

Narcolepsy and psychiatric comorbidity: a review of the literature

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ABSTRACT

Introduction: Narcolepsy is a chronic sleep-wake disorder characterized by recurrent episodes of excessive daytime sleepiness, hypnagogic hallucinations, and sleep paralysis. There are two subtypes: narcolepsy type 1 (with cataplexy) and narcolepsy type 2 (without cataplexy). This review aims to investigate the comorbidity of psychiatric disorders in narcolepsy.

Methods: We examined this association through a systematic literature review conducted on July 20, 2024. Searches were performed in PubMed and Embase.

Results: In general, the prevalence of comorbid psychiatric disorders in patients with narcolepsy varies considerably. Depression, anxiety disorders and ADHD are considerably more prevalent in patients with narcolepsy than in the general population. The prevalence of comorbid psychotic disorders and a formal diagnosis of an eating disorder seems also higher in narcolepsy, albeit to a lesser extent. Neurodegenerative disorders and addictive problems were not more prevalent than in general population. More evidence is needed on bipolar disorder, obsessive compulsive disorder, autism, intellectual disability and personality disorders.

Conclusion: Overall psychiatric disorders are more prevalent in patients with narcolepsy, but prevalence rates vary widely across disorders. High prevalence of comorbid depression, anxiety disorders and ADHD is reported in narcolepsy. For other psychiatric disorders, current evidence is less conclusive. It is important that clinicians and patients are aware of the comorbidity of narcolepsy and psychiatric disorders.

Introduction

Narcolepsy is a chronic sleep-wake disorder characterised by (1) excessive daytime sleepiness (EDS), (2) sleep paralysis (a transient disability to move while falling asleep or awakening), (3) hypnagogic or hypnopompic hallucinations (vivid hallucinations occurring while falling asleep or awakening respectively) and sometimes (4) cataplexy (a sudden loss of muscle tension with remaining consciousness, mostly evoked by strong emotions). There are two subtypes of narcolepsy, defined by the clinical presence (narcolepsy type 1 - NT1) or absence (narcolepsy type 2 - NT2) of cataplexy. Narcolepsy usually begins in adolescence or early adulthood, with two peaks in age of onset: around 15 years and around 35 years, although age of onset can also be later in life (Martens & Van Den Bossche, 2025). The etiology of narcolepsy involves a combination of polygenetic risk factors and environmental factors. The HLA allele DQB1*0602 is associated with an increased risk for NT1, and to a lesser extent for NT2 (Capittini et al., 2018). This points to the hypothesis of an autoimmune reaction, possibly triggered

by environmental factors such as viral or streptococcal infections, leading in NT1 to the destruction of >90 % of hypocretin-1 neurons (Mahlios et al., 2013). Hypocretin is a neuropeptide produced in the hypothalamus that plays a crucial role in the regulation of sleep-wake rhythm. The etiology of NT2 is less clear.

The diagnosis of narcolepsy can be made by polysomnography (PSG), followed by a Mean Sleep Latency Test (MSLT), in which sleep onset latency (SOL) is evaluated (SOL ≤ 8 min is considered indicative of narcolepsy), together with the occurrence of sleep onset REM (rapid eye movement) periods (SOREMPs). For a diagnosis of narcolepsy generally two or more SOREMPs are required. More recently, measurement of the concentration of hypocretin-1 in cerebrospinal fluid (CSF) has enabled more direct diagnosis of NT1. A value of ≤ 110 pg/mL or less than a third of the mean standard value supports the diagnosis of NT1 (Bourgin et al., 2008).

The global prevalence of narcolepsy is estimated at 25 to 50 per 100,000 persons, while the incidence has been estimated at around 0.74 per 100,000 person-years (Longstreth et al., 2007). Males and females

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are affected equally (Baldini et al., 2024a).

In clinical practice, narcolepsy is often found to be comorbid with other psychiatric conditions such as depression, anxiety, and ADHD. High comorbidities are also described in the literature, mainly with mood disorders, anxiety problems and ADHD (Hansen et al., 2023; Krahn et al., 2022; Morse & Sanjeev, 2018), but psychotic disorders and eating problems are also mentioned (Hansen et al., 2023; Morse & Sanjeev, 2018). Psychiatric comorbidity has been hypothesized to result from excessive sleepiness and/or disrupted circadian rhythms, or from shared pathophysiological mechanisms, including hypocretin-1 deficiency (Hansen et al., 2023).

In this literature review, we provide an overview of the comorbidity of narcolepsy with psychiatric disorders. First, the association between narcolepsy and psychiatric disorders in general is discussed, followed by a detailed analysis of specific psychiatric comorbidities and their prevalence in narcolepsy.

Methods

This research involves a systematic literature review, for which PubMed and Embase databases were searched. The literature search was conducted on July 20, 2024. The search terms used in Pubmed were "narcolepsy"[MeSH Terms] combined with ("mental disorders"[MeSH Terms] or "comorbidity"[MeSH Terms]) and "narcolepsy"[All Fields] AND "psychiatric comorbidity"[All Fields]. The search terms used in Embase were "narcolepsy" AND "mental disease" as well as "narcolepsy" AND "psychiatric comorbidity".

In addition, relevant articles from reference lists of the fully screened

articles were included and 2 articles were additionally suggested during the review process.

