cataplexy and without cataplexy in the ICSD-2 is almost unexplored.

Another point of interest was idiopathic hypersomnia because it is in the spectrum of narcolepsy. In idiopathic hypersomnia depressive symptoms are often present, although the diagnosis of idiopathic hypersomnia excludes patients with major depressive disorder (American Academy of Sleep Medicine, 2005). This is because mood disorders can be one of the causes of hypersomnia. However, hypersomnia may have initiated prior to mood changes (Montplaisir and Fantini, 2001).

CLINICAL IMPRESSION

Patients with narcolepsy during an appointment in the sleep laboratory frequently do not seem to be depressed. However, when they are asked about his/her feelings and thoughts, usually underlying depressive symptoms are revealed. Moreover, the same

patients participate in a patients support group and actively organize social meetings even under the presence of depressive symptoms. Thus, this paradoxical behavior- active participation and depressive symptoms- was also an incentive to carry out this work.
The possibility that the depressive symptoms reported by narcoleptics are essentially different from those reported by depressed patients was an opportunity to investigate. This problem was taken into account when comparing narcoleptics and depressives having a similar level of depressive symptoms.

ORGANIZATION OF THE DISSERTATION

The central research topic of this dissertation is embedded within two major fields of research, i.e. sleep and depression. In order to achieve the aim of this dissertation, it is useful to revise the recent findings in narcolepsy and idiopathic hypersomnia as well as to review the core symptoms of depression. This background information will be presented in the theoretical part of the dissertation. In the theoretical part, the concept of daytime sleepiness is initially developed, because it is the most important feature of narcolepsy and idiopathic hypersomnia. Secondly, the characteristics of narcolepsy and idiopathic hypersomnia are described, examining the history, the forms, symptoms and differential diagnoses according to the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2005). Thirdly, the association of hypersomnia with depression disorder is illustrated, analyzing the criteria in the diagnostic manuals DSM-IV and ICD-10, and later on, giving a general sense of the most important theories about depression and sleep abnormalities. To conclude the theoretical part, the dissertation focuses on the depressive symptoms and other psychological characteristics of patients with narcolepsy and idiopathic hypersomnia. In this section, relevant studies on the topic thus far are reviewed and discussed.

In the empirical part, three studies are developed addressing the association between narcolepsy and depression. In the first study of this dissertation, patients with narcolepsy (with and without cataplexy) and with idiopathic hypersomnia are compared. In particular, differences in the depressive symptoms in comparison with a control group are investigated. As a continuation, another study compares those narcoleptic patients with depressive symptoms, with primary depressed patients who are not said to have narcolepsy or a sleep disorder different from insomnia due to depression. The final study is further developed to investigate the relevant items of Beck Depression Inventory contributing to the scores of depression in patients with narcolepsy.

2. THEORETICAL PART

2.1. Definition of excessive daytime sleepiness

During the day, one is expected to be capable of staying awake in spite of being in monotonous situations. Considering that nearly 5% of the population suffers from daytime sleepiness, this symptom is a significant social problem. Excessive daytime sleepiness is not a disease or disorder per se but a symptom of a sleep disorder that cannot easily improve with more hours of sleep (Ohayon, 2008; Aldrich, 1992). An official definition, according to ICSD-2, of daytime sleepiness is “the inability to stay awake and alert during the major waking episodes of the day resulting in unintended lapses into drowsiness or sleep” (American Academy of Sleep Medicine, 2005).

2.1.1. Evaluation of sleepiness

The measurement of sleepiness is not an effortless matter. Sleepiness can be assessed considering the ability to stay awake or the facility to fall asleep. For the assessment of the facility to fall asleep the multiple sleep latency test is the most important method. Among the currently available tests to assess the ability to stay awake here will be discussed the maintenance of wakefulness test and introspective measurements of sleepiness.

MULTIPLE SLEEP LATENCY TEST (MSLT)

Mary Carskadon designed a standard test in 1976, which has been used up to now. She called it multiple sleep latency test (MSLT) based on the observation that the time to fall asleep was a reliable indicator of the somnolence level. This test consists of short nap opportunities -four to six times- during the day in 2-hour intervals. The patient lies down in bed in a dark and quiet room for 20-minute sessions and is instructed not to resist falling asleep (Carskadon, Harvey & Dement, 1981).

MAINTENANCE OF WAKEFULNESS TEST (MWT)

Regarding the evaluation of the ability to stay awake, the maintenance of wakefulness test (MWT) was designed. The main difference from MSLT is the instruction given to the patient: that they should avoid falling asleep. The patient sits comfortably in a bed with low lighting during two or four daytime 20 or 40 min sessions. The end of the test either occurs after 15 seconds of micro sleep or at the end of the session if no sleep occurs (Dauvilliers, 2005). Currently, MWT is not a standard method for the diagnosis of narcolepsy, although it is commonly used in some sleep centers.

INTROSPECTIVE MEASUREMENT OF SLEEPINESS (LONG AND SHORT-TERM OBSERVATION)

The Epworth sleepiness scale (ESS) represents a subjective long-term observation of sleepiness (Details of ESS in subdivision 2.1.2 Methods). The Stanford Sleepiness Scale (SSS) (Hoddes, Dement & Zarcone, 1972) together with Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990) corresponds to the short-term (or actual) observation of sleepiness. SSS and KSS were designed to detect sleepiness over the course of the day. Both scales can be administered repeatedly and are used in experimental environments. Normative data do not exist and are usually not used to make clinical judgments.

2.1.2. Causes of excessive daytime sleepiness

The typical causes of sleepiness comprise sleep deprivation, fragmented sleep and medication side effects (Arand et al., 2005). Specifically, among the causes of EDS is insufficient quality or quantity of night time sleep. Another cause of sleepiness is misalignments of the circadian rhythm (e.g. jet lag, shift work or other circadian rhythm sleep disorders). Some medical illnesses and traumata such as tumors, head trauma, anemia, testosterone disturbances, kidney failure, hypothyroidism and Lyme disease can also cause EDS (Greenberg, Ney, Scharf, Ravdin & Hilton, 1995).

Other triggers that can increase EDS are alcohol, exercise, heavy meals, warm environments (Bassetti & Aldrich, 1997), side effect of medication, abuse of substances, bruxism and gastro-esophageal reflux (Sateia, Doghramji, Hauri & Morin, 2000). Sleepiness can also be caused by psychiatric disorders such as major depressive disorder and is a characteristic symptom of atypical depression (American Psychiatric Association, 2000). In addition, the cause of EDS can be the presence of an underlying sleep disorder, such as narcolepsy, sleep apnea, idiopathic hypersomnia or restless legs syndrome. It is worth mentioning that EDS in sleep apnea and restless legs syndrome is induced by night sleep fragmentation, whereas EDS in idiopathic hypersomnia and narcolepsy is caused by a disorder in the regulation of sleep and wakefulness (American Academy of Sleep Medicine, 2005).

2.1.3. Hypersomnias of central origin

The International Classification of Sleep Disorders second version (ICSD-2) is a manual which classifies 85 sleep disorders into eight major categories (Figure 1).

This dissertation has its focus on “hypersomnia of central origin not due to a circadian rhythm sleep disorder, sleep related breathing disorder or other cause of disturbed nocturnal sleep” (Figure 2). In this category of hypersomnia of central origin, this

dissertation will be centered on narcolepsy and idiopathic hypersomnia (American Academy of Sleep Medicine, 2005). The reason is both disorders share wide similarities in the symptoms and the faintest line of division with narcolepsy without cataplexy.

The explanation for the exclusion of the other hypersomnias of central origin from this dissertation is that they are extremely rare and the symptoms are not constant. In addition, the subcategory behaviorally induced insufficient sleep syndrome seems to be mainly caused by a sleep hygiene problem. Therefore, the inclusion in the category of hypersomnia of central origin is discussible.

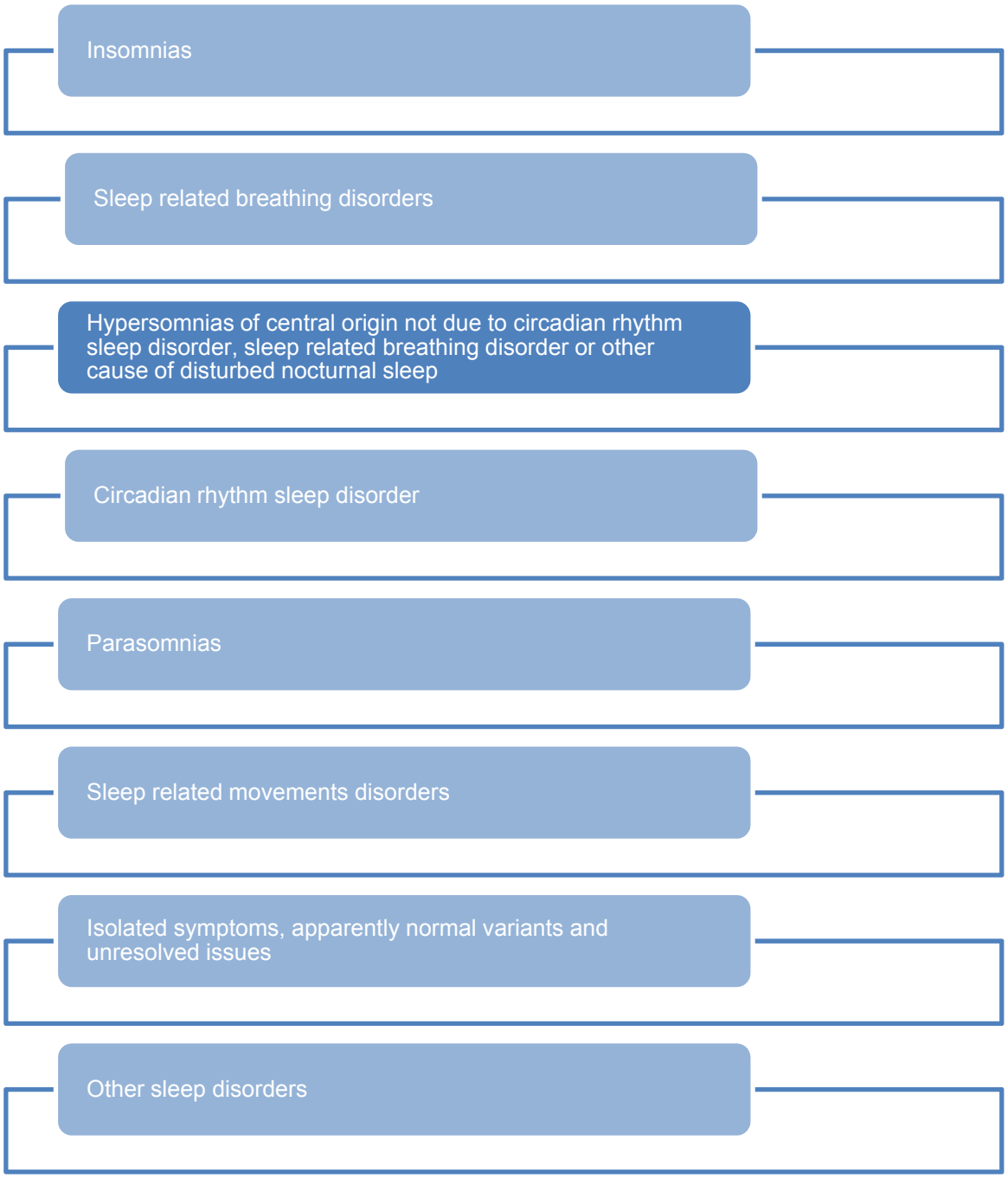

Figure 1. Categories of sleep disorders according to the International classification of sleep disorders 2nd edition (ICSD-2). In dark blue, the selected category of sleep disorders studied in this dissertation.

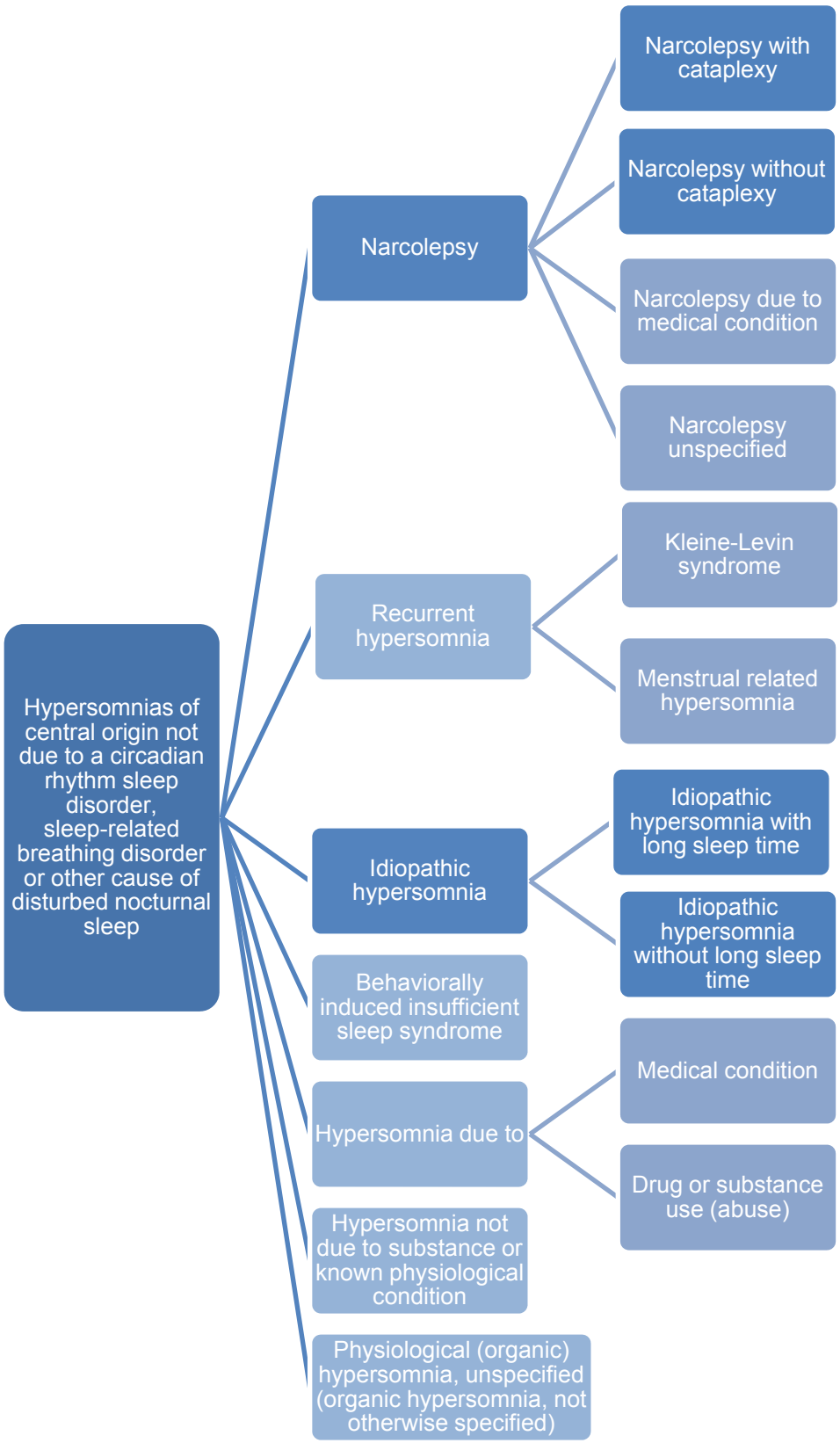

Figure 2. Hypersomnias of central origin due to narcolepsy and idiopathic hypersomnia: In dark blue, the selected sleep disorders studied in this dissertation (adapted from ICSD-2).

2.2. Narcolepsy

2.2.1. The history of the diagnosis of narcolepsy

The German physician, Carl Friederich Otto Westphal from Berlin first described two cases of narcolepsy with cataplexy in 1877 (Westphal, 1877). One year later so did Franz Fisher in Baden-Württemberg (Fischer, 1878). In 1880, Jean-Baptiste-Édouard Gélineau named the disease narcolepsy (Gelineau, 1880). In 1926, Adie reported the younger case of narcolepsy with an onset at the age of 12 years (Adie, 1926). In 1928, Wilson mentioned several causes of narcolepsy such as traumatic, psychopathological, endocrine, epileptic, toxic-infective, circulatory tumor related (a tumor situated in the third ventricle) or with no "Grundkrankheit" (underlying illness) (Wilson, 1928). In 1931 Hoff and Stengel postulated a familiar form (Hoff & Stengel, 1931) although already Westphal in 1877 reported the familiar occurrence of narcolepsy with cataplexy (Westphal, 1877). In 1934, Luman Daniels published a complete description of the symptoms (Daniels, 1934). Afterwards, narcolepsy was considered a type of response to emotional conflicts that patients cannot resolve (Langworthy & Betz, 1944; Spiegel & Oberndorf, 1946).

In the fifties, Aserinsky and Kleitman published the first description of REM sleep considered the beginning of the modern sleep research (Aserinsky & Kleitman, 2003). Only seven years later, Vogel observed that narcoleptic patients have a short REM latency at the sleep onset (Vogel, 1960). Vogel's discovery was central because it was the first objective parameter for narcolepsy. In 1960, Yoss and Daly of the Mayo Clinic described the narcolepsy tetrad which consists of excessive and persistent sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations (Yoss & Daly, 1960).

In the First International Symposium on Narcolepsy held in La Grande Motte (France) in 1975, participants drew up a definition of narcolepsy. This definition included excessive daytime sleepiness (EDS), disturbed night sleep and pathological manifestations of REM sleep as characteristics of narcolepsy. EDS and cataplexy were deemed to be the main symptoms of narcolepsy (Guilleminault, 1976). Richardson proposed the MSLT as an assessment method to attest pathological sleepiness in narcolepsy in 1978 (Richardson et al., 1978).

In the seventies, narcolepsy was reported in dogs in 1973 by Knecht and Mitler (Mignot, 2001). Later, Dement and Mitler contacted several veterinarians in the USA and collected a sample of narcoleptic dogs (Mignot, 2001). The canine model is a resource for the

pharmacological and physiological study of EDS and cataplexy (Nishino, Ripley, Overeem, Lammers & Mignot, 2000).

Later, Bedrich Roth suggested a classification of narcolepsy according to three criteria: etiology, clinical features and pathophysiology (Roth, 1980). Roth described idiopathic and symptomatic forms. The idiopathic form was diagnosed when it was not possible to find causal factors and the symptomatic form when the disease was believed to be a consequence of organic brain lesions such as cranial injuries or encephalitis.

The proportion of Roth's patients with idiopathic and symptomatic forms of narcolepsy was 4:1, respectively. The clinical features were the classic tetrad described by Yoss and Daly. When only one of the four symptoms was present, Roth diagnosed monosymptomatic narcolepsy. Hence, he differentiated monosymptomatic narcolepsy (sleep attacks), monosymptomatic cataplexy and monosymptomatic sleep paralysis (Roth, 1980). Roth did not describe monosymptomatic hypnagogic hallucinations. Using a sample of more than 600 narcoleptics, Roth reported three patients with cataplexy without sleepiness (Roth, 1980).

Other researchers have also described some single cases of cataplexy without sleepiness (van Dijk, Lammers & Blansjaar, 1991; Guilleminault, 1975), but these single cases have not turned into a diagnosis until now. Isolated cataplexy is observed at the onset of the disease, although it is rare (Passouant & Billiard, 1976).

Honda in 1983 described an association of narcolepsy with a certain histocompatibility antigen (Honda, Asaka, Masako & Furusho, 1983). In 1986, when the findings on the HLA-association of narcolepsy were well established, Honda defined very strict criteria for the diagnosis of narcolepsy. These criteria included the presence of sleep attacks, cataplexy, at least one instance of sleep onset REM and the presence of HLA DR2 / DQw1 in immunogenetic typing (Honda et al., 1986).

In the first edition of the International Classification of Sleep Disorders (American Sleep Disorders Association, 1991), the diagnosis of narcolepsy was a single diagnosis (without division of types), always strongly related to cataplexy but including narcoleptics patients without cataplexy when the MSLT demonstrated the presence of two or more sleep onset REM periods (SOREMP) (Table 1).

Table 1. Diagnostic criteria of narcolepsy according to the International Criteria of Sleep Disorders first version (ICSD-1) (American Sleep Disorders Association, 1991).

ICSD-1 diagnostic criteria of narcolepsy	
A.	A complaint of excessive sleepiness or sudden muscle weakness
B.	Recurrent daytime naps or lapses into sleep that occur almost daily for at least three months
C.	Sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy)
D.	Associated features include: 1. Sleep paralysis 2. Hypnagogic hallucinations 3. Automatic behaviours 4. Disrupted major sleep episodes
E.	Polysomnography demonstrates one or more of the following : 1. Sleep latency less than 10 min. 2. REM sleep latency less than 20 min. 3. An MSLT that demonstrates a mean sleep latency of less than 5 min. 4. Two or more sleep-onset REM periods
F.	HLA typing demonstrates DR2 positivity
G.	Absence of any medical or psychiatric disorder that could account for the symptoms
H.	Other sleep disorders may be present, but are not the primary cause of the symptoms, e.g. periodic limb movement disorder or central sleep apnoea

Later, Silber proposed alternative criteria for diagnosing narcolepsy based in the HLA typing that incorporated the following: definite narcolepsy, probable narcolepsy with a laboratory confirmation and probable narcolepsy with clinical confirmation (Silber, Krahn & Olson, 2002). As early as 1998, two research groups reported a deficiency of hypocretin (or orexin) to be a cause of narcolepsy (see details in section 2.2.4 etiology), opening a

new era for the narcolepsy research (Peyron et al., 1998; De Lecea et al., 1998). One consequence of this discovery was that the diagnosis could include a measure of cerebrospinal fluid (CSF) levels of hypocretin-1 although a negative test (values over 110pg/ml) is not a reason to exclude a diagnosis of narcolepsy with cataplexy and there is no special recommendation for this test as diagnostic criterion (American Academy of Sleep Medicine, 2005). Regarding narcolepsy without cataplexy, hypocretin levels are abnormally low only in rare cases (Mignot et al., 2002).

2.2.2. Classification: narcolepsy with and without cataplexy

A new definition of narcolepsy was proposed in the second edition of the ICSD published in 2005 (ICSD-2). Owing to the latest insights into the pathophysiology of narcolepsy related to the role of a hypocretin deficit, two forms of narcolepsy, with (NC+) or without cataplexy (NC-), are distinguished. NC- is diagnosed when EDS and two or more SOREMP, together with a mean sleep latency shorter than 8 minutes in the MSLT, are found (Table 2). The recommendation for a valid MSLT also includes: (a) Adequate sleep documented by sleep log or actigraphy for two weeks prior to testing; (b) At least 6 hours of polysomnographically defined sleep recorded prior to MSLT; and (c) Keeping patients awake before and between MSLT naps (American Academy of Sleep Medicine, 2005).

Table 2. Diagnostic criteria of narcolepsy with and without according to the International Criteria of Sleep Disorders second version (ICSD-2) (American Sleep Disorders Association, 1991).

ICSD-2 diagnostic criteria for narcolepsy	
I. Criteria for narcolepsy with cataplexy	
A.	The patient complains of excessive daytime sleepiness occurring almost daily for at least three months.
B.	A definite history of cataplexy, where cataplexy is defined as sudden and transient episodes of loss of motor tone triggered by emotions is present.
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 8 min and two or more SOREMP are observed following sufficient nocturnal sleep (minimum 6h) during the night prior to the test. Alternatively, hypocretin-1 levels in the cerebrospinal fluid are less than or equal to 110pg/ml or one third of mean normal values.
D.	The hypersomnia is not better explained by another sleep disorder or neurological disorder, mental disorder, medication use or substance use disorder.
II. Criteria for narcolepsy without cataplexy:	
A.	The patient complains of excessive daytime sleepiness occurring almost daily for at least three months.
B.	Typical cataplexy is not present, although doubtful or atypical cataplexy-like episodes may be reported.
C.	The diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal polysomnography followed by an MSLT. In narcolepsy without cataplexy, the mean sleep latency on MSLT is less than or equal to 8 min and two or more SOREMP are observed following sufficient nocturnal sleep (minimum 6h) during the night prior to the test.
D.	The hypersomnia is not explained better by another sleep disorder, medical or neurological disorder, mental disorder and medication use or substance use disorder.

2.2.3. Clinical symptoms

The main symptom of narcolepsy is EDS and the most specific one is cataplexy. Associated symptoms of narcolepsy are hypnagogic hallucinations (HH), sleep paralysis (SP), and nocturnal sleep disruption.

EXCESSIVE DAYTIME SLEEPINESS (EDS)

EDS is the core symptom of narcolepsy and occurs in episodes of urgent need to sleep several times per day (Billiard et al., 2006). These episodes take place in monotonous situations and also in situations where the patient should stay awake, for example, during talking, eating, driving a car or being in a business meeting. The episode has a duration which varies from minutes to hours. After a sleep episode, a narcoleptic patient will wake up refreshed and the next episode will occur 2 or more hours later. In consequence, narcolepsy is characterized by a marked disorganization of sleep/wake behavior (Scammell, 2003). Patients can experience extreme drowsiness causing memory lapses and automatisms also called automatic behavior. This means that the patient will continue with the activity despite the sleepiness automatically without consciousness of the task. For example, patients will write a note or scribble words that do not make any sense.

CATAPLEXY

Cataplexy is the second most common symptom of narcolepsy after EDS (Billiard et al., 2006). The word cataplexy comes from the Greek word kataplēxis which means the fixation (of the eyes) and from kataplēssein, to astound or terrify. In addition, it comes from the Latin word cataplēxis, which means “hoc est stupor, mens attonita, admiratio” (Forcellini, 1965), the English translation of which is astonishment, amazement, admiration.

In the etymological analysis, the origin of the word cata in English was borrowed from other languages. “Most English words with cata were borrowed, often through Latin, after the 1500´s as part of Greek words (…) *Cata* was known in Latin (as in catacomb), it is a borrowing from Greek *kata*-, from *katá* down, against, over, and is cognate with Old Welsh *cant* with, Old Irish *cēt*, Hittite *katta* down, under, with and possibly with Latin *com”* (Barnhart, 1988, p.149). The origin of the word lepsy is also originated from Greek and Latin words, it comes from “combining form meaning ´a violent attack´ as in catalepsy, epilepsy (medicine) from Greeκ ληψια, literally a seizing, from ληψ the future stem of λαμβανειν (lambanein) to take grasp, seize” (Klein, 1967, p.880). The word cataplexy was

coined by Henneberg (Henneberg, 1916) and adopted ten years later by Adie (Adie, 1926).

Cataplexy is characterized by sudden bilateral loss of muscle tone triggered by strong emotions. All striated muscles except the diaphragm may be affected (American Academy of Sleep Medicine, 2005) causing the collapse of the patient. Yoss and Daly described that narcoleptic patients report “that pleasure or a sense of exaltation on completion of a difficult task also may provoke attacks” (Yoss & Daly, 1960).

Indeed, current studies show that the emotions triggering cataplexy are mainly positives, such as laughter, pride, elation or surprise, although negative emotions can also provoke cataplexy (Anic-Labat et al., 1999; Krahn, Lymp, Moore, Slocumb & Silber, 2005). However, the emotional trigger must be spontaneous because during experiments, even in patients with frequent cataplexy, it is not easy to trigger an episode of cataplexy (Dauvilliers et al., 2010). The attacks can also be triggered by a sensation of elation while watching a movie or listening to music, remembering a funny situation, telling a joke or when a patient anticipates saying something amusing (American Academy of Sleep Medicine, 2005).

Cataplexy can affect all skeletal muscle groups simultaneously or can be localized in parts of the body that can be regionally affected such as limbs (lower or upper), neck, mouth or eyelids (American Academy of Sleep Medicine, 2005). The episode of cataplexy can be short and partial, and for that reason it can go undetected during a medical examination (Guilleminault, Huang & Lin, 2006). Regarding the reflexes, deep tendon reflexes are temporarily suppressed during cataplexy and the H-reflex is normally absent. In healthy subjects, the H-reflex can be diminished during laughter but a long-lasting complete lack of this reflex is characteristically seen in an episode of cataplexy (Guilleminault, Lee & Arias, 2006). Checking deep tendon reflexes is reported as a simple and definitive test that confirms transient areflexia and atonia of voluntary muscles. During cataplexy, increased phasic muscle activity (twitches) may be present.

Consciousness and awareness of the environment are maintained throughout the episode. It has been described that patients have slurred speech but are able to hear (Krahn et al., 2005). This description is useful for clinicians when the episodes are not typical. The electroencephalogram (EEG) during a cataplexy episode shows a pattern of wakefulness in humans and animals. When the cataplectic attack is longer, the subjects report dreaming and EEG showed typical features of REM sleep (Guilleminault & Gelb, 1995). The onset of cataplexy is variable, but in a sample of young narcoleptics (14-23 years),

49% of the cases developed cataplexy simultaneously with EDS (Passouant et al., 1976). Cataplexy seems to decrease with age (Guilleminault et al., 2006).

SLEEP PARALYSIS

Sleep paralysis (SP) has been described as “hypnagogic cataplexy” due to the similarity between SP and cataplexy (Yoss et al., 1960). Weir Mitchell, the neurologist, first described the condition as “nocturnal paralysis” (Mitchell, 1890). It consists of temporary episodes where the patient is incapable of moving although he is aware of his surroundings (Yoss et al., 1960). In rare cases, relatives of SP subjects have observed temporary breathlessness during sleep paralysis (Yoss et al., 1960) which has been also self-reported by the subject (American Academy of Sleep Medicine, 2005).

Cheyne has proposed that SP can be divided in three categories according to the type of hallucinations related to it (Cheyne, 2005). These are intruder, incubus and vestibular-motor experiences. Intruder experiences are characterized by the sense of a presence with the feeling of being touched and hearing noises. Incubus experiences are characterized by the sensation of suffocation, bodily pressure and thought of imminent dead. Both of them include high levels of fear. Vestibular experiences are different because they include sensations of linear and angular acceleration in the form of floating, flying and falling. In this type, patients experience out of body experiences, seeing oneself from an external point and motor movements. This one is less correlated with fear (Cheyne, 2005). SP has been associated with sleep onset REM which is consistent with the vivid dreams that are reported (Hishikawa, 1975). Isolated incidence of SP can occur in healthy persons who have no symptoms of narcolepsy and may differ among ethnic groups (Dahlitz & Parkes, 1993). Isolated SP is not associated with the HLA haplotype typical for narcolepsy (Dahlitz et al., 1993).

HYPNAGOGIC HALLUCINATIONS

Hypnagogic hallucinations (HH) are dream like, often fear-provoking hallucinations that characteristically occur at sleep onset (American Academy of Sleep Medicine, 2005) during the phase between wakefulness and sleep. The hallucinations are usually visual with reports of seeing people or animals, but can also be tactile, auditory or vestibular such as a sense of sudden falling (Scammell, 2003).

The explanation for the association of hallucinations with sleep paralysis has been hypothesized as a link with gamma loop (motoneuron which control muscles) suggesting a reflex contraction of the entire muscles (Kryger, Roth & Dement, 2005).

The hallucinations in narcolepsy are different than the kind of hallucinations that people with schizophrenia experience (Dahmen, Kasten, Mittag & Muller, 2002), as well as hallucinations that go along with bipolar depression, depression with psychotic symptoms and Morvan´s Syndrome (Jouvet, 1998). The differences in type, quality and body posture dependence of hallucinations between narcoleptics and schizophrenics do not support the hypothesis of a common pathophysiological mechanism such as REM intrusion for hallucinations (Dahmen & Kasten, 2001).

Symptoms similar to narcolepsy can be associated with psychiatric disorders. Curt Rosenthal described in 1934 hallucinations and some kind of "sleep paralysis" similar to the real sleep paralysis in narcolepsy which were related to fear. This is known in German as "halluzinatorisch - kataplektisches Angstsyndrom" (Hallucinatory- Cataplectic Anxiety syndrome) and occurs in the context of schizophrenia (Bassetti, Billiard & Mignot, 2007).

Further, HH is well recognized in Parkinson's disease (Barnes, Connelly, Wiggs, Boubert & Maravic, 2010).

NOCTURNAL SLEEP DISTURBANCES

Narcolepsy patients have normal amounts of sleep over 24 hours but disrupted nighttime sleep (American Academy of Sleep Medicine, 2005). Patients show a polyphasic sleep, with preserved circadian rhythms and with a homeostatic sleep regulation (Plazzi, Serra & Ferri, 2008). Broughton demonstrated that patients with good or relatively normal nighttime sleep still have a pathological daytime sleepiness. According to this, nocturnal disturbances would be just a little contributor for sleepiness during the day (Broughton, Dunham, Weisskopf & Rivers, 1994).

OTHER SYMPTOMS ASSOCIATED WITH NARCOLEPSY

- *Cognitive impairment:*

Narcoleptic patients frequently complain about impaired memory. A Canadian study shows that narcoleptic patients do not have a memory deficit compared to controls. They interpret the subjective memory deficit as a motivational problem (Aguirre, Broughton & Stuss, 1985). The authors suggest that when the test is shorter and challenging the patients may stay alert (Aguirre et al., 1985).

In another study measuring cognitive impairment of 700 narcoleptics, researchers found that 38% subjectively reported moderate or severe memory problems, 39% had problems with forgetfulness, 40% with concentration and 26% with general learning (Smith et al, 1992).

Some authors have gathered evidence that narcolepsy patients have a decreased cognitive performance in comparison with controls due to the complaints of memory problems (Fulda & Schulz, 2001) but until now it is not clear if decreased cognitive performance is due to the daytime sleepiness or if is due to the pathophysiology of the illness. Researchers at the University of Bochum reported that narcoleptics showed a mild verbal memory deficit and increased forgetting rates, which may be explained by a reduced encoding efficiency (Naumann, Bierbrauer, Przuntek & Daum, 2001). This reduction is probably because patients with narcolepsy need to use cognitive resources to stabilize vigilance levels at the same time (Naumann et al., 2001).

- *Obesity and eating disorders:*

Obesity is another feature of narcolepsy already distinguished by Daniels (Daniels, 1934). Different authors (Kok et al., 2003; Hara et al., 2001; Schuld et al., 2000) report an increased BMI in patients with narcolepsy. Some of them suggest that a higher BMI is related to the pathological link that involves hypocretin deficiency in narcoleptic patients (Schuld et al., 2000). Although hypocretin deficiency should theoretically be a predictor of a reduced food intake, this is not the case (Willie, Chemelli, Sinton & Yanagisawa, 2001), probably due to multiple factors involved in the pathology of narcolepsy. Narcoleptic patients are prone to develop obesity while idiopathic hypersomnia patients are less obese. This supports the hypothesis that destruction of hypocretin neurons is involved in the pathogenesis of obesity in narcolepsy (Kok et al., 2003). This link between narcolepsy and obesity is consistent also with animal models of narcolepsy (Hara et al., 2001).

Bixler mentioned that several studies have shown that obesity is associated with reduced nocturnal sleep (Bixler et al., 2005). The above mentioned study evidently could be linked to the poor night's sleep in narcolepsy and the high BMI, which is well documented in the literature (Chabas et al., 2007; Kok et al., 2003; Dahmen, Bierbrauer & Kasten, 2001; Krahn, Moore & Altchuler, 2001b).

Obesity in narcoleptics can also be explained by eating disorders. According to a Dutch study, there is a high prevalence of narcoleptic patients with cataplexy reporting symptoms of eating disorders such as craving for food or binge eating behavior (Fortuyn et al., 2008). The exact mechanism associating narcolepsy with obesity is still unknown.

- *Olfactory dysfunction:*

Recently, investigators linked narcolepsy with olfactory dysfunction. The study, performed with only 20 patients, suggests that olfactory dysfunction may be a predictor of local degeneration of hypocretinergic mucosa cells (Stiasny-Kolster, Clever, Moller, Oertel & Mayer, 2007). This is remarkable because olfactory dysfunction is one of the first signs of

a neurodegenerative disorder. In line with this finding, a recent French study showed that patients with Parkinson disease (PD) could suffer from cataplexy episodes (Arnulf et al., 2000). The Francophone study and other two studies simultaneously reported that there is a loss of hypocretin cells in Parkinson patients. The similarities with Parkinson patients are not only related to the possible olfactory dysfunction but also with the typical EDS and to a lesser extent to the hallucinations present in Parkinson patients. Moreover, another link with PD is REM-behavior disorder, which was described in narcolepsy patients, especially in children (Nevsimalova, Buskova, Kemlink, Sonka & Skibova, 2009b; Arnulf et al., 2000)

2.2.4. Etiology

HLA ASSOCIATION

The family of genes called human leukocyte antigens (HLA) located on chromosome six codes for mechanisms that trigger an immune response. In the case of narcolepsy, a specific variant of the HLA gene DQB1 has been identified to be strongly associated with this sleep disorder (Langdon, Welsh, van, Vaughan & Parkes, 1984).

Initially, this association was believed to be with HLA DR2, later the association most closely linked to narcolepsy was found to be HLA DQB1*0602 (Honda et al., 1986).

Recently, a study reported that the haplotype DQB1*0603 is a protective HLA haplotype in narcolepsy vulnerability. This haplotype is seldom seen in patients with narcolepsy and is recognized as one of the main protective alleles against autoimmune disorders such as diabetes type 1 and rheumatoid arthritis (Hor et al., 2010).

NEUROTRANSMITTER HYPOCRETIN

In 1998, two different research groups identified a new neurotransmitter in the hypothalamus relevant to narcolepsy. One group named it “orexin” due to its role in food intake (Sakurai et al., 1998) and the other group “hypocretin” because it is similar to the hormone secretin and due to its hypothalamic origin (De Lecea et al., 1998).

Hypocretin 1 is a 33 amino-acid peptide (3562Da) and hypocretin 2 (2937Da) has 46% of the amino-acids identified in the sequence of hypocretin 1 (Korotkova, 2003). These peptides are produced only by a cluster of neurons in the posterior half of the lateral hypothalamus (Saper, Scammell & Lu, 2005).