The search strategy focused on English-language publications since 1945. Exclusion criteria were: (1) no full text available, (2) no clear diagnosis of narcolepsy, (3) animal studies, (4) absence of psychiatric comorbidity, (5) no clear diagnosis of psychiatric disorder, (6) sleep disorders without psychiatric conditions, and (7) somatic comorbidity. Inclusion criteria were: (1) clear diagnosis of narcolepsy type 1 or type 2, (2) psychiatric comorbidity, (3) a clear psychiatric diagnosis based on DSM criteria or made by means of validated instruments. No age restriction was applied.

After systematic screening of the databases, a total of 201 articles were identified and evaluated based on their abstracts. Of these, 134 articles met the inclusion criteria for full text review. After this review, 1 article was excluded because of the unavailability of the full text, 37 articles because of the lack of a clear diagnosis of psychiatric comorbidity or narcolepsy, 8 articles because of the lack of a distinction between narcolepsy and idiopathic hypersomnia, 11 articles because of no prevalence data available and 2 articles because of the presence of an organic brain disorder. Finally, 78 articles were included, consisting of 19 reviews, 14 case reports/case series, 20 case-control studies, 10 cross-sectional studies and 14 cohort studies (Fig. 1).

Results

General psychiatric comorbidity

The study by Krishnan et al. showed that two-thirds of patients with

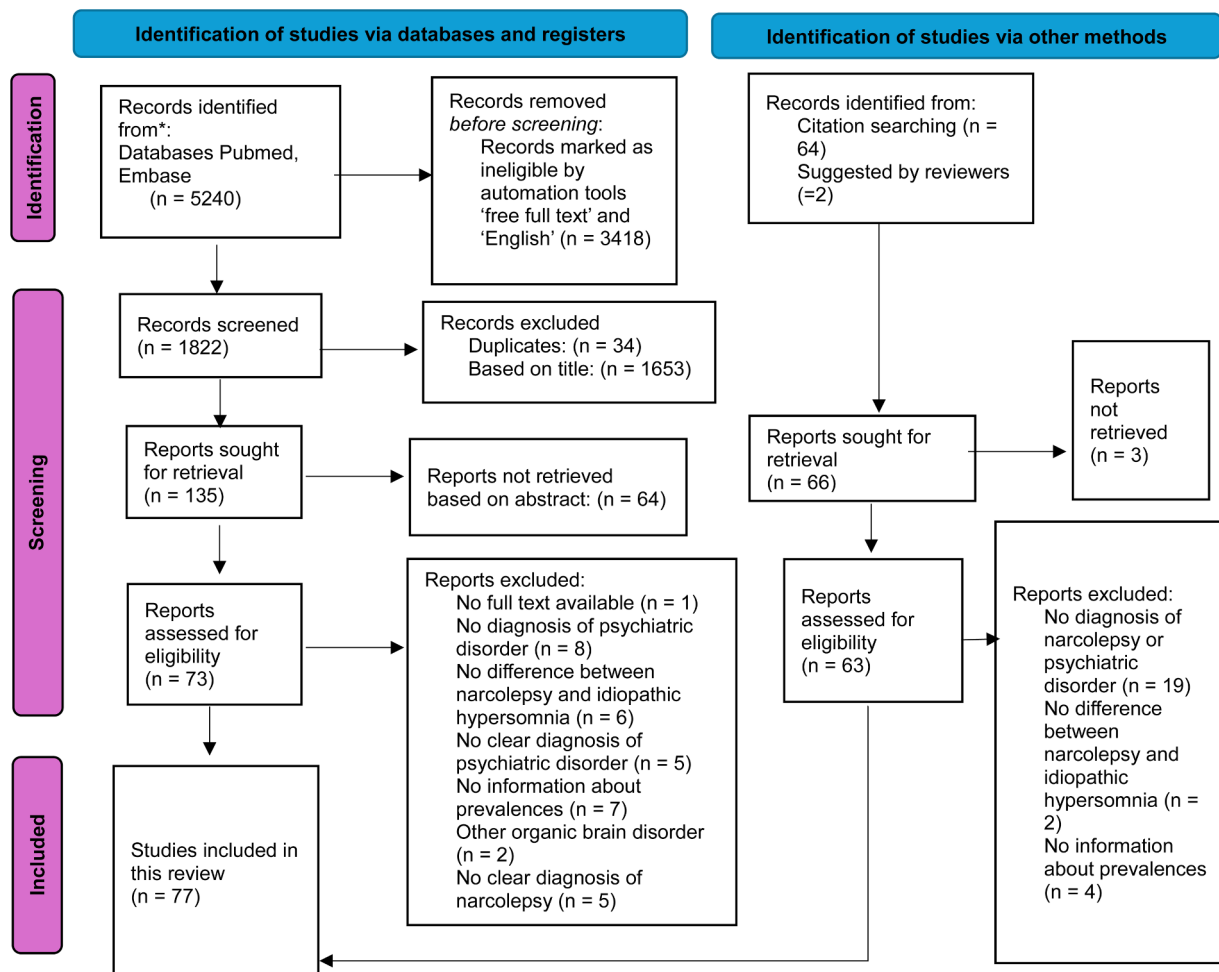


Fig. 1. PRISMA 2020 flow diagram of our literature search.

narcolepsy had a comorbid psychiatric disorder (formal diagnosis based on patient charts), although these findings were based on a small population of 24 patients and no control groups were included (Haba-Rubio, 2005; Krishnan et al., 1984).

A cross-sectional study by Hansen et al. examined 59 patients with NT1 for psychiatric comorbidity, with 30.5 % of participants having a single psychiatric disorder and 22 % having two or more psychiatric disorders according to clinical evaluation through a semi-structured interview (Hansen et al., 2023). Similarly, in a sample of 38 patients with narcolepsy, Szakács et al. found through clinical evaluation that 37.8 % (14/37) had at least one psychiatric comorbidity (Szakacs et al., 2015). A third study conducted by Nevsimalova et al. analyzed 148 patients with narcolepsy and idiopathic hypersomnolence. This showed that 38.1 % of the NT1 group and 45.5 % of the NT2 group had some form of psychiatric comorbidity based on self-report questionnaires (Nevsimalova et al., 2022). In contrast to these results, a study by Frauscher et al. discovered comorbid psychiatric problems in only 8 % based on patient charts (Frauscher et al., 2013). The reason for this lower prevalence could be due to the incompleteness of the files. The lack of control groups was a limitation in all these studies.

In a cross-sectional study by Kales et al. about 50 % of the 50 patients with narcolepsy studied were found to have psychiatric comorbidity according to clinical evaluation, consisting mainly of depressive disorders and personality problems (Kales et al., 1982). Cohen et al. observed in a cohort of 68 patients with narcolepsy that psychiatric comorbidity was present in 45.6 % at baseline and 57.4 % at follow-up, compared with 17.3 % and 28.7 %, respectively, in controls (Cohen et al., 2018). This result was statistically significant. Psychiatric diagnosis in this study was based on clinical evaluation. Yet another study by Alasim et al. found comorbid psychiatric disease in 45 % of 74 patients with narcolepsy compared to 15 % of the control group, a result that was statistically significant (Alasim et al., 2020). The most common comorbidity here was depression and psychotic disorders (diagnoses obtained from medical records).

However, a 2013 study analyzed a comprehensive cohort of 757 patients with narcolepsy and 3013 controls, where only 4 % of patients were found to have psychiatric comorbidity compared with 1.8 % of controls, a difference that was not statistically significant (Jennum et al., 2013). In an even larger study with data from medical claims, where 9312 patients with narcolepsy were compared with 46,559 control subjects for comorbidities, an excess prevalence of 31.1 % was found for mental illness, the highest of all categories (62.3 % versus 31.2 %) (Black et al., 2017).

Finally, Feketeova et al. showed that 20 % of patients with narcolepsy had a comorbid psychiatric disorder based on clinical evaluation, and that the presence of narcolepsy doubled the risk of a psychiatric disorder (Feketeova et al., 2020).

A summary of the above studies can be found in Table 1.

Affective disorders

Depressive disorder

Depression is often identified as the most common comorbidity in narcolepsy. In a meta-analysis of 31 studies, 32 % of patients with narcolepsy were found to have a comorbid depression (Li et al., 2021).

The prevalence of depression in patients with narcolepsy is between 10.55 % and 37.9 % according to several controlled studies, while in control groups it was only between 5 % and 13.8 % (Morse & Sanjeev, 2018). Most studies gave a similar prevalence of around 30 % for a comorbid depressive problem with a statistically significant difference compared to the control group although study designs and methods used for psychiatric diagnosis differed between studies (Alasim et al., 2020; Black et al., 2017; Cohen et al., 2018; Feketeova et al., 2020; Huang et al., 2016; Kales et al., 1982; Lee et al., 2017; Ohayon, 2013; Ruoff et al., 2017). In the study by Cohen et al. an increase of this percentage to 50 % was even observed at follow-up (Cohen et al., 2018). Furthermore,

it was found that patients with narcolepsy showed more frequent depressive symptoms and had higher scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) than control groups (Chabas et al., 2007; Filardi et al., 2017).

However, three studies could not retain a significant difference with the control group (Fortuyn et al., 2010; Kamada et al., 2024; Vourdas et al., 2002). One of these is the study by Kamada Y. et al. which examined a large population of 4594 patients, but one of the control groups consisted of people with schizophrenia in which depressive disorder is also very common which could lead to a distorted picture (Kamada et al., 2024). Another study, where psychiatric diagnosis was based on a structured psychiatric interview, found no difference between the two groups, but those findings were based on small sample sizes of 45 narcolepsy patients and patients from a psychiatric service were excluded from the study (Vourdas et al., 2002). Finally, the study by Fortuyn et al. used the SCAN method to arrive at a DSM-IV diagnosis of depression, but in this method somatic complaints of sleep disturbance and fatigue are excluded, therefore potentially leading to a lesser overlap (Fortuyn et al., 2010).

In clinical studies without a control group, Krystal et al. showed that 28.1 % had a history of depression (Krystal et al., 2022), while Nevsimalova et al. reported a history of mixed anxiety-depressive disorder in 22 % NT1 patients (Nevsimalova et al., 2022) and in the French Harmony study 26.3 % had mild depressive disorder, 23.2 % moderately severe depressive disorder and 5.6 % severe depression (Dauvilliers et al., 2009). In a recent study of 88 narcolepsy children, 25 % were diagnosed with depressive symptoms, although a diagnosis of major depression was rare (Rocca et al., 2015). Three other studies recorded similar findings: two cohort studies showed a comorbid depressive disorder in 28 % of 120 narcoleptic patients (Chin et al., 2023) and 26 % of 100 narcoleptic patients (Chin et al., 2024), similarly, a third study found a comorbid depression in 26 % of 111 NT1 patients and 11 % of 46 NT2 patients (Huang et al., 2017).

Finally, Chepke et al. describe a 31-year-old man with ADHD and depression in his past, but who also developed narcolepsy later in life (Chepke, 2023).