Hypocretin (Hcrt) regulates sleep and wakefulness. The hypocretinergic system is involved in other functions like the regulation of food intake, autonomic control, sensory control and energy balance (Baumann & Bassetti, 2005). Narcolepsy with cataplexy and positive HLA DQB1*0602 is linked with low or undetectable levels of Hcrt (Nishino et al., 2000).

HYPOCRETIN IN NARCOLEPSY

The first experimental studies regarding Hcrt system were carried out in animal models of narcolepsy. Lin et al (1999) observed that in canine narcolepsy is due to the mutation of Hcrt-2 and this result in an REM sleep abnormality such as cataplexy (Lin et al 1999). Hcrt-2 knockout mice show a typical narcolepsy behavior (Willie et al., 2001). As a consequence of the experimental studies of Hcrt in the animal narcolepsy model, the human narcolepsy model began to be studied. Nishino and collaborators first reported low levels of Hcrt-1 in around 90% of narcolepsy patients with cataplexy and HLA type DQBI*0602 (Nishino et al., 2000).

Using the Fos protein as a index of neuronal activity, it was demonstrated that Hcrt neurons are activated only when there is motor activity during wakefulness and inactive during slow wave sleep. Therefore the Hcrt system would be predominantly involved in the enhanced arousal of motor activity mediated by histamine (Torterolo & Vanini, 2003). A subpopulation of Hcrt neurons is active during REM sleep.

The main function of Hcrt system is probably the facilitation of the motor system which accompanies the wakefulness. This was confirmed by Kiyashchenko and collaborators (2002) who, using microdyalisis, described an increase of the release of Hcrt during motor activity (Kiyashchenko et al., 2002).

HYPOCRETIN DESTRUCTION

The destruction of Hcrt neurons either genetically or with chemical toxins, is, hypothetically, the cause of facilitated REM sleep (Scammell, 2003). The probable place where the neurons are destroyed was recently reported. The study revealed that a lesion in the ventral lateral periaqueductal gray neurons increased REM sleep at night, but does not trigger cataplexy (Kaur et al., 2009). In most of cases, it is a destruction of the hypocretinergic neurons that causes a low level of Hcrt-1 (Torterolo, Yamuy, Sampogna, Morales & Chase, 2003). However, a Norwegian study revealed that only 72% of patients with NC+ had low levels of Hcrt (≤134pg/ml) (Heier et al., 2007). The difference in the study results is not clear, but could be due to the ethnically diverse patient population or due to the inclusion of some patients in the cataplexy group who had the so called “pseudocataplexy” (Krahn, Hansen & Shepard, 2001a).

Recently, a study showed that not only narcolepsy with cataplexy loses Hcrt cells but also narcolepsy without cataplexy. However, the depletion is not as much as those levels found in patients with cataplexy (Thannickal, Nienhuis and Siegel, 2009). Thannickal based his study only on two postmortem brains specimens of patients with narcolepsy without

cataplexy. The small sample is because it is difficult to obtain such brain samples and therefore, this study needs replication.

AUTOIMMUNE HYPOTHESIS FOR THE HYPOCRETIN DEFICIENCY

In addition to genetics, an autoimmune process could explain the above mentioned Hcrt destruction. This hypothesis is supported by a study suggesting a streptococcal infection and a recently published study regarding antibodies.

- *Streptococcal infections:*

Several patients have claimed that environmental factors triggered narcolepsy, but few studies directly tested this hypothesis. Recently, Aran and fellow researchers, in a sample of 200 patients with recent onset of narcolepsy in comparison with age matched controls, showed that the rate of increased antistreptococcal antibodies is increased in narcoleptic patients (Aran et al., 2009). The presence of streptococcal infections could start or cause an autoimmune response resulting in the destruction of Hcrt neurons.

- *Tribbles homolog-2:*

Recently, the research group of Tafti in Switzerland found evidence that supports the hypothesis that narcolepsy is an autoimmune disorder. They report that sera from narcolepsy patients with cataplexy had higher Tribbles homolog-2 (Trib2) specific antibody levels compared with healthy controls, patients with narcolepsy without cataplexy, idiopathic hypersomnia, multiple sclerosis or other inflammatory diseases. Additionally, they found a positive correlation between Trib2 and cataplexy (Cvetkovic-Lopes et al., 2010).

VOXEL-BASED MORPHOMETRY STUDIES

Several studies have investigated structural brain changes in the hypothalamus of narcoleptics. Three of them revealed areas of reduced gray matter in the hypothalamus of narcoleptics (Kim et al., 2009; Buskova, Vaneckova, Sonka, Seidl & Nevsimalova, 2006; Draganski et al., 2002). The remaining studies found no structural abnormalities in the hypothalamus of patients with narcolepsy (Brenneis et al., 2005; Overeem et al., 2003; Kaufmann, Schuld, Pollmaecher & Auer, 2002). Interestingly, among the studies without significant abnormalities, one researcher's group found a reduction in bilateral cortical gray matter but not subcortical gray matter alterations (Kaufmann et al., 2002).

2.2.5. Pathophysiology

An explanation for cataplexy, sleep paralysis and hypnagogic hallucinations is that narcoleptic patients have abnormal manifestations of REM sleep that intrude into

wakefulness (Scammell, 2003). The pathophysiology of cataplexy seems to be an imbalance between pontine monoaminergic and cholinergic neuronal populations (Overeem, Lammers & van Dijk, 2002). The cataplexy event is produced by the activation of the neural systems responsible for the typical REM without muscular tonus during wakefulness (Torterolo et al., 2003). Researchers have found an increase in postsynaptic dopamine type 2 receptors in the amygdala with an impairment of dopamine discharge in dogs (American Academy of Sleep Medicine, 2005). Other brain regions such as the basal forebrain/anterior hypothalamus play a role in the modulation of cataplexy.

THE FLIP-FLOP SWITCH MODEL: EXPLANATION OF THE WAKE-SLEEP TRANSITIONS

A flip-flop switch is a circuit to design two stable states with immediate transitions. This kind of circuit tends to avoid transitions states. This is because when one of the states begins to decline, the other one will rapidly increase and the system will "flip" to the alternative state. The existence of such a flip-flop switch explains the sudden transition sleep-wakefulness. Humans and animals spend no more than 1 to 2% of each day in a transition state. There are two reasons of adaptation for the sleep wake system of the flip-flop switch. First, it is because it would be dangerous for an animal to have an impaired attention during wakeful behavior. Second, it would be inefficient to use the time spent sleeping in a half wake state. The flip-flop circuit would involve the VLPO (ventrolateral preoptic nucleus) and monoaminergic cell groups (Saper et al., 2005).

- *Hcrt and state stability:*

Hcrt neurons have ascending and descending projections in the cerebral cortex. There are mutual projections between VLPO and Hcrt neurons but VLPO neurons do not express receptors of Hcrt. Consequently, Hcrt neurons can reinforce the arousal system but do not inhibit VLPO neurons. This is called an asymmetrical relationship. This asymmetric link can stabilize the change flip-flop, preventing unwanted transition into sleep (Saper et al., 2005). The flip-flop switch is relatively unstable but Hcrt neurons help to stabilize this switch.

- *Flip-flop switch in narcoleptics with hypocretin deficiency:*

Narcoleptic patients have EDS and will take several naps during the day. This is because they do not have the influence of Hcrt neurons in the VLPO. Therefore, it is hypothesized that the flip-flop switch is destabilized in narcoleptics (Saper et al., 2005).

The flip-flop system explains sleepiness in patients with Hcrt deficiency but does not explain sleepiness in patients without Hcrt deficiency.

CATAPLEXY AS AN ATAVISM (REAPPEARANCE OF ANCESTRAL CHARACTERISTICS) OF TONIC IMMOBILITY.

A different hypothesis considers cataplexy as a form of tonic immobility. Tonic immobility (TI) is an animal response, described when an animal is confronted with an extreme risk. The EEG shows that the animal is totally awake similar to cataplexy episodes and the animal may fall asleep after long-lasting immobility (Overeem et al., 2002). The authors recognize that TI does not occur in humans. Nonetheless, cataplexy and TI share the strong emotional trigger. This hypothesis needs further confirmation.

2.2.6. Epidemiology

The most important study was performed in Finland with 11,354 subjects; the researchers found that the prevalence of narcolepsy in the population was 0.026% (Hublin et al., 1994). Other studies in England, France, the Czech Republic and the USA show a similar prevalence of about 0.02 to 0.067%. The center for narcolepsy at Stanford University suggests that the prevalence of narcolepsy with cataplexy is within a range of 0.02 and 0.18% (Nishino, Okura & Mignot, 2000).

In general, the prevalence of narcolepsy in Europe and North America is estimated to be about 1 in 3000 (0.03%). In South America there are no data on the prevalence until now. Interestingly, in Japan, the prevalence is much higher: between 0.16 and 0.18% while in Israel it is considerably lower at about 0.002%.

According to Billiard, the methodology used in the studies of prevalence performed in Japan is a matter of discussion. In contrast, the data from Israel are consistent with the low rate of HLA-DQB1*0602 found in the Jewish population. Nonetheless, it is still necessary to perform population studies to establish such low prevalence (Billiard et al., 2006).

Narcolepsy (as a whole) is more common in men than in women with a prevalence rate of 1.8:1 in narcolepsy. In narcolepsy with cataplexy, the male predominance is lower (1.4:1) but is still present (Silber, Krahn, Olson & Pankratz, 2002). This study confirmed previous findings reported by Roth (Roth, 1980). With respect to age at onset, in narcolepsy with cataplexy there is evidence for a bimodal distribution with two peaks, the first one occurring at 14.7 years and the second one at 35 years of age (Dauvilliers et al., 2001). The onset of narcolepsy is not correlated with sex or HLA type (Longstreth, Jr., Koepsell, Ton, Hendrickson & van Belle, 2007).

2.2.7. Diagnosis

Regarding to the clinical diagnosis, the definite presence of cataplexy is the specific symptom which characterizes narcolepsy with cataplexy (Table 2). In the case of doubtful

cataplexy, the patient with two or more SOREMP on the MSLT should be included in the category non cataplexy. It is known that some of these patients will develop cataplexy later on (American Academy of Sleep Medicine, 2005). A cataplexy episode should be differentiated from the common experience of muscle weakness during sport or when laughing uncontrollably. Additionally some subjects feel weak after stressful events which should be not considered cataplexy. Cataplexy must be differentiated from hypotension, transient ischemic attacks, drop attacks, akinetic seizures, neuromuscular disorders, vestibular disorders, sleep paralysis and psychological or psychiatric disorders. In psychiatric disorders, cataplexy should be carefully differentiated from a pseudocataplexy (Krahn et al., 2001a), for instance, in the context of a conversion disorder (American Psychiatric Association, 2000).

Patients with narcolepsy can have other diagnoses such as obstructive sleep apnea, periodic limb movement disorder or behaviorally induced insufficient sleep syndrome. However, this does not explain the symptom of excessive daytime sleepiness.

Regarding to the diagnosis using the MSLT, when two or more SOREMP along with mean sleep latency shorter than 8 minutes are found (Table 2) without the explicit presence of cataplexy, the diagnosis is narcolepsy without cataplexy and when SOREMP are less than two, the diagnosis of idiopathic hypersomnia must be kept in mind. Patients with narcolepsy do not normally have long episodes of sleep during the day, which is more typical for idiopathic hypersomnia with long sleep time.

2.2.8. Treatment of narcolepsy

Sleepiness and cataplexy persist throughout life and often improve after retirement probably due to better management of activities and napping schedules (Dauvilliers et al., 2004). Although medication can increase alertness, avoiding cataplexy and diminishing nocturnal disturbances to the patients, there is no complete cure for narcolepsy.

MEDICATION USED FOR EXCESSIVE DAYTIME SLEEPINESS AND IRRESISTIBLE EPISODES OF SLEEP

According to the guidelines of the European Federation of Neurological Societies (EFNS) for the treatment of EDS and irresistible episodes of sleep, modafinil should be the first-line therapy and the second-line should be methylphenidate. In case of high severity of these symptoms, the combination of modafinil and sodium oxybate is recommended (Billiard et al., 2006).

- *Amphetamines and amphetamine-like CNS stimulants:*

  The treatment with stimulants (ephedrine and amphetamine) began in 1931 by Dr. Janota in patients with narcolepsy (Daniels, 1934).

The mechanism of action of amphetamines is dependent on the dose. If it is used at low doses, the effect is to discharge dopamine and, to a lesser extent, norepinephrine and serotonine. If it is used at high doses, the result is a monoaminergic decrease with an inhibition of the reuptake (Billiard et al., 2006).

The adverse effects are similar to those previously described by Yoss and Daly: irritability, hyperactivity, mood changes, headache, palpitations, sweating, tremors, anorexia and insomnia (Yoss & Daly, 1959). Side effects of some medication perhaps influenced the results of psychopathological findings in patients with narcolepsy. For instance, in MMPI, elevations in the scales psychasthenia or schizophrenia (Kales et al., 1982) may be biased not only by the physical symptoms but also by the use of stimulants.

- *Methylphenidate:*

Yoss and Daly (1959) accurately described the treatment with methylphenidate hydrochloride with a daily dosage of 40 to 80mg in 60 patients with narcolepsy and followed some of them for eight to 27 months. They report side effects such as nervousness, anorexia, insomnia, tachycardia and in some rare cases skin rash (Yoss et al., 1959). The action is the same as for amphetamine with the difference that there is no reuptake (Billiard et al., 2006).

The adverse effects are similar but with the considerations that clinically it seems to be slightly better than amphetamines and there is a smaller decrease of appetite and an increase in blood pressure (Billiard et al., 2006).

- *Modafinil:*

The way of action of modafinil is not completely understood. The possible mechanisms of action are associated with adrenergic alpha-1 stimulation, interactions of the dopamine systems and the compromise of serotonergic/GABAergic mechanisms (Billiard et al., 2006).

Some adverse effects described are headache, nausea and rhinitis in a range of 11 to 13% compared with 2 to 3% in the placebo group (US modafinil in narcolepsy multicenter study group, 2000). Modafinil affects the mood in narcoleptics and a randomized study shows that modafinil improved mood also in healthy subjects and had a significant effect in positive life scale events (Taneja, Haman, Shelton & Robertson, 2007). Studies also show that narcolepsy patients under treatment with modafinil report improvement in psychological well-being and self-esteem between other variables (Beusterien et al., 1999).

In a study about the effect of modafinil on fatigue, mood and quality of life in narcoleptics, a significant improvement in vigor and cognition was reported (Becker, Schwartz, Feldman

& Hughes, 2004). In addition, the authors found a reduced fatigue in the patients assessed by the Profile of Mood States. Besides, in the Short Form Health Survey (SF-36) specific improvements were seen in vitality, role-physical and social functioning (Becker et al., 2004). Side effects of stimulants include insomnia, headaches, anxiety and palpitations (Mitler, Aldrich, Koob & Zarcone, 1994). It has been argued that stimulants may complicate some psychiatric and interpersonal problems of patients with narcolepsy. But side effects may be less pronounced with modafinil in comparison to other stimulants (Mitler et al., 1994). To a lesser extent, there are also negative reports using modafinil. Recently, a case was reported about a patient with narcolepsy with cataplexy and HLA-DQB1*0602 with pathological gambling associated with modafinil. The 39-year-old patient had no psychiatric history or medical co morbidity except narcolepsy but did have a prior history of minor gambling. When modafinil was interrupted, the gambling habits disappeared although somnolence increased (Tarrant, Cavanna & Rickards, 2010). The authors suggest that due to the potentiation of the dopaminergic system, modafinil can have as a side effect pathological gambling in individuals with a predisposition for this kind of impulse control disorder. Another case-report describes a narcoleptic patient without cataplexy who developed a psychotic episode under 500mg of modafinil. The patient's dosage was increased (settled in 400mg divided on two doses per day) because of a test to assess the capacity to drive (Wu, Jones, Ryan, Michail & Robinson, 2008). The authors mention three other similar reports of modafinil inducing psychosis.

- *Phenelzine:*

Phenelzine is a non-selective inhibitor of the monoamine oxidase (MAO) and the treatment has the potential risk of a hypertensive crisis if the patient consumes too much food containing tyromine or dopamine. This is therefore an inadequate long-term treatment.

- *Selegiline:*

Selegiline is an irreversible MAO-B selective inhibitor and is metabolized in methamphetamines, amphetamine and desmethylselegiline. The use of selegiline is restricted due to possible sympathomimetic (substances that mimic the effects of the sympathetic nervous system) side effects and interaction with other drugs (Billiard et al., 2006).

- *Gamma-hydroxyburate (GHB) also known as Sodium oxybate:*

GHB is produced naturally in the body and is the most recent medication approved for the management of narcolepsy patients. Currently, this represents an alternative treatment for hypersomnia, cataplexy and a poor night's sleep. GHB is a neurotransmitter or neuromodulator present in the central nervous system that possibly acts to silence

dopaminergic neurons (Billiard et al., 2006). GHB was discovered in 1960 and became renowned for its therapeutic value as well as for being a substance open to abuse. In 1979, Broughton and Mamelak recommended the prescription of GHB as a treatment for cataplexy (Broughton & Mamelak, 1979). During the 1980´s, GHB increased in popularity for the use in weight loss, bodybuilding and the treatment of sleeplessness. Also it was known as a substance used in sexual assaults. The adverse effects are nausea, nocturnal enuresis, confusional arousals and headache (Billiard et al., 2006). Recently, Rossetti and his team reported two cases of young male narcolepsy-cataplexy patients (18 and 25 year old) who developed depression after sodium oxybate in combination with Modafinil (Rossetti, Heinzer, Tafti & Buclin, 2010).

Both cases recovered completely after sodium oxybate discontinuation. The case is interesting as modafinil itself is known to produce nervousness (Mitler et al., 1994) and suggests that the combination of both medications might trigger depression in vulnerable subjects. The mechanism of action may be associated with the GABA-B receptors although the exact pathway remains unclear (Rossetti et al., 2010).

MEDICATION USED FOR CATAPLEXY

GHB and clomipramine (a non specific monoamine uptake inhibitor) are indicated for cataplexy. All other medications are off-label.

- *Gamma-hydroxyburate (GHB):*

GHB reduces cataplexy in a large number of patients. The cessation of GHB in the placebo group produced an increase in the number of cataplexy episodes compared to those patients who continued on treatment. As previously mentioned (see above in medication used for EDS), GHB has adverse effects but patients do not report tolerance (Billiard et al., 2006).

- *Non-specific monoamine uptake inhibitors:*

For the control of cataplexy episodes, tricyclic antidepressants like imipramine, desmethylimipramine, clomipramine and protriptylin have been used.

Clomipramine is the most evaluated treatment for cataplexy and demonstrated efficacy. The adverse effects are typical for anticholinergics which include dry mouth, sweating, weight increase, tachycardia, constipation, hypotension, impotence and difficulty urinating (Billiard et al., 2006).

- *Newer antidepressants for cataplexy:*

The newer antidepressants for cataplexy are selective serotonin reuptake inhibitors (including femoxetine, fluoxetine and fluvoxamine). The daily doses are higher than for

tricyclics and the effects are less marked. Side effects include central nervous system excitation, gastrointestinal troubles, movement disorders and sexual dysfunctions (Billiard et al., 2006). Noradrenalin uptake inhibitors (viloxazine) reduce cataplexy and have few side effects. Serotonin and noradrenalin reuptake inhibitors (venlafaxine) do not have the side effects of tricyclic antidepressants. The adverse effects are increased heart rate and blood pressure.

BEHAVIORAL TREATMENTS FOR EDS AND CATAPLEXY

It is recommended that the patient take naps according to his or her daily activities and that he or she maintain a regular sleep schedule (Billiard et al., 2006). Naps can increase alertness and decrease the use of stimulants in some patients (Bassetti, 1999).

TREATMENT OF ADDITIONAL SYMPTOMS OF NARCOLEPSY -HALLUCINATIONS, SLEEP PARALYSIS AND POOR NIGHT SLEEP-

The treatment for HH and SP is a therapy for REM-associated phenomena, therefore the recommendation is the same as for cataplexy. Nonetheless, there are few studies based on evidence. For nocturnal sleep disturbances, the use of benzodiazepines or non-benzodiazepines is recommended. Patients under treatment with modafinil report a notable improvement. Currently, the best option for night sleep disturbances is GHB (Billiard et al., 2006).

2.3. Idiopathic hypersomnia

2.3.1. History of the diagnosis of idiopathic hypersomnia

After narcolepsy was relatively well described, a diagnostic problem become visible with those patients who where excessively sleepy, although did not meet the criteria for narcolepsy.

In Prague, Bedrich Roth described for the first time a syndrome with a characteristic of excessive daytime sleepiness, prolonged sleep and sleep drunkenness but without sleep attacks, cataplexy, sleep paralysis, or hypnagogic hallucinations (Roth, 1980). Due to the typical drunkenness, Roth coined the term “hypersomnia with sleep drunkenness” or “independent sleep drunkenness” (Roth, 1980). Roth described two clinical forms of idiopathic hypersomnia called monosymptomatic and polysymptomatic. The first referred to patients with marked non-imperative daytime sleepiness with sleep attacks with a length of 30 minutes to several hours. The second included also daytime sleepiness but in co-occurrence with abnormally prolonged nocturnal sleep with rapid falling asleep and sleep drunkenness upon awakening (Roth, 1975). This condition is now known as idiopathic hypersomnia (IH) and was defined in 1979 in the first International Classification of Sleep Disorders (Table 3) (American Sleep Disorders Association, 1991).

Until now, this diagnosis is an issue of discussion. This matter was re-discussed during the revision of ICSD-2 by the task force in 2007. Currently, the diagnosis of IH is separated in two conditions: IH with long sleep time and without long sleep time. Some members of the American Academy of Sleep Medicine proposed to integrate IH without long sleep time with narcolepsy without cataplexy but this suggestion was not accepted (Billiard, 2009).

Table 3. Diagnostic criteria of idiopathic hypersomnia (IH) according to the International Classification of Sleep Disorders-first version (ICSD-1) (American Sleep Disorders Association, 1991).

	ICSD-1 diagnostic criteria of idiopathic hypersomnia
A.	A complaint of prolonged sleep episodes, excessive sleepiness or excessively deep sleep
B.	Presence of a prolonged nocturnal sleep period or frequent daily sleep episodes
C.	The onset is insidious, and typically before age 25 years
D.	The complaint is present for at least six months
E.	The onset does not occur within 18 months of head trauma
F.	Polysomnography demonstrates one or more of the following: 1. A sleep period that is normal or prolonged in duration 2. Sleep latency less than 10 min. 3. Normal REM sleep latency 4. An MSLT that demonstrates sleep latency less than 10 min. 5. Less than two sleep-onset REM periods
G.	Absence of any medical or psychiatric disorder that could account for the symptom
H.	Does not meet the diagnostic criteria of any other sleep disorder causing excessive sleepiness, e.g. narcolepsy, obstructive sleep apnea syndrome or posttraumatic hypersomnia

2.3.2. Classification: idiopathic hypersomnia with and without long sleep time

In IH with and without long sleep time, sleep drunkenness and few or not awakenings during sleep are typical characteristics. The difference between the condition with long sleep time and without is the sleep time. If it is prolonged, which means more than 10 hours, the condition is called with long sleep time but if the sleep time is not prolonged, which means more than 6 hours but less than 10 hours, then the condition is called without sleep time (Table 4).

Table 4. Diagnostic criteria of idiopathic hypersomnia (IH) according to the International Criteria of Sleep Disorders-second version (ICSD-2) (American Sleep Disorders Association, 2005).

ICSD-2 diagnostic criteria of idiopathic hypersomnia (IH).	
I. Criteria for IH with long sleep time.	
A.	The patient has a complaint of excessive sleepiness occurring almost daily for at least three months
B.	The patient has prolonged nocturnal sleep time (more than 10h) documented by interview, actigraphy or sleep logs. Waking up in the morning or at the end of naps is usually laborious
C.	Nocturnal polysomnography has excluded other causes of daytime sleepiness
D.	The polysomnogram demonstrates short sleep latency and a major sleep period that is prolonged to more than 10h in duration
E.	If an MSLT is performed following overnight polysomnography, a mean sleep latency of less than 8 min is found and fewer than two SOREMP are recorded Mean sleep latency in IH with long sleep time has been shown to be 6.2±3 min
F.	The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder
II. Criteria for IH without long sleep time	
A.	The patient has a complaint of excessive sleepiness occurring almost daily for at least three months
B.	The patient has normal nocturnal sleep (greater than 6h but less than 10h) documented by interviews, actigraphy or sleep logs
C.	Nocturnal polysomnography has excluded other causes of daytime sleepiness
D.	The polysomnogram demonstrates a major sleep period that is normal in duration (greater than 6h but less than 10h)
E.	An MSLT following overnight polysomnography demonstrates a mean sleep latency of less than 8 min and fewer than two SOREMP. Mean sleep latency in IH has been shown to be 6.2±3 min
F.	The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, and medication use or substance use disorder

2.3.3. Clinical symptoms

This sleep disorder presents the characteristics of severe excessive daytime sleepiness with not-refreshing naps of up to three or four hours, a major sleep episode prolonged to at least 10 hours typically even 12 to 14 hours with few or no awakenings. The patients have problems waking up in the morning or at the end of a nap with sleep drunkenness upon awakening (Billiard, 2009; American Academy of Sleep Medicine, 2005). Although these symptoms are features of IH and narcolepsy, they are also present in other illness such as psychiatric disorders and hypersomnia linked to other neurological disorders (Kryger et al., 2005). Some IH patients have spontaneous improvement for more than 6 months. However this cannot be predicted because the clinical and polysomnographic features are similar between individuals who improve and those who do not (Anderson, Pilsworth, Sharples, Smith & Shneerson, 2007).

EXCESSIVE DAYTIME SLEEPINESS, NAPS AND SLEEP EFFICIENCY

Unlike in narcoleptic patients, EDS in idiopathic hypersomniacs is not imperative yet permanent (American Academy of Sleep Medicine, 2005). The consequence is frequent naps that are not refreshing. Some patients report that they avoid the naps as much as possible because of the subsequent sleep drunkenness; nonetheless, this can increase automatic behaviours (Kryger et al., 2005). Although planned naps are unfavourable, authors mention that some IH patients can have short and refreshing naps (Bassetti et al., 1997). The sleep of IH patients is typically undisturbed. In comparison with narcoleptics, the sleep efficiency of IH is significantly better (Anderson et al., 2007), with fewer awakenings and reduced wake duration (Bruck & Parkes, 1996).

SLEEP DRUNKENNESS

Sleep drunkenness is a typical symptom of IH and is characterized by a difficulty to wake up. It is associated with automatic behavior, confusion and recurrent returns to sleep (Anderson et al., 2007). Patients commonly report that they do not awake with clocks (American Academy of Sleep Medicine, 2005) which render it necessary to use other creative ways to get out of bed. The sleep inertia also called the “time to get going” can be considerably long during the morning (Kryger et al., 2005).

OTHER ASSOCIATED SYMPTOMS

IH patients often have SP and HH although these symptoms are commonly described in narcoleptics (Vernet & Arnulf, 2009; Bassetti et al., 1997). Associated symptoms are headaches; orthostatic hypotension with syncope and peripheral vascular complaints

(Raynaud´s type phenomena with cold hands and feet) but normally they do not require medical care (Bassetti et al., 1997). A study shows evidence that IH, particularly with long sleep time, is associated with evening type (chronotype) and young age (Vernet et al., 2009).

2.3.4. Etiology

The etiology is unknown. In contrast to narcolepsy, the disorder is not related to certain HLA types or Hcrt levels and a precipitating factor has not been identified. Guilleminault (2001) suggests the possibility that IH is a consequence of undiagnosed encephalitis but this is difficult to investigate.

2.3.5. Pathophysiology

Little is known about the pathophysiology of IH with and without long sleep time. A Norwegian study affirmed that narcolepsy patients without cataplexy could not be distinguished of IH by biochemical findings (Heier et al., 2007). There is evidence that IH patients have normal Hcrt-1 concentrations in the cerebrospinal fluid and a decreased histaminic transmission (American Academy of Sleep Medicine, 2005). A Czech study found a lower nocturnal level of melatonin in IH compared with controls (Nevsimalova et al., 2000). The same group found a phase delay in the rhythm of melatonin and cortisol secretion in patients with polysymptomatic form of IH (Nevsimalova et al., 2009). Kanyabashi and collaborators found decreased histamine in the cerebrospinal fluid in 14 IH patients (Kanbayashi et al., 2009).

Regarding polysomnography data in IH patients, a research group hypothesized that there is a decreased slow wave sleep during the first two sleep cycles, suggesting that non restorative night sleep might be the cause of EDS (Sforza, Gaudreau, Petit & Montplaisir, 2000). However, this finding requires replication. Studies exist that have documented a consistent familial predisposition to IH with long sleep time (Billiard et al., 2001a).

2.3.6. Epidemiology

IH is a rare condition whose prevalence is unknown but is estimated to be about 10 times less than narcolepsy. There is no sex predominance (American Academy of Sleep Medicine, 2005) but one study reports a female: male ratio of 1.8:1 (Bassetti et al., 1997). The beginning of the illness is in the first two decades of life (Anderson et al., 2007; Haba-Rubio, 2005; Kryger et al., 2005; Bassetti et al., 1997; Bruck et al., 1996).

2.3.7. Diagnosis

For the diagnosis of IH, the minimal criteria are a complaint of EDS, difficulty waking up in the morning or after a nap, duration at least six months, exclusion of other conditions that can explain the cause of the symptoms and the absence of a recent (within 18 months) head trauma. For the exclusion of conditions that may cause the symptoms of IH, it is necessary to perform sleep studies such as PSG and the patient must complete sleep diaries. The manual of sleep disorders advises for the correct interpretation of PSG that the recordings should be performed when the patient is free of drugs that influence sleep for at least 15 days. Seven days before, the sleep wake schedule must be standardized and nocturnal PSG must be performed on the night immediately preceding the MSLT (American Academy of Sleep Medicine, 2005).

An alternative method to diagnose IH is a continuous 24-h polysomnography where the subject is allowed to sleep ad libitum (Latin word that means “at will”). However, this method is until now not standardized with a large number of patients and normal controls to become reliable (Bastuji & Garcia-Larrea, 1999). Another method to assess sleep drunkenness is using evoked potentials but this technique has some inconveniences due to the inter-subjects variability (Bastuji et al., 1999).

DIFFERENTIAL DIAGNOSIS

IH is not easy to diagnose clinically since a variety of other causes of hypersomnia must be excluded. For instance, mood disorders, chronic fatigue syndrome, post-viral infections, endocrine disorders and other forms of excessive daytime sleepiness which are due to perturbed nocturnal sleep (Nevsimalova et al., 2000). Patients with the disorder may need a monitoring of esophageal pressure during sleep to exclude upper airway resistance syndrome and must have a psychiatric evaluation in order to exclude another reason for daytime sleepiness such as a medical or mental disorder that could explain the symptoms (ICSD-10). The presence of multiple brief arousals occurring periodically during PSG may suggest a need for monitoring esophageal pressure (American Academy of Sleep Medicine, 2005).

Mood disorders are part of the differential diagnosis of IH. This criterion is part of a dilemma because if hypersomnia symptoms come before the beginning of mood changes, it is not diagnosed (Billiard, 2001). Because of the similarity of the symptoms in some cases IH can be confused with “atypical depression” (Haba-Rubio, 2005). Therefore, it should be checked whether the onset of EDS is associated with a depressive or hypomanic state (Roth, 1980). Sleep drunkenness is uncommonly related with narcolepsy

without cataplexy and can be a symptom also in subjects under sleep deprivation diagnosed with a phase delay syndrome (Nevsimalova et al., 2000).

2.3.8. Treatment of idiopathic hypersomnia

In keeping with the guidelines of the European Federation of Neurological Societies (EFNS), the treatment of IH is the same described for EDS in narcolepsy without cataplexy (see treatment for EDS). In IH the response to stimulants is variable and side effects such as headaches, tachycardia or irritability are reported (American Academy of Sleep Medicine, 2005).

2.4. Depression

2.4.1. Historical aspects of depression

Depression or melancholia is a clinical syndrome that has been recognized for over 2000 years, yet there are still major unresolved issues related to its nature, classification and etiology. The term melancholia, at the beginning used synonymously with depression, comes from the Greek words meaning “black bile” (Beck, 1967). Hippocrates gave the first clinical description of melancholia in the fourth century B.C. (Beck, 1967). According to Hippocrates, the black bile was secreted by the spleen and was responsible for darkening the mood. He hypothesized that this was the cause of melancholia. Hippocrates describes melancholia as “food aversion, desperation, insomnia, irritability and worry, accompanied by a characteristic sad mood”. Afterwards, Hippocratic text associated melancholia with fear (Sadek & Nemeroff, 2000).

Robert Burton, who wrote “Anatomy and melancholia” in 1621 suggested that melancholic persons are born from melancholic parents and identified some environmental factors in the development of depression (Sadek et al., 2000).The Danish neurologist Carl Lange in 1886 was one of the earliest to establish the term depression to psychological medicine (Benca et al., 1997).

2.4.2. Classification and different names for depression

The classification of depression has been in constant change along the years and these changes are associated with the assumed causes and response to different treatments. Between 1905 and 1915, the German psychiatrist Emil Kraepelin created a new nosological system to organize psychiatric disorders and defined the expressions dementia praecox and involutional melancholia (Wong & Licinio, 2001). During the history of depression, there has been a huge change in the classification, moving from a descriptive strategy based on Kraepelin´s ideas and the American Psychiatric Association to more interpretative strategies such as Freud´s theories (Wong et al., 2001).

Some classifications were endogenous versus reactive, melancholic versus non-melancholic, psychotic versus neurotic and major versus minor depression (Cobo-Gómez, 2005). Martin Roth and colleagues developed the distinction in endogenous and exogenous or reactive depressions (Wong et al., 2001). Endogenous occurred in the absence of environmental factors and exogenous or reactive depression is seen as the response to external stressors. However, depression often appears with biological and environmental variables (Benca et al., 1997). The division of endogenous and reactive

depression had the primary focus on the treatment. Another classification is primary and secondary depression. The term primary is used when it does not appear after another psychiatric illness, while secondary is used when it occurs following or during another psychiatric illness (Cobo-Gómez, 2005).

CONCEPT OF ENDOGENOMORPHIC DEPRESSION

In 1974, Donald Klein, an American psychiatrist who introduced a difference between neurotic and endogenophormic depression proposed a model mixing categorical and dimensional constructs (Klein, 1974). This concept, which refers to the “doctrine of the two depressions”, distinguishes between the melancholic depression and non-melancholic depression (Shorter, 2007). Neurotic depression has the features low self-esteem, feelings of helplessness, irritability, anger, unhappiness and histrionic attitude. The concept of endogenomorphic depression which can or cannot be precipitated results “in a sharp, un-reactive pervasive impairment of the capacity to experience pleasure or to respond with affect to the anticipation of pleasure …” (Klein, 1974). Indeed, this refers to anhedonia or the loss of pleasure which seems to be a central feature of major depression (Stein, 2008).

DEFINITION OF DEPRESSION WITH MELANCHOLIC AND WITH ATYPICAL FEATURES

The category referred to as melancholic features was proposed to describe patients with loss of the ability to feel pleasure in almost all activities (anhedonia) and the lack of reactivity to stimuli that were a source of satisfaction for the person (mood non-reactivity). Furthermore, the patient should have at least one of the following symptoms: depression is worst during the morning, waking up early in the morning at least 2 hours earlier every day, psychomotor retardation or agitation, significant anorexia or loss of weight, excessive guilt or feelings of inadequacy. In contrast, the atypical features of depression are mood reactivity in response to real and/or positive situations. Additionally, major depression or dysthymia must be present, as well as two of the following four associated symptoms: significant increase of weight or appetite, hypersomnia, leaden paralysis (feeling of arms or legs heavy or inert), long term pattern of sensitivity to interpersonal rejection that has a significant negative effect in the social or work relations. The sensitivity to be rejected appears with an early onset and continues throughout life. In patients with atypical depression, the presence of personality disorders such as avoidant personality disorder and anxiety disorders such as social phobia is more frequent (American Psychiatric Association, 2000).

THE CONCEPT OF DEPRESSION ACCORDING TO AARON BECK

Beck argues that depression can be understood as a paradox. The paradox is because of the huge contrast between the self-image of the person with depression and the objective facts (Beck, 1967). This means that in spite of the patient's idea, there is no objective evidence or as Beck wrote: "no logical demonstration of the irrationality of these ideas" (Beck, 1967 p.24). It makes sense that Beck, having obtained solid training in psychoanalysis before his fundamental contributions to cognitive therapy, suggests that depression is contradictory with one of the concepts from psychoanalysis, the so called pleasure principle which states that people seek satisfaction and minimal pain (Beck, 1967).

According to this US-American psychiatrist, depression may be defined by some attributes such as an alteration of mood characterized by sadness, loneliness and apathy, and a negative self-concept associated with self-reproach and self-blame. Other aspects are regressive and self-punitive wishes together with vegetative changes and modification in activity level. In the development of depression, one central aspect is the negative self-concept or low self-esteem. Following Beck, this is "the tendency to extract personally relevant meanings from unpleasant situations … of depression-prone individuals" (Beck, 1974, p.9). The cause of an adverse situation can have different possible explanations but the depressed patient will opt for those that are due to a defect in him or herself.

Another aspect is self-reproaches and self-criticism. As previously mentioned, Beck explains this characteristics of depression using some concepts from psychoanalysis. Freud proposed that the depressed patient has hostility toward the "loved object" but he did not allow himself to feel this hostility and therefore turned this anger upon himself. The goal of this self-blame is self-rejection similar as he would do were he rejecting another person. The patient reacts feeling hurt, sad and humiliated (Beck, 1974). In depression, the person has lost the capacity to respond with mirth to happy situations replacing them with apathy or sadness, also in anger to situations that normally would exasperate this person.