Detailed overview of these studies can be found in Table 2. A description of the case reports can be found in Table 9.

Bipolar disorder

A study by Feketeova et al. found affective disorders in 21 % of patients with narcolepsy, although this disorder was not specified (Feketeova et al., 2020). Two cross-sectional studies with large sample sizes reported a statistically significant difference with about 8 % of patients with narcolepsy diagnosed with comorbid bipolar disorder, compared with only about 2 % in the control group (Ohayon, 2013; Ruoff et al., 2017). The study by Ohayon et al. examined 320 patients with narcolepsy; psychiatric diagnosis was obtained by clinical interview (Ohayon, 2013). The study by Ruoff et al. examined as many as 9312 patients with narcolepsy (Ruoff et al., 2017). Two other studies also reported similar results, with 2 % to 5 % of patients having comorbid bipolar disorder (Fortuyn et al., 2010; Frauscher et al., 2013). However, one of these studies lacked a control group and psychiatric diagnosis was solely based on patient charts (Frauscher et al., 2013). In the other study, the result was statistically significant and here psychiatric diagnosis was obtained from a semi-structured interview (Fortuyn et al., 2010).

The above results are presented in Table 2.

In addition, two case reports were included in which, based on clinical symptoms, PSG and MSLT, the comorbid diagnosis of narcolepsy and bipolar disorder was made (Crosby et al., 2011; Trzepacz, 1987). Detailed data on these case reports can be found in Table 9.

Psychotic disorders

Results regarding the prevalence of psychotic disorders in narcolepsy

Table 1

Overview of articles on narcolepsy and general psychiatric comorbidity.

Title	Study design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Comorbidities in a community sample of narcolepsy	<i>Cohort study</i>	Cohen A. et al.	2018	n = 68	?	?	n = 272	PSG + MSLT	Clinical evaluation documented in the medical record	t1: 45.6 % with psychiatric comorbidity versus 17.3 % of the controls. t2 (after years of follow-up): 57.4 % with psychiatric disorder versus 28.7 % of the controls. Both statistical significant.
Associations between psychiatric comorbid disorders and executive dysfunctions in hypocretin-1 deficient pediatric narcolepsy type 1	<i>Cross-sectional study</i>	Hansen, B.H. et al.	2023	n = 59	n = 59	/	none	PSG + MSLT and CSF level hypocretin-1	DSM 5 Semi-structured diagnostic interview obtained by a psychiatrist – clinical evaluation	52.5 % psychiatric comorbidity; 30.5 % one and 22 % two or more psychiatric disorders.
Narcolepsy: Preliminary Retrospective Study of Psychiatric and Psychosocial Aspects	<i>Retrospective study</i>	Krishnan et al.	1984	n = 24	n = 19	n = 5	none	Selection from a narcolepsy clinic	Psychiatric comorbidity according to DSM-III based on patient charts	66 % with psychiatric diagnosis.
Psychiatric Comorbidity and Cognitive Profile in Children with Narcolepsy with or without Association to the H1N1 Influenza Vaccination	<i>Cross-sectional study</i>	Szakács A. et al.	2015	n = 38	?	?	none	ICD-10 + ICSD 2005	DAWBA, ASSQ, ADHDRS, PANNS questionnaires. DSM-IV. Diagnostic interview consisting of structured interviews, questionnaires, and rating techniques. Final rating made by a psychiatrist – clinical evaluation	34.84 % with psychiatric comorbidity.
Central Disorders of Hypersomnolence: Association with Fatigue, Depression and Sleep Inertia Prevailing in Women	<i>Cross-sectional study</i>	Nevsimalova S. et al.	2022	n = 148	n = 87	n = 22	none	PSG + MSLT and clinical information	HADS, FSS and SIQ questionnaire – self-report	38.1 % of NT1 with psychiatric comorbidity and 45.5 % of NT2.
Delayed Diagnosis, Range of Severity, and Multiple Sleep Comorbidities: A Clinical and Polysomnographic Analysis of 100 Patients of the Innsbruck Narcolepsy Cohort	<i>Cohort study</i>	Frauscher B. et al.	2013	n = 100	n = 87	n = 13	none	Sleep history, PSG and MSLT, HLA typing and hypocretine-1 level in CSF.	Psychiatric comorbidity based on patient records and clinical interview	8/100 had a psychiatric disorder.
Narcolepsy-Cataplexy II. Psychosocial Consequences and Associated Psychopathology	<i>Cross-sectional study</i>	Kales A. et al.	1982	n = 50	?	?	n = 50	Selection from the Sleep Disorders Clinic + cataplexy	Psychiatric interview, MMPI and SCL-90 – clinical evaluation	30 % comorbid depressive disorder.
Comorbid psychiatric disorders among patients with narcolepsy	<i>Cross-sectional study</i>	Alasim H. et al.	2020	n = 74	n = 30	n = 44	n = 265	ICSD-3, PSG and MSLT	MINI version 6 based on DSM-IV – clinical evaluation	45 % psychiatric disorder compared with 15 % of the control group; statistically significant.
Comorbidity and Mortality of Narcolepsy: A	<i>A Case-Controlled Retro- And</i>	Jennum P. et al.	2013	n = 757	?	?	n = 3013	PSG + MSLT, LP or clinical information	Diagnosis based on ICD-10 Information	4 % with a psychiatric disorder

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Table 1 (continued)