The phenomena of depression can be recognized in exploring the theme of loss, where the person has cognitive distortions regarding evaluations of his world, himself and his future. The depressed patient will exaggerate or misinterpret the loss or will give an extravagant meaning to the loss. Beck mentions in his cognitive model "certainly when the loss of appetite or sleep occurs as the result of a debilitating physical illness it does not produce the other symptoms of depression" (Beck, 1974, p.5). This suggests that for Beck, the depressive symptoms in patients with a physical illness are not necessarily the source

of core symptoms of depression. The concept of depression for Beck is more related to a melancholic depression. The vegetative symptoms of interest in this study related with hypersomnia are focused on the tendency to morning awakenings, loss of appetite and weight loss.

THE CONCEPT OF DEPRESSION ACCORDING TO WILLIAM ZUNG

Zung was interested in depression as an emotional disorder. He focused on the questions of how it is possible to diagnose depression, how it is possible to assess the changes in the severity of depression when patients are being treated, whether some physiological changes are features of depression and if it is possible to associate some brain structure with the behavioral dysfunctions of depression (Zung, 1978). In the seventies, Zung recruited patients with depression and found diverse opinions about what a depressive disorder is. He decided to reduce the large list of symptoms into four basic categories that he denominates "(1) psychic-affective, (2) physiological (3) psychomotor (4) psychological". In each category he included symptoms that would be possible to associate with brain structure.

Zung proposed the following formula to investigate psychopathology: $I=i_1 +i_2 +\ldots+in +x +r$.

"I" represents the Indicator of psychopathology; the investigator can use signs and symptoms as indicators of change in quality and quantity. The ies correspond to the methods of measurements performed. The numbers down (sub index) of the "i´s" correspond to the number of techniques used; this can be subjective, semi objectives and objectives. X corresponds with the experimental noises, which according to the author represent all that cannot always be controlled such as the intelligence of the subject, the affect or emotional situation of the person at the moment of the test, the motivation, the adaptation or the amount of learning, habituation or satiation, the introspection which is the cognitive elaboration of the subject. Zung mentions that motivation and affect are also under the influence of the pre-morbid personality, cultural background and experimental environment. The r symbolizes the residues which are all the unmeasured psychopathology which remains unaccounted for (Zung, 1973). In developing his questionnaire, the author included the most common characteristics of depression with the purpose of minimizing the symptoms related with somatic anxiety and in an effort to maintain depression and anxiety as two different units. He operationalized depression with four criteria: (1) Pervasive affective disturbance, (2) Physiological disturbances: diurnal variation was conceptualized as an exaggeration of the symptoms in the morning with relief at the end of the day, sleep with early and frequent waking. In the item sleep, the

author states that the problems of falling asleep are more typically present in anxiety and early awakening and is more representative of patients with depression, (3) Psychomotor disturbances and (4) Psychological disturbances: confusion, emptiness, hopelessness, indecisiveness, irritability, dissatisfaction, personal devaluation and suicidal rumination (Zung, 1973).

ASSESSING DEPRESSIVE SYMPTOMS: ZUNG SELF-RATING DEPRESSION SCALE (SDS) AND BECK DEPRESSION INVENTORY (BDI)

Both authors developed a scale to assess depressive symptoms based in their concept of depression. Zung's concept of depression is a melancholic type of depression and is slightly more focused on aspects related with the vegetative dimension of depression than Beck. There are some differences in the content of questions between SDS and BDI, although, according to Hautzinger (1995), both tests show a high correlation of rho= .72 (Spearman´s rank correlation coefficient). The number of questions is almost the same; only BDI has one more question. The differences in the questions' content are slight, and when comparing both tests, SDS has five questions that are not equally asked in BDI, such as diurnal variation, tachycardia, confusion, psychomotor agitation and emptiness. BDI also has five questions that are not present in the SDS, all of which are related with the cognitive dimension of depression like failure, guilt, punishment, self-blame and feeling ugly.

2.4.3. Diagnosis of depression according to DSM-IV and ICD-10

The International Statistical Classification of Diseases and Related Health Problems (ICD-10) published by the World Health organization and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV- TR) published by the American Psychiatric Association are manuals for mental disorders during adulthood, childhood and adolescence (Schulte-Markwort M., 2003). Both are official classification and coding systems in most of the countries with systematic records of psychiatric diagnoses.

Table 5. Diagnostic criteria of Major Depressive Disorder (MDD) according to the International Statistical Classification of Diseases and Related Health Problems [ICD-10] (World Health Organization, 1992).

ICD-10 criteria of major depressive episode	
Marked tiredness after only slight effort is common. Individuals usually suffer from depressed mood, loss of interest, enjoyment and reduced energy leading to increased fatigability and diminished activity. Other symptoms are:	
A.	Reduced concentration and attention.
B.	Reduced self-esteem and self-confidence.
C.	Ideas of guilt and unworthiness (even in mild type episode).
D.	Bleak and pessimistic views of the future.
E.	Ideas or acts of self-harm or suicide.
F.	Disturbed sleep.
G.	Diminished appetite.

DSM-IV is widely used in North and South America. DSM-IV is more a rule description while ICD-10 -the European system- is more like a guideline description. The DSM-IV system generally follows more psychopathologic principles while the chapters of ICD-10 are structured pathogenetically (Schulte-Markwort M., 2003).

Table 6. Diagnostic criteria of Major Depressive Disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV- TR) (American Psychiatric Association, 2000)

DSM-IV criteria of major depressive episode	
A.	Five or more of the following symptoms are present during the same two week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or lost of interest or pleasure
1.	Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
2.	Markedly diminished interest or pleasure in all or almost all activities most of the day nearly every day (as indicated for either subjective account or observation made by others)
3.	Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day
4.	Insomnia or hypersomnia nearly every day
5.	Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6.	Fatigue or loss of energy nearly every day
7.	Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self reproach or guilt about being sick)
8.	Diminished ability to think or concentrate, or indecisiveness, nearly every day
9.	Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B.	The symptoms do not meet criteria for a mixed episode (maniac and depressive)
C.	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
D.	The symptoms are not due to the direct physiological effects of substance or a general medical condition (e.g. hypothyroidism)
E.	The symptoms are not better accounted for by bereavement, that is, after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms or psychomotor retardation

The presence of symptoms of depression does not automatically indicate that a person would be diagnosed as being clinically depressed. There are different criteria organized to assure an accurate diagnosis. For depressive episodes of all three grades of severity (mild, moderate and severe) a duration of at least 2 weeks is required for the diagnosis but the ICD-10 suggests that shorter periods may also be reasonable if symptoms are "unusually severe and of rapid onset" (World Health Organization, 1992).

One of the cardinal symptoms of depression is sleep disturbance. In some cases where depression is accompanied by hypersomnia rather than insomnia, such patients report increased duration of nocturnal sleep, often with problems in waking up and increased napping. This hypersomnia tends to occur in bipolar patients during major depressive disorder (Benca, Obermeyer, Thisted & Gillin, 1992). In patients with hypersomnia who have somatic symptoms of depression the diagnosis may be difficult. Some symptoms in narcolepsy patients and in patients with depression can be indistinguishable. In particular, these are reduced energy leading to increased fatigability and diminished activity, reduced concentration and attention due the excessive daytime sleepiness and fragmented night sleep.

2.4.4. Severity of depression according to DSM-IV and ICD-10

The clinical presentation of the symptoms may vary from person to person. The two manual systems described above (ICD-10 and DSM-IV), have different criteria to classify whether the severity or degree of depression is mild, moderate or severe (Table 7).

Table 7. Depression severity criteria according to DSM-IV and ICD-10.

Depression Severity	DSM-IV criteria	ICD-10 criteria
Mild	1. Depressed mood or loss of interest/pleasure + four other depressive symptoms. 2. Minor social/occupation impairment.	1. Two typical symptoms. 2. Two other core symptoms.
Moderate	1. Depressed mood or loss of interest/pleasure + four or more other depressive symptoms. 2. Variable social /occupational impairment.	1. Two typical symptoms. 2. Three or more other core symptoms.
Severe	1. Depressed mood or loss of interest/ pleasure + four or more depressive symptoms. 2. Major social /occupational impairment-or with psychotic features.	1. Three typical symptoms 2. Four or more other core symptoms. Also sub typed as with or without psychotic symptoms.
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2.4.5. Core symptoms of depression

ANHEDONIA

Anhedonia is a core symptom of depression. Ribot defined anhedonia in 1897 as the loss of the capacity to experience pleasure (Loas, 1996). In the beginning of the last century, Myerson (1922) suggested a state permanent of anhedonia together with low energy, pessimism and introspection. Afterwards he used the expressions of “constitutional anhedonia” and “anhedonic constitutional personality”. With the term constitutional, the author means not only hereditary but also environmental factors. Genetic studies confirm this hypothesis. For example, Kendler found that in 29 pairs of twins the correlation for anhedonia was higher in the monozygotic twin pairs (r=.94) than in the dizygotic twins (r=-.18). The personality is characterized by low sensation seeking, avoiding emotional involvement and sometimes huge interest in work activities. ICD-10 and DSM-IV support the notion that anhedonia is a symptom of pre-schizophrenia personality and is a recognized negative symptom of this psychopathology.

PSYCHOLOGICAL VARIABLES ASSOCIATED WITH ANHEDONIA

Loas (1996) described the association between anhedonia and psychological variables, such as displeasure capacity, introversion, autonomy, dysfunctional attitudes and sensation seeking (Loas, 1996). Displeasure capacity refers to the inhibitory role of anhedonia in negative emotions such as anger, sadness, irritation or fear. Introversion shows a positive correlation with anhedonia in healthy subjects. Autonomy is related to attitudes and aims, giving a high value to independence and freedom to the detriment of close interpersonal relationships. This is, according to the cognitive therapy of Beck, a vulnerability factor for depression. When an autonomous person confronts a problem, which is perceived as a loss of control, he or she will tend to protect him or herself by withdrawing from the environment. The characteristic of autonomous subjects becoming depressed is similar to the concept of endogenomorphic depression, defined for the first time by Klein. For this author anhedonia is the central symptom of depression (Klein, 1974).

Dysfunctional attitudes are, according to Beck´s cognitive theory, a substrate of depression. Beck in a life interview says that his idea about dysfunctional attitudes began during a clinical interview with a patient. Dr. Beck asked him, just as an intuitive idea, what he was thinking about his conflict right at that moment of their dialogue. The patient told him that he constantly thought he was boring, tedious and unintelligent. Beck asked him if

this was only during that interview but the patient revealed that it happened when talking with other persons as well (video life interview to Aaron Beck in DGPPN, Berlin, 2009)

From this and other patients, Beck and Weismann derived a questionnaire called Dysfunctional Attitudes Scale (DAS) which attempts to predict subsequent depressive episodes. The Physical and Anhedonia Scales (PAS) correlates with DAS. The last variable is sensation seeking, which is related with the necessity to maintain high levels of cortical activation or arousal (Loas, 1996). Once again, the sensation seeking scale shows a correlation with PAS.

SLEEP DISTURBANCES

Poor sleep is a fundamental aspect of depression; sleep-disturbances in depression include insomnia, the more common form and hypersomnia (Jindal & Thase, 2004). Kraepelin mentioned the association of depression with hypersomnia for the first time in 1904 (Roth et al., 1975). A strong correlation exists between excessive daytime sleepiness and depression consistent with larger epidemiological studies. An epidemiological study with 1007 adults aged 26 to 35 years showed a significant connection between severity of excessive sleepiness and MDD. The authors report an association of daytime sleepiness with employment, marital status, snoring and MDD remaining when hours of sleep and other determinants of daytime sleepiness were held constant (Breslau, Roth, Rosenthal & Andreski, 1996). Nevertheless, in a previous study the same authors did not find support for an association between hypersomnia and major depression, meaning that hypersomnia is not a cause for developing a depression, although it could be associated (Benca et al., 1992).

Frequently, patients with major depression-unipolar complain about insomnia, but hypersomnia symptoms are reported mostly by patients with bipolar and seasonal affective disorder (Benca et al., 1992). Sleepiness implies an increased vulnerability to fall asleep but the complaint about sleepiness is frequently used to describe physical tiredness for example in depression (Hublin, Kaprio, Partinen, Heikkila & Koskenvuo, 1996). A study performed in Idaho, USA, using the ESS to evaluate the symptoms of excessive sleepiness in major depressive disorder (MDD), found that approximately half of the patients with MDD also experience excessive sleepiness (Lundt, 2005). Sleep disturbances are an important component of depression, but on the other hand, depression is not an obligatory component in hypersomnia patients, although some studies demonstrate a high prevalence of depressive symptoms in hypersomnia patients (Dauvilliers et al., 2009).

SLEEP DISTURBANCE AS A PREDICTOR OF RECURRENT DEPRESSION

Disturbed nocturnal sleep is a characteristic symptom of depression. After an effective treatment, most of the symptoms will disappear while REM sleep abnormalities are maintained. The persistence of sleep disturbance after the recovery of the other symptoms can be a predictor of recurrence of depression (Modell & Lauer, 2007). Reduced REM latency is a biological marker of major depression and correlates inversely with the severity of symptoms (Kupfer & Foster, 1972) although during normal aging, REM sleep begins to shorten, this process is pronounced in patients with depression (Modell et al., 2007).

DEPRESSION AS CAUSE OR AS CONSEQUENCE

Some authors question whether depression is a cause for sleep disorders or if depression is the origin of sleeps abnormalities. Many people with depression fail to display short REM sleep latency, reduced slow wave sleep (SWS) or sleep disruption (Kryger et al., 2005). Studies in psychiatric disorders such as schizophrenia, mood disorders, anxiety disorders, borderline personality disorder, eating disorders and alcoholism, reported a short or reduced REM latency. The same has been reported in patients after the end of treatment with REM sleep suppressing drugs such as benzodiazepines and antidepressants or during alcohol withdrawal (Nishino, Taheri, Black, Nofzinger & Mignot, 2004). In a study within the Finnish population, approximately 25% of patients with excessive daytime sleepiness had BDI scores suggesting a state of moderate to severe depression (Hublin et al., 1996).

In the sleep centers, the differential diagnosis of depression is frequent. A Dutch study regarding the prevalence of depressive feelings in patients diagnosed in a center for sleep and wake disorders found that depression symptoms occurred in more than half of patients with psychophysiological insomnia, inadequate sleep and wake hygiene, sleep state misperception and periodic limb movement disorder, or restless legs syndrome (Vandeputte et al., 2003). However, they report that moderate to severe depression was found only in 3.5% of the patients using BDI. This study suggests that mood disorders are common in patients with sleep disorders and the authors recommend performing a depression scale in the daily routine of diagnosing and treating sleep disorders (Vandeputte et al., 2003). Consistent with this study, another author, also based on self rating questionnaires, reported that 67% of patients from a sleep centre reported an episode of depression within the previous 5 years and 26% described themselves as depressed at presentation (Mosko et al., 1989).

2.4.6. Problems in the diagnostic of depression related to hypersomnia

DSM-IV-TR and ICD-10 take into account self reported sleep disturbances, instead of using an objective parameter. In contrast, the International Classification of Sleep Disorders [ICSD-2] (American Academy of Sleep Medicine, 2005) recommends a PSG to probe the reduced sleep efficiency and the increased numbers of arousals during the night. ICSD-2 is the only manual that includes the discussion about time in bed but none of these three classification systems include the amount of hours of sleep in the context of a depression (Kaplan et al., 2009).

Table 8. Criteria for hypersomnia related to another mental disorder according to DSM-IV-TR.

A.	The predominant complaint is excessive sleepiness for at least 1 month as evidenced by either prolonged sleep episodes or daytime sleep episodes that occur almost daily.
B.	The excessive sleepiness causes clinically significant distress or impairment in social, occupational or other important areas of functioning.
C.	The hypersomnia is judged to be related to another Axis I or II disorder (MDD, dysthimic disorder) but is sufficiently severe to warrant independent clinical attention.
D.	The disturbance is not better accounted by another sleep disorder (narcolepsy, breathing- related sleep disorder, parasomnia) or by an inadequate amount of sleep.
E.	The disturbance is not due to the direct physiological effects of a substance (drug of abuse, medication) or a general medical condition.

The criterion C for non-organic hypersomnia in the ICD-10 is noteworthy because around 30% of the normal population present hypnagogic hallucinations or sleep paralysis in the absence of excessive daytime sleepiness (Table 8).

Table 9. Criteria for non-organic hypersomnia according to ICD-10

A.	EDS or sleep attacks, not accounted for by an inadequate amount of sleep, and/or prolonged transition to the fully aroused state upon awakening (sleep drunkenness).
B.	Sleep disturbance occurring daily for more than one month or for recurrent periods of shorter duration, causing either marked distress or interference with social or occupational functioning.
C.	Absence of auxiliary symptoms of narcolepsy (cataplexy, sleep paralysis, hypnagogic hallucinations) or of clinical evidence for sleep apnea (nocturnal breath cessation, typical intermittent snoring sounds)
D.	Absence of any neurological or medical condition of which daytime somnolence may be symptomatic.

In the proposed DSM-V (2010), which is still in revision, hypersomnia included the category of narcolepsy without cataplexy, while narcolepsy with cataplexy is referred to as Hcrt deficiency. Both hypersomnia/narcolepsy without cataplexy and narcolepsy with cataplexy/Hcrt deficiency have the criteria C: “do not occur exclusively during the course of another mental or medical disorder but may occur simultaneously with these disorders”. This new proposal, not yet official but programmed for 2013, would broaden the diagnosis of hypersomnia in patients with depression and will probably revive the dilemma of those patients with IH and depression.

2.4.7. Epidemiology

Depression is a common but a serious condition. Around 13% of the population will experience an episode of MDD during their lifetimes (Table 10). Depression is the leading cause of disability in developed countries and the fourth leading cause of disability worldwide (Lam & Mok, 2008).

Table 10. Prevalence of major depressive disorder in studies performed in the general population of several countries according to the criteria from DSM-IV and ICD-10.

Location (study)	Criteria	Current/1 month	12 month	Lifetime
Prevalence rates (%)				
Europe (ESEMeD)	DSM-IV	-	3.9	12.8
Germany	DSM-IV	5.6	10.7	17.1
Netherlands (NEMESIS)	DSM-III-R	2.7	5.8	15.4
UK(NSPM)	ICD-10	2.1		
Canada	DSM-IV	-	7.4	-
USA (NCS-R)	DSM-IV		6.6	16.2
USA (NCS)	DSM-III-R	4.9		17.1
Australia	DSM-IV	3.2	-	-
Australia	ICD-10	3.3	-	-
Japan	DSM-III-R	-	1.2	2.9

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DEPRESSION BY SEX AND AGE

- *Sex:*

Women are more depressed than men, the lifetime prevalence of depression is 1.6 to 3.1 higher in women than in men (Lam & Mok, 2008). The prevalence of MDD ranges from 2.6% to 5.5% for men and between 6% and 11.8% for women. The difference in the prevalence of depressive symptoms is much higher than MDD, with rates from 10% to 19% in men and 18% to 34% in women (Loue & Sajatovic, 2008). In the global burden of disease study (Murray & Lopez, 1998), depression is the leading cause of disability among all diseases in women "and accounted for 41.9% of their [women] disability burden from neurological and psychiatric disorders as compared to 29.3% among men" (Blehar, 2006).

There are many interpretations for these differences between men and women, one being that men experience similar depressive symptoms but attempt to cope with them in a different way such as substance abuse and antisocial behavior, which is more prevalent in men than in women (Loue et al., 2008).

The theories on stressful life events explain the difference as being caused by the tendency women have of taking care of and being concerned for others, which increases

the exposure to adverse life events and as a result leads to depression. Another theory is associated with rumination. Ruminative thinking maintains a negative emotion and is more frequent in females than in men (Blehar, 2006).

- *Age:*

Sex differences already begin during adolescence and aggravate at the onset of menstruation, diminishing after menopause (Lam et al., 2008). In German adolescents screened in Munich and Bremen, the male: female ratio of depression is 1:7 (Kuehner, 2003). Nowadays, depression is the second cause of disability in the age category 15-44 years. By the year 2020 depression will be the second cause of disability for all ages and both sexes (American Psychiatric Association, 2000). The mean age for the depression onset is 26 years old. An earlier age for the onset of depression is associated with higher levels of medical co-morbidity, greater depressive symptom severity and a more negative view of life and self, among other characteristics (Zisook et al., 2007). Depressive symptoms differ with age. In childhood there tends to be more somatic complaints combined with irritability and withdrawal, while during adolescence, symptoms appear more atypical, such as hypersomnia and overeating. In the elderly, melancholic features as anhedonia or a lack of reactivity are more present (Lam et al., 2008).

2.4.8. Theories about depression related to sleep abnormalities

The precise pathogenesis of depression is still unknown but there are multiple processes that can explain it, biological, psychological and social factors are involved (Lam et al., 2008). Here the principal theories about depression related with sleep disturbances will be described.

TWO PROCESS MODEL OF SLEEP REGULATION: DEFICIENCY OF PROCESS S

Borbely proposed a model of sleep regulation integrating two processes: the process S and the process C (Borbely, 1982). The first one is sleep dependent and describes a physiological correlate of increase and decrease of sleep necessity. The second is independent of sleep and is controlled by a circadian oscillator. According to this model, the combined action of both processes determines the need and duration of sleep. The author exposes that the increase of process S during wakefulness is deficient in depression (Borbely, 1982). This means that depressive patients accumulate process S slowly. The classical problems of patients with depression in initiating and maintaining sleep are an attribute of low need of sleep, which is a consequence of a low level of process S.

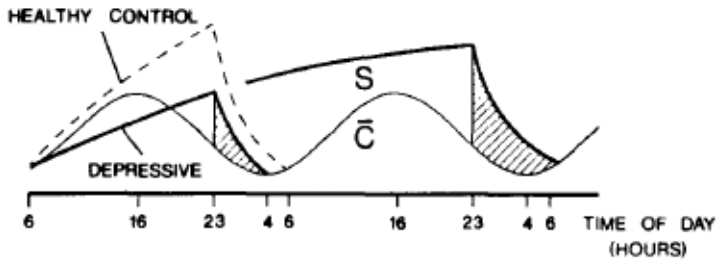

Figure 3. Two process model of sleep in depression. The interrupted curve represents process S and C in a healthy control, and the continuous curve represents it in a depressive patient. In the left part, a regular sleep waking cycle is represented and in the right part the situation under sleep deprivation is shown. The shading corresponds to the sleep periods of a depressive patient (Borbely, 1987, p.23).

The hypothesis of Borbely consists of two parts:

A. The deficiency in process S can explain the sleep disturbances in depression: the sleep in depressives is characterized by a prolongation of sleep latency, more night awakenings and the premature end of sleep (Figure 3). The diminished process S will determine a superficial and short sleep. Typical changes are the reduction of slow wave sleep and alterations in the REM sleep patterns. Process S is by definition measured from the EEG activity of SWS in NREM sleep. It has been suggested that the increase in REM activity is also due to the inhibition of process S. Typical features of sleep in patients with depression are the short REM latency and a longer first REM period.

B. A causal relation between the level of S and depressive symptoms is postulated to account for the antidepressant action of sleep deprivation: sleep deprivation decreases depressive symptoms because the low level of process S is normalized with the prolongation of wakefulness. Nevertheless, this effect has a short duration because the level of S is again reduced by the next sleep period (Borbely, 1987).

CHOLINERGIC- AMINERGIC IMBALANCE

Janowsky and his collaborators originally proposed the hypothesis of cholinergic-aminergic imbalance in depression in 1972 (Janowsky, el Yousef, Davis & Sekerke, 1972). REM sleep has been suggested to be promoted by cholinergic activation and inhibited by aminergic activation. The imbalance could also be responsible for reductions in total sleep time and in sleep efficiency (Benca, 2000). This theory suggests an imbalance of the

neurotransmitters acetylcholine, serotonin and norepinephrine. Janowsky and collaborators proposed that the aetiology of mood disorders is influenced by cholinergic and adrenergic factors. These authors thought that depression is a disease of central cholinergic predominance and mania a disease of central adrenergic (or serotonergic) predominance (Janowsky et al., 1972). This theory of a high cholinergic and low monoaminergic neurotransmission has been supported by several experiments (Adrien, 2002). According to this hypothesis, depressive patients are sensitive to the cholinergic muscarinic agonists that provoke REM (Nishino et al., 2004). One critical point of this theory is that it does not explain the antidepressant effect of sleep deprivation.

INCREASED REM SLEEP PRESSURE

Patients with depression have sleep abnormalities already at the beginning of the disease. Vogel has postulated that depression may be caused by excessive amounts of REM sleep and a decrease in REM sleep pressure (Vogel, 1999). In line with this theory, sleep deprivation and especially REM sleep deprivation have antidepressant effects (Borbely & Wirz-Justice, 1982). The finding that antidepressants suppress REM sleep for long periods supports this hypothesis. According to Vogel, two lines of evidence disclose the relationship between REM sleep and depression (Vogel, 1999):

A. Depression has sets of REM sleep abnormalities: the studies suggest that REM sleep is disinhibited during depression.

B. Sleep deprivation: REM sleep deprivation has the effect of improved depressive symptoms. Some antidepressant drugs improve depression by arousal type deprivation of REM sleep.

Evidence for this theory is the known REM rebound following the interruption of REM sleep deprivation or tricyclic antidepressants, although some antidepressants do not reduce REM sleep. This suggests that REM suppression is not always a necessary effect (Nishino et al., 2004).

CIRCADIAN PHASE ADVANCE

This theory suggests that in depressed patients, the circadian oscillator controlling REM sleep and temperature are phase advanced. Wehr and cols. in 1979 tested the hypothesis of a phase advance of the circadian sleep-wake cycle, revealing that an advancement of the sleep-wake schedule of 6 hours in maniac depressed patients causes a remission of the symptoms (Wehr, Wirz-Justice, Goodwin, Duncan & Gillin, 1979). In the polysomnography analysis, they were able to show that after this phase advance, several indices approach normal values. In addition, this study shows that the antidepressant

effect of the phase advance is transitory and the authors make an analogy with the circadian desynchronization triggered by jet lag in normal subjects (Wehr et al., 1979).

HYPOTHALAMIC-PITUITARY- ADRENAL (HPA) AXIS DYSREGULATION

There is evidence showing that the relationship between sleep and the HPA axis is bidirectional. This means that HPA hormones influence sleep and that alterations on sleep affect the discharge of these hormones (Steiger, 2002). During the sleep period, low and higher levels of secretion of adrenocorticotropin (ACTH) and cortisol will occur. Corticotropin releasing hormone (CRH) impairs sleep, augments vigilance and promotes REM sleep. A REM period, especially during the first four sleep cycles, is associated with a decrease in cortisol levels. Furthermore, ACTH and cortisol were higher in a group of normal subjects with short sleep in comparison with those with long sleep.

Cortisol secretion is sex dependent; women have a higher secretion of cortisol compared to men. In addition, there is a positive correlation between age and cortisol levels in female patients with depression. In depression there are well-described endocrine changes revealing elevated cortisol and ACTH although the circadian pattern is preserved (Steiger, 2002). Some studies show a causal connection between superficial sleep, low growth hormone (GH) and HPA hyperactivity in depression, supporting that HPA is a state marker of depression in adults (Steiger, 2002). After recovery of depression, the changes in sleep such as superficial sleep and REM sleep disinhibition will persist together with blunted GH secretion.

2.5. Hypersomnia and depression

2.5.1. Similarities

DAYTIME SLEEPINESS

Patients with depression and hypersomnia have the main complaint of being “tired” but sleepiness and fatigue are distinct phenomena (Shen, Barbera & Shapiro, 2006). The measurements of fatigue are mainly subjective and the measurements of sleepiness are subjective and objective. In hypersomnia, the patient has a complaint of excessive daytime sleepiness, which is conceptually different to the fatigue experienced by a patient with depression. Therefore, the concept fatigue is not included in the diagnostic criteria of hypersomnia although the expression could be used by the patient to explain his or her daytime sleepiness. Fatigue is the consequence of prolonged physical activity. In contrast, sleepiness does not necessarily imply a previous physical activity and can decrease after a sleep period (Cluydts, De Valck, Verstraeten & Theys, 2002).

SHORT REM SLEEP LATENCY

Changes in the sleep pattern are associated with depression in a classic study involving sleep onset rapid eye movement (SOREM) in patients with depression (Kupfer et al., 1972). Owing to the short REM latency reported in narcolepsy, researchers grounded the idea that depression might be endogenous to narcolepsy (Roth et al., 1975). Although, narcolepsy patients with short REM sleep latency and with all the symptoms of the illness are not invariably depressed (Kryger et al., 2005), this hypothesis was supported by other common features such as nocturnal sleep disruption and increased REM density (Serra, Montagna, Mignot, Lugaresi & Plazzi, 2008; Aldrich, 1992; Broughton et al., 1981).

The comparison of narcolepsy and depression has been done in the structure of sleep due to the apparent similarities in REM. An American study compared nocturnal sleep in patients with narcolepsy and depression (Reynolds, III, Christiansen, Taska, Coble & Kupfer, 1983). The authors found that 60% of the sample did not meet the criteria for any present or past psychiatric disorder and narcoleptics reported less frequently a history of depression compared to depressive patients. Polysomnography revealed that Non-REM (NREM) sleep differences and sleep continuity measures are the most authentic differences between narcoleptic and depressive patients regardless of age or SOREM positivity. This suggests that sleep in depression is different from sleep in narcolepsy (Reynolds, III et al., 1983). The researchers leave open the possibility that depression is inherent to narcolepsy but the results plainly support the idea that depression might be a

reaction to the imperative sleepiness. Another study, performed in Germany, addressed the same issue but with the hypothesis that narcolepsy and depression share a common mechanism of REM sleep disinhibition at sleep onset (Pollmaecher, Mullington & Lauer, 1997). The researchers concluded that narcolepsy and depression do not have a common pathophysiology of REM sleep disinhibition and showed that REM sleep disinhibition is not caused by depressive symptoms. Unfortunately, the authors of the study excluded narcolepsy patients with past or current major depressive disorder.

The American and the German researchers found that narcoleptic patients exhibit shorter sleep onset latency, longer sleep period and total sleep times, as well as higher amounts of stage 1 and awakenings than depressives. However, the German study differed with the American one in the higher REM density and the shorter mean REM latency described in narcoleptics (Pollmaecher et al., 1997; Reynolds, III et al., 1983). The differences are probably due to the selection criteria regarding the inclusion of only narcoleptics with cataplexy in the German study.

COGNITIVE DEFICIT

The psychomotor retardation and decreased concentration can be very similar in hypersomnia patients and in those with depression. The cause for the cognitive deficit in hypersomnia patients is mostly attributable to the instability of vigilance, which is normalized when better controlled by medication (Aguirre et al., 1985). Cerebral imaging studies in depressives show a dysfunction in the dorsolateral prefrontal cortex, the amygdala and hippocampus (Jouvent, 2008). Fossati hypothesized that cognitive deficits in MDD can be explained by an increasing effort to maintain a high performance level prior to the presentation of a demanding task (Fossati, 2008).

WEIGHT INCREASE

An increased body mass index is frequent in patients with hypersomnia and at least in narcolepsy patients it is independent of gender and medication, which suggests a disturbance in food intake, metabolism, or in both (Schuld et al., 2000). Yet some studies have found differences in the body mass index within the spectrum of hypersomnia (Dauvilliers et al., 2009; Martinez-Rodriguez, Iranzo, Casamitjana, Graus & Santamaria, 2007). There has been a disagreement in the literature as to whether there is a connection between obesity and mood disorders. In patients with depression, obesity is specifically associated with females and in depression with atypical symptoms, abdominal obesity is associated with depression in females and males. However, in the opposite scenario, most overweight and obese persons do not have mood disorders (McElroy et al., 2004). Another

study showed that obesity measurements were associated with depressive symptoms and found that women were maybe more influenced by body size than their current amount of body fat, while for men, depressive symptoms were relatively unrelated to diverse measures of obesity. Nevertheless, it is of high interest that in sleep disorders, the percent of fat was more associated with fatigue than with depression (Lim et al, 2008).

2.5.2. Possible causes of depression in narcolepsy and idiopathic hypersomnia

CHRONIC ILLNESS

The association between chronic illness and depression is widely reported in the literature (Moussavi et al., 2007; Cavanaugh, 1984). Recently, the WHO corroborated that depression occurs more frequently in persons with physical illness rather than in those without illness. Depression and physical illness share some common symptoms of depression. Moreover, physical symptoms of depression may not only confound but also perhaps add to the diagnosis of depression.

Clark et al analyzed the internal consistency of the BDI responses from two different patient samples: medical inpatients and psychiatric inpatients. They tried to test whether BDI items explore a single underlying dimension of depressive severity and if some, but not all, BDI scales items measured depressive severity well in both samples of patients. The authors found that the two symptoms related to the subject's pleasure capacity were the most relevant symptoms in both samples. These are anhedonia (item D) and social anhedonia (item L) (Clark, vonAmmon & Gibbons, 1983). Several authors have highlighted the need to distinguish between somatic symptoms and the cognitive component of depression especially in medical populations. Beck suggested that somatic symptoms should be cautiously treated when they can be attributed to the medical condition (Beck, 1967).

A polysomnographic study aimed to differentiate patients with IH versus those with psychiatric hypersomnia and found that psychiatric hypersomnia should be a disorder of hyperarousal and IH a disorder of hypoarousal (Vgontzas, Bixler, Kales, Criley & Vela-Bueno, 2000). The authors emphasized that psychiatric hypersomnia patients show a lower sleep propensity than persons with IH (Vgontzas et al., 2000).

Some studies have tried to eliminate somatic items from depression rating scales, arguing that in patients with physical illness, the scores obtained are inflated by bodily symptoms (Clark et al., 1983). Nonetheless, some authors have disagreed because this would diminish the diagnostic properties of the test. According to DSM-IV, major depressive

disorder (MDD) can be associated with chronic medical illness. Up to 20 or 25% of the patients with specific chronic illness, for example: diabetes, heart attack, stroke, and carcinoma will present MDD during the illness (American Psychiatric Association, 2000). In this context, it can be expected that a similar percentage of patients with narcolepsy or IH will display MDD.

STRESSFUL LIFE EVENTS

Depressive symptoms can have their origin in a stressful event in a person's life. Orellana et al (1994) reported that in narcoleptics, the weight of life events in the year preceding the beginning of EDS and cataplexy was higher than life events reported by controls in the equivalent year. Indeed, some patients connect the onset of narcolepsy with a stressful event such as a major change in sleeping habits, a major personal injury or illness, and major changes in the health of a family member, among others (Orellana et al., 1994).

Although that study was searching for the association between stressful life events and illness onset, this also could suggest that narcolepsy patients can have depressive symptoms not only due to the impact of the illness but also due to other stressful events that occurred in the years preceding the onset of illness.

DELAY OF DIAGNOSIS

Patients with narcolepsy usually will visit several doctors until they have a diagnosis. A study in a normal population found that a high frequency of medical visits is an aspect that increases the chance of patients to be misdiagnosed as depressed (Perez-Stable, Miranda, Munoz & Ying, 1990). Even today, narcoleptic patients often have to see several physicians until the correct diagnosis is made (Paterack & Faria, 2009). This has been confirmed by a study showing that narcoleptic patients are often misdiagnosed with depression (Kryger, Walid & Manfreda, 2002).

RESTLESS LEGS SYNDROME (RLS) IS ASSOCIATED WITH DEPRESSION AND NARCOLEPSY

Recently, a multicenter study reported a higher prevalence of RLS in NC+ patients (14.7%) in comparison with age matched controls (3%) (Plazzi et al., 2010). Because there is a well documented high prevalence of depressive symptoms in RLS patients (Winkelmann et al., 2005), this could suggest that an increased rate of depression in narcoleptic patients might be related to the presence of RLS in this population. Plazzi and his team found that depression is not a predictor for having or not having RLS but rather the opposite, namely that it is possible that RLS may play a role in depressive symptoms as in other RLS patients without narcolepsy (Plazzi et al., 2010).

SEXUALITY PROBLEMS IN NARCOLEPTIC PATIENTS

Severe sleepiness can result in loss of sexual and libidinal drive, thereby causing psychological distress. There are few studies focused on the sexual activity of narcolepsy patients in spite of the psychosocial importance (Bruck, 2001). An old study found that all women with narcolepsy of the sample (n=10) suffered from anorgasmia. The author suggests that an explanation can be aversive learning, producing a phobia of orgasm. Roy hypothesized that women with narcolepsy avoided sexual intercourse to prevent cataplexy (Roy, 1976). Karacan et al reported in 1992 that men with narcolepsy frequently experienced erectile problems (Karacan et al., 1992). In a more recent study, from 29 patients with narcolepsy-cataplexy only 3 reported cataplexy during sexual intercourse and orgasm (2 females, 1 male) (Poryazova, Khatami, Werth & Bassetti, 2009). In conclusion, narcoleptic patients report problems with sexual life but this it seems to be not necessarily associated with cataplexy.

SELF-HELP GROUP

Many patients with narcolepsy and patients with depression participate in a self-help group. They receive social support which may improve depressive symptoms (Karp, 1992). The participation in a self-help group could be also a disadvantage for patients because according to the theory of Coyne, the interpersonal process can contribute to the development of depression (Haeffel, Voelz, Joiner, 2007). Coyne postulates that some mildly dysphoric persons (not depressed) who excessively look for reassurance and have little social support can be vulnerable to develop depressive symptoms. This author states that this group of patients would be more susceptible to diminished social support or to perceive less social aid and therefore be more prone to have depressive symptoms (Coyne & Bolger, 1990).

In the literature on narcolepsy, others have mentioned this point, arguing that perhaps only narcoleptics with severe symptoms would participate in a self-help group but at the same time, patients could improve their status of health (Daniels et al., 2001).

The importance of a support group has been documented due to their ability to normalize the participants' feelings and experiences. The following is a comment of one patient cited by Alaia: "Having narcolepsy has been a lonely experience. Only recently have I come to know others with it. A support group through the 40+ years would have helped me cope so much. Family and friends have understood, but they do not really know my feelings and frustration…only persons with it (narcolepsy) can understand" (Alaia, 1992).

HYPOCRETIN DEFICIENCY AND DEPRESSION

Hcrt plays an important role in the regulation of complex behaviors such as feeding, sleeping and being awake. Hcrt can modulate the mesocorticolimbic dopamine circuit and therefore seems to be implicated in the pathology of schizophrenia, depression, addiction (Borgland & Labouebe, 2010) and panic anxiety (Johnson et al., 2010).

A loss of Hcrt neurons is believed to be the cause of narcolepsy in humans (Peyron et al., 2000; Thannickal et al., 2000). There is sufficient evidence that this deficiency of Hcrt is present in patients with narcolepsy with cataplexy, but a smaller amount of evidence for narcoleptics without cataplexy (Thannickal, Nienhuis & Siegel, 2009). These findings suggest that in patients with narcolepsy with cataplexy depression may be caused or augmented by Hcrt deficiency. The connection between depression and Hcrt is due to the hypocretinergic innervations in all the important areas of the brain implicated in the neurobiology of depression. This topic can be analyzed from at least two points of view. The first one is due to the role of Hcrt in the aminergic and cholinergic cell groups (Salomon et al., 2003). The second one is related to the fact that both narcolepsy and depressive patients are treated with agents that increase monoaminergic activity and affect the physiology of sleep (Salomon et al., 2003).

It has been hypothesized that deficiency of Hcrt is related to psychiatric symptoms such as depression (Ganjavi & Shapiro, 2007). Low levels of Hcrt in narcolepsy are associated with depression but, on the other hand, there is no important decrease in the CSF Hcrt baseline levels in depressive patients (Salomon et al., 2003). Hcrt most likely takes part in the regulation of the monoaminergic tone that is high during wakefulness and diminishes sleep. Monoaminergic tone decreases during REM sleep (see 2.4.8 Theories about depression related to sleep abnormalities) and Hcrt is active during wakefulness and REM sleep and inactive during rest and non REM sleep. In narcolepsy, low Hcrt would decrease monoaminergic activity, provoking sleepiness and short REM sleep latency.

According to the hypothesis of Janowski, REM is promoted by cholinergic activation and is inhibited by aminergic activation (Janowsky et al., 1972). Hence, Hcrt deficit in narcoleptic patients could cause an imbalance of the aminergic and cholinergic systems. The cholinergic-aminergic imbalance has been described in depression and in narcolepsy. In both diseases, there are indicators of a deficiency in the monoaminergic neurotransmission and an increased sensitivity to muscarinic-M2-cholinergic agonists (Mamelak, 2009). Salomon and colleagues examined levels of Hcrt in 14 depressed subjects before and after antidepressant treatment. In patients with depression, a small variation of Hcrt-1 in CSF during the day is reported but the authors also suggest that Hcrt

deficiency is an improbable cause for depression (Salomon et al., 2003). This would be an argument against the difference between patients with and without cataplexy (with or without Hcrt deficiency). Antidepressant drugs which are also anticataplectic drugs will improve the monoaminergic transmission and will re-establish the balance between noradrenergic and cholinergic transmission (Mamelak, 2009).

ROLE OF HYPOCRETIN IN OBESITY

Hcrt deficiency in narcoleptic patients is associated with abdominal obesity (Kok et al., 2003). Zhang, in an animal model, confirmed that Hcrt ligand deficiency could be one of the critical factors in the tendency for obesity in narcolepsy. However, multiple other factors are also likely to affect this phenotype, and a sex specific alteration of leptin-Hcrt signaling may be involved (Zhang, Zeitzer, Sakurai, Nishino & Mignot, 2007).

Dauvilliers (2003) found no association between CSF Hcrt-1 level and sex, body mass index, severity of cataplexy, mean sleep latencies in MSLT and the number of SOREM periods. He confirmed prior findings showing that Hcrt-1 levels are significantly reduced or indetectable in patients with cataplexy, but not in narcolepsy without cataplexy, where the levels are within the normal range (Dauvilliers, 2003).

2.5.3. Prevalence of depression in narcolepsy

Depression is considered common in narcolepsy (Daniels et al., 2001; Goswami, 1998; Broughton et al., 1994; Merrit et al., 1992). One of the first studies regarding narcolepsy and depression reported that 17 narcoleptics out of a group of 100 were depressed (Roth et al., 1975). The same study found that in narcolepsy patients without cataplexy, depression occurred in 28.6% of the cases, while in narcolepsy with cataplexy they found depression in 17.2% of the cases. In IH, the occurrence of depression was 26.1%. Furthermore, the authors reported a relatively frequent occurrence of depression in the families of the patients suffering from depression associated with IH or narcolepsy (Roth et al., 1975). In 1992, a North-American study found that the prevalence of depressive symptoms in narcolepsy patients was 49%. Additionally, it was reported that although the drugs used by narcoleptic patients could have an effect on mood, in the sample studied this was not a factor that affected depressive symptoms. Younger patients experienced significantly more depressive symptoms, as well as narcoleptics with less education and lower income levels. Narcoleptics who are married experienced significantly less depressive symptoms (Merrit et al., 1992).

Another study describes the health status and psychosocial aspects of narcolepsy patients in the UK compared with normative data using BDI and SF-36. The authors found in BDI

that 56.9% of 305 subjects had some degree of depression (Daniels et al., 2001). A Brazilian study using BDI and HAM-D, reported that in a sample of 12 narcoleptic patients, 3 patients showed depressive symptoms in BDI and 5 patients in HAM-D. Only one patient reported severe depressive symptoms according to both questionnaires (Adda et al., 1997). All these investigations remain controversial because of the enormous differences in the prevalence of depression. Consequently, it is not yet clear whether depression is a genuine comorbidity of narcolepsy, or if the finding of an increased rate of depressive symptoms is merely an assertion artifact.

NO EVIDENCE OF CULTURAL DIFFERENCES

The psychosocial impact of narcolepsy was the same in populations from North America (Canada and USA), Japan and the Czech Republic (Czechoslovakia at the time of the study) demonstrating that the genetic origin or cultural experiences have no significant influence (Broughton et al 1983). Suicidal thoughts were more common in Japanese patients, whose culture has a tradition of using suicide as a means of escape. Driving accidents were significantly less frequent in the Czech Republic probably because of the severe restrictions and penalties for driving narcoleptics (Broughton et al., 1981).

PERSONALITY

Using MMPI, one study found higher scores in the scales for schizophrenia, depression, and hysteria (Kales et al., 1982). Another study reported that also scales hypochondriasis and psychasthenia were elevated (Ramos-Platón, 1998). Others found that only the scales of hysteria and hypomania are significantly elevated in patients with narcolepsy compared with controls (Jara, Loubat & Castillo, 2003). As Kales mentions, some items of MMPI may not distinguish between symptoms of narcolepsy and daily life feelings, but there is no way to reduce the elevation of scales due to content related with physical symptoms (Kales et al., 1982).

In 1990, Stepanski et al compared a group of 56 narcoleptics with patients diagnosed with excessive daytime sleepiness of other causes. Both groups showed greater scores using MMPI (Stepanski, Markey, Zorick & Roth, 1990). The results suggest that the psychopathology related to narcolepsy is not specific and may be generalized to other disorders with excessive sleepiness. Beutler et al (1981) found that narcoleptics are most often characterized by personality patterns which emphasize coping with stress by sensitization to sources of anxiety and social withdrawal compared to the control group (Beutler, Ware, Karacan & Thornby, 1981). Narcoleptics were distinguished from controls as being relatively more depressed, anxious, fatigued and having less vigor. Moreover,

Broughton in another study discovered that narcoleptic patients are more anxious and emotionally changeable than normal controls (Broughton, 1976).

2.5.4. Prevalence of depression in idiopathic hypersomnia

A study performed in Montpellier that compared dysthymic patients who complained of excessive night and daytime sleepiness with IH patients found that patients with dysthymia did not have reduced mean sleep latency on the MSLT. However, they exhibited an abnormal macrostructure of sleep with enhanced sleep stage 1 and a decreased stage 3 and 4 (Dolenc, Besset & Billiard, 1996). Roth reported that in patients with IH, the prevalence of psychiatric symptoms is circa 50% and specifically for depression between 14 to 26% (Roth, 1980; Roth et al., 1975). One study found that the prevalence of psychiatric symptoms was 57% (Bassetti et al., 1997) It seems that psychiatric symptoms in IH patients are reactions to chronic illness but at the same time the symptoms of IH have common characteristics with psychiatric symptoms (Bassetti et al., 1997). Bassetti and Aldrich suggested that there are three arguments to maintain the link between IH and mood disorders: (a) Fluctuations of EDS and psychiatric complaints with intensification of EDS in winter or during menstrual period, (b) Hypersomnia is commonly reported by young depressed patients who spend 16-20 hours in bed per day and (c) Patients with depression frequently sleep longer when they are allowed to sleep as much as they want, which is significantly more than in the controls (Bassetti et al., 1997). Supporting this results, Chellappa (2006) evaluated EDS related with depression, and examined the association with severity of depression and suicide ideation. The authors reported that daytime sleepiness in outpatients with depressive disorder is related with suicide ideation (Chellappa, 2006).

One study with a considerable number of IH patients used depression as an exclusion criterion (Anderson et al., 2007), which decreased possibilities for a psychiatric approach. Only in the absence of a depression is it possible to diagnose IH with short or long sleep time. This can be a bias in the studies of IH. Billiard et al (2001) reported that IH patients with mood disorders are often excluded from the diagnosis spectrum because of the criteria “no medical or mental disorders as a possible cause of the symptoms” (Billiard, 2001).

2.5.5. Key references related to depression and daytime sleepiness

To provide an insight into the pertaining literature, table 33 (in appendix) shows crucial work concerning the topic of narcolepsy, idiopathic hypersomnia and depression. The papers are listed in alphabetical order of the first author. The majority of studies are

prospective (62%). After the division narcolepsy with and without cataplexy in 2005, the studies are principally focused in patients with cataplexy. The following review of the literature, summarized in the table, shows that although patients have depressive symptoms and have a low quality of life (which includes some items regarding depression) most of the studies fail to probe whether they have a major depressive disorder (MDD).

2.6. Research questions and hypothesis

Depression and depressive symptoms are consistently reported as a problem for narcoleptic patients in various studies, but the lifetime prevalence of depressive disorders based on internationally accepted diagnostic criteria is not increased, as pointed out in the previous section. This obvious discrepancy leads us to hypothesize that depression in narcoleptics is a phenomenon that can be differentiated from the symptoms in patients with MDD by a distinct constellation of single symptoms (**Hypothesis I**). Depending on varying sets of criteria, these symptoms may or may not result in the formal diagnosis of a depressive disorder. Accordingly, the key question of this dissertation is:

ARE DEPRESSIVE SYMPTOMS OF NARCOLEPTIC PATIENTS DIFFERENT FROM THE DEPRESSIVE SYMPTOMS OF NON-NARCOLEPTIC PATIENTS WITH MAJOR DEPRESSIVE DISORDER?

The main hypothesis implicitly presupposes that narcoleptic patients are indeed more depressed than a comparable control group from the general population (**Hypothesis II**). Given the large variance in previous results on this topic, this hypothesis was to be tested in a first step. This was formulated as a first research question:

ARE NARCOLEPTIC PATIENTS MORE DEPRESSED THAN CONTROLS FROM THE GENERAL POPULATION?

In the latest version of the International Classification of Sleep Disorders, the diagnosis of narcolepsy has been split into two distinct subcategories, and the delimitation against IH was changed. This may in many ways influence the characteristics and the distribution of depressive symptoms. Therefore, an additional step of analysis was introduced to lay the foundation to approach the primary research question. Based on previous research, it was hypothesized that narcoleptics with cataplexy show more depressive symptoms than those without cataplexy (**Hypothesis III**), and that IH patients are equally depressed as narcolepsy patients without cataplexy (**Hypothesis IV**). This resulted in a second research question:

DO THE TWO NEWLY DIFFERENTIATED FORMS OF NARCOLEPSY (WITH AND WITHOUT CATAPLEXY) AND IH DIFFER WITH RESPECT TO THE DEGREE OF DEPRESSIVE SYMPTOMS?

To answer these questions, a first study was performed with the title: “Depressive symptoms in narcolepsy with and without cataplexy and in IH” (**Study I**).

For methodological reasons, an approach with self-rating scales was chosen to compare depressive symptoms between depressed narcoleptic patients and patients with primary

depression. The type of depressive symptoms narcoleptic patients report may be different from those seen in primary depression. Physical symptoms may elevate the scores obtained by narcoleptic patients. Consequently, it is expected that depressed narcoleptics report less cognitive symptoms than patients with primary depression with equal mean scores in the same rating scales (**Hypothesis V**).

In terms of a research question, this was worded as:

ARE SELF-REPORTED DEPRESSIVE SYMPTOMS IN PATIENTS WITH NARCOLEPSY DIFFERENT FROM THOSE IN PATIENTS WITH A PRIMARY DEPRESSIVE EPISODE, WHEN INTENSITY OF DEPRESSION IS CONTROLLED?

To address this question, a second study was performed with the title “Narcoleptics with depressive symptoms compared with patients with primary depression” (**Study II**).

Based on the results of study II, the analysis of the specific symptom constellation was followed up concentrating on the BDI, which had proven to be the most promising candidate for a factor analysis. A large number of factor analysis studies have been performed in many depressed and non-depressed populations, and in various medically ill populations. Despite the extensive use of BDI in narcoleptic patients, so far, this method of statistical analysis has not been previously explored on this population. This resulted in the following research question:

WHAT ARE THE CENTRAL ITEMS OF BECK DEPRESSION INVENTORY (BDI) THAT EXPLAIN THE SCORES OBTAINED BY NARCOLEPTICS?

Different studies using BDI factor analyses have identified three factors: (1) negative attitudes toward self, (2) performance impairment and (3) somatic disturbances.

The expectations are that in narcoleptic patients the components related to somatic items of BDI will be more relevant when compared to components associated with cognitive items. (**Hypothesis VI**). Accordingly, a third study was performed with the title: “Factor analysis of Beck Depression Inventory in patients with narcolepsy” (**Study III**).

3. EMPIRICAL PART I: "DEPRESSIVE SYMPTOMS IN NARCOLEPSY WITH AND WITHOUT CATAPLEXY AND IDIOPATHIC HYPERSOMNIA"

3.1. Introduction

Narcolepsy is a chronic sleep disorder first described by Westphal more than 130 years ago (Westphal, 1877). Over time, it has been a matter of discussion as to whether or not the symptom of cataplexy should be necessary to diagnose narcolepsy. Notably, in 15% of the cases, cataplexy will develop more than 10 years after the onset of sleepiness (Yoss et al., 1960). In the second edition of the ICSD (ICSD-2) two forms of narcolepsy, with (NC+) or without cataplexy (NC-), are distinguished (American Academy of Sleep Medicine, 2005). The difference between both is the definitive presence of cataplexy in the first form and absent or questionable cataplexy in the second form (American Academy of Sleep Medicine, 2005). Narcolepsy without cataplexy is distinguished from IH based on the presence of two or more sleep onset REM periods in the MSLT. IH is divided into two groups, depending on whether the duration of night sleep is more than 10 hours or not, referred to as IH with long sleep time or without long sleep time, respectively.

An association between narcolepsy and depression was observed in 1975 when Roth and Nevsimalova reported that 17 narcoleptics out of a group of 100 were depressed, as assessed by clinical interviews (Roth et al., 1975). This is higher than the prevalence of major depression in Europe, which is between 3.1% and 10.1% (Wittchen & Jacobi, 2005). After these studies, several authors using a variety of diagnostic systems and assessment scales reported depressive symptoms in 6% to 56% of the narcolepsy patients (Rovere et al., 2008; Vandeputte et al., 2003; Daniels et al., 2001; Adda et al., 1997; Broughton et al., 1994; Merrit et al., 1992; Kales et al., 1982; Roth, 1980; Sours, 1963). A study performed with a structured interview found that only 7% of NC+ patients met criteria for depressive disorder not otherwise specified according to DSM-IV (Vourdas et al., 2002) while Daniels found that 56.9% of patients were on the border of a depression (BDI >10 points), and 15.1% were at least mildly to moderately depressed (BDI >20 points) (Daniels et al., 2001). The variation in these studies could reflect unlike assessments, the use of different research instruments, varying cut-off scores or specific questions in the psychometric tests related to sleep and overlap between symptoms of depression and narcolepsy.

Five out of the nine symptoms of Major Depressive Disorder according to DSM-IV (American Psychiatric Association, 2000) are common symptoms of narcolepsy, including fatigue, psychomotor retardation, decreased concentration, hypersomnia and weight increase.

Nonetheless, the high rates of depressive symptoms in narcolepsy suggest a relevant relation between these two disorders. In the discussion of possible causes, several lines of evidence have been mentioned. The core question, brought up more than 45 years ago (Sours, 1963), of whether the psychiatric findings are epiphenomena or if they are inherent to the disease, remains unanswered.

The distinction between NC+ and NC- raises the question of whether there is a difference in depressive symptoms between both groups. Most authors reported no significant differences between narcoleptics NC+ and NC- in quality of life scales such as the SF-36 scale or in depression (e.g. BDI) scores (Morrish, King, Smith & Shneerson, 2001). A Japanese study with drug naïve patients showed that quality of life did not differ across different categories of hypersomnia of central origin (NC+, NC-, and IH without long sleep time) (Ozaki et al., 2008). In contrast, the “Harmony study”, performed in France with medicated patients found that NC+ patients have more depressive symptoms than a combined group of NC- and IH (Dauvilliers et al., 2009). Several studies suggest that narcolepsy patients have many limitations and difficulties managing their daily activities (Goswami, 1998; Broughton et al., 1994) and untreated narcoleptics with or without cataplexy do not differ in terms of quality of life. Others found that the impact of narcolepsy in daily life is unrelated to medication (Rovere et al., 2008; Dodel et al., 2007; Ervik, Abdelnoor, Heier, Ramberg & Strand, 2006; Vignatelli et al., 2004; Daniels et al., 2001; Beusterien et al., 1999). Usually, antidepressant medication in narcolepsy patients is given for cataplexy and not to diminish depressive symptoms. Therefore, the prescribed dose is low. There is no clear evidence that antidepressants improve the quality of life (Vignatelli et al., 2004). Whether stimulants will diminish depressive symptoms is not well established. Amphetamines can increase anxiety and in some patients can lead to mania (Roy, 1976) but modafinil has been associated with improvement in quality of life and mood in narcolepsy patients (Becker et al., 2004).

Hcrt deficiency is mainly observed in NC+ (Nishino et al., 2000). The interest to compare both groups is increasing because this peptide plays a role in modulating the reward system in the brain in addition to regulating appetite, metabolism and sleep. Therefore, Hcrt may be relevant in depression (Ganjavi et al., 2007). A direct comparison of depressive symptoms in NC+, NC-, IH and a sex and age matched control group has not been performed yet. Given these considerations, depressive symptoms in narcoleptic and IH patients and controls were assessed. Furthermore, a comparison of depression scores of patients with and without cataplexy and IH were performed.

3.2. Methods

3.2.1. Participants

Eighty-six narcolepsy patients of Caucasian origin were studied (46 women, 40 men, age range 19 to 78 years) and a total of 15 patients with IH were studied (three women, 12 men) (Table 4).
Diagnosis according to ICSD-2 criteria (American Academy of Sleep Medicine, 2005) was established in the Sleep Disorders Centre, department of Psychiatry, Psychosomatics and Psychotherapy, University Medical Centre Regensburg (n= 36) or in another German sleep laboratory, based on polysomnography (PSG) and Multiple Sleep Latency Test (MSLT). Patients were rated NC+ when a history of current or past definite cataplexy was present (n = 65). No specific exclusion criteria were applied.From the narcoleptic sample, 70% were members of the German narcolepsy association, a patient support group.
All IH patients were diagnosed in the sleep centre in Regensburg according to the ICSD-2 criteria. Because of the small number of patients the group was not divided into the categories of with or without long sleep time as recommended by the ICSD-2.There was a significant difference in age between the whole sample of controls and IH patients. Therefore, from the sample of controls, a sub sample was regrouped to match each IH patient.Each narcoleptic patient was matched to a control subject of the same sex and equal age (± five years). The matching variables were chosen because these are known predictors of depressive symptoms (Slone et al., 2006).
The ethics committee of the University of Regensburg approved the study. All patients and controls signed informed consent.

CONTROL GROUP

The control group for the narcoleptic patients group was composed by 86 healthy subjects. From them (86 subjects) 15 were matched to the IH patients group for statistic comparison. This group of 15 subjects was called IH controls (Table 12). The purpose of this extraction of the control group was to have groups similarly distributed by age. The control group (86 subjects) was recruited from volunteers among the employees of the Psychiatric University Hospital, students of the University of Regensburg and visitors of a senior citizen center in Regensburg. Exclusion criteria for controls were use of hypnotics, antidepressants, current diagnosis of depressive disorder, Restless Legs Syndrome according to ICSD-2, and insomnia complaints (Pittsburgh Sleep Quality Index [PSQI] (American Academy of Sleep Medicine, 2005; Buysse, Reynolds, III, Monk, Berman & Kupfer, 1989) score > 5, or > 8 points for subjects 60 years or older (Eser, Khorshid & Cinar, 2007;

American Academy of Sleep Medicine, 2005)). Although a diagnosis of depression was an exclusion criterion, controls with depressive symptoms were not excluded of the sample to avoid a bias.

3.2.2. Procedure and questionnaires

Following a prospective study design, self-administered questionnaires were given to the patients during their visit in the sleep disorders centre in Regensburg or at a meeting of the German narcolepsy association. The scales used were the German versions of Beck Depression Inventory (BDI), Zung Self-rating Depression Scale (SDS), Global Impression of Severity of Depression (GSD), Profile of Mood States (POMS) and Epworth Sleepiness Scale (ESS), and a questionnaire on demographic data and symptoms, diagnosis, and pharmacological treatment.

BECK DEPRESSION INVENTORY (BDI)

The BDI is a self-rating scale, which is comprised of 21 questions related to depressive symptoms. For each item, the possible score ranges from 0 to 3 points, resulting in a possible total score from 0 to 63 points. The score increases with the severity of depression and originally is graded as follows: from 0-9 points: no or minimal depression, 10-14 points: on the border of depression, 15-20 points: mild depression, 21-30 points: mild to moderate depression, 31-40 points: moderate to severe depression, and 41-63 severe depression (Hautzinger, 1991; Beck, Ward, Mendelson, Mock & Erbaugh, 1961). The first version of the test was used because the second one version (Kühner, Bürger, Keller & Hautzinger, 2007) was not yet available in the German language at the beginning of the study.

Table 11. Items of Beck Depression Inventory (BDI) according to Beck et al. (1961)

BDI items			
A.	Sadness	K.	Irritability
B.	Hopelessness	L.	Social anhedonia
C.	Sense of failure	M.	Indecisiveness
D.	Anhedonia	N.	Change of body image
E.	Guilt	O.	Push to work
F.	Expectation of punishment	P.	Insomnia
G.	Self hate	Q.	Fatigue
H.	Self blame	R.	Loss of appetite
I.	Suicidal ideation	S.	Loss of weight
J.	Crying spells	T.	Health worries
		U.	Loss of libido

ZUNG SELF-RATING DEPRESSION SCALE (SDS)

The SDS consists of 20 items. The scores for each item are 1 to 4 points, so the minimum score is 20 and the maximum score is 80 points.The scores were graded following the original cut off values from Zung: 20-39 points: normal, 40-47: mild depression, 48-55 points: moderate depression and 56-80 points: severe depression (Zung, 1965).

Table 12. Items of Zung Self-Rating Depression Scale (SDS) according to William Zung (1965).

Items SDS			
1)	I feel down-hearted and blue	11)	My mind is as clear as it used to be
2)	Morning is when I feel the best	12)	I find it easy to make decisions
3)	I have crying spells or feel like it	13)	I am restless and can´t keep still
4)	I have trouble sleeping at night	14)	I feel hopeful about the future
5)	I eat as much as I used to	15)	I am irritable than usual
6)	I still enjoy sex	16)	I find it easy to make decision
7)	I notice that I am losing weight	17)	I feel that I am useful and needed
8)	I have trouble with constipation	18)	My life is pretty full
9)	My heart beats faster than usual (tachicardia)	19)	I feel that others would be better off if I were dead
10	I get tired for no reason	20)	I still enjoy the things I used to do

In a secondary analysis, items specifically related to sleep in BDI and SDS (“sleep items”) were excluded. These items were in BDI „I can sleep as well as before” and “I do not get more tired than usual” and in SDS “I have trouble sleeping at night” and “I get tired for no reason”.

GLOBAL IMPRESSION OF SEVERITY OF DEPRESSION (GSD)

The GSD is a visual analogue scale (range 0 to 10) with the question “Do you feel depressed” with expressive faces at each one of the extremes, with low values corresponding to depressive feelings. GSD was performed in this study based on the validated scales used in pain research studies (Wewers & Lowe, 1990). This was used to compare the subjective feelings of depression of narcoleptic patients without mentioning the field of sleepiness.

PROFILE OF MOOD STATES (POMS)

The POMS consists of 65 items grouped into five negative and one positive mood dimension. As for time frame, the question “How have you been feeling during the past week including today?“ was used. The subscales are tension-anxiety (9 items), depression (15 items), anger-hostility (12 items), vigor-activity (8 items) fatigue (7 items), and confusion-bewilderment (7 items) (McNair, Lorr

& Droppleman, 1992). The total of mood disturbance score (TMD, range 0 -200) is calculated by adding all the negative mood dimensions and subtracting the positive one (vigor). In some analyses, the focus was on the subscale depression of POMS because it is specifically related to depressive symptoms.

EPWORTH SLEEPINESS SCALE (ESS)

Daytime sleepiness was assessed with the ESS. The ESS asks about the tendency to fall asleep during eight different situations that are commonly encountered in daily life, yielding a score range of 0-24, 11 points or over was considered indicative of pathological sleepiness (Johns, 1991). The normative value of the German version of the ESS for healthy controls is 6.6±3.5 [mean± SD] (Sauter et al., 2007).

3.2.3. Statistical analysis

Data analyses were processed using the Statistic Package for Social Sciences 16.0 (SPSS). The significance level was set to .05 for all analyses. The effect size is reported because "a result statistically significant at conventional levels is not necessarily "practically significant" as judged by the magnitude of the effect" (Rosenthal, Rosnow & Rubin, 2000, p.4). Cohen´s d was carried out to calculate the effect size. To address the problem of multiple comparisons, the Bonferroni correction was carried out where indicated. A square root transformation was performed in some cases of variables with non-Gaussian distribution. Sex and age matched groups were compared by Mann Whitney U-test. For categorical variables, the Pearson Chi-square test followed by Fisher's exact test was employed. The effect and interaction of type of drug and sex was evaluated by analysis of variance (ANOVA). For post-hoc comparison, tests not assuming equal variances (Games-Howell) were used.

The associations between the sleep related items in BDI and SDS, and the ESS were analyzed with the Spearman correlations. Bilateral tests for significance were used in all cases. The Pearson Chi-square test was employed to contrast the hypothesis of independence between two categorical variables (levels of depressive symptoms) followed by Fisher's exact test.

A multiple linear regression analysis using the backward method was conducted to explore and quantify the relation between the depressive symptoms and multiple independent variables such as age, sex, use of stimulants, antidepressants, combination of stimulants and antidepressants, the illness duration, cataplexy symptom, severity of sleepiness, body mass index, age at the onset of narcolepsy and diagnosis age. IH patients were not included in this analysis because the goal of

the regression was to analyze the effect of cataplexy, which is specific to narcolepsy. The backward method includes all the independent variables and then proceeds to eliminate each variable one at a time. A logistic regression was used to confirm the results obtained in the linear regression, because some of the variables were dichotomous. For this analysis, the variables of depressive symptoms were transformed into yes (BDI > 9, SDS > 39) or no. We analyzed by age group (19-29, 30-39, 40-49, 50-59, 60-69 and 70-78 years old) and body mass index (BMI) classification according to the WHO (Underweight<18.50, normal range 18.50-24.99, overweight ≥25-29.99 and obese ≥30) (World Health Organization, 2000).

3.3. Results

3.3.1. Demographic and clinical characteristics

AGE, SEX, BODY MASS INDEX

The difference between sexes in the control group was not significant (p>.05). In the BDI test, the control group scores were in the normal range with a percentage of participants arranging a higher level referred to by Beck as “on the border of a depression” without a diagnosis of MDD. This was part of the exclusion criteria (see methods). The total scores are represented in the Table 14.

COURSE OF THE ILLNESS

Patients with IH had shorter illness duration than narcoleptics because almost all were younger than patients the comparison group.

Table 13. Demographic and clinical characteristics of study sample.

Group	Age *M* ± *SD*	Sex female: male	Body Mass Index (in kg/m²) *M* ± *SD*	Age at onset of excessive sleepiness *M* ± *SD*	Illness duration (in years) *M* ± *SD*	Years living without diagnosis *M* ± *SD*
NC+ *n*=65	45.4 ± 16.4	35:30	29.5 ± 6.2	21.4 ± 10.1	27.5 ± 16.2	14.2 ± 1.6
NC- *n*=21	51.7 ± 15.2	11:10	28.5 ± 4.4	23.2 ± 13.2	26.5 ± 17.6	20.4 ± 3.6
IH *n*=15	31.6 ±12	3:12	24.0±3.5	19.6±12.4	12.4±7.8	10.2±8.5
C (NC+ & NC-) *n*=86	45.2 ± 16.5	46:40	23.8 ± 4.0	NA	NA	NA
C (IH) *n*=15	33.5 ±12	3:12	23.9±2.7	NA	NA	NA

NC+, narcoleptics with cataplexy; NC-, narcoleptics without cataplexy; IH, idiopathic hypersomnia patients; C (IH), matched control group for IH patients; C (NC+ & NC-), matched control group for NC+ and NC- patients; M, arithmetic mean; SD, standard deviation; NA, not applicable.

MEDICATION USE

Sixteen patients were unmedicated for narcolepsy at the time of the study (NC+: 10, NC-: 6), 39 were using stimulants only (NC+: 27, NC-: 12), eight (all NC+) were taking anticataplectics only, and 20 NC+ patients were taking both (stimulants and anticataplectics). Three NC- patients were taking antidepressant medication in combination with stimulants, one of them for recurrent depression and the other two for unknown reasons. The anticataplectic drugs used were tricyclic antidepressants (n=12), selective serotonin reuptake inhibitors (n=8), serotonin-norepinephrine reuptake inhibitors (n=5), norepinephrine reuptake inhibitors (n=8), monoamine oxidase inhibitors (n=1), and sodium oxybate (n=6). Eight patients were taking a combination of two anticataplectic drugs. The stimulant drugs used were modafinil (n=46), methylphenidate (n=9), fenethylline (n=1) and pemoline (n=1). Twenty-nine patients were not taking stimulants at the time of the study. These had been just diagnosed (n=8) or had chosen not to use stimulants at this time.

EPWORTH SLEEPINESS SCALE (ESS)

Daytime sleepiness (measured by ESS scores) was compared between patients groups and controls (Figure 4). Although all but 16 patients were taking medication against narcolepsy and 57 were taking stimulants, the ESS-score at the time of the study was in the normal range (below 11 points) for only five patients (5.8%), with a mean of 16.7 points (Standard deviation (SD) 3.9 range 4 to 23 points). Patients on stimulants showed the same mean as the rest (ON stimulants: ESS-score mean=16.7, SD= 3.8; OFF stimulants: ESS-score mean=16.6, SD=4.0, $p>.05$). In the control group, the ESS mean score was 5.1, SD 3.3, with 10.5% scoring more than 10 points. This is similar to the normative values of the German version of ESS for healthy controls (See methods).

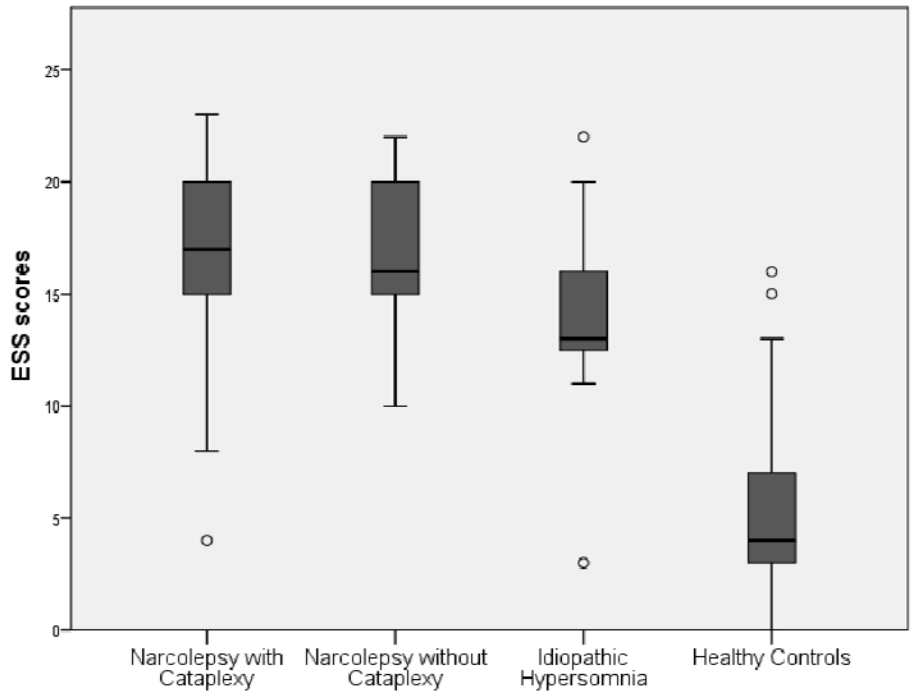

Figure 4. Average of scores in the Epworth Sleepiness Scale (ESS). Higher scores indicate a higher level of impairment. Lines denote the median values; box denotes specific interquartile range. Maximum and minimum scores are indicated by the upper and lower markers, respectively (See interpretation of boxplots in section appendix).

3.3.2. Depressive symptoms – Univariate analysis

COMPARISON NARCOLEPTIC PATIENTS WITH, WITHOUT CATAPLEXY, IDIOPATHIC HYPERSOMNIA

No significant differences between NC+ and NC- in the total scores in BDI, SDS, GSD, TMD or any of the subscales of POMS were found. The analysis shows that NC+ and NC- have significantly lower scores in the subscale Fatigue than IH (Figure 5). In addition, NC- have significantly lower scores in the subscale Confusion than IH, however NC+ shows no significant differences with NC- or IH (Table 14).

NC+ women showed a significant increase in depressive symptoms compared to men. This difference was neither present in NC- nor in controls. Nevertheless, no significant differences were found in BMI by gender.

Table 14. Depression, mood ratings and sleepiness in narcoleptics with and without cataplexy and idiopathic hypersomnia patients.

Measure		NC+ (*n*=65) *M* ± *SD*	NC- (*n*=21) *M* ± *SD*	IH *(n*=15*)* *M* ± *SD*	*Kruskal Wallis (df=2)*	*p value*
Depression	BDI	11.8 ± 8.8	7.8 ± 6.0	11.6±10.8	2.78	.25
	BDI –sleep items	9.8±7.8	6.1±5.4	10.1±10.1	4.03	.13
	SDS	40.2± 10.0	37.1± 7.8	39.1±11.3	1.40	.50
	SDS – sleep items	34.9±9.4	32.3±7.3	34.6±11.1	0.99	.61
	GSD	2.9 ± 2.6	2.9 ± 2.6	3.3±3.0	0.23	.89
Mood	POMS-TMD	39.3±37.3	27.5±21.7	53.2±41.9	3.60	.17
	Tension	11.7±6.7	8.9±4.5	11.7±8.7	3.27	.19
	Depression	13.3±12.9	7.8±7.7	16.9±15.8	4.10	.13
	Anger	10.1±7.5	9.2±6.3	11.4±9.4	0.17	.92
	Vigor	16.1±6.2	18.0±5.3	13.5±6.6	3.77	.15
	Fatigue	11.7±6.1	10.8±4.5	15.7±5.5	7.32	.03*
	Confusion	8.6±5.0	6.8±4.0	11.1±5.1	7.05	.03*
Sleepiness	ESS	16.6 ± 3.8	16.8 ± 3.8	14.1±4.3	3.60	.10

NC+, narcoleptics with cataplexy; NC-, narcoleptics without cataplexy; IH, idiopathic hypersomnia patients; *Kruskal*-Wallis Test; this is a non-parametric test here performed to compare NC+, NC- and IH. *M*, arithmetic mean; *SD*, standard deviation; BDI, Beck Depression Inventory (21 item version); BDI-sleep items, BDI scores excluding 2 sleep items (see Methods); SDS, Zung Self-Rating Depression Scale; SDS-sleep items, SDS scores excluding 2 sleep items (see methods); GSD, Global impression of Severity of Depression; POMS, Profile of Mood States; TMD, Total Mood Disturbance; ESS, Epworth Sleepiness Scale; **: significance level= .01 after Bonferroni correction (k=5, adjusted for comparison of BDI, SDS, GSD, POMS (total) and ESS).

To avoid the problem of multiple comparisons, a one factor ANOVA with post hoc was performed. The Levene tests shows that the variance is equal (p>.05), therefore the Tukey post-hoc test was performed confirming that fatigue and confusion are significantly different between the groups.

Table 15. Depression and mood ratings in narcoleptic patients with and without cataplexy.

Measure		NC+ (*n*= 65) *M* ± *SD*	NC- (*n*= 21) *M* ± *SD*	*U*	*p value*
Depression	BDI	11.8 ± 8.8	7.8 ± 6.0	-1.70	.09
	BDI –sleep items	9.8±7.8	6.1±5.4	-2.01	.04
	SDS	40.2± 10.0	37.1± 7.8	-1.10	.26
	SDS – sleep items	34.9±9.4	32.3±7.3	-.96	.33
	GSD	2.9 ± 2.6	2.9 ± 2.6	-.12	.89

M, arithmetic mean; *SD*, standard deviation; *U*, computed value Mann-Whitney U-Test; NC+, narcoleptics with cataplexy; NC-,narcoleptics without cataplexy; BDI, Beck Depression Inventory (21 item version); BDI-sleep items, BDI scores excluding 2 sleep items (see methods); SDS, Zung Self-Rating Depression Scale; SDS-sleep items, SDS scores excluding 2 sleep items (see Methods); GSD, Global impression of Severity of Depression; POMS, Profile of Mood States; TMD, Total Mood Disturbance; ESS, Epworth Sleepiness Scale; **: significance level= .01 after Bonferroni correction (k=5, adjusted for comparison of BDI, SDS, GSD, POMS (total) and ESS).