Title	Study design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Controlled Retro- and Prospective National Study	<i>Prospective Study</i>								abstracted from the database	versus 1.8 % of the controls. Not statistical significant.
Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study	<i>Retrospective data-analysis</i>	Black, J. et al.	2017	n = 9312	n = 1890	n = 7422	n = 46,559	Medical claims data, diagnosis code for narcolepsy	Diagnosis code, clinical classification system	62.3 % mental illness in narcolepsy group versus 31.2 % in control group
Narcolepsy in Slovakia e Epidemiology, clinical and polysomnographic features, comorbid diagnoses: a case-control study	<i>Case-control study</i>	Feketeova E. et al.	2019	n = 61	n = 51	n = 10	n = 244	PSG + MSLT, HLA typing and hypocretin-1 level in CSF	Diagnosis obtained by medical records review or based on a telephone interview	20 % with comorbid psychiatric disorder.
Narcolepsy and psychopathology: is there an association?	<i>Case-control study</i>	Vourdos, A. et al.	2002	N = 45	?	?	N = 50	PSG + MSLT	Diagnosis made by a structured psychiatric diagnostic interview obtained by a psychiatrist	4/45 patients with Comorbid psychotic disorder compared to none in the control group; statistically significant. But all related to amphetamine use. 7/45 patients compared to 9/60 controls had a major depression; not statistically significant. 2/45 patients and none of the controls met criteria for anxiety disorder NOS; not statistically significant.

vary considerably. A 2005 review by Haba-Rubio et al. reported that between 0 % and 14 % of patients with narcolepsy would have comorbid schizophrenia (Haba-Rubio, 2005). This spans a range of a very significant increased risk to no increase at all, as the lifetime prevalence of schizophrenia is estimated to be between 0.3 % and 0.66 % (van Os & Kapur, 2009). Similarly, a study by Vourdas et al. found no evidence of an increased prevalence of schizophrenia in patients with narcolepsy (Vourdas et al., 2002). A 2011 review by Fortuyn et al. also seems to confirm these findings, with the majority of studies showing no increased prevalence of schizophrenia compared with a control group (Fortuyn et al., 2011). The 2018 review by Morse & Sanjeev additionally confirmed that the co-occurrence of narcolepsy and schizophrenia is rare (Morse & Sanjeev, 2018). However, none of these reviews has a detailed methodology.

A recent 2021 systematic review by Hanin C. et al. collected data from 100 articles. This showed that older studies suggested a relatively high prevalence, but that these results could not be confirmed in newer, methodologically better designed studies (Hanin et al., 2021). For example, Dauvilliers et al. studied 542 NT1 patients, of whom 1.8 % had a history of schizophrenia spectrum disorder (however no formal diagnosis was made) (Dauvilliers et al., 2016). In a prospective study 10 out of 102 NT1 patients had comorbid schizophrenia based on clinical evaluation through a psychiatrist (Huang et al., 2014). In contrast, none of the 38 narcolepsy children in a population-based study had a

psychotic disorder (Szakacs et al., 2015). These inconsistencies can be due to difference in study design. As for the study of Szakacs et al., this was a cross-sectional study of children and adolescents with mean age of 15.3 years old. As we know that schizophrenia mostly starts at adolescent age, it is clear that there can be an underestimation of comorbidity rate in this study (Szakacs et al., 2015). The study of Huang et al. on the contrary followed patients with narcolepsy for four years, thereby probably leading to a greater comorbidity rate of psychotic disorders. Furthermore, in all studies patients used stimulants as a treatment for their narcolepsy but it is not known to which dosage. Some authors argue that (higher doses of) stimulants could play a role in inducing or aggravating psychotic symptoms (Auger et al., 2005). A lack of formal psychiatric diagnostic measures in the study of Dauvilliers et al. could have affected both the frequency and diagnosis of psychotic disorders (Dauvilliers et al., 2016).

A 2023 retrospective cohort study examined 69 patients with narcolepsy, of whom 4 % had experienced a psychotic episode and 1.5 % had a formal diagnosis of schizophrenia (Feketeova et al., 2022). Similarly, in another recent retrospective study 6 % of 120 narcolepsy patients had comorbid schizophrenia (Chin et al., 2023). In a cross-sectional study from 2022 conducted in 87 NT1 and 22 NT2 patients, only two patients had comorbid schizophrenia, although diagnoses were based on self-report questionnaires and since people with schizophrenia often lack insight in their own disorder, this may

Table 2

Overview of articles on narcolepsy and affective disorders.