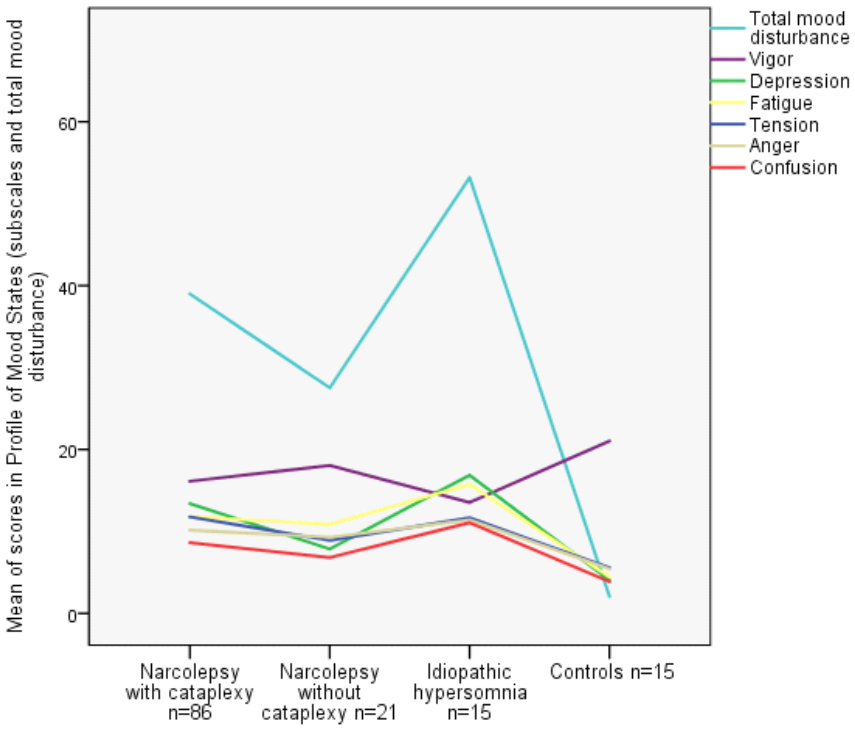

Figure 5. Average of scores in the six subscales of Profile of Mood States and in the total mood disturbance (total of subscales excluding Vigor). Higher scores indicate a higher level of impairment.

SEVERITY OF DEPRESSION

In BDI and SDS, the distribution among the graded categories of depression severity showed no significant differences between the NC+ and the NC- groups (Pearson Chi-square, Fisher's exact test, p >.05). The distribution over the graded score groups of the BDI and the SDS was clearly different between narcoleptics and controls (BDI: Pearson Chi-squared=27.03 p<.0001, Fisher's exact test=27.84 p<.0001, SDS: Pearson Chi-squared=38.21 p<.0001, Fisher's exact test=40.15 p<.0001).

In BDI, none of the narcoleptic patients were in the "severe depression" group, but three patients (3%) scored "moderate to severe depression". In SDS, seven patients (8%) scored in the highest category ("severe depression"), and 10 patients (12%) had "moderate depression". Only about half of the patients scored normal values in SDS and BDI. In the control group, 94 % (SDS) or 90 % (BDI) were in the normal range, while the remainder scored in the range of mild depression (Figure 6 and 7). None of the

narcoleptics showed severe depression in the BDI, and none of the controls had more than mild depression in either of the scales.

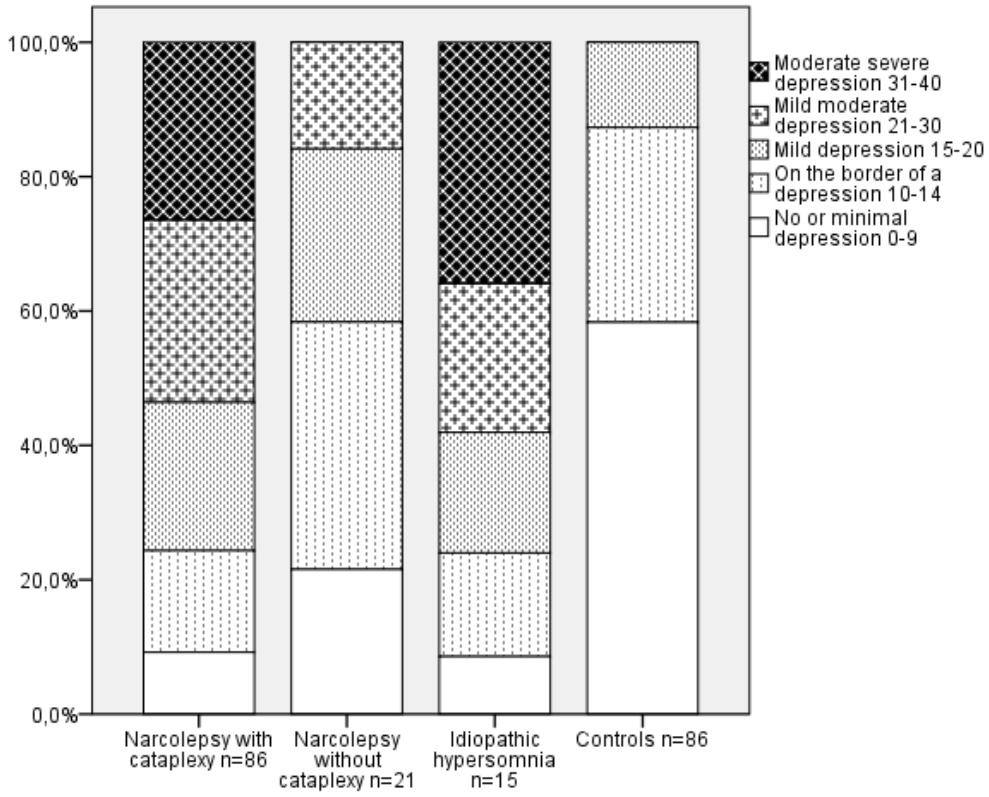

Figure 6. Graded distribution of depressive symptoms in narcoleptics with and without cataplexy, idiopathic hypersomniacs and controls according to Beck Depression Inventory.

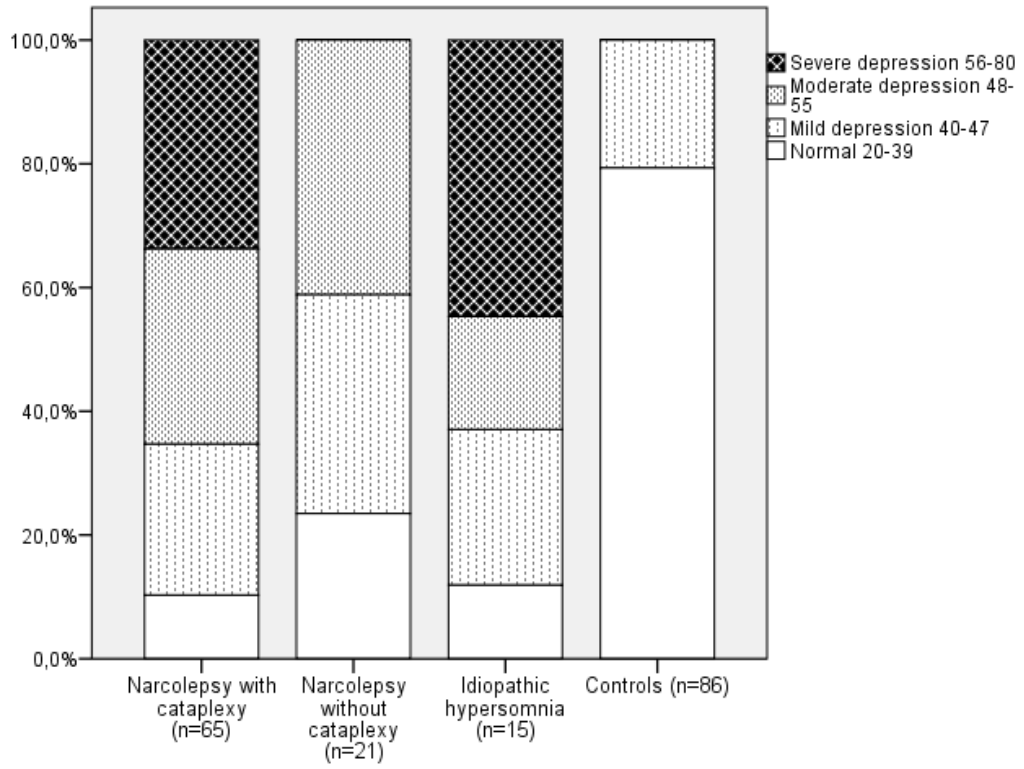

Figure 7. Graded distribution of depressive symptoms in narcoleptics with and without cataplexy, idiopathic hypersomniacs and controls according to Zung Self-rating Depression Scale.

As not substantial differences between NC+ and NC- were found, both groups were combined for subsequent analyses.

Table 16. Depression and mood ratings in narcoleptic patients and control subjects.

	Measure	Narcoleptic patients (n= 86) *M* ± *SD*	Controls (n=86) *M* ± *SD*	*U*
Depression	BDI	10.8 ± 8.4	3.8 ± 3.9	-6.25****
	BDI - sleep items	8.9 ± 7.4	3.2±3.5	-5.98****
	SDS	39.4 ± 9.7	28.1 ± 6.2	-6.73****
	SDS - sleep items	34.3 ± 8.9	25.5±5.8	-6.29****
	GSD	2.9± 2.6	1.0 ± 1.6	-5.59****
Mood	POMS - TMD	36.4±34.4	2.0±21.9	-6.35****
	Anxiety	11.1±6.4	5.5±4.5	-5.77****
	Depression	12.0±12.1	4.0±6.3	-5.70****
	Anger	9.9±7.2	5.4±5.3	-4.47****
	Vigor	16.6±6.0	21.0±6.2	-4.40****
	Fatigue	11.6±5.8	4.4±4.6	-6.78****
	Confusion	8.2±4.9	3.8±2.9	-6.01****

M, arithmetic mean; SD, standard deviation; *U*, computed value Mann Whitney test; BDI, Beck Depression Inventory (21 item version); BDI-sleep items, BDI scores excluding 2 sleep items (see Methods); SDS, Zung Self-Rating Depression Scale; SDS-sleep items, SDS scores excluding 2 sleep items (see Methods); GSD, Global impression of Severity of Depression; POMS, Profile of Mood States; TMD, Total mood disturbance; ****p<.0001.

COMPARISON -NARCOLEPTIC PATIENTS AND CONTROLS

Patients with narcolepsy revealed a significantly higher level of depressive symptoms in the total scores of BDI, SDS and GSD than controls (p<.0001 for all scores). This difference remained significant when the sleep items in BDI and SDS were excluded. In the POMS, narcoleptics scored higher on the TMD and on all negative sub scales, and lower on the positive sub scale (vigor). As expected, the ESS score was significantly higher in the narcoleptics (Figure 4).

CORRELATION BETWEEN ESS AND DEPRESSIVE SYMPTOMS IN PATIENTS AND CONTROLS

In narcoleptics, BDI items correlating with ESS scores were: item L Social withdrawal (r=.26, p=.002), item 0 Retardation (r=.25, p=.02), item Q Fatigability (r=.25, p=.02). The item P Insomnia showed a statistical tendency which was not significant (r=.21, p=.052).

In controls, BDI items correlating with ESS scores were: item B Hopelessness (r=.23, p=.03), G Dislike of self (r=.23, p=.03), N Change of body image (r=.36, p=.001), Q Fatigability (r=.27, p=.01) and U Loss of Libido (r=.25, p=.02). There was no correlation between ESS and items of BDI and SDS in the sample of 15 IH patients.

Table 17. Correlation between Epworth sleepiness scale and Beck Depression Inventory items in narcoleptic, idiopathic hypersomnia patients and controls.

Beck Depression Inventory (BDI) items	Narcoleptic patients n=86	Healthy controls n=86	Idiopathic hypersomnia patients n=15
		rho	
Sadness	.15	.12	-.05
Hopelessness	.21	.23*	-.27
Sense of failure	.07	.01	-.15
Dissatisfaction	.09	.06	.41
Guilt	-.06	.08	.09
Punishment	.05	.02	.08
Dislike of self	.07	.23*	-.03
Self accusation	-.09	.17	.37
Suicidal ideation	.15	0	-.05
Crying spells	.04	.08	.10
Irritability	.03	.11	.13
Social withdrawal	.26*	.20	.36
Indecisiveness	.03	-.04	.42
Body image	.14	.36**	.44
Push to work	.25*	.11	-.17
Insomnia	.21	.12	.26
Fatigability	.25	.27*	.03
Loss of appetite	-.01	.05	.21
Loss of weight	.01	-.03	.36
Healthy worries	.00	.08	.07
Loss of libido	.11	.25*	.40
rho, Spearman´s rank correlation coefficient; *p value<.05; **p value<.01. After Bonferroni correction p value is considered significant when <.0024, (alpha divided by the number of tests (k= 21).			

In narcoleptic patients, the items of SDS correlating with ESS scores were: I feel down and blue (r=.22, p=.04), I get tired for no reason (r=.33, p=.002), my mind is as clear as it used to be (r=.26, p=.01) and I find it easy to do the things I used to (r=.29, p=.008). In controls, no items of SDS correlate with ESS scores.

Table 18. Correlation between Epworth sleepiness scale and Zung Self rating Depression scale items in narcoleptic patients, controls and idiopathic hypersomnia patients.

Items of SDS	Narcoleptics patients n=86	Healthy controls n=86	Idiopathic hypersomnia patients n=15
		r	
Depressed affect	.22*	.01	.13
Diurnal variation	.04	-.08	.03
Crying spells	.05	.18	.11
Sleep disturbance	.21	.00	-.03
Decreased appetite	.03	.01	.51
Decreased libido	.17	.16	.25
Weight loss	-.02	.07	.46
Constipation	-.01	.18	.19
Tachycardia	.03	-.01	.32
Fatigue	.33*	-.01	.36
Confusion	.26*	.14	.38
Psychomotor retardation	.29**	.07	.12
Psychomotor agitation	.17	.07	.45
Hopelessness	.03	.12	.03
Irritability	.15	.08	.29
Indecisiveness	-.00	.06	-.20
Personal devaluation	.10	.19	-.07
Emptiness	.01	-.08	-.32
Suicidal rumination	.19	0	.13
Dissatisfaction	.15	-.04	.42
SDS, Zung Self-rating Depression Scale; r, sample correlation coefficient of Pearson. After Bonferroni correction p value is considered significant when <.0025, (alpha divided by the number of test k= 20)			

CORRELATION OF ESS AND DEPRESSION SUBSCALE OF POMS

As predicted, the subscale fatigue correlates with ESS. Similarly as in BDI and SDS, there was no correlation between ESS and POMS (total and subscales) in the sample of 15 IH patients.

Table 19. Correlation between Epworth sleepiness scale and Profile of mood states in narcoleptics, idiopathic hypersomnia patients and healthy controls.

POMS	Narcolepsy patients n=86	Healthy controls n=86	Idiopathic hypersomnia patients n=15
		r	
TMD	.24*	.22*	.34
Tension- anxiety	.14	.22*	.40
Depression- dejection	.24*	.27*	.34
Anger-hostility	.20	.15	.18
Vigor-activity	-.17	-.16	-.22
Fatigue-inertia,	.28*	.16	.15
Confusion-bewilderment	.17	.09	.31
POMS, Profile of Mood States; TMD; Total mood disturbance (calculated as total of subscales excluding Vigor); r, sample correlation coefficient of Pearson; *p<.05			

EFFECT SIZE

The effect size is a measure of the power of the relationship between two variables in a statistical population. In consequence, the effect size is a complement of inferential statistics such as p-values. According to Cohen "effect sizes of .20 are small, .50 are medium, and .80 are large enables us to compare an experiment's effect-size results to known benchmarks" (Thalheimer, W. & Cook, S., 2002) (Table 20).

Table 20. Effect size of the independent groups

Test	Narcoleptics and controls		NC+ and NC-	
	Cohen´s *d*	Effect-size *r*	Cohen´s *d*	Effect-size *r*
BDI	1.07	0.47	0.53	0.25
SDS	1.39	0.57	0.35	0.17
GSD	0.88	0.40	0	0
POMS	1.18	0.51	0.39	0.19
Anxiety	1.01	0.45	0.49	0.24
Depression	0.83	0.38	0.46	0.22
Anger	0.71	0.34	0.13	0.064
Vigor	-0.72	-0.34	-0.32	-0.16
Fatigue	1.37	0.56	0.17	0.08
Confusion	1.09	0.48	0.40	0.19
Anxiety	1.01	0.45	0.49	0.24
ESS	3.2	0.84	-0.053	-0.026

BDI, Beck Depression Inventory (21 item version); SDS, Zung Self-Rating Depression Scale; SDS-sleep items, GSD, Global impression of Severity of Depression; POMS, Profile of Mood States; TMD, Total Mood Disturbance; ESS, Epworth Sleepiness Scale; Cohen´s d is defined as the difference between two means divided by a standard deviation for the data.

3.3.3. Variables influencing depression- Multivariate analysis

CONSTRUCTION OF THE MODEL

The final model was constructed including each independent variable using the backward method. The variables excluded from the final model in BDI, SDS, GSD and depression subscale of POMS scores were: Epworth sleepiness scale scores, age at onset of sleepiness, illness duration, age at the time of the study, age at diagnosis of narcolepsy (in a sleep laboratory), body mass index, symptom of cataplexy, participation in the narcolepsy support group and intake of stimulants only.

Multiple linear regression analysis showed that for BDI and SDS, the same set of variables contributed significantly to the final model, which explained 20 to 27% (BDI, SDS, GSD and Depression subscale of POMS) of the variance in patients with narcolepsy (Table 21). These variables were for BDI, SDS and depression subscale of POMS, a combination of drugs (anticataplectic and stimulants) and female sex.

In controls, none of the possible predictor variables (age, sex, sleepiness, BMI) were associated with depressive symptoms in BDI, SDS or GDS. Only in depression subscale of POMS, the variables age and sleepiness (ESS-score) together explained 13% of the variance (R^2 =.13, Age: Beta [B] =0.30 p=.005, 95% CI [-0.04,-0.01]; Sleepiness [B] =0.24 p=.02, 95% CI [0.02, 0.19]).

When probed by ANOVA, neither cataplexy nor the interaction of “type of drug” and cataplexy had an influence on depressive symptoms. Rather, “type of drug” alone had an influence on such symptoms. Post hoc-analysis (Games-Howell) showed that narcolepsy patients using stimulants and antidepressants (combination) presented more depressive symptoms than those using only stimulants, only anticataplectics or unmedicated patients.

Table 21. Multiple linear regression models for depressive symptoms in patients with narcolepsy

Independent Variables	**Dependent variables**			
	BDI	SDS	GSD	Depression subscale of POMS
	B [95%CI]			
Constant	5.536*** [3.88, 7.51]	34.117*** [31.36, 36.97]	0.824*** [0.39, 1.44]	4.322*** [2.34, 6.92]
Combination A+S	1.476*** [0.46, 3.06]	0.357*** [0.07, 0.85]	-	2.730** [0.81, 5.81]
Only A	-	-	-2.500** [3.88, 0.27]	-
Any A at all	-	-	0.706*** [0.17, 1.59]	-
Sex (Female)	0.403** [0.02, 1.25]	0.516** [0.02, 0.52]	0.362** [0.06, 0.92]	0.690* [0.02, 2.31]
r^2	.241	.201	.270	.222
F	13.15***	10.42***	9.84***	11.81***

Analyses were performed with square root transformed variables, but in the table original value are given for better comprehension. Table data correspond to the final model of each independent variable, using the backward method; the variables excluded from the final model in BDI, SDS, GSD and depression subscale of POMS scores were: Epworth sleepiness scale scores, age at onset of sleepiness, illness duration, age at the time of the study, age at diagnosis of narcolepsy (in a sleep laboratory), body mass index, symptom of cataplexy, participation in the narcolepsy support group and intake of stimulants only; A, antidepressants; S, stimulants; r^2, coefficient of determination unadjusted; BDI, Beck Depression Inventory; SDS, Zung Self-Rating Depression; Scale; GSD, Global impression of Severity of Depression; Depression subscale of POMS, Profile of Mood Disturbance; B, unstandardized Coefficient Beta; CI, confidence interval; * p<.05, ** p<.01, *** p<.001.

LOGISTIC REGRESSION

The results obtained from the regression analysis were further tested by binary logistic regression. Again, the patients using antidepressants and stimulants (combination) and females had a higher probability for depressive symptoms independent of cataplexy, BMI and age group (Table 22).

Because of the fundamental effect of antidepressants and stimulants, a logistic regression without the patients taking that combination of drugs (n=63) was carried out. Also in this analysis, cataplexy does not have an effect on depressive symptoms,

(Odds ratio [OR] = 2.05, Standard Error [SE] =1.56, Z=0.94, p=.345, 95%CI [0.46, 9.14] but sex plays a significant role (OR=7.72, SE=6.39, Z=2.47, p=.014, 95%CI [1.52, 39.10].

Table 22. Logistic regression for patients with narcolepsy with the dependent variables BDI and SDS.

BDI and SDS n=86	Odds Ratio	*SE*	*Z*	p value	95% CI [LL, UL]
Sex	8.39	5.78	3.09	.002**	[2.17,32.38]
Age group	0.91	0.17	-0.51	.612	[0.63, 1.31]
Cataplexy	0.91	0.58	-0.15	.881	[0.26,3.18]
BMI	1.68	1.14	0.77	.443	[0.44, 6.37]
Combination A+S	16.2	11.6	3.90	.000***	[4.01,66.12]

BDI, Beck Depression Inventory, SDS, Zung Self-Rating Depression Scale; dichotomized in yes (BDI > 9, SDS > 39) or no; for age group division see Methods; BMI, Body Mass Index (kg/m²) BMI classification of adults according to WHO see Methods ; A, antidepressants; S, stimulants; *SE*, standard error; LL, lower limits; UL, upper limits; CI, confidence interval;**p<.01***p<.001.

4. EMPIRICAL PART II: "NARCOLEPTICS WITH DEPRESSIVE SYMPTOMS COMPARED WITH PATIENTS WITH DEPRESSION".

4.1. Introduction

At the beginning of the last century, the etiology of the symptoms of narcolepsy was often misunderstood as psychiatric symptoms, probably because it could be not explained as a physical disease. For example, in 1924, an Austrian physician, in the heyday of psychoanalysis, described a case of a young narcoleptic man who recovered after a psychoanalytic treatment (Missriegler, 1941).

Currently, the etiology of narcolepsy is associated with a deficiency of Hcrt in the lateral hypothalamus (Nishino et al., 2000). Hcrt is associated with stress, appetite (Ganjavi et al., 2007; Taheri & Hafizi, 2002), psychiatric disorders (Borgland et al., 2010) and is involved as an antidepressant effect in a model of depression in mice (Lutter et al., 2008). This finding has again opened the debate and increased the interest in mood disorders in narcolepsy. Recently, a study from the Netherlands reported that anxiety and social phobias are more prevalent than depression in patients with narcolepsy (Fortuyn et al., 2010). This conclusion is not supported by another study showing that patients with panic anxiety had a higher CSF Hcrt concentration than patients without panic anxiety (Johnson et al., 2010).

Narcolepsy has been associated with depression for several reasons. One of them is the REM similarities at sleep onset. Another reason is that narcolepsy is a chronic illness that has a negative impact on the patients' quality of life.

Many authors have described the presence of depressive symptoms to different degrees in patients with narcolepsy (Dauvilliers et al., 2009; Rovere et al., 2008; Vandeputte et al., 2003; Daniels et al., 2001; Broughton et al., 1994; Merrit et al., 1992; Kales et al., 1982; Broughton et al., 1981; Beutler et al., 1981; Roth, 1980; Roth et al., 1975). Some authors have argued that this is an overrepresentation caused by similar symptoms between narcolepsy and depression (Vourdas et al., 2002; Adda et al., 1997). The misdiagnosis of depression is reinforced because some symptoms in narcoleptics and in patients with depression can be identical. Among these symptoms especially are the reduced energy leading to increased fatigability and diminished activity, reduced concentration and attention due to the excessive daytime sleepiness, increased weight and fragmented night sleep (American Psychiatric Association, 2000; American Sleep Disorders Association, 1991).

In the first study of this dissertation, the results confirmed that several but not all patients with narcolepsy with and without cataplexy have depressive symptoms independent of the presence of cataplexy. Therefore, in this second part, the group of narcoleptics (with and without cataplexy) was not divided into these two categories.

Several studies have compared narcoleptic patients to patients with diseases such as obstructive sleep apnea, epilepsy and IH (Broughton et al., 1994). Only two studies have compared narcolepsy patients to patients with a diagnosed depression disorder. All of these studies are focused on the polysomnography (Pollmaecher et al., 1997; Reynolds, III et al., 1983). It is not yet clear if patients with narcolepsy and high scores in questionnaires of depression exhibit similarities to patients diagnosed with depression. Furthermore, is not well known if the somatic symptoms of depression are inflating the rate of depressive symptoms reported in the literature as in other chronic diseases.

The severity of depressive symptoms in patients with narcolepsy is most frequently reported in the range of mild to moderate depression (Dauvilliers et al., 2009; Vandeputte et al., 2003). The severity of the symptoms was taken into account. In consequence, this study was conducted on patients with mild to moderate depression with the purpose of having an equal severity of depressive symptoms. This allowed the analysis of the items because BDI item means vary widely and increase at different rates relative to the total score (Beck *et al.*, 1988). For example, less “pathological” items reflecting high base rate problems (e.g., low self-esteem) approach a maximum level more rapidly than the suicidality item, which may not be endorsed unless depression is marked (Aikens et al., 1999). Furthermore, in medically ill patients, several authors using identical self-rating scales have made the distinction between physical symptoms (somatic/vegetative) and non-physical symptoms (cognitive/affective). The goal of this second study was to examine if there are differences in the self reported depressive symptoms of patients with narcolepsy from those with a primary depressive episode.

4.2. Methods

4.2.1. Procedure and questionnaires

The intensity of depression in patients with narcolepsy and depression was controlled. The procedure used was to include only patients with mild to moderate depression, defined by a score in the BDI between 10 and 40 points. According to this questionnaire, 10 points are the minimum score to describe a subject on the border of depression (Hautzinger, 1991; Beck, 1967; Beck et al., 1961).

In BDI, more than 40 points correspond to severe depression. On the one hand, the cut-off score of at least 10 points was selected because previous studies show reasonable specificity and sensitivity for predicting a depressive episode. On the other hand, depressive symptoms in narcoleptics are often presented as moderate.

The upper limit of 40 points was chosen to reduce the variance in the data. The limit seems appropriate, because none of the narcoleptic patients scored more than 40 points in BDI. The items of BDI and SDS have been described above (see section 3.2.1.Table 11 and 12). For the group of narcoleptic patients, data obtained in study 1 were used (see section 3.2.2). The depressive patients selected were those with 10 or more points but less than 41 points in Beck Depression Inventory. For the group of depressive patients, self-administered questionnaires were given to the patients during their regular medical visits. These were three validated questionnaires: the German versions of Beck Depression Inventory (BDI), Zung Self-rating Depression Scale (SDS), Global Impression of Severity of Depression (GSD), Profile of Mood States (POMS) and Epworth Sleepiness Scale (ESS). In SDS, the division between somatic and affective dimensions was not performed because is not well validated as in BDI (see results 4.3.5)

A general questionnaire regarding demographic data and questions about symptoms, diagnosis, and pharmacological treatment was given to participants together with the testing and informed consent.

4.2.2. Participants

Thirty-six narcoleptics (10 men, 26 women) with a Beck Depression Inventory (BDI) score ≥10 points and <41 points were selected from the sample of 86 narcoleptic patients in the first study (section 3). In patients with narcolepsy, the mean age at the onset of excessive daytime sleepiness (EDS) was 20.5±11.1. All were diagnosed in a Sleep Disorders Center according to ICSD-2 criteria (American Academy of Sleep Medicine, 2005). Twenty-nine were NC+ and seven were NC-. The age was between 20 and 76 years (mean 44.7±SD15.5). The mean of body mass index in patients with narcolepsy, according to the world health organization (WHO), was in the overweight range (mean 29.6±7.3) and 41.7% of them had a BMI>30.

Thirty-four outpatients with depression (12 men, 22 women) were recruited from the Bezirksklinikum (Dr. Lübbers, Dipl. Psych. Hauser) and from the private practices of psychiatrists in Regensburg (Drs. Eckl, Zacher and Kühnl). Because patients with narcolepsy are out-patients, only out-patients with a depressive episode as described

above were included. The group of patients with depression was diagnosed with mild or moderate depression (Table 23) [F32.0 and F32.1 codes ICD-10].

The age of the patients was between 19 and 74 years (mean 42.8±SD 14.6). The mean of body mass index in patients with depression was in the overweight range (mean 25.3±SD 4.9), 23.5% of them had a BMI>30.

Table 23. Description of the levels of depression with emphasis on mild to moderate depression according to ICD-10

Classification	Description
Mild depression Episode	The individual is normally distressed due to the symptoms and difficulties of continuous working and social activities but will not discontinue functioning entirely (can be with or without a somatic syndrome).
Moderate depression Episode	The individual has considerable difficulties working, with social activities or activities at home.

The control group (11 men, 25 women) was recruited from volunteers among the employees of the Bezirkskrankenhaus (psychiatric regional hospital) of Regensburg, students of the University of Regensburg and visitors of a senior citizen centre. None of the patients or control subjects were paid to participate. The age was between 19 and 78 years old (mean 44.7±SD 15.8).

The mean of body mass index in the control group was in the normal range (mean 23.4±SD 4.5) and only 2.8% of the controls had a BMI>30. Each narcoleptic patient was matched to a depressive patient by age (± 3 years), sex and mean score of Beck's depression inventory. They were also age (± 3 years) and sex matched with a healthy control subject. Exclusion criteria for the controls were the same as for the first study (see section 3.2.1). The age range of the whole sample was 19 to 78 years. Age and sex were chosen as matching variables because these are known predictors of depressive symptoms (Slone et al., 2006). There were no significant differences in the matching variables between groups. BMI was significantly different between narcoleptic patients (with depressives symptoms) ($p=.008$) and controls ($p<.001$). In BMI, there were no significant differences between controls and patients with depression ($p=.09$).

4.2.3. Statistical analysis

The significance level was set to .05 for all analyses (two tailed). To address the problem of multiple comparisons, the Bonferroni correction was used when indicated.

All data were checked for a normal distribution using the nonparametric Kolmogorov-Smirnov test. Non parametric-tests were employed to assess differences between the depressive group and the narcolepsy group (Mann-Whitney test) and for comparison with the age matched healthy control group (Kruskal-Wallis test for 3 or more independent samples). ANOVA was carried out to explore if depression (BDI, SDS, GSD, POMS) is different between women and men (effect of the first factor) and at the same time whether different age groups had different scores in depression. This analysis was done on the three groups (narcoleptics, depressives and healthy control group). A two-way ANOVA was performed to analyze if the dimensions affective/cognitive and somatic in BDI were different between groups of patients and if sex or age groups had an effect of interaction on these scores. For categorical variables, the Pearson´s chi-square test was employed followed by Fisher's exact test. After comparing the differences in items mean scores, an item by item analysis was performed using custom tables. The focus was in the hypothesis that the structure of the depressive symptoms in patients with narcolepsy is different than in patients with depression. Because multiple tests were performed, the Bonferroni adjustment was applied to column proportion tests to ensure that the alpha level (or false positive rate) specified on the test statistics tab applies to each set of tests. A post-hoc comparison test not assuming equal variances (Games-Howell) was performed when needed. Data analyses were processed using the Statistic Package for Social Sciences 16.0 (SPSS Inc. Chicago, Illinois).

4.3. Results

4.3.1. Medication use

In the narcoleptic group, the anticataplectic drugs were tricyclic antidepressants (TCA, seven patients), selective serotonin reuptake inhibitors (SSRI, five patients), serotonin-norepinephrine reuptake inhibitors (SNRI, one patient), norepinephrine reuptake inhibitors (NRI, two patients) and sodium oxybate (three patients). Five patients were taking a combination of two anticataplectic drugs (monoamine oxidase inhibitors (MAOI) and SSRI (one patient), SNRI plus SSRI (one patient), TCA plus SSRI (one patient) and sodium oxybate plus NRI or TCA (one patient). The stimulant drugs used were modafinil (20 patients), methylphenidate (four patients), and fenethylline (one patient).

In the depression group, the antidepressants were SSRI 11 patients, TCA six patients, SNRI six patients and tetracyclic antidepressants (TeCA) two patients. Nine patients were not taking antidepressant medication (Figure 8). These patients had been just diagnosed at the time of the study. None of the healthy controls were taking antidepressant.

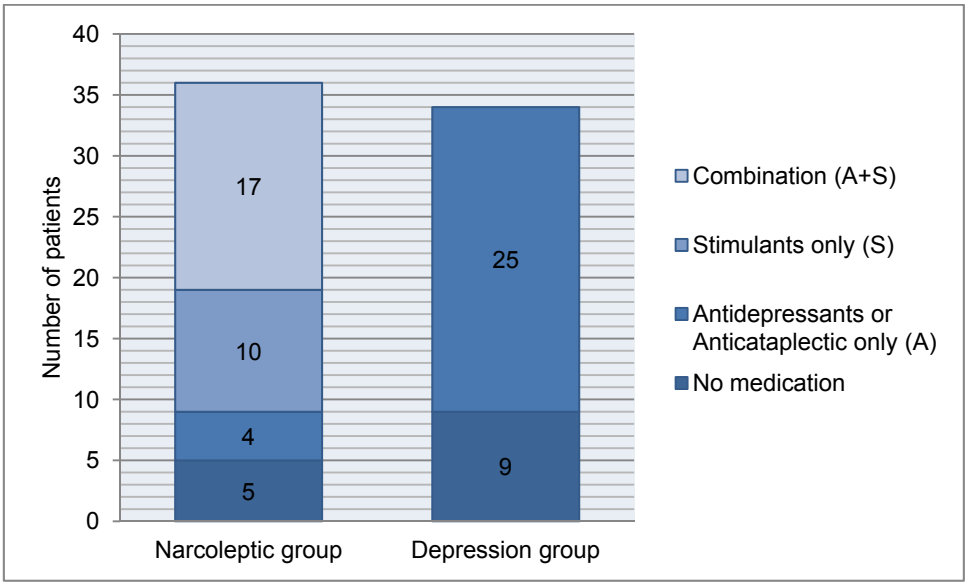

Figure 8. Patients with narcolepsy (n=36) and depression (n=34) on or not on medication; A, antidepressants; S, stimulants.

4.3.2. Comparison of mean scores and grading distribution of depressive symptoms in questionnaires

MEAN SCORES IN DEPRESSION QUESTIONNAIRES

As intended, the intensity of depressive symptoms in patients with narcolepsy was similar to patients with depression. The mean scores in measures of depression (BDI, SDS and GSD scores) for the narcoleptic group were not different from the mean scores for the same measures for the depression group. A Mann-Whitney U test did not reject the hypothesis of equals mean scores at a 5% significant level ($p>.05$). Similarly, POMS (total of mood disturbances [TMD] and sub scales) showed no significant differences between the two groups of patients ($p> .05$). For all scales (BDI, SDS, GSD, POMS [TMD and subscales]) the differences between both patient groups and the healthy controls were significant ($p> .001$). The daytime sleepiness measured by the ESS (mean score) in the narcoleptic group (mean=17.6) was higher than in the depressive group (mean=8.2). A Mann-Whitney U test demonstrated that this difference was significant ($p<.001$). The

healthy controls had a lower mean ESS score (mean=5.0) than both patients groups (p<.001, Table 24)

Table 24. Clinical data, depressive symptoms, Mood (POMS) and sleepiness (ESS) of narcoleptic patients, patients with primary depression and healthy controls.

	narcoleptic patients with depression¹ M ±SD (n=36)	*patients with depression² M±SD (n=34)*	*p value ¹vs² (two-tailed)*	*Healthy control group³ M ±SD (n=36)*	*p value ² vs³*	*p value ¹vs³*
BMI	29.6±7.3	25.3±4.9	.008	23.4±4.5	.09	<.001
%BMI>30	41.7	23.5	.020	2.8	<.001	<.001
ESS	17.6±3.3	8.2±3.6	.001	5.0±3.2	<.001	<.001
%ESS>10<16	97.2	32.4	.03	11.1	<.001	<.001
%ESS>16	61.1	0	<.001	0	0	<.001
BDI	18.6±7.3	19.6±5.9	.49	3.9±4.5	<.001	<.001
BDI-sleep items	15.8±6.6	16.47±5.6	.41	3.2±3.9	<.001	<.001
SDS	47.5±8.0	46.8±9.0	.99	28.7±7.3	<.001	<.001
SDS-sleep items	41.9±7.5	42.3±8.6	.63	26.1±6.9	<.001	<.001
GSD	4.9±2.4	5.1±2.1	.94	1.2±1.8	<.001	<.001
POMS (TMD)	61±35.8	67.8±36.2	.27	4.8±22.9	<.001	<.001
Anxiety	15.2±6.1	16.9±7.1	.15	5.3±1.3	<.001	<.001
Depression	21.8±12.4	24.4±13.1	.31	5.4±6.8	<.001	<.001
Anger	13.2±7.5	14.3±8.4	.66	5.3±4.5	<.001	<.001
Vigor	13.1±6.7	12.2±5.9	.43	19.7±7.4	<.001	<.001
Fatigue	14.7±6.0	15.2±6.8	.63	4.5±5.2	<.001	<.001
Confusion	11.4±5.2	10.7±4.9	.54	4.1±3.2	<.001	<.001

M, arithmetic mean; *SD*, standard deviation; *vs.*, versus; BDI, Beck Depression Inventory (21 item version); BDI-sleep items, BDI scores excluding 2 sleep items (see Methods); SDS, Zung Self-Rating Depression Scale; SDS-sleep items, SDS scores excluding 2 sleep items (see Methods); GSD, Global impression of Severity of Depression; POMS, Profile of Mood States; TMD, Total Mood Disturbance; ESS, Epworth Sleepiness Scale; BMI, Body Mass Index(kg/m²), significance level (two tailed)= .01 after Bonferroni correction (k=5, adjusted for comparison of BDI, SDS, GSD, POMS (total) and ESS). The Mann-Whitney or Kruskal Wallis tests statistics were performed to compare the groups depending of two or three groups.