Title	Study Design	Author	Year	Narcolepsy (n=)	NT1 (n=)	NT2 (n=)	Controls (n=)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study	<i>Retrospective data-analysis</i>	<i>Black, J. et al.</i>	2017	n = 9312	n = 1890	n = 7422	n = 46559	Medical claims data, diagnosis code for narcolepsy	Diagnosis code, clinical classification system	37.9% mood disorders in narcolepsy group versus 13.8% in control group
Comorbidities in a community sample of narcolepsy	<i>Cohort study</i>	<i>Cohen A. et al.</i>	2018	n = 68	n = 28	n = 40	n = 272	PSG+MSLT	Clinical evaluation documented in the medical record	t1: 39.7% comorbid depressive disorder and t2 (after follow-up): 50%.
Associations between psychiatric comorbid disorders and executive dysfunctions in hypocretin-1 deficient pediatric narcolepsy type 1	<i>Cross-sectional study</i>	<i>Hansen, B.H. et al.</i>	2023	n = 59	n = 59	/	none	PSG + MSLT and hypocretin-1 level in CSF	DSM 5 Semi-structured diagnostic interview obtained by a psychiatrist – clinical evaluation	11.9% comorbid depressive disorder.
Psychiatric Comorbidity and Cognitive Profile in Children with Narcolepsy with or without Association to the H1N1 Influenza Vaccination	<i>Cross-sectional study</i>	<i>Szakács A. et al.</i>	2015	n = 38	?	?	none	ICD-10 and ICSD (2005)	DAWBA, ASSQ, ADHDRS, PANNS questionnaires. DSM-IV. Diagnostic interview consisting of structured interviews, questionnaires, and rating techniques. Final rating made by a psychiatrist – clinical evaluation	In the post vaccination group, 6/30 had a major depression.
Central Disorders of Hypersomnolence: Association with Fatigue, Depression and Sleep Inertia Prevailing in Women	<i>Cross-sectional study</i>	<i>Nevsimalova S. et al.</i>	2022	n = 148	n = 87	n = 22	none	PSG+MSLT	HADS, FSS and SIQ questionnaire – self-report	4.1% depressive disorder of which 3.5% of the NT1 group and 0% of the NT2 group.
Delayed Diagnosis, Range of Severity, and Multiple Sleep Comorbidities: A Clinical and Polysomnographic Analysis of 100 Patients of the Innsbruck Narcolepsy Cohort	<i>Cohort study</i>	<i>Frauscher B. et al.</i>	2013	n = 100	n = 87	n = 13	none	Sleep history, PSG with MSLT, HLA typing and hypocretin-1 determination in CSF.	Psychiatric comorbidity based on patient records and clinical interview	2/100 had bipolar disorder and 1/100 a first manic episode with psychotic features
Narcolepsy-Cataplexy II. Psychosocial Consequences and Associated Psychopathology	<i>Cross-sectional study</i>	<i>Kales A. et al.</i>	1982	n = 50	?	?	n = 50	Selection from the Sleep Disorders Clinic + cataplexy	Psychiatric interview, MMPI and SCL-90 – clinical evaluation	30% comorbid depressive disorder.
Comorbid psychiatric disorders among patients with narcolepsy	<i>Cross-sectional study</i>	<i>Alasim H. et al.</i>	2020	n = 74	n = 30	n = 44	n = 265	ICSD-3, PSG and MSLT	MINI version 6 based on DSM-IV – clinical evaluation	30% comorbid major depressive disorder compared with 9% of the controls; statistically significant. No one had bipolar disorder (in neither group).
Narcolepsy in Slovakia: Epidemiology, clinical and polysomnographic features, comorbid diagnoses: a case-control study	<i>Case-control study</i>	<i>Feketeova E. et al.</i>	2019	n = 61	n = 51	n = 10	n = 244	PSG, MSLT, HLA typing and hypocretin-1 deficiency.	Diagnosis obtained by medical records review or based on a telephone interview	21% had affective disorder.

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Table 2 (continued)

Title	Study Design	Author	Year	Narcolepsy (n=)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Comorbidity of narcolepsy and depressive disorders: a nationwide population-based study in Taiwan	Cohort study	Lee M.-J. et al.	2017	n = 258	?	?	n = 258	ICD-9-CM	DSM IV Diagnosis based on patient medical records	32.7%, 24.8% and 10.9% depressive, dysthymia or major depressive disorder respectively versus 6.3%, 4.4% and 1.6% of controls.
High rates of psychiatric comorbidity in narcolepsy	Cross-sectional study	Ruoff C.M.	2017	n = 9312	?	?	n = 46 559	ICD-9	Diagnosis based on ICD-9 obtained from the database	35.8% depressive disorder compared to 13% in controls; statistically significant.
Brain imaging and cognition in young narcoleptic patients	Case-control study	Huang Y.-S.	2016	n = 71	?	?	n = 20	ICSD-3 criteria + clinical interview, actigraphy, PSG, MSLT and HLA typing. In some, hypocretin-1 level in CSF	Clinical interview	24.6% of narcolepsy patients had depressive disorder compared to 0% in the control group.
Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population	Cross-sectional study	Ohayon M.	2013	n = 320	?	?	n = 1464	ICSD-2 criteria and DSM-IV-TR	Diagnosis based on DSM IV-TR obtained by clinical interview	17.1% major depressive disorder compared to 6.4% of controls; statistically significant. 2.4% dysthymia compared to 1.2% in controls; not statistically significant.
Eating Disorder and Metabolism in Narcoleptic Patients	Case-control study	Chabas D. et al.	2007	n = 13	?	?	n = 9	Clinical symptoms, PSG + MSLT and HLA typing	CIDI-2 EAT-40 EDI-2 MADRS Combination of self-report and clinical evaluation	Higher MADRS scores in narcolepsy than controls.
Attention impairments and ADHD symptoms in adult narcoleptic patients with and without hypocretin deficiency	Case-control study	Filardi M. et al.	2017	n = 36	n = 21	n = 15	n = 22	ESS, PSG + MSLT and HLA typing	ANT, ASRS, OCIR, BDI and STAI questionnaires – self-report	More depressive symptoms than controls.
Anxiety and mood disorders in narcolepsy: a case-control study	Case-control study	Fortuyn Droogleeveer, H.A.	2010	n = 60	?	?	n = 120	ICSD-2 criteria	Semistructured interview SCAN (DSM-IV) – clinical evaluation	13% had a mood disorder compared to 5% of the controls. Of these, 7% major depressive disorder compared to 3% of the controls and 0% dysthymia compared to 3% of the controls. None statistically significant.
Burden of narcolepsy in Japan: A health claims database study evaluating direct medical costs and comorbidities	Retrospective cohort study	Kamada, Y. et al.	2024	n = 4594	?	?	n = 18376 (schizophrenia) n = 18376 (epilepsy) n = 4594 (ulcerative colitis)	ICD-10	ICD-10 Clinical evaluation	14% comorbid depression; not statistically significant relative to controls.
Solriamfetol treatment of excessive daytime sleepiness in participants with narcolepsy or obstructive sleep apnea with a history of depression.	Post hoc analysis	Krystal A.D. et al.	2022	n = 236	?	?	none	ICSD-3 or DSM-5 criteria	History of depression at screening (recall)	28.1% history of depression.
Psychological health in central hypersomnias: the French Harmony study	Cohort study	Y Dauvilliers	2009	n = 517	n = 424	n = 68	none	ICSD-2 + PSG and MSLT	S-BDI Self-report	26.3% had mild depressive disorder, 23.2% moderately