In the questionnaires, BDI and SDS two items are directly associated with sleepiness. These items are: „I can sleep as well as before" and "I do not get more tired than usual" and in SDS are "I have trouble sleeping at night" and "I get tired for no reason".

When these two items were excluded respectively from BDI and SDS, the total scores were still higher in the patients with narcolepsy than in controls and patients with depression (Table 24).

GRADING DISTRIBUTION OF DEPRESSIVE SYMPTOMS

When the clinical grading of the BDI and the SDS scores was applied, the distribution over the resulting groups was not different between narcoleptic and depressive patients (BDI: Pearson´s chi-square=4.86 p>.05, Fisher's exact test=4.84 p>.05, SDS: Pearson Chi-square = p>.05, Fisher's exact test= p>.05, Figure 9 and 10).

A significant difference in the grading of BDI and SDS was found between narcoleptics and healthy controls. The same result was obtained when comparing depressives and controls (p<.05). ANOVA shows that in BDI, SDS and ESS, the difference between groups was significant (p<.001). Post-hoc comparisons were performed using the method of Games-Howell. When both groups were compared in the grading of ESS (%ESS score >10<16 and %ESS>16), depressive patients and controls were found to be significantly lower than narcoleptics (p<.001), but no differences between depression group and controls were found. Seven narcoleptics and six depressive patients showed severe depression in the SDS. In BDI, three narcoleptics and two depressive patients were in the „moderate to severe depression" category. None of the patients were in the "severe depression" group, and none of the controls had more than mild depression on either of the scales.

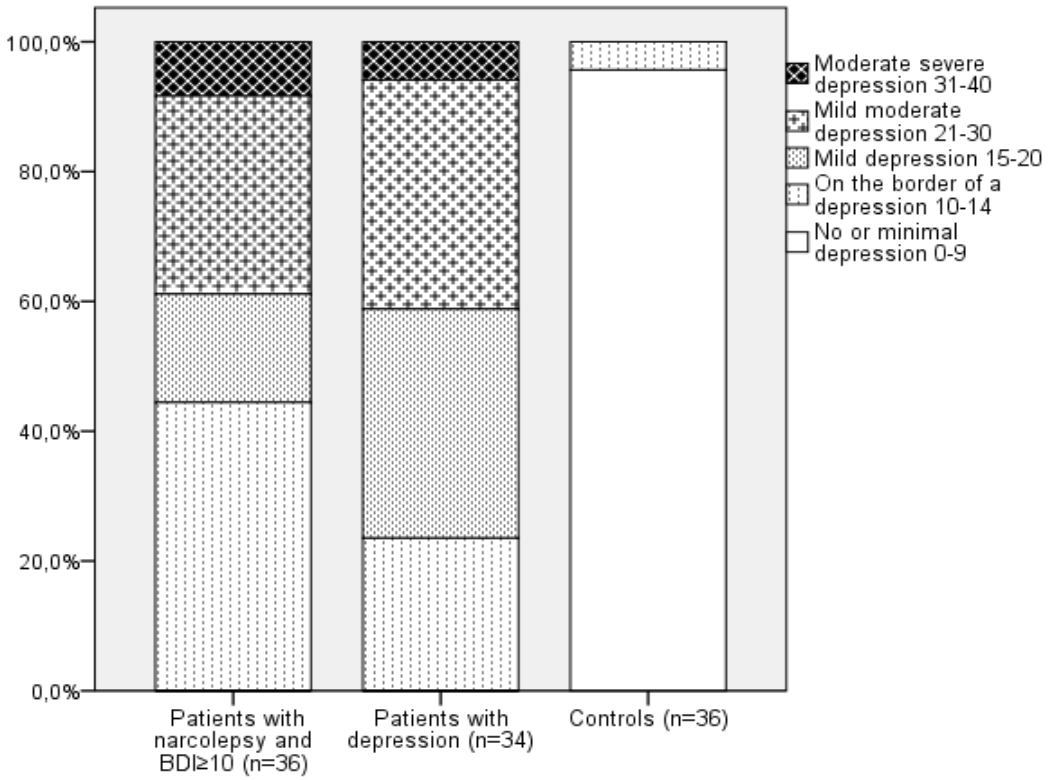

Figure 9. Graded distribution of depressive symptoms in patients with narcolepsy, depression and in controls according to Beck Depression Inventory. Patients with narcolepsy and primary depressive patients showed no differences. Both patient groups are different to healthy controls.

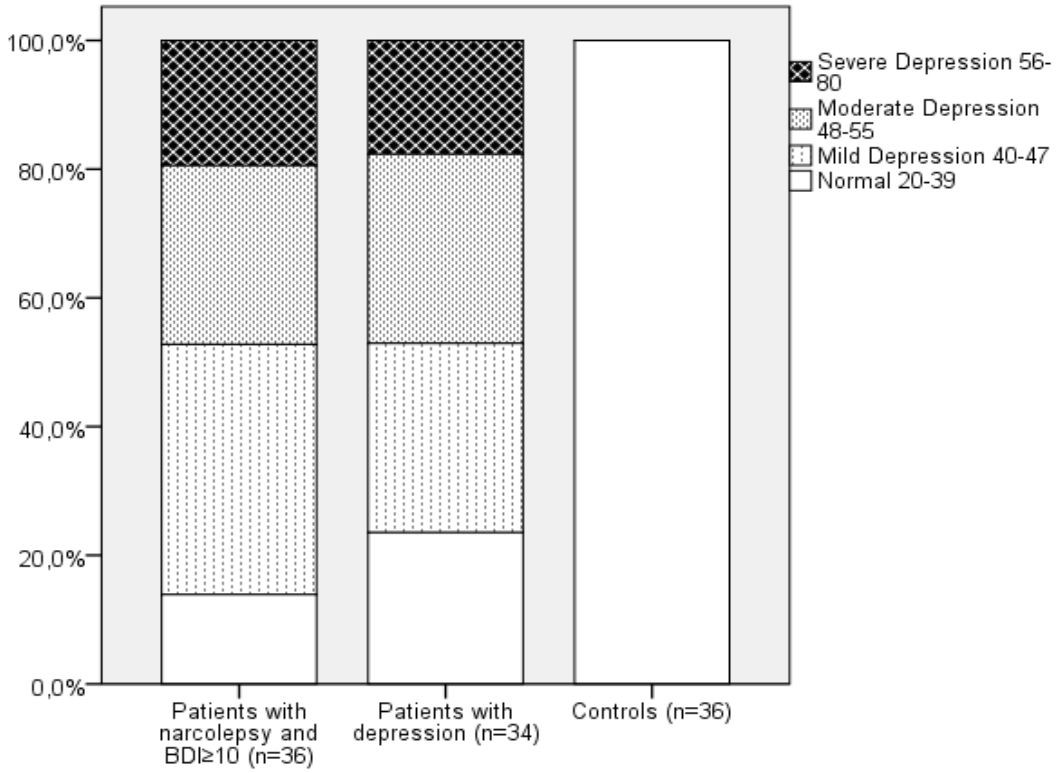

Figure 10. Graded distribution of depressive symptoms in patients with narcolepsy, depression and in controls according to Zung self-rating Depression scale. Patients with narcolepsy and primary depressive patients showed no differences. Both patient groups are different to healthy controls.

4.3.3. Correlations between different measures of depression

The narcoleptic, depressive patients and the control group showed a positive correlation among all scales of depression used in this study (Table 25).

Table 25. Pearson's correlations between tests assessing symptoms of depression in patients with narcolepsy, primary depression and controls.

Measure	Patients with narcolepsy n=36	Patients with depression n=34	Healthy controls n=36
		r	
SDS vs. BDI	**.73****	**.71****	**.75****
SDS vs. GSD	**.51****	**.69****	**.73****
BDI vs. GSD	**.41***	**.69****	**.56****

r= Pearson correlation, two sided p value *p<.05, **p<.01. SDS: Zung Self-rating Depression Scale, BDI: Beck Depression Inventory, GSD: Global impression of Severity of Depression.

No correlation was found between the ESS and the total scores in the depression scales (BDI, SDS; GSD) within the groups (Table 26). However, several items correlate with ESS points obtained by narcoleptics, patients with primary depression and controls.

Concerning the correlation between ESS and items of BDI and SDS in the sub-sample of 36 narcoleptic patients with depressive symptoms, in BDI, there were no items correlating with ESS scores in this group. In SDS, the items correlating with ESS scores were: “I get tired for no reason” (item 10) and “my mind is as clear as it used to be” (item 11). Both items had the same degree of correlation ($r=.36$, $p=.03$).

Table 26. Spearman correlations between ESS scores and items of BDI in narcoleptics, depressive patients, and healthy controls.

Items BDI	Epworth sleepiness scale (total scores)		
	Narcoleptic patients n=36	Depression patients n=34	Controls *n*=36
	rho		
Sadness	.31	.38	.18
Pessimism	.14	.29	.34
Sense of failure	-.00	.10	-.13
Dissatisfaction	.06	.16	.16
Guilt	-.17	.19	.09
Expectation of Punishment	-.19	-.22	-.29
Dislike of self	.02	.00	.24
Self accusation	-.10	.09	.21
Suicidal ideation	.11	-.05	0
Crying spells	-.14	.07	.24
Irritability	-.07	.06	.06
Social withdrawal	.20	.28	.28
Indecisiveness	-.20	.01	-.02
Change of body image	.13	-.23	.32
Push to work	.31	.29	.12
Insomnia	.21	-.13	-.01
Fatigability	.18	.30	.18
Loss of appetite	-.06	.25	.17
Loss of weight	-.07	.13	0
Health worries	-.10	.10	.17
Loss of libido	.03	-.38	.14

ESS, Epworth Sleepiness Scale; BDI, Beck Depression Inventory; rho, Spearman´s rank correlation coefficient. Note: after Bonferroni correction, p value is considered significant when <.0024, (alpha divided by the number of test (k= 20).

Concerning the correlation between ESS and items of BDI and SDS in the sample of 34 patients with primary depression, in BDI, the items correlating with ESS scores were: item A “sadness” (r=.38, p=.03) and negative correlation with item U “loss of libido” (r=-.38, p=.03). In SDS no items correlated with ESS scores in this group.

Concerning the correlation between ESS and items of BDI and SDS in the sample of 36 matched controls, in BDI only the item B “pessimism” correlated with ESS scores (r=.34, p=.04). In SDS, there were no items correlating with ESS scores in this group.
Finally, a correlation shows that the items “sadness” and “loss of libido” of BDI correlate with sleepiness (ESS) (Table 27).

Table 27. Spearman correlations between ESS scores and items of SDS in narcoleptics with depressive symptoms, in depressive patients, and in healthy control group.

Items SDS	ESS (total scores)		
	Narcoleptic patients n=36	Depression patients n=34	Healthy controls
		rho	
Depressed affect	.28	.21	.15
Diurnal variation	.09	.33	.11
Crying spells	-.03	-.11	.21
Sleep disturbance	.21	-.23	-.18
Decreased appetite	.04	-.09	-.16
Decreased libido	.06	-.16	-.05
Weight loss	-.06	.15	.20
Constipation	-.09	.05	.19
Tachycardia	-.18	.16	.08
Fatigue	.36	.32	.08
Confusion	.36	-.01	.25
Psychomotor retardation	.18	.24	-.00
Psychomotor agitation	.18	-.06	.10
Hopelessness	.07	.16	.31
Irritability	.30	.09	.04
Indecisiveness	-.08	.18	.04
Personal devaluation	.18	.14	.25
Emptiness	-.01	-.06	-.14
Suicidal rumination	.10	.09	0
Dissatisfaction	.21	.10	-.02

ESS, Epworth Sleepiness Scale; SDS, Zung Self-rating Depression Scale; rho, Spearman´s rank correlation coefficient.After Bonferroni correction, p value is considered significant when <.0024, (alpha divided by the number of test (k= 21).

Table 28. Spearman correlation between ESS (total scores) and POMS (total and sub scales) in narcoleptics, depressive patients, and healthy controls.

POMS	ESS (total scores)		
	Narcoleptic patients n=36	Depressive patients n=34	Healthy controls n=36
		rho	
TMD	.25	.21	.30
Tension- anxiety	.32	.24	.26
Depression- dejection	.32	.20	.20
Anger-hostility	.20	.13	.06
Vigor-activity	-.20	-.30	-.31
Fatigue-inertia,	.27	.24	.18
Confusion-bewilderment	.15	.23	.08

ESS, Epworth Sleepiness Scale; POMS, Profile of Mood States; TMD; Total mood disturbance (calculated as total of subscales excluding Vigor); rho, Spearman´s rank correlation coefficient. Note: after Bonferroni correction, p value is considered significant when <.01 (alpha divided by the number of subscales of POMS (k= 5)

4.3.4. Age and sex differences

When age (as continous variable) was considered in controls (partial correlation), Vigor [sub scale POMS] was the unique factor that correlated with ESS scores (r=-.37, p=.03).

When age was controlled in patients with narcolepsy (partial correlation), Depression and Fatigue [sub scales POMS] correlated with ESS (respectively r=.41, p=.01, r=.35, p=.04).

When age was controlled in patients with depression, it was found for a second time that no factor correlated with ESS.

Women with narcolepsy had higher scores than men with narcolepsy in BDI scores excluding items of sleep and in Tension [sub scale POMS]. This difference was significant using a Mann-Whitney U test (respectively U=67, p=.03; U=61, p=.01 (two-tailed)). Comparing the depression group and controls, no differences were found in any of the measures with respect to sex.

4.3.5. Somatic and affective items: differences between groups

In narcoleptics and depressive patients the scores in cognitive and somatic dimensions had a normal distribution using the Kolmogorov-Smirnov test (Cognitive dimension p=.271, Somatic dimension p=.122).

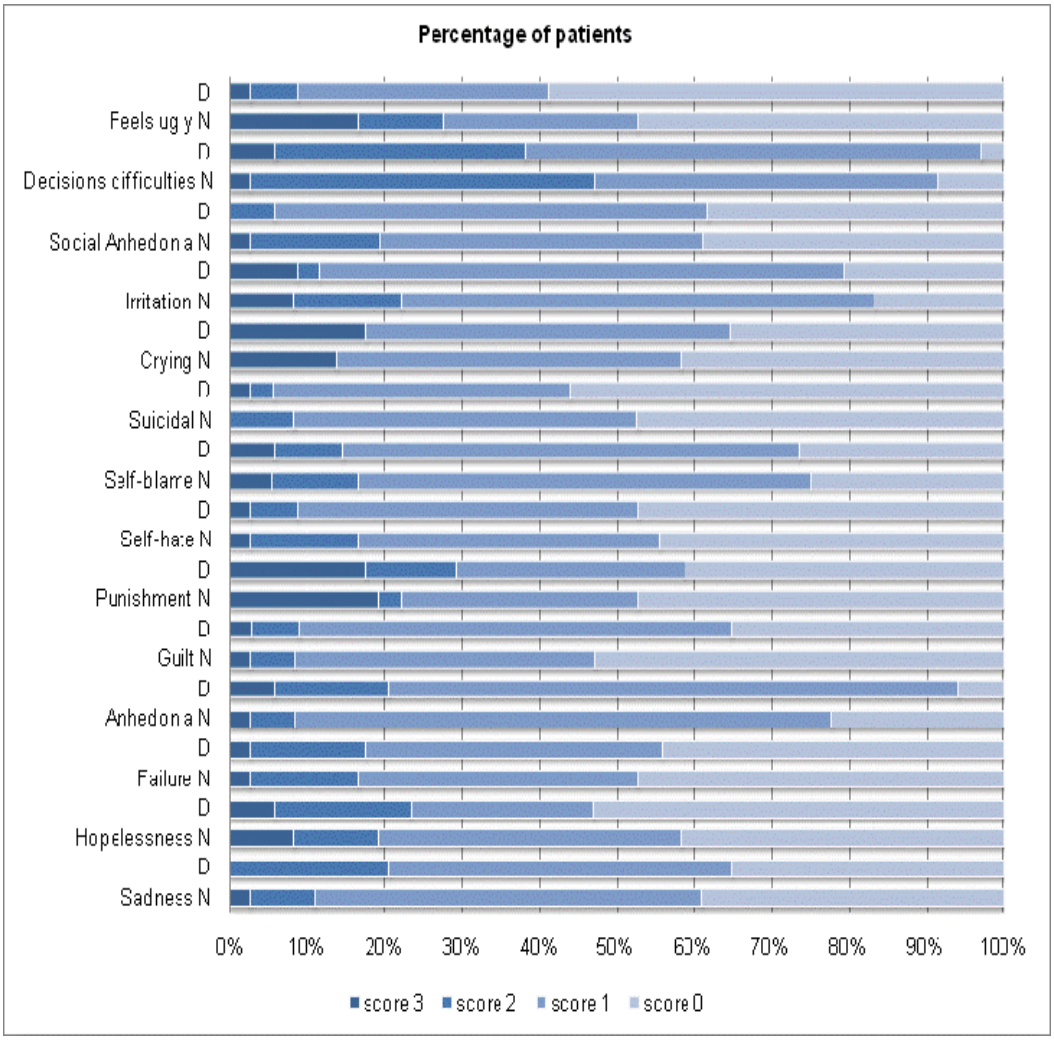

Figure 11. Characteristics of the cognitive dimension of depressive symptoms according to the Beck Depression Inventory in narcoleptic [N] (n=36) and depressive patients [D] (n=34). The highest score in a single item is three, and the lowest score is zero.

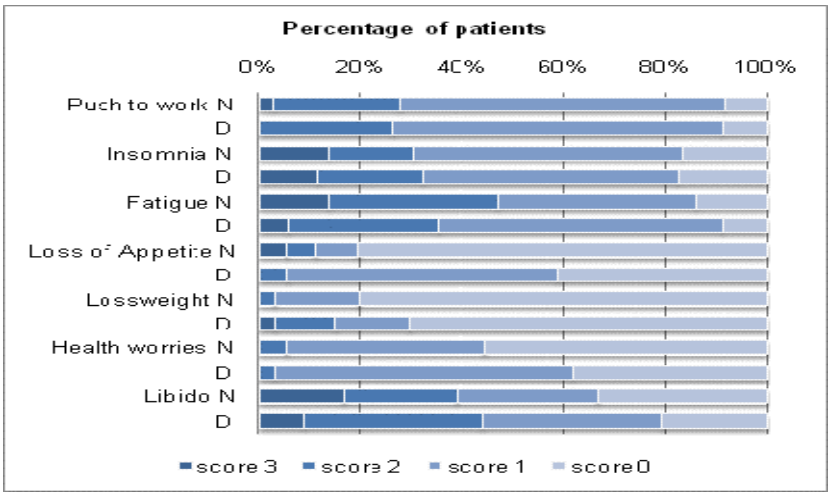

Figure 12. Characteristics of somatic dimension of depressive symptoms according to the Beck Depression Inventory in narcoleptic [N] (n=36) and depressive patients [D] (n=34). The highest score in a single item is three, and the lowest score is zero.

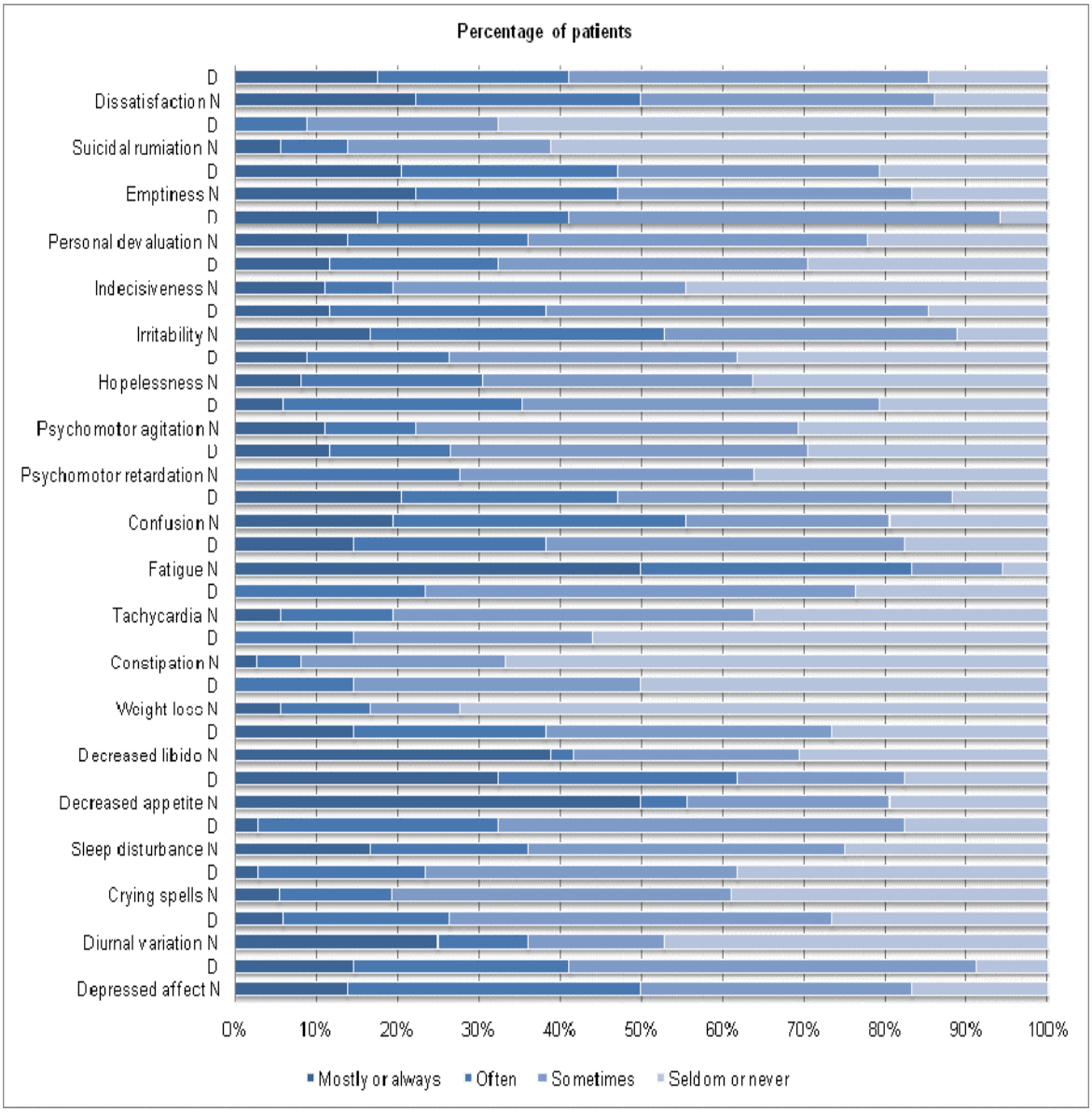

Figure 13. Characteristics of depressive symptoms according to the Zung Self-rating Depression Scale (SDS) in narcoleptic [N] (n=36) and depressive patients [D] (n=34). The highest score in a single item is four (i.e. mostly or always), and the lowest score is one (i.e. seldom or never).

Regarding to the differences in the dimensions, both patients groups had higher scores in somatic and affective items (Figure 11 and 12) compared to controls (respectively mean ranks narcoleptics=68, depressives=72 and controls=22, Kruskal-Wallis [KW] test x^2 (df 2) =59; p<.001; narcoleptics=69.1, depressives=71 and controls=21.4. KW test x^2 (df 2) =60; p<.001).

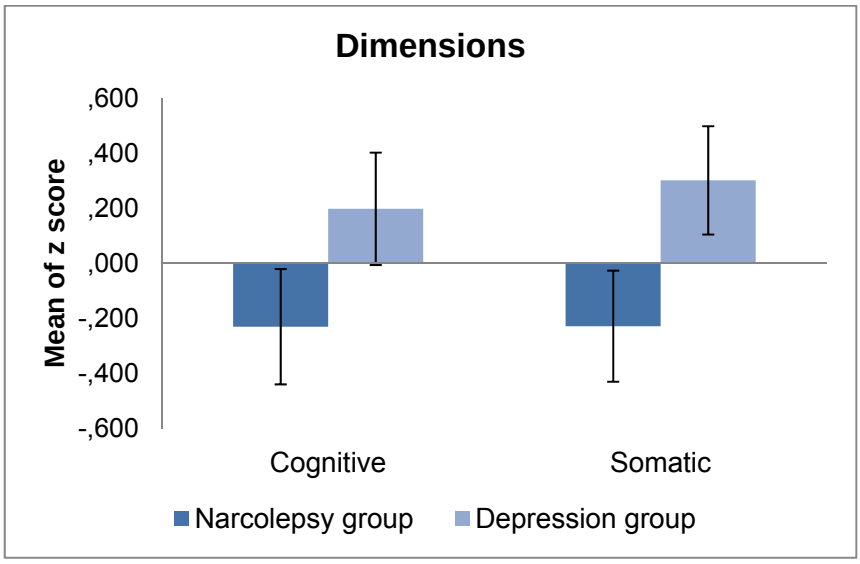

Figure 14. Mean of z scores of narcolepsy and patients group in cognitive and somatic dimension of Beck Depression Inventory. The raw scores were standarized in z scores. Z scores represents the distance between the raw score and the population mean in units of the standard deviation. The mean of z score is negative when the raw score is below the mean and is positive when above.

When the dimensions were tested with a mixed-design ANOVA, the main effect of the groups (depressive and narcoleptics) was significant. The depressive group showed higher scores in both dimensions ($F(1,50)=4.07$, $MSE=5.85$, $p<.05$, partial-eta-squared=.075). The variables sex or age group were not significant (respectively $F(1,50)=.003$, n.s.; $F(1,50)=1.33$, $MSE=1.91$, n.s). Moreover, the interactions of these three factors (illness group, sex and age group) were not significant (respectively $F(1,50)=.29$ $MSE=.43$, n.s; $F(4,50)=.99$, $MSE=1.43$,n.s., $F(4,50)=.45$, $MSE=.65$, n.s., $F(4,50)=.07$, $MSE=.10$, n.s.).

4.3.6. Differences in the structure of depressive symptoms between narcoleptic and depressive patients

The mean scores of BDI items showed significant differences between narcoleptic and primary depressive patients in the item anhedonia and loss of appetite (Mann-Whitney U test z=-2.993, p=.003, z=-2.697, p=.007 respectively). The depressive group reported higher scores in both items (Figure 15).

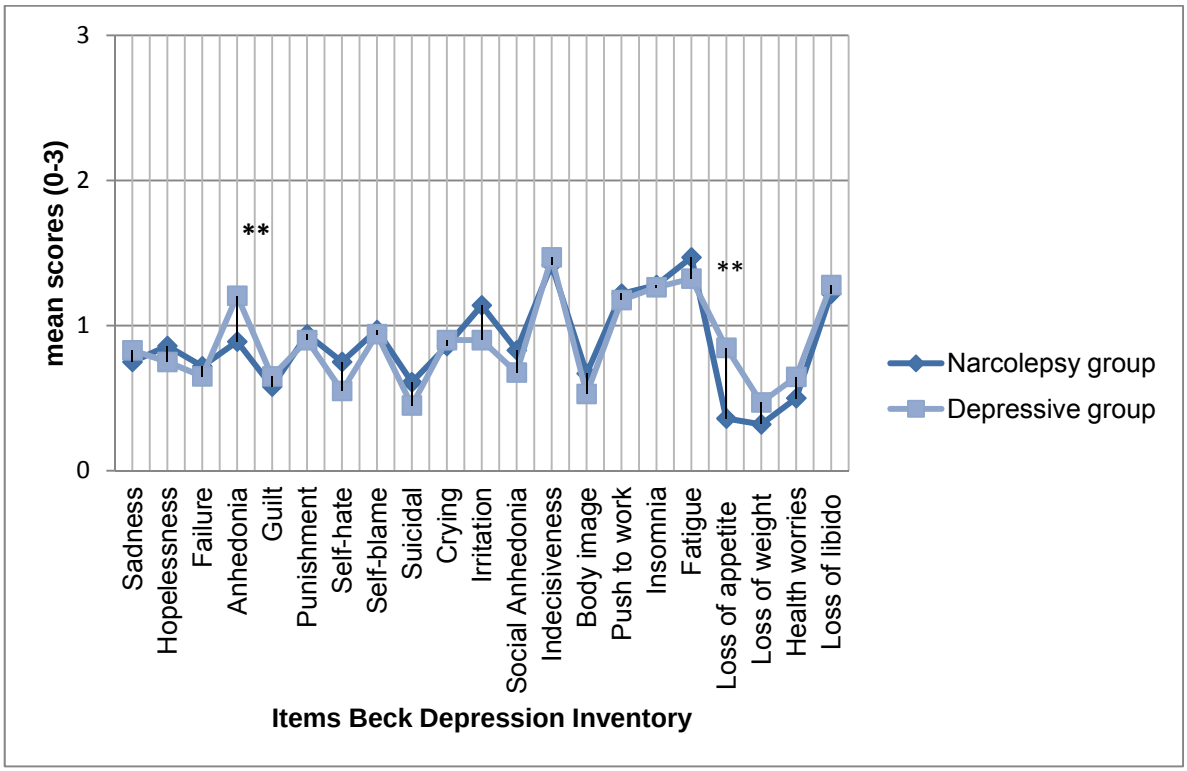

Figure 15. Mean scores of Beck Depression Inventory items. ** p value<.001.

The mean scores of SDS items showed significant differences between narcoleptic and primary depressive patients only in the item fatigue (Mann-Whitney U test z=-3.769, p=.0001). As expected narcoleptic patients reported higher scores in the item “I get tired for no reason” (Figure 13 and 15)

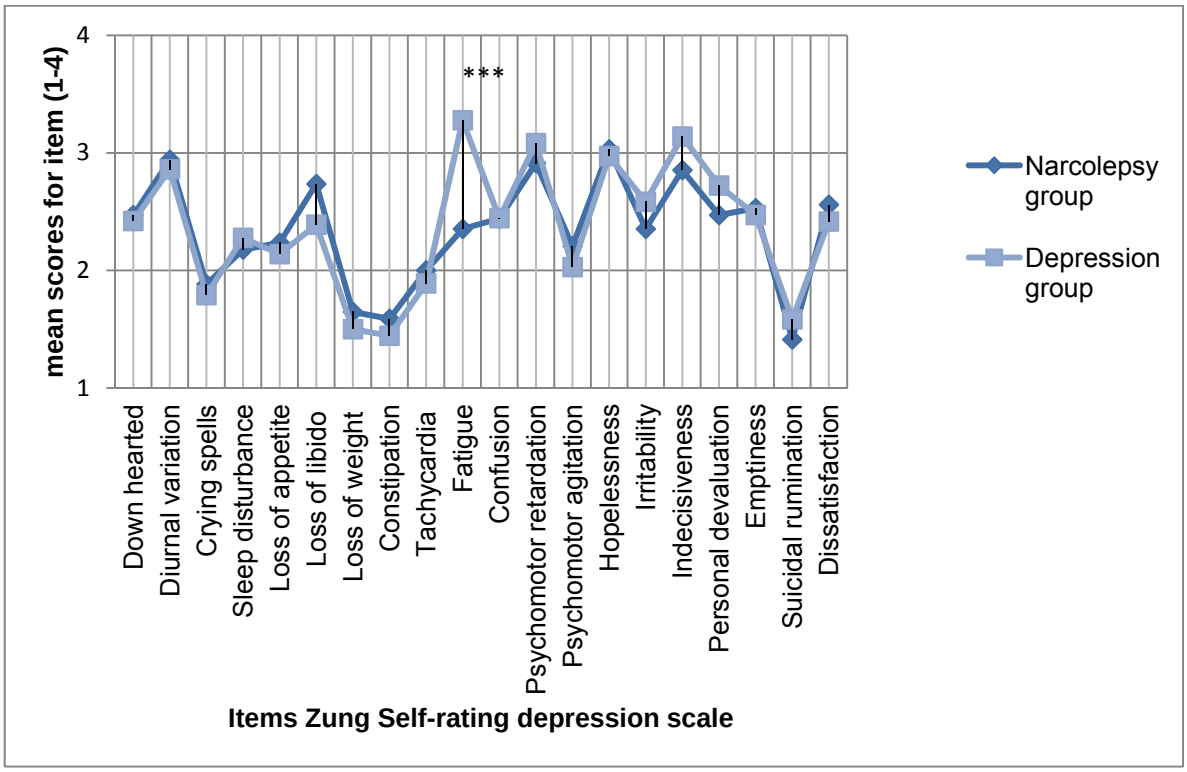

Figure 16. Mean scores of Zung Self-Rating Depression Scale items in narcoleptic and depressive patients. *** p value<.0001.

A finer analysis of the answers showed that the results reaching statistical differences using the Bonferroni adjustments for multiple answers in BDI were items D, R and T (see methods). In item D, dissatisfaction/anhedonia, narcoleptic patients were more likely to continue to feel pleasure than before compared to patients with depression.

For item R, loss of appetite, narcoleptic patients responded more often that their appetite was not worse than usual compared to patients with depression, and for the same question (second category also significant), patients with depression declared that in fact their appetite was not as good as it used to be.

Finally, for the item T, health worries, narcoleptic patients answered more often that they were not worried about physical problems compared to patients with depression who mostly answered that they were, in fact, very worried about physical problems..

The results reaching statistical differences using the Bonferroni method for multiple answers in SDS were Items 2 (Morning is when I feel the best), 5 (I eat as much as I used to), 6 (I still enjoy sex), and 7 (I notice that I am losing weight) . Patients with narcolepsy were less impaired in diurnal variation (2), appetite (5), loss of libido (6) and loss of weight (7) than patients with depression.

5. EMPIRICAL PART III: "FACTOR ANALYSIS OF BECK DEPRESSION INVENTORY IN PATIENTS WITH NARCOLEPSY".

5.1. Introduction

Depressive symptoms in varying degrees are typically reported in narcoleptics using mostly the Beck Depression Inventory (Dauvilliers et al., 2009; Vandeputte et al., 2003; Morrish et al., 2001; Daniels et al., 2001; Adda et al., 1997; Pawluk, Hurwitz, Schluter, Ullevig & Mahowald, 1995), in addition to other assessment tools (Mosko et al., 1989; Beutler et al., 1981; Roy, 1976; Roth et al., 1975). In line with these findings, instruments evaluating quality of life have emphasized the presence of a high level of depressive symptoms (Ozaki et al., 2008; Dodel et al., 2007; Ervik et al., 2006; Vignatelli et al., 2004). Others using structured psychiatric interviews have reported that patients with narcolepsy do not meet the criteria for a lifetime depression in a greater degree compared to control subjects (Vourdas et al., 2002). These conflicting results suggest that depressive symptoms in narcolepsy patients are over represented due to somatic symptoms. Nonetheless, the first study of this dissertation shows that even when the questions directly related with sleep were excluded, narcoleptics exhibited more depressive symptoms than sex and age matched controls. Emmons et al (1987), who found that there was no difference in the total BDI scores between medically ill patients and psychiatric inpatients, did find significant differences in the cognitive/affective items. In patients seeking a surgery for weight loss, Munoz et al (2007) found that patients were more likely to display somatic items than cognitive items. This is relevant because of the overlapping physical symptoms of depression and obesity. This is similar to the situation of patients with narcolepsy, which is even more difficult because most of these patients are pathologically sleepy. Furthermore, most of them are obese. An analogous condition is in patients with an obstructive sleep apnea syndrome where depressive symptoms are widely reported (Kjelsberg, Ruud & Stavem, 2005; Schroder & O'Hara, 2005; Sharafkhaneh, Giray, Richardson, Young & Hirshkowitz, 2005; Bardwell, Berry, Ancoli-Israel & Dimsdale, 1999). A study using BDI found that the association between sleep apnea severity and depressive symptoms is related with the subset of somatic items more than with cognitive items (Aloia et al., 2005).

As shown in the first study, women with narcolepsy were more depressed than men. Further, women are traditionally believed to be more sensitive to weight than men. These beliefs have been probed in the study of Lim et al 2008, who reported that women are

more influenced by body size, and that depression scores in men are relatively independent of different measures of obesity. It would therefore not be surprising if body image played a role in the depressive symptoms of narcoleptics and especially in women.

Regarding BDI, cut off scores are used to indicate the presence of depression. These cut off scores can vary when used in medical populations as a consequence of the overlap between symptoms of depression and physical symptoms. Therefore, some authors found an overestimation in the prevalence and severity of depression in medically ill patients compared with a clinical assessment of depression (Clark et al., 1983).

Previous research in BDI has identified a two factor approach to depression: the cognitive/affective items and somatic items. BDI cognitive/affective represents the sum of the first 13 items of the BDI and BDI somatic items is formed by the sum of the scores of the last eight items (Beck & Steer, 1993).The purpose is to facilitate find out the primary cause of a patient´s depression.The first one describes depressive thoughts, feelings and beliefs and the second one reflects the health worries or physical discomfort (Beck et al., 1961) Somatic items can be less useful in patients with chronic illness but can also help in the diagnosis (Cavanaugh, 1984).