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Table 2 (continued)

Title	Study Design	Author	Year	Narcolepsy (n=)	NT1 (n=)	NT2 (n=)	Controls (n=)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Narcolepsy and psychopathology: is there an association?	Case-control study	Vourdos, A. <i>et al.</i>	2002	n = 45	?	?	N = 50	PSG + MSLT	Diagnosis made by a structured psychiatric diagnostic interview obtained by a psychiatrist	severe depressive disorder and 5.6% severe depression. 7/45 patients compared to 9/60 controls had a major depression; not statistically significant
Impact of Taiwan's 2021 COVID-19 lockdown on the symptom severity and quality of life of patients with narcolepsy	Retrospective study	Chin, W.-C. <i>et al.</i>	2022	n = 120	n = 80	n = 40	/	PSG, MSLT, HLA typing, actigraphy	Diagnosis based on records from the database	28% of the narcolepsy patients had depression.
Long-term follow-up of symptom and quality of life changes in patients with narcolepsy during and after the COVID-19 pandemic	Retro- and prospective cohort study	Chin, W.-C. <i>et al.</i>	2024	n = 100 zelfde cohort?	n = 67	n = 33	/	PSG, MSLT, HLA typing, actigraphy	Diagnosis based on records from the database	26% of the narcolepsy patients had a comorbid depression.
Multiple sleep latency test in narcolepsy type 1 and narcolepsy type 2: A 5-year follow-up study	Cohort study	Huang, Y. <i>et al.</i>	2018	n = 157	n = 111	n = 46	/	PSG + MSLT	General clinical evaluation, diagnosis based on DSM-IV	26% of NT1 patients had a major depression and 11% of NT2.

influence these results (Nevsimalova *et al.*, 2022).

On the other hand, in an older 2005 study, Auger *et al.* concluded that 17 of 116 (14.6 %) patients with narcolepsy had a comorbid psychotic disorder (Auger *et al.*, 2005) and Huang *et al.* showed that 12 % of 111 NT1 patients had comorbid schizophrenia, but none of the 46 NT2 patients, which could be due to the smaller sample size and the fact that comorbidity is often more frequent among NT1 patients (Huang *et al.*, 2017). Similarly, Chin *et al.* revealed that 10 % of the 171 people with narcolepsy studied had comorbid schizophrenia (Chin *et al.*, 2021).

It cannot be ruled out that the use of stimulants partly influenced these (higher) numbers. Stimulants can sometimes induce or exacerbate psychotic symptoms which are sometimes difficult to distinguish from psychotic symptoms due to schizophrenia. In the above studies all patients received at least 200 mg of modafinil (Auger *et al.*, 2005; Huang *et al.*, 2017; Chin *et al.*, 2021). Additionally, in the studies by Auger *et al.* and Chin *et al.* psychiatric diagnosis was obtained through screening of medical records and it is not clear how initial diagnoses were made.

A limitation of all these studies is the lack of a control group.

When comparing studies with a control group, results continue to vary. Four studies showed a statistically significant outcome between both the narcolepsy group and the control group. In a first retrospective cohort study from 2020, 8.1 % of patients with narcolepsy had a comorbid psychotic disorder based on patient records, compared with 1.5 % in the control group (Yeh *et al.*, 2020). Another cross-sectional study found schizophrenia in 3.4 % of patients with narcolepsy compared with 0.9 % in the control group (Ruoff *et al.*, 2017), a third study found 14.1 % compared with 0 % in controls (Huang *et al.*, 2016) and a fourth cross-sectional study showed a prevalence of 8 % (based on clinical evaluation by a psychiatrist) in patients with narcolepsy compared with 0 % in control subjects (Alasim *et al.*, 2020). In the study by Huang *et al.*, comorbidity in narcolepsy was not the set-up of the study but schizophrenia was present in the demographic data of the study population (Huang *et al.*, 2016).

In contrast, the cross-sectional study by Fortuyn *et al.* discovered no difference in prevalence between the two groups. Diagnosis was based on clinical evaluation through a semi-structured interview (Fortuyn *et al.*, 2009). The study by Feketeova *et al.* diagnosed only three patients with comorbid psychotic disorder through review of the medical records or based on a telephone interview at the moment of their medical visit, while information on the control group was missing (Feketeova *et al.*, 2020). The study by Feketeova *et al.* was a case-oriented study in which data were manually reviewed and information was added through interviews leading to a better quality in assessment of the psychotic symptoms (Feketeova *et al.*, 2020). Sample sizes of the latter studies were smaller.