A factor analysis was conducted to explore the relationships among items in the BDI and to determine if these relationships can be summarized in a small number of latent constructs. The purpose of performing a factor analysis is to reduce the items of BDI to explain the results obtained by narcoleptics. The goal is to find the minimal factors that clarify most of the information given by narcoleptics in the 21-item version of BDI.

Beck, Steer and Garbin identified three factors from a review of 13 factor analysis studies: Negative attitude toward self, performance impairment and somatic disturbance (Beck, Steer & Garbin, 1988).The relevance of this concern is that patients with narcolepsy may appear to be depressed based on total scores while, in fact, this is more representative of their medical stress rather than cognitive and affective features of depression. Moreover, this could be the case not only for the items of BDI specifically related with sleep but also for the rest of the somatic items. Factor analysis of the BDI has been reported for many psychiatric and non-psychiatric populations. Despite the extensive use of BDI in narcoleptic patients, there are no studies investigating the factor structure on patients with narcolepsy.

The BDI was developed to assess depression as a syndrome but not as a nosologic entity. This means that depressive symptoms are supposed to be present in affective disorders but are not necessarily excluded from, for example, anxiety or schizophrenia. Within the same argument, Kendall emphasizes that high scores can also reflect stressful life events

or transitory distresses that are not always part of an affective disorder and that individuals with very low scores may have other forms of psychopathology such as psychopathy or hypomania (Kendall, 1987). The aim was to find the minimal factors that explain depressive symptoms in narcoleptic patients and the hypothesis is that the components related to somatic items of BDI will be more relevant when compared to components associated with cognitive items.

5.2. Method

5.2.1. Participants

The total number of patients was increased to meet the basic requirements of a factor analysis. The sample size must be considered in an exploratory factor analysis. The recommended is not less than 100 individuals for any analysis.

The sample was made up of 114 Caucasian narcoleptic patients (62 women, 52 men) with and without cataplexy. 28 patients were recruited during the annual meeting of the German narcolepsy association (a patient support group). They complemented the sample of 86 narcoleptic patients in study 1 (section 3) to run the analysis. All patients were diagnosed according to the ICSD-2 and were between the ages of 19-79 years (mean=47±.17.2).

5.2.2. Procedure and questionnaire

The Beck Depression Inventory (BDI) is a self-rating scale comprised of 21 questions related to depressive symptoms. The score increases with the severity of depression and originally is graded as follows: from 0-9 points: no or minimal depression, 10-14 points: on the border of depression, 15-20 points: mild depression, 21-30 points: mild to moderate depression, 31-40 points: moderate to severe depression, and 41-63 severe depression (Hautzinger, 1991; Beck et al., 1961). It has been translated into a variety of languages. A German manual is provided by Hautzinger, and its reliability and validity is well documented (Hautzinger, 1991). The cognitive/affective items of BDI as identified by Beck et al. (1988) are sadness, hopelessness, sense of failure, anhedonia, guilt, punishment, self-hate, self-blame, suicidal, crying, irritation, social anhedonia, difficulty in making decisions and feeling ugly. The somatic items are a push to work, late insomnia, tiredness, loss of appetite, weight loss, health worries and loss of libido.

5.2.3. Statistical analysis

An exploratory factor analysis (EFAs) was processed using the Statistic Package for Social Sciences 16.0 (SPSS). Components were restricted to those with characteristic

roots or eigenvalues > 1. Only variables with rotated loadings ≥.5 are included to generate components with unique variables, a only post rotation components are reported with percentages of variance explained. The approach used to decide how many factors were retained was the statisitical significance test according to Barlett. The extraction method performed was a principal component analysis (PCA) and the rotation method used was promax with Kaiser Normalization. Promax was selected because it is an oblique method which allows factors to correlate with each other, as expected for BDI factors.

5.3. Results

5.3.1. Somatic and cognitive items of BDI

The scale reliability (Cronbach`s alpha) for the present study participants was .89, indicating a high internal consistency of the items. The mean BDI score for the sample was 10.9 (SD=8.8, median=9, CI 95% [9.3, 12.5]). The mean for cognitive items 6.5 (SD=6.8) and for somatic items was 4.3 (SD=2.6).

Table 29. Descriptive statistics for each item of the Beck Depression Inventory (BDI) in patients with narcolepsy (n=114) in descending order.

Item type	Name of the BDI item	*M*±*SD*	95% CI [UL, LL]
Somatic	Fatigue	0.99±.85	[0.99, 1.15]
Somatic	Insomnia	0.91±.93	[0.74, 1.08]
Somatic	Push to work	0.86±.66	[0.74, 0.98]
Somatic	Sexuality	0.82±1.01	[0.64, 1.01]
Cognitive	Decisions	0.82±.79	[0.67, 0.96]
Cognitive	Irritable	0.71±.77	[0.57, 0.85]
Cognitive	Self-criticism	0.61±.72	[0.47, 0.74]
Cognitive	Anhedonia	0.55±63	[0.44, 0.67]
Cognitive	Crying spells	0.47±.90	[0.31, 0.64]
Cognitive	Body image	0.46±.86	[0.30, 0.63]
Cognitive	Punishment	0.46±.82	[0.30, 0.61]
Cognitive	Failure	0.42±.75	[0.28, 0.56]
Somatic	Health worries	0.39±.54	[0.29, 0.49]
Cognitive	Sadness	0.38±.64	[0.26, 0.50]
Cognitive	Future	0.37±.74	[0.23, 0.51]
Cognitive	Social anhedonia	0.36±.64	[0.24, 0.48]
Cognitive	Self-disappointment	0.35±.64	[0.23, 0.47]
Cognitive	Guilt	0.33±.63	[0.22, 0.45]
Cognitive	Suicidal thoughts	0.28±.51	[0.19, 0,37]
Somatic	Loss of appetite	0.18±.57	[0.08, 0.29]
Somatic	Weight loss	0.18±.52	[0.08, 0.27]
M, Mean ; SD, standard deviation ; CI, Confidence interval ; UL,upper limit ; LL lower limit.			

When the group was divided by sex, women reported more depressive symptoms in the cognitive area (Table 30).

Table 30. Comparison of somatic and cognitive items of BDI in narcoleptic patients by sex.

BDI items	**Narcoleptic patients**		**U**	**Z**	**p value (two sided)**
	Women n=62 *M*±*SD* 95%CI [LL, UL]	Men n=52 *M*±*SD* 95%CI [LL, UL]			
Total scores	13.4±10.1 [10.1, 16.0]	7.9±5.8 [6.3, 9.5]	1078	-3.04	.002
Somatic items	4.8±3.0 [4.1, 5.6]	3.7±2.0 [3.2, 4.3]	1274	-1.94	.053
Cognitive items	8.6±7.8 [6.6, 10.6]	4.1±4.3 [2.9, 5.3]	1058	-3.16	.002

M, arithmetic mean; *SD*, standard deviation; BDI, Beck Depression Inventory; CI, confidence interval; LL, lower limit; UL, upper limit, U, Mann –Whitney test statistic, Z, standardized score, the value of U divided by its standard error.

5.3.2. Exploratory factor analysis (EFAs)

The Barlett test of sphericity [Chi-square (df= 210) =1.029E3, p>.001] indicating sufficient overlap among Beck items (variables) was used to perform this analysis. The Kaiser-Meyer-Olkin (KMO) measure of sample adequacy was 0.866, which indicates that the factor matrix was adequate for data reduction.

Table 31. Eigenvalues and percentage of variance explained by each component of the model.

Component	Eigenvalues	% variance	% cumulative variance explained
1	7.11	33.87	33.87
2	1.86	8.84	42.71
3	1.41	6.72	49.43
4	1.25	5.97	55.41
5	1.19	5.64	61.05
6*	1.02	4.84	65.89

Note: Eigenvalues represents the explanatory importance of the factors with respect to the variables. *This component comprises only one item and therefore was eliminated.

The obtained solution comprised five components model. These first five components explained a prudent level of variance (Table 31). The total of variance explained by this model is 60.7%. Solutions with more components were unacceptable because contain only one item and each component must consist of at least two items.

Table 32. Factor loadings for exploratory factor analysis with promax rotation of Beck Depression Inventory (BDI) items.

	Item BDI	Negative attitude toward self 36% of variance	Negative mood 7.5% of variance	Interpersonal relations 6.1% of variance	Sleep 5.5% of variance	Eating 5.1% of variance
Affective /Cognitive items	A. Sadness	.150	**.756**	**.**049	.114	.055
	B. Hopelessness	.079	**.668**	.237	.030	.061
	C. Sense of failure	**.725**	.228	.265	.044	.023
	D. Anhedonia	**.**156	**.651**	.252	.326	.108
	E. Guilt	**.710**	.219	.049	.072	.024
	F. Punishment	**.805**	.257	.286	.039	.174
	G. Self hate	**.753**	.191	.189	.131	.050
	H. Self blame	**.909**	.219	.017	.121	.201
	I. Suicidal ideation	.125	**1.013**	.306	.019	.043
	J. Crying spells	.311	.286	**.656**	.021	.186
	K. Irritability*	.003	.216	.183	.298	.271
	L. Social Anhedonia	.064	.270	**.659**	.031	.032
	M. Indecisiveness*	.418	.357	.057	.158	.134
	N. Body image*	.327	.187	.330	.141	.203
Somatic items	O. Push to work *	.133	.367	.148	.194	.007
	P. Insomnia	.013	.148	.285	**1.087**	.141
	Q. Fatigue	.110	.041	.092	**.521**	.149
	R. Loss of appetite	.291	.016	.154	.195	**.747**
	S. Loss of weight	.230	.016	.334	.302	**.809**
	T. Health worries*	.096	.101	.004	.146	.163
	U. Loss of libido	.151	.051	**.981**	.253	.224

Factor loadings>.50 are in boldface. Items were considered to load on a factor if the rotated factor loadings was at least 0.5. *factor loadings<.50. Each component must consist of at least two items (here loading refer to pattern coefficients). Porcentage of variance in the data accounted by the rotated factor solution. The total of variance explained by this model is 61%.

Solutions with fewer factors revealed an inadequate amount of residual variation. The five solution generated distinct components, each composed of between two and four items. Some items of BDI did not load on a factor with minimum expected (0.5), these items are reported with an asterisk (Table 32).

The first component was called negative attitude toward self, which accounted for the 36% of the variance and was composed of five items: self-hate, self-blame, expectations of punishment, guilt and sense of failure. The second component, called negative mood, explained 7.5% of the variance and was composed of four items: suicidal ideation, sadness, anhedonia and hopelessness. The third component, social interpersonal relations, explained 6.1% of the variance and was composed of three items: loss of libido, social anhedonia and crying spells. The fourth component was sleep which made up 5.5% of the variance. It was composed of the two items insomnia and fatigability. The fifth component, eating, explained 5.1% of the variance and was composed of two items: loss of appetite and lose of weight.

6. DISCUSSION

6.1. Discussion empirical part I: "Depressive symptoms in narcolepsy with and without cataplexy and idiopathic hypersomnia"

In this study, the question of whether depression in narcolepsy is an epiphenomenon or if it is inherent to the disease itself was attempted to answer. An epiphenomenon is defined as "an accidental or accessory event or process occurring in the course of a disease but not necessarily related to that disease" (Dictionary Merriam-Webster online, 2010). The results provide an argument for depression as an epiphenomenon. A central finding of this study is that 40% of the narcoleptic patients were at least mildly depressed as it is for more severe depression with at least 15% of the narcoleptic patients experiencing a clinically significant level of depressive disorder. This was almost four times as much as in controls. The control group was selected from the general population and one of the criteria of exclusion was the absence of a current depression diagnosis. However, some participants did show a mild degree of depressive symptoms. The proportion of participants with mild depression was similar to an unselected general population, in which it is 11% (Oliver & Simmons, 1985).

The use of self-rating scales was preferred for several reasons. The first one is because the patients were mostly contacted in different social meetings of the self-help group. In consequence, the patients were interviewed for demographic data and filled in the questionnaires in a quiet place. Most of them returned the questionnaires during the meeting and some of them decided to send it by post later. The second one was the fact that the interviews and analysis of the data were done by the same person. For these reasons, self-rating scales were an advantage because they decreased the possibility of a bias in the analyses and interpretation of the results. In addition, others investigating this group of patients have used the same approach before. Therefore, this procedure facilitates comparison with quantitative data from previous research studies performed with similar approach and equivalent populations.

6.1.1. Predictors of depressive symptoms

The major predictors for depressive symptoms were sex (being female) and the intake of a combination of stimulants and anticataplectic drugs, while cataplexy and the ESS score had no influence. These findings make it unlikely that depressive symptoms in narcoleptics are closely linked to the Hcrt deficit, which is predominantly found in NC+ patients. ESS, which was assessed under current treatment, may not be a valid indicator for sleepiness in this population comprising many medicated patients. Severely affected patients may be

more prone to take stimulants and thus reduce their ESS score. It cannot be ruled out that the intake of antidepressants in 33% of the narcoleptic sample masked the presence of even more depressive symptoms. The findings are in keeping with previous studies, which reported that the severity of sleepiness is not related to depression (Nevsimalova, Buskova, Kemlink, Sonka & Skibova, 2009; Daniels, King, Smith & Shneerson, 2001). Items in BDI and SDS directly related to EDS appeared to have only a minor influence. According to Beck's cognitive model (Beck, 1967), depressed narcoleptics could perceive themselves without control of their vigilance and sleepiness, and this deficit is attributed as a weakness damaging to self-esteem.

6.1.2. Presence of cataplexy

Another major result of this study is that despite the psychological impact of cataplexy reported by the patients in clinical interviews, depressive symptoms were not associated with the presence of cataplexy. The lack of difference between NC+ and NC- in the level of depression supports the assumption that the major psychosocial burden in narcolepsy is not necessarily associated with the presence of cataplexy. This data are in line with the findings of Morrish et al. (2001) who used older criteria for the differentiation between NC+ and NC- (Morrish et al., 2001). Another study established that “irresistible episodes of sleep” is the major symptom affecting quality of life. There is no significant influence of the other symptoms of narcolepsy, such as cataplexy (Dodel et al., 2007).

These results are also in good agreement with a previous longitudinal study by Bruck and Costa (2003) who reported that excessive daytime sleepiness (EDS) had the greatest impact on life across the 10-year period of the study compared to other symptoms of narcolepsy (Bruck & Costa, 2003). In addition, Vignatelli et al. (2004) found that cataplexy does not correlate with the scales of the SF-36 (Vignatelli et al., 2004). A possible explanation is that cataplexy is frequently better controlled by medication than EDS. Even with the intake of stimulant medication, sleepiness is merely reduced but not eliminated (US Modafinil in narcolepsy multicenter study Group, 2000; Broughton & Mamelak, 1979). Most but not all other studies found that NC+ patients tend to be sleepier than NC- patients (Dauvilliers et al., 2009; Martinez-Rodriguez et al., 2007). This was not the case in this sample, perhaps due to pharmacological treatment. The difference in sleepiness between NC+ and NC- plus IH patients in the “Harmony study” may be explained by the influence of the IH group (Dauvilliers et al., 2009). In fact, in the results, it is possible to detect a difference between IH and narcolepsy patients regarding general mood state (fatigue and confusion). Consequently this difference supports the idea that it is not appropriate to

group IH patients with NC- ones. This finding once more demonstrates the negative impact of narcolepsy on psychosocial performance (Broughton et al., 1981), although the results revealed a lesser degree of depressive syndrome than some earlier studies (Dauvilliers et al., 2009; Daniels et al., 2001).

6.1.3. Similarities with other studies

The results furthermore indicate that the pharmacological treatment used in narcolepsy is closely associated with depressive symptoms. Supporting this data, Daniels and colleagues showed that narcolepsy patients taking stimulants and antidepressants had a higher BDI score than patients taking none or only one of these compounds (Daniels et al., 2001). It is likely that individual personality characteristics influence the decision for drug intake. In addition, life circumstances that permit coping strategies such as taking regular naps may reduce the necessity to take medications. Simultaneously, this could reduce distress and the resulting depression. Of particular concern is the role of sex in depressive symptoms. Narcoleptic women were more depressed independent of other factors, which is in line with studies performed in the general population (Slone et al., 2006). A Norwegian study found that women with narcolepsy experience more social limitations than men do. The authors explained this by considering that women are more socially active, or that they have the ability to express their experiences more easily (Ervik et al., 2006). Supporting that notion, an Israeli study found that untreated sleepy women with obstructive sleep apnea have higher scores in depression than men (Pillar & Lavie, 1998). Another explanation could be that women are more prone to report their symptoms than men, which might be due to early socialization, traditional sex roles or differences in social standing (Van Wijk & Kolk, 1997). In conclusion, this data suggest that depression is an epiphenomenon of narcolepsy, not a primary feature of the disease itself. The results reconfirm the psychosocial impact of narcolepsy and the subsequent effect on mood state. Sleepiness appears to be the best candidate explaining depressive symptoms, and the use of medication to combat it may be a better indicator for this than the ESS score. Inevitable sleepiness is a symptom less impressive than cataplexy and for that reason often misinterpreted as laziness by peers (Stores, 2006; Kales et al., 1982). This may be the reason why depression is associated rather with sleepiness than with cataplexy (Vignatelli et al., 2004). Since sex and a combination of antidepressants and stimulants contributed to depressive symptoms, future research should focus on the role of psychotropic drug intake and sex for depression in narcolepsy. Furthermore, depressive symptomatology in narcoleptic patients needs to be studied in more detail.

6.2. Discussion empirical part II: "Narcoleptics with depressive symptoms compared with patients with depression".

6.2.1. Sleepiness

As expected, there is a significant difference in the ESS total scores between narcoleptic and depressive patients. However, the sleepiness present in narcolepsy is considered conceptually different from tiredness, fatigue and sleep disturbances characteristic to depression (Lessov-Schlaggar, Bliwise, Krasnow, Swan & Reed, 2008). The fact that a group of patients with depression has clinically relevant high scores in the ESS is consistent with previous studies (Ferentinos et al., 2009; Lundt, 2005) which found that one fourth to half of the patients with depression experience on average moderate daytime sleepiness (ESS>10 points). However, it is not possible to assume that this one third of patients with depression with more than 10 points in ESS scores experience the same type of sleepiness as patients with narcolepsy. The ESS is a validated scale in sleep disorders research but probably is not sensitive to the type of sleepiness experienced by patients with depression (Kaplan, 2009).

SLEEPINESS ASSOCIATED WITH DEPRESSIVE SYMPTOMS

There is disagreement in the literature as to whether the somatic symptoms of depression should be included in the diagnosis of depression of patients with chronic illness or not. Some but not all authors suggest the solution of excluding items related with fatigue, weight loss, or disturbed sleep from depression questionnaires such as BDI (Clark et al., 1983, Aikens et al., 1999). In this sample, depressive symptoms (mean total scores) were not correlated with sleepiness scores (ESS). In addition, ESS scores did not correlate with the items of BDI directly related to sleepiness in any of the groups. These findings support that it is not necessary to omit items of BDI when evaluating narcoleptic patients. This is also suggested in a study evaluating patients with multiple sclerosis who also have symptoms related with somatic items such as sleepiness and fatigue (Aikens, 1999).

OBESITY, GENDER AND MEDICATION STATUS

The finding that BMI is higher in narcoleptics than in the normal population is in agreement with data found in the literature. One study performed with 129 Swiss and German narcoleptic patients found that at least a third of them were obese, which is similar to the results here presented (Dahmen et al., 2001). This finding is supported by the result that narcoleptic patients have fewer difficulties with appetite than patients with depression.

Women have higher scores in the “Tension- Anxiety” scale of POMS which is in line with the first study showing that women with narcolepsy are more depressed than men and with another study reporting that the female group of patients with narcolepsy perceived more social limitations than men (Ervik et al., 2006). In the other questionnaires, no differences were found between men and women, which must be interpreted with caution because of the small sample size.

Regarding medication status, 21 patients with narcolepsy of the sample were on antidepressants. Although this was prescribed to reduce cataplexy, patients were still reporting depressive symptoms. The most reasonable explanation is that the dosage of antidepressants was probably not enough to reduce depressive symptoms in these patients. Another reason can be the type of antidepressant. Stewart et al. (2009) proposed that the response to tricyclic antidepressants is reduced in patients with atypical depression.

ITEM BY ITEM ANALYSIS ON BDI AND SDS: ANHEDONIA

This study shows that narcoleptic patients with depressive symptoms are more hedonistic than patients with depression. This result should be interpreted with caution. It is not sufficient evidence that narcolepsy patients with depressive symptoms maintain a normal hedonic level. Rather, a significant difference is reported compared to depressed patients in spite of the same level of depression. An explanation for this finding in patients with narcolepsy may be double-sided. On the one hand, anhedonia is one of the core symptoms of depression and a normal hedonic tone is characteristically maintained in subjects with atypical depression. In consequence, one might hypothesize that the patients with narcolepsy and depression as comorbidity are more prone to an atypical depression than to melancholic depression.

Rye et al (1998) describes a single patient with narcolepsy diagnosed with atypical depression. Characteristically, the patient reacted when presented with positive events. In this case, the patient was treated with 100 mg Bupropion (NDRI) and recovered not only in terms of depressive symptoms, but also in terms of narcoleptic symptoms such as decreased daytime sleepiness (ESS points), SOREMP and increased REM sleep latency (Rye, Dihenia & Bliwise, 1998). The hypothesis that narcoleptic patients with depressive symptoms are possibly more prone to an atypical depression is in agreement with the emotive reactivity typically present in a cataplexy episode, which would be impossible for a narcoleptic patient with a melancholic depression. This premise is concordant with a recent study showing that phobias and anxiety are often present in narcoleptic patients

(Fortuyn et al., 2010). These characteristic are related to an atypical depression (American Psychiatric Association, 2000). On the other hand, this finding can suggest a link with the pathophysiology of narcolepsy. Hcrt neurons are important in regulating motivation and stress states (Siegel, 2004). Although we do not have data on the Hcrt status of this group of patients, this peptide could play a role in modulating the recompense system in the brain and may therefore be relevant in depression (Ganjavi et al., 2007).

This study shows that narcoleptics are less worried about health problems than depressive patients. This can imply that even with depressive symptoms, narcoleptics are more concerned with "daily problems" such as falling asleep or having cataplectic attacks during inappropriate situations than with physical problems. Narcoleptic patients reported fewer diurnal variations of mood; this can be explained because narcoleptics are more wakeful during the morning due to the recent night's sleep. Diurnal mood variation can also be related with disrupted social rhythms in depressed patients (Germain, 2008). For this reason, the results suggest that the refreshed feeling in the early morning for narcoleptic patients can be a protecting factor because it helps maintain social rhythms at least during the first hours of the day. According to Bech (2008), diurnal variations of mood are more an indicator for depression and not for sadness related to stress or when under adversity, which is in line with a chronic illness such as narcolepsy. Diurnal variation is also a feature of depression more related to melancholic features of depression in DSM-IV.

6.2.2. Subjective and unspecified question: Do you feel depressed?

When patients with narcolepsy were asked if they felt currently depressed, avoiding any question associated with symptoms, they answered positively and on the same level as patients with depression. Considering that depressive symptoms were, in this study, based on the patient's self report, it is not possible to argue that patients were only taking into account his/her somatic symptoms that are included in DSM-IV or in ICD-10 in the criteria of depression. Furthermore, this is concordant with the finding that in these patients the somatic dimension of BDI was not more dominant than the cognitive dimension.

These data provide only a partial answer to the question on the features of depressive symptoms in patients with narcolepsy, leaving the question open on whether the kind of depression described by narcoleptic patients is prone to an atypical depression or not. According to DSM-IV, the diagnosis of atypical depression is characterized by mood reactivity (also called paradoxical anhedonia) and should include two or more symptoms, which include hypersomnia, increased weight or appetite, sensation of heaviness in limbs, and a long-term pattern of hypersensitivity to perceived personal rejection. If it were

possible to demonstrate that mood reactivity is present in narcolepsy despite other depressive symptoms, it would be very difficult to fulfill the criteria because three of the symptoms are similar features of narcolepsy. The exception is the criterion of subjective personal rejection, which should be further investigated in narcoleptic patients with a coexisting depression. Previous reports of psychosocial consequences and psychopathology in narcoleptic patients with cataplexy show that in the symptom checklist-90 (SCL-90), one of the three dimensions with the highest scale elevations is interpersonal sensitivity while the other one is depression and obsessive-compulsiveness. These interpersonal difficulties can be seen as a consequence of negative reactions from others toward his or her illness (Kales et al., 1982).

It will be an issue of future studies to evaluate the presence of atypical depression in narcoleptic patients with depressive symptoms using structured or semi-structured interviews.

6.3. Discussion empirical part III: "Factor analysis of Beck Depression Inventory in patients with narcolepsy".

Because symptoms of narcolepsy and depression can be similar, there is a risk of misdiagnosing narcoleptic patients as depressives. The rate of depressive symptoms in a one-dimensional model would show that around 45% of patients of this sample are at least moderately depressed according to the total BDI scores. In this study, the factor structure of the BDI was derived from a relatively large sample of patients with narcolepsy considering the low prevalence of narcolepsy in the population. This data indicates that there is a moderately robust structure to the BDI responses of patients with narcolepsy, which can shed light on the phenomena of depressed mood and major depressive disorder in patients with narcolepsy, having important clinical repercussions.

6.3.1. Negative attitude toward self

The exploratory factor analysis revealed a five components solution. In a meta-analysis of the factor structure of BDI, others found that the average of components reported in 33 studies (also using the varimax rotation) was a four components solution (Shafer, 2006). This average of components found in a meta-analysis corresponds to studies with healthy participants and with patients.

Negative attitude toward self is the most relevant component in BDI which explains 36% of the variance of the factor analysis, much more than all other factors. This is a central finding, because only cognitive items of BDI load in this factor. Based on this result, it is not possible to support the theory that somatic items were responsible for the severity of depressive symptoms in narcolepsy. The second factor is clearly the negative mood. The highest loading items included sadness, hopelessness, anhedonia and suicidal ideation. The association between hopelessness and suicide is well documented in Beck's theory.

As reported, factors emerged related to somatic items, including those related with eating and sleep, although they were not the most important in explaining the depressive symptoms. This means that the symptoms can be not understood as inflating the scores in BDI. The low degree of somatic items endorsed versus the high degree of cognitive symptoms of depression refutes the idea that depressive symptoms in narcoleptics are just an expression of typical symptoms of the sleep disorder.

In a sample of 477 depressive patients, Hautzinger (1994) reported a first factor or component called performance impairment (19.2% of the variance), which consists of a push to work, fatigability, social anhedonia, sadness, indecisiveness, crying, anhedonia

and health worries. A second component in the depressive sample, the so called negative attitude toward self, explained 18.6% of the variance and shows guilt, self blame, sense of failure, self hate, hopelessness and suicide ideation. A third component, somatic disturbance, explained 7.6% of the variance and included weight loss, loss of appetite and insomnia. Compared to the results of Hautzinger (1994) in patients with depression, the components obtained in this sample of narcoleptics have only few similarities. Negative attitude toward self explained also the most of the variance in patients with depression (18%) but in narcoleptics this component explains twice as much of the variance obtained (36%). This is the most similar component. The others are not comparable because they include different items. Women with narcolepsy showed a higher severity of depressive symptoms related to the cognitive dimension. In consequence, they should be largely screened during an interview with a physician. It is not clear why women with narcolepsy are more depressed than men. This is also seen in the non-narcoleptic population and is explained by different theories.

6.3.2. Cognitive dimension

The results of this sample suggest that the cognitive symptoms play an important role in women. The item related with body image could not be identified in any factor, indicating that this is not a central theme in the context of depressive symptoms neither in men nor in women. This suggests that the treatment could be oriented, for instance, to a cognitive therapy focussing on the negative attitude toward self. This factor structure means that the content of these scores shows a relatively large amount of symptoms which are not necessarily only related with a chronic illness but which also characterize a depression. Interestingly, among the items with weak loadings were irritability, indecisiveness, change of body image, push to work and health worries. The lower importance of push to work and health worries suggests that patients discriminate between the impact of the illness and the motivation to work. Furthermore, patients are aware of the characteristics and consequences of the illness.

Further work needs to be done to establish the utility of the current factor solution. This study requires replication using confirmatory factor analytic methods, preferably. Furthermore, it would be important to compare this factor solution with another population of hypersomnia patients.

6.4. Overall findings of all three studies

One of the central findings is that 40% of narcoleptic patients are at least mildly depressed according to self-report questionnaires. This is four times as much as in controls. This result is in line with a review of current literature on narcolepsy and depression, which leads to the conclusion that patients with narcolepsy show an increased prevalence of depressive symptoms when compared to controls (Dauvilliers et al., 2009; Daniels et al., 2001; Pawluk, Hurwitz, Schluter, Ullevig & Mahowald, 1995; Stepanski et al., 1990; Beutler et al., 1981). Although depressive symptoms are often reported, a diagnosis of major depressive disorder is infrequent (Fortuyn et al., 2010; Adda et al., 1997; Roy, 1976). Previous reports demonstrate that although patients have depressive symptoms and have a low quality of life (which includes some items regarding depression) most of the studies fail to probe whether they have a major depressive disorder (MDD). In the cases where MDD was diagnosed, literature suggests that it was not more prevalent than in the general population.

6.4.1. Similar severity of depression in NC+ and NC-

One issue was to distinguish if the two newly differentiated forms of narcolepsy (with and without cataplexy) have a role on depressive symptoms. This question is primarily founded in the neurotransmitter Hcrt (See 1.2.4 Etiology). The Hcrt deficiency, which is observed in most cases of NC+ but rarely in cases of NC-, generates an interesting hypothesis because of the possible role of Hcrt in depression.

Salomon and colleagues already described that there is no outstanding decrease of CSF Hcrt values in depressed subjects (Salomon et al, 2003). This suggests that Hcrt deficiency is an improbable cause of primary depression. The results reported here found no evidence to state that patients with cataplexy are more depressed than those without cataplexy. Further research could be performed looking for a correlation between the level of Hcrt in CSF and the severity of depressive symptoms in patients with narcolepsy.

Another topic on this point was to find out the determinants of depression in patients with narcolepsy. The key result in this part was that the presence of cataplexy alone is not enough to predict depressive symptoms. This is in line with Dodel and colleagues, who reported that sleep episodes have a major impact on the quality of life of patients with narcolepsy (Dodel et al., 2007).

Nevertheless, this result should be treated with fine consideration because it is not possible to conclude that the severity of cataplexy is not associated with depression. This result reveals only that the presence of the symptom does not explain “by itself” the

presence of depressive symptoms. The severity and frequency of cataplexy should be analyzed in further studies because this factor could have an influence on the depressive symptoms. There may also be some patients under anticataplectic medication in almost the same condition as patients without cataplexy.

Furthermore, narcolepsy patients with cataplexy can have mild cataplectic episodes, for instance, only affecting the face. This does not necessarily affect social relationships or quality of life compared to patients who have cataplectic episodes with a total loss of muscular tone, thereby making them more dependent on their peers. The current data are contrary to a previous study carried out in France that reported that narcolepsy patients with cataplexy are more depressed than those without cataplexy (Dauvilliers et al., 2009). One possible explanation is the fact that this French study grouped NC- patients together with IH.

6.4.2. Daytime sleepiness scores and mood state

Daytime sleepiness seems to be the major symptom affecting mood states. The fact that daytime sleepiness was not significantly different between narcoleptics (with and without cataplexy) and IH patients, has been previously reported (Martinez-Rodriguez et al., 2007). IH patients showed higher scores in total mood disturbances in POMS. In particular, they reported more impairment in the sub-scales fatigue and confusion than patients with narcolepsy without cataplexy. This difference in fatigue and confusion could be explained by the typical unrefreshing naps for IH patients. Not-refreshing naps are more characteristic in IH than in narcolepsy. Unlike in patients with narcolepsy, daytime sleepiness in IH is not imperative but it is permanent (American Academy of Sleep Medicine, 2005). The consequences of this permanent daytime sleepiness are frequent naps that are not refreshing. Another interpretation may be that IH patients are very heterogeneous and IH may have multifactorial pathogenesis (Bassetti et al., 1997). According to the results, there are no differences in the depressive symptoms reported by narcoleptics and IH patients.

6.4.3. Excluding items related to sleepiness from depression questionnaires

In the literature of depression and narcolepsy, it was unclear if the symptoms of depression were masked by the symptoms of the sleep disorder, or if they were independent. Indeed, questionnaires measuring depression always include questions regarding sleep disturbances. However, the items of the depression questionnaires (BDI and SDS) that enquire specifically about sleep do not have as relevant an influence on the

total scores of these questionnaires as expected. This suggests that these items should be not excluded when the tests are used as a routine in patients with narcolepsy. This is consistent with studies performed in other clinically ill populations (e.g. patients with diabetes, chronic pain), which conclude that removing items did not improve their accuracy. As a consequence, full BDI is also considered valid in those populations (Geisser, Roth & Robinson, 1997; Lustman, Griffith & Clouse, 1997).

6.4.4. Determinants of depression in narcolepsy

SEX

Data reporting differences between men and women with narcolepsy regarding depression in the literature are rare and conflicting. The results of this dissertation show that women with narcolepsy are more depressed than men. In IH most of the patients are men, hence it is not possible to examine a possible difference. Male narcoleptics are more impaired in some studies while female narcoleptics are more impaired in others. Bruck reported that men were more affected than women, specifically regarding sexual problems and Ervick and colleagues further suggested that women have more social limitations than men (Ervik et al., 2006; Bruck, 2001). Therefore, this is an unsettled matter. The fact that women report more depressive symptoms is an interesting finding because this was not emphasized until now except for some contradictory results from previous studies. Such a difference is widely reported in epidemiologic studies in the normal population. It is not possible to establish whether this significant difference between men and women is explained by the same reasons as in the normal population or if it can be attributed to narcolepsy per se.

IMPACT OF MEDICATION

The results show that medication, specifically the combination of stimulants and antidepressants are associated with depressive symptoms in patients with narcolepsy. Some authors consent that the combination of antidepressants and stimulants can play a negative role in depressive symptoms (Bruck, 2001, Daniels et al., 2001, Dauvilliers et al., 2009). More than a few of the studies reviewed suggest that medication may have an influence on depressive symptoms and on the quality of life of patients with narcolepsy. However, in the span of the last 10 years, the pharmacological treatment for narcolepsy has been substantially improved. This implies a factor difficult to be compared and controlled.

For instance, old stimulants such as amphetamines had side effects associated with anxiety such as hypomania, tremble, fast heart beat or wet hands. Modafinil changed the scenario in a positive way. As treatment for daytime sleepiness has been promoted to improve patients' quality of life, so has the treatment of cataplexy. The use of sodium oxybate, a newly approved medicament for cataplexy, has a definite important benefit for the symptoms of narcolepsy that can also explain positive changes in the depressive symptoms of patients. This does not mean that sodium oxybate acts as an antidepressant, but can be a consequence of the improvement of the symptoms. Moreover, and no less important, the use of sodium oxybate is responsible for weight loss in some obese patients and, consequently, diminishes the probability of developing sleep apnea. The improvement of the medication is a big change. This is not yet well investigated but could be an implicit explanation of the differences found in the current literature. It is worth mentioning that in the sample of narcoleptics only three patients were taking sodium oxybate.

6.4.5. Distinctive depressive symptoms between narcolepsy and depression

The second study was performed in the subgroup of narcoleptics reporting depressive symptoms. The goal was to find out whether depressive symptoms of narcoleptic patients are different than in depressed non-narcoleptics. Indeed, there were differences in the depressive symptoms of both groups. This was observed even when the intensity of depressive symptoms was similar. The differences were associated to hedonic tone, health worries and diurnal variation of depressive symptoms.

HEDONIC TONE

The central finding on this part of the dissertation is that narcoleptics are less impaired in their capacity to feel rewarded, called anhedonia. This is important because anhedonia is one of the core symptoms of depression. The maintenance of interest and enjoyment in the activities reported by depressed narcoleptic patients was significantly higher than in patients with depression. As a consequence of this finding, it has been discussed whether patients with narcolepsy and depression as a comorbidity are more prone to atypical depression than to melancholic depression. The reason is that depression with atypical symptoms is differentiated from the melancholic type by the maintenance of the reactivity under positive experiences. Depressive patients frequently report that they have lost their sense of humor, for instance they do not get happiness from a joke or a cartoon. Beck called this loss of mirth response (Beck, 1967). In narcolepsy, this symptom of depression

is rare because patients react with positive experiences but nonetheless can be depressed. This is concordant with a report showing that phobias and anxiety are often present in narcoleptic patients (Fortuyn et al., 2010) because phobias and anxiety are associated with atypical depression (American Psychiatric Association, 2000).

Anhedonia should be further studied and can hint to a link with the pathophysiology of narcolepsy, considering that Hcrt neurons are central in regulating arousal, motivation and stress (Siegel, 2004).

HEALTH WORRIES

Another distinction between both groups was that depressed narcoleptics were less worried about health problems than depressive patients. This can imply that even with depressive symptoms, narcoleptics are more concerned with "daily problems" such as falling asleep during inappropriate situations than with physical problems.

The sample of depressed narcoleptics studied was under medical treatment because of the diagnosis of narcolepsy. Therefore, this might be an explanation as to why depressed narcoleptic patients do not need to worry about a physical disease. In contrast, depressed patients may attribute their negative mood state to somatic symptoms (Beck, 1967).

DIURNAL VARIATIONS

An additional difference was that narcoleptic patients reported less diurnal variations of mood in the depression questionnaires. A possible interpretation for this result is that narcoleptics are more wakeful during the morning due to the recent night's sleep. Diurnal mood variation can also be related to disrupted social rhythms in depressed patients (Germain, 2008). Moreover, diurnal variation is a feature of depression more related to melancholic features of depression in DSM-IV (American Psychiatric Association, 2000) which is concordant with the results.

6.4.6. Relevant items contributing to depression in narcolepsy patients

NEGATIVE ATTITUDE TOWARD SELF

The factor analysis of Beck Depression Inventory represents an important contribution because it recognizes the kind of symptoms that build the components of the depressive symptoms in a large sample of patients with narcolepsy. This was an exploratory factor analysis that offered a more precise definition of the relationship between items in one of the most used tests in the assessment of depressive symptoms on narcoleptics.

The negative attitude towards self was the component that explained most of the symptoms of depression. Even though this is a component also found in patients with depression without narcolepsy, it is interesting because in patients with narcolepsy it is more manifest than in depressives without this sleep disorder. Yet, why do patients with narcolepsy report having a sense of failure, guilt, an expectation of punishment, self-hate and blame as the most important components of their depressive symptoms? It can be hypothesized that the attribution of the cause of the symptoms has been re-directed to themselves. Additionally, patients without cataplexy are informed at the time of diagnosis that cataplexy may turn up soon or later or maybe never. This can also be a source of anxiety and a false self-attribution of the causes of the beginning of cataplexy.

EARLY IDENTIFICATION OF DEPRESSIVE SYMPTOMS

Patients already diagnosed with narcolepsy, who report depressive symptoms should be screened for a major depressive disorder independent of the physical condition and not only focusing on the somatic dimension of depression but also on the cognitive one.

Sleep specialists should be provided of basic training on identification of patients suffering from depressive disorders. Early identification of depressive symptoms means more effective treatment not only for depression but also for narcolepsy. Furthermore, sleep specialists should be more aware of the importance of engaging family and peers of patients (also adults) during treatment. The emphasis is on patients with an onset in adulthood probably because when the onset is during childhood, familial support is greater. The family of patients with depressive symptoms could help to develop coping strategies more easily, which could increase the chance of a chronically ill patient's integration in society. Furthermore, failure in school or in the workplace together with obesity and the fear of not being understood are situations that every patient with daytime sleepiness struggles with throughout life.

6.4.7. Limitations of the dissertation

SAMPLE AND METHODS

The presence of depressive symptoms or suspicion of a psychiatric condition in the clinical interview carried out in the sleep center was an exclusion criterion for the IH patients. There is a dilemma on this topic because patients who have depressive symptoms because of the IH symptoms will have fewer possibilities of being diagnosed due to these ICSD-2 criteria (Billiard & Dauvilliers, 2001b). Therefore, possibly two things occur: the first is that some real patients were excluded following this criterion and the second is that as a

consequence, a bias on this group has been unintentionally generated. During this study, it was possible to have contact with the patients, some of whom were very engaged in the organization of the meetings, even when they reported high scores in depression questionnaires. This seemed very contradictory but was in line with the finding of the second study that shows that narcoleptics with depressive symptoms are more interested in participating in activities, which produce satisfaction than non narcoleptic patients with a similar level of depression but are non narcoleptic. The type of depression in narcoleptic patients is, in summary, best described as an atypical depression.

While one advantage of the present study was the matching of patients in order to have a similar level of depression, some limitations were encountered such as not having exact data on the dosage of antidepressants. This dosage was possibly higher in patients with depression.

6.4.8. Future research directions

One of the results of this dissertation shows that narcoleptic patients with depressive symptoms are more hedonistic than patients with depression. This does not state that narcolepsy patients with depressive symptoms maintain a normal hedonic level. Rather, the results are evidence of a significant difference in comparison with depressed patients in spite of the same level of depression. This outcome is interesting because anhedonia is a cardinal symptom of major depression and the experience of enjoyment is the typical trigger of a cataplexy episode. Therefore, it is possible to hypothesize that narcolepsy patients with cataplexy are in some way protected from the symptom of anhedonia. Looking at this point from a different perspective, it appears that patients who maintain a good level hedonic experience are more prone to experience cataplexy, because they expose themselves to more emotional stimuli. Meehl suggested that there is a normal-range of individual differences in the hedonic capacity in the general population and a reduced capacity to feel pleasure in non-clinical individuals may be associated with brain abnormalities that constitute neural markers of vulnerability for some psychiatric disorders (Meehl, 2001). A possible future research question would be to identify the brain regions whose activity during the processing of hedonic information varies in function of anhedonia severity in control subjects and narcolepsy patients. So far, functional neuroimaging studies of anhedonia have focused exclusively on two clinical populations, either schizophrenia or MDD (Harvey, Armony, Malla & Lepage, 2010). It is not yet known if narcolepsy patients differ from controls in the range of hedonic levels.

The possibility that narcoleptic patients with a depression are prone to an atypical depression is an interesting likelihood which needs further confirmation. An exploration of this topic should re-test this result and corroborate the presence of other symptoms of atypical depression such as subjective personal rejection by others.

7. CONCLUSION

a) Depressive symptoms are present in a significantly higher proportion in patients with narcolepsy and IH than in healthy controls. This is four times more than the controls and shows that depression in these patients is not overestimated as suspected. However, patients experiencing clinically significant depression made up no more than 15% of the sample.

b) Patients with cataplexy are not more depressed than those without cataplexy. The presence of cataplexy alone is not enough to predict depressive symptoms. Daytime sleepiness seems to be the major symptom affecting mood states but is a symptom less impressive than cataplexy, and therefore, it is often misinterpreted by peers as laziness. Further research should be performed to test if the severity and frequency of cataplexy are associated with depression.

c) In spite of the differences in fatigue and confusion, there are no differences in depression scores between patients with narcolepsy and IH.

d) Regarding the determinants of depressive symptoms, combination of antidepressants and stimulants, and sex contributed to depressive symptoms. Although it is possible that the use of stimulants and antidepressants in the treatment of narcolepsy may increase the occurrence of depression, this result needs to be studied in more detail. Women with narcolepsy are more depressed than men and have a higher risk of developing depression. This difference is reported in the general population, and it is not possible to establish if this difference is explained by the same reasons or can be attributed to narcolepsy per se.

e) This dissertation attempted to answer the question of whether depression in narcolepsy is an epiphenomenon or if it is inherent to the disease itself. The results provide an argument for depression as an epiphenomenon.

f) The items of the depression questionnaires used which enquire about sleep do not show a relevant influence in the total scores of these questionnaires as expected.

Hence, removing items did not improve their accuracy. In addition, somatic items were not responsible for the severity of depressive symptoms in narcolepsy.

g) The key difference between patients with narcolepsy and depression under similar intensity of depression is associated with the level of anhedonia, i.e. the capacity to feel rewarded. This distinction should be further studied and can hint to a link with the pathophysiology of narcolepsy. This is particularly the case considering that Hcrt neurons are central in regulating arousal, motivation and stress.

8. SUMMARY

8.1. English summary

Depression and depressive symptoms are consistently reported as a problem for patients with daytime sleepiness in various studies. The present dissertation attempts to compare depression severity and daytime sleepiness in patients with narcolepsy and Idiopathic Hypersomnia. The main objective of this dissertation is to determine whether the depressive symptoms of narcoleptic patients are different from the depressive symptoms of depressed non-narcoleptics. Given the large discrepancy in previous results on this topic, this hypothesis was to be tested in steps, therefore this dissertation is divided into three studies.

The first study assesses depressive symptoms in 86 narcoleptic patients with (NC+) and without (NC-) cataplexy (46 women, 40 men), idiopathic hypersomnia (IH) patients (three women, 12 men) and age- and sex- matched healthy controls. Seventy patients were under treatment with stimulants and/or anticataplectics.

The second study compares depressive symptoms between 36 narcoleptics (26 women, 10 men) and 34 outpatients with mild to moderate depression (22 women, 12 men). The group of narcoleptics was selected from the sample of patients of the first study (n = 86) who had ≥10 points in the Beck Depression Inventory (BDI). All subjects completed the Beck Depression Inventory (BDI), the Zung Self-Rating Depression Scale (SDS), the Global Impression of Severity of Depression (GSD), the Profile of Mood States (POMS) and Epworth Sleepiness Scale (ESS).

The third study identifies the components of depressive symptoms of narcoleptic patients using BDI. The total number of patients had to be increased to meet the basic requirements of a factor analysis. The sample was made up of 114 Caucasian narcoleptic patients (62 women, 52 men). The results show that patients with narcolepsy were more depressed than controls (higher scores in BDI, GSD, SDS, and POMS [in the total score and in all sub scale scores]); however, between the NC+ and NC- patient groups, no differences were found. Women and the patients using antidepressants and stimulants (combination) have a higher probability for depressive symptoms independent of the presence of cataplexy. The daytime sleepiness measured by the ESS (mean score) for the narcoleptic group was higher than the mean scores for the depressive group ($p<.001$). In the item analysis, differences between the narcoleptic group and depressive disorder group in BDI were found regarding anhedonia. Narcoleptic patients were more likely to

continue to feel pleasure compared to patients with depression. Further differences were found in the items loss of appetite and health worries. In SDS, narcoleptics were less impaired in diurnal variation, loss of libido, appetite and weight than patients with depression. Narcoleptics and depressives were more impaired in POMS (total and all sub scales) compared to controls. The factor analysis of BDI revealed that the negative attitude towards self was the component that explained most of the symptoms of depression. Even though this is a component also found in patients with depression without narcolepsy, it is interesting because in patients with narcolepsy it is more manifest than in depressives without this sleep disorder.

Taken together, the findings support the assumption that the major psychosocial burden in narcolepsy is associated with sleepiness and not with cataplexy. Female sex and the intake of antidepressants and stimulants together are two determinants connected with depressive symptoms in patients with narcolepsy. The prevention of depressive symptoms should have special focus in women with narcolepsy independent of the presence of cataplexy. Furthermore, with regards to prevention, the focal point should be the negative attitude toward self as the most relevant component. Future studies should concentrate on the impact of medication on depression in patients with narcolepsy.

8.2. German summary

Wie verschiedene Studien konsistent zeigen konnten, stellen Depressionen und depressive Symptome ein Problem für Patienten mit Tagesschläfrigkeit dar. Die vorliegende Arbeit zielt darauf ab, Depressionsschweregrad und Tagesschläfrigkeit bei Patienten mit Narkolepsie und Idiopathischer Hypersomnie (IH) zu vergleichen. Das Hauptziel dieser Dissertation ist es, festzustellen, ob die depressiven Symptome von Narkolepsie-Patienten sich von den depressiven Symptomen von nicht-depressiven Narkolepsie-Patienten unterscheiden. Angesichts der großen Diskrepanz der bisherigen Studienergebnisse zu diesem Thema, musste die Ausgangshypothese in einzelnen Schritten getestet werden. Aus diesem Grund ist die vorliegende Dissertation in drei Studien unterteilt.

Die erste Studie erfasst depressive Symptome bei 86 Narkolepsie-Patienten (46 Frauen, 40 Männer) mit (NC+) und ohne (NC-) Kataplexie, bei IH-Patienten (drei Frauen, 12 Männer) sowie einer nach Alter und Geschlecht angepassten gesunden Kontrollgruppe. Siebzig Patienten waren unter Behandlung mit Stimulanzien und/oder Antidepressiva (Anticataplectics).

Die zweite Studie vergleicht depressive Symptome zwischen 36 Narkolepsie-Patienten (26 Frauen, 10 Männer) und 34 ambulanten Patienten mit leichter bis mittelschwerer Depression (22 Frauen, 12 Männer). Die Gruppe der Narkolepsie-Patienten wurde aus der Stichprobe von Patienten der ersten Studie (n = 86) ausgewählt, die ≥ 10 Punkte in der Beck Depressions-Inventar (BDI) aufwiesen. Alle Versuchspersonen füllten neben dem Beck Depressions-Inventar (BDI), die Zung Selbstbeurteilung Depressionsskala (SDS), ein Globalmaß für die Schwere der Depression (Global Impression of Severity of Depression, GSD), sowie das Stimmungsbarometer „Profile of Mood States“ (POMS) und die Epworth Schläfrigkeitsskala (ESS) aus.

In der dritten Studie werden auf der Grundlage des BDI die Komponenten der depressiven Symptome von Narkolepsie-Patienten identifiziert. Die Gesamtzahl der Patienten musste erhöht werden, um den grundlegenden Anforderungen einer Faktorenanalyse gerecht zu werden. Die Stichprobe bestand aus 114 kaukasischen Narkolepsie-Patienten (62 Frauen, 52 Männer). Die Ergebnisse zeigen, dass Narkolepsie-Patienten depressiver als Kontrollpersonen waren (höhere Werte im BDI, GSD, SDS und POMS [sowohl in der Gesamtwertung als auch in den Subskalen]), aber zwischen den beiden Patientengruppen NC+ und NC- keine Unterschiede gefunden wurden. Frauen und Patienten, die Antidepressiva und Stimulanzien (auch in Kombination) einnahmen, haben eine höhere Wahrscheinlichkeit für depressive Symptome unabhängig vom Vorliegen der Kataplexie. Die Tagesschläfrigkeit

gemessen an Hand der ESS (mittlere Punktzahl) war für die Narkolepsie-Gruppe höher als die Mittelwerte für die depressive Gruppe ($p<.001$). In der Item-Analyse des BDI wurden Unterschiede zwischen der Narkolepsie-Gruppe und der Gruppe mit depressiver Störung in Bezug auf Anhedonie gefunden. Narkolepsie-Patienten waren nach wie vor besser in der Lage, Freude und positive Gefühle zu empfinden als depressive Patienten. Weitere Unterschiede wurden bei den Items Appetitlosigkeit und Gesundheitsbesorgnis gefunden.

In der SDS wiesen Narkolepsie-Patienten weniger Beeinträchtigungen in Bezug auf zirkadianen Rhythmus, Libidoverlust, Appetitverlust und Körpergewicht als depressive Patienten auf. Gemessen am POMS (Gesamtwert und Subskalen) waren Narkolepsie-Patienten und depressive Personen stärker beeinträchtigt als die Kontrollpersonen.

Die Faktor-Analyse des BDI zeigte, dass die negative Lebenseinstellung die Komponente ist, welche die meisten depressiven Symptome aufklärte. Obgleich diese Komponente auch bei Patienten mit Depression ohne Narkolepsie gefunden werden kann, ist dies interessant weil bei Patienten mit Narkolepsie es sich mehr äußert als bei depressiven Personen ohne diese Schlafstörung.

Zusammengefasst unterstützen diese Ergebnisse die Annahme, dass die größte psycho-soziale Belastung bei Narkolepsie mit Schläfrigkeit und nicht mit Kataplexien verbunden ist. Weibliches Geschlecht und die Einnahme von Antidepressiva in Kombination mit Stimulanzien sind zwei Determinanten, welche depressiven Symptomen von Patienten mit Narkolepsie beeinflussen.

Bei der Prävention von depressiven Symptomen sollte ein besonderer Fokus auf Frauen mit Narkolepsie gelegt werden, unabhängig davon, ob sie Kataplexie haben.

In Bezug auf präventive Maßnahmen sollte weiterhin der Schwerpunkt auf die negative Lebenseinstellung gelegt werden, da diese die wichtigste Komponente darstellt.

Zukünftige Studien sollten sich auf die Auswirkung von medikamentöser Behandlung von Narkolepsie-Patienten konzentrieren.

8.3. Spanish summary

La presencia de depresión o de síntomas depresivos son frecuentemente reportados por pacientes que experiencian somnolencia diurna en diversos estudios. La presente disertación está dividida en tres estudios que se concentran en la temática de la asociación entre la somnolencia diurna (presente en la narcolepsia y la hipersomnia idiopática) y la depresión.

El primer estudio evalúa los síntomas depresivos en 86 pacientes narcolépticos con (NC+) y sin (NC-) cataplejía (46 mujeres, 40 hombres), pacientes con hipersomnia idiopática (IH) (3 mujeres, 12 hombres) y un grupo control sano pareado por edad y sexo. De estos pacientes, 70 estuvieron bajo tratamiento ya sea con estimulantes y/o con anticatapléjicos.

El segundo estudio compara síntomas depresivos entre 36 narcolépticos (26 mujeres, 10 hombres) y 34 pacientes ambulatorios con depresión leve a moderada (22 mujeres, 12 hombres). El grupo de pacientes narcolépticos fue seleccionado desde la muestra del primer estudio, participaron aquellos que tuvieran al menos 10 puntos o más en el inventario de depresión de Beck. Todos los sujetos que participaron tanto en el primer como en el segundo estudio completaron el Inventario de depresión de Beck (BDI), la escala de autoevaluación de la depresión de Zung (SDS), impresión global de la severidad de depresión (GSD), el perfil de estados de ánimo (POMS) y la escala de somnolencia de Epworth (ESS).

El tercer estudio que conforma esta disertación tiene como objetivo identificar los componentes de los síntomas depresivos en pacientes narcolépticos usando el BDI. Para esta parte, fue necesario aumentar el número de sujetos de manera tal que se cumplan los requisitos básicos para realizar un análisis factorial. La muestra total fue de 114 pacientes narcolépticos de origen caucásico (62 mujeres, 52 hombres). Todos ellos completaron BDI y ESS. Los resultados muestran que los pacientes con narcolepsia están más deprimidos que los sujetos de control (puntajes más altos en BDI, GSD, SDS y POMS [tanto en el puntaje total como en el puntaje de todas las subescalas]); sin embargo, entre los grupos de pacientes NC+ y NC-, no se hallaron diferencias. Mujeres y pacientes usando antidepresivos y estimulantes (combinación) tienen mayor probabilidad de presentar síntomas depresivos independientemente de la presencia de cataplejia. La somnolencia diurna medida a través del ESS (puntaje promedio) para el grupo narcoléptico fue más alta que los puntajes promedio en el grupo de pacientes con depresión ($p<.001$). En el análisis de los ítemes, se encontraron diferencias entre el grupo de pacientes narcolépticos y de aquellos con depresión asociados con la Anhedonia. Específicamente los pacientes con narcolepsia

y síntomas depresivos tuvieron más probabilidades de continuar sintiendo la misma satisfacción de antes que los pacientes con depresión. Otras diferencias fueron halladas en los ítemes sobre pérdida del apetito y preocupaciones por la salud. En el SDS, los pacientes con narcolepsia tuvieron menos problemas de variabilidad durante el día, pérdida de líbido, apetito y peso que los pacientes con depresión. Ahora bien, tanto narcolépticos como depresivos tuvieron puntajes más altos en el POMS (puntaje total y todas las subescalas) en comparación con los controles. El análisis factorial del BDI reveló que el componente que mayormente explica los síntomas depresivos en los pacientes con narcolepsia es la actitud negativa hacia sí mismos. A pesar de que este componente es reconocido en personas con depresión al usar este test, en pacientes narcolépticos se sitúa como el componente que explica la varianza más alta a diferencia de otros pacientes deprimido sin este trastorno de sueño

Tomado en conjunto, los resultado apoyan el supuesto de que la carga psicosocial más pesada en la narcolepsia está asociada a la somnolencia y no a la cataplejia. El sexo femenino y la ingesta de antidepresivos en combinación con estimulantes serían dos determinantes que estarían relacionados con los síntomas depresivos en pacientes con narcolepsia. La prevención de síntomas depresivos debiera entonces estar enfocada a las pacientes con narcolepsia de sexo femenino independientemente de la presencia de cataplejía. Dentro de la prevención la temática parece centrarse en la actitud negativa hacia sí mismo como el componente más relevante. En el futuro, los estudios debieran concentrarse en el impacto de la medicación sobre la depresión en estos pacientes.

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11. APPENDICES

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A. Interpreting a boxplot diagram

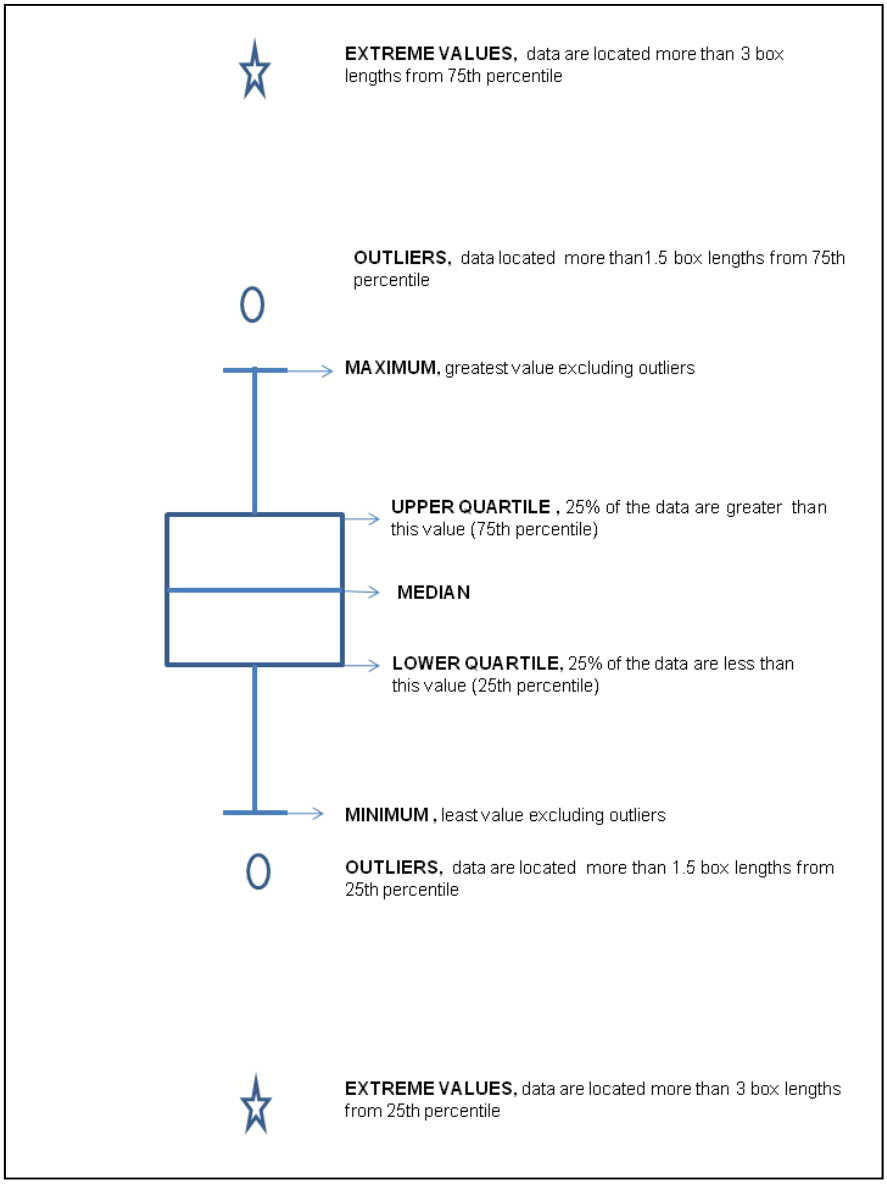

Figure 17. Interpretation of a boxplot (www.cms.murdoch.edu.au/areas/maths/statsnotes/samplestats/boxplot.html)

B. Key references

Table 33. Key references related to depression and daytime sleepiness

Authors	Study design & considerations	Sample	Aim	Sex (M:F)	Age range (mean)	Tests	Results
Adda et al., 1997	Retrospective. No statistical analysis. Questions regarding sleep in both instruments were excluded but not specified how many and which questions were excluded.	12 N	Evaluate depressive disorder in patients with narcolepsy.	5:7	20-65 (53)	BDI, HAM-D	Three patients showed depressive symptoms in BDI and 5 patients in HAM-D. Only one patient (8.3%) reported severe depressive symptoms according to both questionnaires.
Becker et al., 2004	Open label multicenter study, no placebo control group. Prospective. During 6 weeks narcoleptic patients received modafinil. Patients with psychiatric disorders and/or prior experience with modafinil were excluded.	123 N	Determine if treatment with modafinil for EDS improves fatigue, mood and HRQOL	70:81	18-68 (39)	SF-36, POMS	Modafinil improved HRQOL based on SF-36. Modafinil reduced fatigue, and improved vigor and confusion (POMS subscales).

Beutler, 1981	Prospective	50 OSA (20) N (20) C (10)	Investigate personality and mood characteristics	50:0	OSA (45.6) N (42.3) C (41.7)	POMS, MMPI	OSA and N patients are different in POMS and MMPI than controls. OSA patients had hypochondrical and hysterical personality characteristics and N were characterized by anxiety and social introversion. N were relatively more depressed and show higher scores in fatigue than OSA do.
Broughton et al. ,1984	Prospective	120 Epilepsy (60) NC+ (60)	Compare the life effects attributed to epilepsy an those attributed to narcolepsy	54: 66	32, Epilepsy group and 41, N group.	Questionnaire published in previous study.	Narcolepsy has a greater overall negative impact than epilepsy on quality of life.

Bruck, 2001	Prospective	129 N	Assess psychological adjustment, disruption due to symptoms and medication problems in N.Compared to normative values for other illness groups.	57:72	18-81 (53)	PAIS-SR	High psychological distress in N patients. Males report more psychosocial adjustment problems than females. ESS was not correlated with any variable assessed in this study. Patients on tricyclic medication were more disturbed during the daily activities and during night than other groups
Daniels et al., 2001	No control group. Presence of cataplexy not addressed. Prospective.	305 N	Describe the health related quality of life of people with narcolepsy residing in UK	120:185	18-89 (median 56)	BDI and SF-36	56.9% had more or equal to 10 points (on the border of depression) in BDI and 15.1% more or equal to 20 points (moderate to severe depression). In SF-36, N showed lower scores in all scales than normative data. N taking stimulants and anticataplectics had poorer health status than the rest of the sample

Dauvilliers et al., 2009	PSG, MSLT and HLA of patients included were retrospectively examined. The sample of NC- and IH was regrouped as one group for statistical reasons. No control group.	517 EDS (NC+=424, NC-=68, IH=25)	Clarify the relationships between severity of the condition, psychological health and treatment response.	246:271	15 or more (41.2)	Face to face standardized clinical interviews and ESS, S-BDI, PSQI and SF36.	55.1% had depressive symptoms in S-BDI (26.3% had mild , 23.2%moderate and 5.6% severe).NC+ had higher scores in S-BDI and PSQI, lower in SF-36 than NC- and IH together. NC+ using anticataplectic had higher S-BDI and lower SF-36 than NC+ using stimulants alone.
Fortuyn et al., 2010	Case-control study Age and sex matched controls. Prospective.	60 NC+ 120 C	Assess symptoms and diagnostic classifications of mood and anxiety disorders	28:32	(43)	SCAN semi-structured interview.	A third of patients reported depressed mood and the highest odds ratio in the depressive symptoms was anhedonia. Prevalence of mood disorders was less preponderant than anxiety or panic attacks. No influence of age, sex, duration of illness or medication treatment in the prevalence of mood or anxiety disorders or in symptoms.
Ervik et al., 2006	Cross-sectional study. No control group. Just 40% of the sample had a PSG and MSLT. Prospective	77 NC+	Describe HRQOL in Norwegian patients with narcolepsy.	23:54	10-82 (53)	SF-36	Impairment in social function, bodily pain and general health; women were socially more affected than men. No treatment related differences in SF-36.

Kales, 1982	Prospective. A Psychiatrist blinded for the sleep problem of the patient interviewed each patient.	50 NC+	Assess personality of patients with sleep attacks and cataplexy. Evaluate the psychosocial consequences of the illness.	22 :28	(43)	MMPI. A sub-group of 40 NC+ completed also SCL-90, Rorschach and TAT	In MMPI, high scores in Schizophrenia, depression and hysteria. In SCL-90 elevated scores for obsessive-compulsiveness,interpersonal sensitivity and depression. Projective tests showed a lack of emotional expressiveness.
Lundt et al., 2005	Retrospective chart review	161 MDD	Evaluate incidence of excessive daytime sleepiness in MDD.	-	18-65	ESS, BDI	Correlation between ESS scores and BDI scores. 50% of patients with MDD experience Excessive Daytime sleepiness.
Morrish et al., 2001	Post survey No control group. Only abstract.	285 N (260 NC+, 25 NC-)	Assess if there are differences in HQOL and mood between NC+ and NC-	-	-	BDI and SF-36	No difference between NC+ and NC-.

Mosko et al., 1989	Retrospective.	151(patients in sleep laboratory) plus 82 with PSG and diagnosis of OSA (22), PLM(11), N (22), sleeping pill group (11)	Prevalence of self reported symptoms of major affective disorders in patients of a sleep lab. Relationship between sleep disorders and mood associated with treatments	160:73	12-51 (46)	POMS, questionnaire based in DSM-3 criteria.	67% of patients who presented in a sleep center reported an episode of depression within the previous 5 years and 26% described themselves as depressed at presentation. No differences in POMS with or without stimulant medication.
Nevsimalova et al., 2009	Longitudinal study	105 N (NC+87, NC-18)	Compare the course and severity of narcolepsy in relation to age at onset and find out if childhood onset narcolepsy does have a more severe course.	44:61	(45.4)	SSS, ESS and MSLT	The severity of narcolepsy does not depend on the age at onset. Smoking is associated with the risk of hypnagogic hallucinations. BMI increases in linear proportion to age and decreased the MSLT values.

Ozaki et al., 2008	Prospective. No control group.	137 EDS (NC+28, NC-27, IH=82)	Evaluate HRQOL of drug naïve NC+, NC- and IH without long sleep time. Explore the factors influencing HRQOL.	66:71	20-61 (31.2)	SF-36, ESS, socio-demographics and driving habits.	Low HRQOL in all disease categories unrelated with severity. NC+ showed higher ESS scores in comparison with the other 2 groups.
Pawluk et al., 1995	Prospective. Small sample. No control group.	11 NC+	Assess whether narcoleptic patients on chronic high dose methylphenidate develop psychosis and if they would be less prone to depression.	6:5	(54.5)	MMPI, SCL-90, BDI, BAI. Two weeks later: BPRS, HAM-D and SSS.	45.4% met DSM-III criteria for dysthymia, 9.1% for major depression. Two patients had symptoms of psychosis induced by stimulant.
Roth & Nevsimalová, 1975	Retrospective study. No control group.	130 (N 100, IH 30)	Analyze the association between narcolepsy and depression.	-	-	Psychiatrist who treated the patients for depression. Mentioned questionnaires but no specified.	In NC- depression occurred in 29% of the cases, in NC+ depression in 17% of the cases. In IH, depression in 26.1%.
Rovere et al., 2008	Prospective. Not addressed if cataplexy.	40 N 40 C	Evaluate the perception of QL in Brazilian patients with narcolepsy	12:28	20-72 (41.5)	WHOQOL-BREF	N show lower scores than controls in all domains of questionnaire.

Roy, 1976	Prospective. Not addressed if cataplexy No control group. Unclear instruments in method.	20 N	Explore psychiatric aspects of patients with narcolepsy	10:10	(40)	Psychiatric interview, intelligence test and personality questionnaire (Eysenck)	Intelligence was normal, no characteristic personality or psychopathology. 40% current psychiatric disorder (only one diagnosis of depression)
Sours, 1963	Retrospective. Diagnosis under Yoss and Daly's criteria. Historical paper.	75 N (54 NC+, 21 NC-)	Review the role of psychological disturbances in and the association of schizophrenia with narcolepsy.	45:30	(18.2)	No instruments. Revision of clinical records regarding psychiatric and neurological evaluation.	Principal findings without statistical corroboration: Anxiety, depression, headaches, obesity, vivid dreams and irritability.
Stepanski et al , 1990	Prospective. Not addressed if cataplexy. Age and sex matched with controls. N and EDS patients matched by level of sleepiness.	56 N, 56 EDS controls and 48 C	Relation between psychopathology and narcolepsy.	36:20 N 36:20 EDS 32:16 C	(51.8)	MMPI and CMI.	Both EDS groups higher scores in MMPI scales of hypochondriasis, depression, hysteria, psychasthenia and schizophrenia and in CMI than controls. N had higher depression scores than EDS. Psychopathology related to narcolepsy is not specific and may be generalized to other disorders with excessive sleepiness.
	BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory (with S, Short form); BPRS, Brief Psychiatric Rating Scale; C, controls; CMI, Cornell Medical Index; EDS, excessive daytime sleepiness; ESS, Epworth sleepiness scale; HAM-D, Hamilton Rating Scale for Depression; HRQOL, Health-Related Quality Of Life; IH, idiopathic hypersomnia; OSA, obstructive sleep apnea; MDD, major depressive disorder; MMPI, Minnesota Multiphasic Personality Inventory; MSLT, Multiple Sleep Latency Test; N, narcolepsy patients (no division with and without cataplexy); NC-, narcolepsy without cataplexy; NC+, narcolepsy with cataplexy; PAIS-SR, Psychosocial Adjustment to Illness Scale-Self Report; PLM, periodic leg movements; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; SCAN interview, Schedules for Clinical Assessment in Neuropsychiatry interview; SCL-90, Symptom Check List 90; SF-36, Medical Outcomes Study 36-Item Short Form Health-Survey; SSS, Stanford Sleepiness Scale; TAT, Thematic Apperception Test; WHOQOL-BREF, World Health Organization Quality of Life instrument Brief Version.						

C. Information for patients and control subjects

PATIENTENINFORMATION ZUM PROJEKT

“Depression und mit Schlaf verbundene depressive Symptome bei Narkolepsie und anderen Störungen mit Tagesschläfrigkeit“

Sehr geehrte Dame, sehr geehrter Herr,

vielen Dank für Ihre Bereitschaft, an unserer Untersuchung teilzunehmen.

Schlafstörungen sind für die Betroffenen oft eine große Belastung im Alltagsleben. Das kann auch zu einer nachhaltigen Beeinträchtigung der Stimmung führen, bis hin zu den Anzeichen einer Depression. Auf der anderen Seite gibt es Symptome der Schlafstörung selbst, die dem Erscheinungsbild einer Depression sehr ähneln. Das Ziel unserer Untersuchung ist es, hier die Unterschiede und Gemeinsamkeiten genauer zu betrachten. Dazu bitten wir Sie, eine Reihe von Fragebögen auszufüllen.

In den Fragebögen werden zum Teil sehr persönliche Dinge abgefragt. Wir versichern Ihnen, dass Ihre Angaben streng vertraulich behandelt und nur für die Zwecke dieser Untersuchung verwendet werden. Die Weiterverarbeitung erfolgt pseudonymisiert, das heißt ohne Bezug zu Ihrem Namen.

Für weitere Fragen stehen wir Ihnen jederzeit gerne zur Verfügung. Die Projektleiterin ist Frau Cecilia Jara. Sie ist über das Schlaflabor des Bezirksklinikums Regensburg zu erreichen (Tel. 0941-941-2843)

Vielen Dank für Ihre Mitarbeit

Dr. Peter Geisler	Cecilia Jara	Unterschrift Teilnehmer
Oberarzt	Licenciada en Psicología Universidad de Santiago de Chile	

INFORMATION ZUM PROJEKT

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Vielen Dank für Ihre Mitarbeit

Dr. Peter Geisler	Cecilia Jara	Unterschrift Teilnehmer
Oberarzt	Licenciada en Psicología Universidad de Santiago de Chile	

D. Informed consent

EINVERSTÄNDNISERKLÄRUNG ZUM PROJEKT:

“Depression und mit Schlaf verbundene depressive Symptome bei Narkolepsie und anderen Störungen mit Tagesschläfrigkeit“

Ich habe die Aufklärung für Studienteilnehmer über die genannte wissenschaftliche Untersuchung gelesen und verstanden. Mir wurden alle Fragen, die ich zu dieser Untersuchung habe, beantwortet und ich bin mit der Durchführung der Untersuchung einverstanden.

Die gesetzlichen Datenschutzbedingungen werden eingehalten.

Ich erkläre, dass ich mit der im Rahmen der klinischen Prüfung erfolgenden pseudonymisierten Aufzeichnung von Krankheitsdaten/ Studiendaten einverstanden bin.

_____, den_____

_____

Unterschrift des Patienten

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Unterschrift der aufklärenden Psychologin

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Unterschrift Aufklärender Arzt

12. ACKNOWLEDGMENTS

I would like to thank Prof. Jürgen Zulley, Prof. Gorän Hajak and Dr. Peter Geisler for the great opportunity to take part in the sleep lab in Regensburg and to develop my dissertation there. I appreciate the valuable advice of Prof. Zulley in all aspects of the project presented in this dissertation. I am especially in debt to Dr. Geisler, because he supported every step of my research. His deep interest in narcolepsy and hypersomnia stimulated my own curiosity in this theme. And as he said, narcolepsy is an illness that affects people throughout life, but also people doing research in narcolepsy maintain the interest on this fascinating illness throughout life. Furthermore, he is responsible for gaining the enthusiasm from the German association of narcolepsy to participate on this project. Dr. Geisler has supported unselfishly this association for more than 20 years.

I would also like to thank all the people working at the sleep lab for the warm human atmosphere that I felt from the first day, even without knowledge of the German language. Therefore, this dissertation means for me not only a large process of learning about sleep research but also the personal wisdom to live in a foreign country with a different culture. Employees working at the sleep lab received me in a friendly atmosphere that facilitated the adaptation process. Hence, I want to express special gratitude for Drs. Roland Popp, Tatjana Crönlein, Christiane Hirn and more at the end Christoph Pieh. I am in debt to Ms. Sabine Weigl, Ulla Götz, Karin Völlner, Annette Suttner and Karin Berger. And also I am thankful to Ms. Maria Wiechmann, Michaela Christl, Josefa Gawarkiewicz and Nina Effhauser. Moreover, inside the hospital, there were other individuals who have further been protagonists of this process, to whom I would also like to express my gratitude. They are Simone Hauser, Günter Gürlach and although no longer with us, Claudia Lübbers. I would like to express my gratitude to Drs. Eckl and Kühnl who helped me in the city of Regensburg to contact most of the patients with depression.

Furthermore, I am very grateful for the support of my family and friends in Chile, who were always thoughtful about every step of these years.

In addition, the Chilean government trusted in me through CONICYT, which provided me the financial support to work on this dissertation and at the end the University of Regensburg through the Frauenförderung program.

Last but not least, I am thankful for the enormous patience of Christian for motivating me to persevere.

13. DECLARATION

The project to perform this dissertation was approved by the university ethics committee (Number 06/201).

A part of this dissertation was recently published in an international journal. The citation of the article is the following:

Jara, C., Popp, R., Zulley, J., Hajak, G., Geisler, P. Determinants of depressive symptoms in narcoleptic patients with and without cataplexy. J Nerv Ment Dis 2011; 199 (5):329-34.