In two additional studies, patients with a known diagnosis of schizophrenia were screened for the presence of comorbid narcolepsy. Douglass *et al.* reported in a 1993 study that 3.8 % of schizophrenia patients had comorbid narcolepsy (Douglass *et al.*, 1993). However, in a well-designed 2016 cohort study, this result could not be replicated; no patients with schizophrenia were diagnosed with narcolepsy (Sansa *et al.*, 2016).

See for a detailed overview (Table 3).

In addition, 8 case reports/case series were also included, a detailed description of which can be found in Table 9.

Anxiety disorders

Most reviews report an increased prevalence of anxiety disorders in patients with narcolepsy (Krahn *et al.*, 2022; Morse & Sanjeev, 2018; Rocca *et al.*, 2015; Thorpy & Krieger, 2014). These are mainly panic attacks and social anxiety disorders (up to 53 % of patients with narcolepsy), but generalized anxiety disorders also occur (Morse & Sanjeev, 2018; Rocca *et al.*, 2015).

A list of studies on comorbid anxiety disorders in narcolepsy is presented in Table 4. A 2023 cross-sectional study showed that 13 out of 59

Table 3
Overview of articles on narcolepsy and psychotic disorders.

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Comorbidity of Narcolepsy and Psychotic Disorders: A Nationwide Population-Based Study in Taiwan	<i>Retrospective cohort study</i>	Yeh J-Y. et al.	2019	n = 258	?	?	n = 2580	ICD-9 criteria	Patient records were screened to find a psychiatric diagnosis based on ICD-9 criteria.	8.1 % comorbid psychotic disorder compared with 1.5 % of controls; statistically significant.
Psychiatric Comorbidity and Cognitive Profile in Children with Narcolepsy with or without Association to the H1N1 Influenza Vaccination	<i>Cross-sectional study</i>	Szakács A. et al	2015	n = 37	?	?	none	ICD-10 and ICSD (2005)	DAWBA, ASSQ, ADHDRS, PANNS Diagnostic interview consisting of structured interviews, questionnaires, and rating techniques. Final rating made by a psychiatrist – clinical evaluation	None with psychotic symptoms
Central Disorders of Hypersomnolence: Association with Fatigue, Depression and Sleep Inertia Prevailing in Women	<i>Cross-sectional study</i>	Nevsimalova S. et al	2022	n = 109	n = 87	n = 22	none	Clinical examination, actigraphy, PSG and MSLT.	HADS, FSS and SIQ questionnaire – self-report	2 individuals in the NT1 group developed schizophrenia.
Comorbid psychiatric disorders among patients with narcolepsy	<i>Cross-sectional study</i>	Alasim H. et al	2020	n = 74	n = 30	n = 44	n = 265	ICSD-3, PSG and MSLT	MINI version 6 based on DSM-IV – clinical evaluation	8 % with psychotic disorder compared to no one in the control group; statistically significant.
Narcolepsy in Slovakia e Epidemiology, clinical and polysomnographic features, comorbid diagnoses: a case-control study	<i>Case-control study</i>	Feketeova E. et al.	2020	n = 61	n = 51	n = 10	n = 244	PSG, MSLT, HLA typing and hypocretin-1 deficiency	Review of medical records or telephone interview	3 patients with a psychotic disorder. No info on the control group
High rates of psychiatric comorbidity in narcolepsy	<i>Cross-sectional study</i>	Ruoff C.M.	2017	n = 9312	?	?	n = 46 559	ICD-9	Diagnosis based on ICD-9 obtained from the database	3.4 % with comorbid schizophrenia compared to 0.9 % in controls; statistically significant.
Brain imaging and cognition in young narcoleptic patients	<i>Case-control study</i>	Huang Y-S. et al.	2016	n = 71	?	?	n = 20	ICSD-3 criteria + clinical interview, actigraphy, PSG, MSLT and HLA typing. In some, hypocretin-1 level in CSF	Clinical interview	14.1 % comorbid diagnosis of schizophrenia compared with 0 % of the control group.
Absence of NMDA receptor antibodies in the rare	<i>Cohort study</i>	Dauvilliers Y. et al.	2016	n = 542	n = 542	/	none	PSG + MSLT, HLA typing, hypocretin-1 level in CSF	DSM-IV-TR Medical records	1.8 % comorbid schizophrenic disorder, of

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Table 3 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
association between Type 1 Narcolepsy and Psychosis										which 9 patients had schizophrenia and 1 schizotypal personality disorder.
Narcolepsy–cataplexy and schizophrenia in adolescents	Retrospective case-control study	Huang Y-S. et al.	2014	n = 102	n = 102	/	none	PDSS, ESS, sleep diary, HLA typing, PSG and MSLT	K-SADS-E, PANNS, BDI and CGI-SS. Clinical evaluation	9.8 % developed schizophrenia.
Psychotic Episode and Schizophrenia in Slovakian Narcolepsy Database	Retrospective cohort study and case analysis	Feketeová E. et al.	2022	n = 69	n = 69	/	none	ICSD2/ 3	ICSD2/ 3 Clinical evaluation	4 % with psychotic episode and 1.5 % with schizophrenia.
Risks of High-Dose Stimulants in the Treatment of Disorders of Excessive Somnolence: A Case-Control Study	Case-control study	Auger R. et al.	2005	n = 116	?	?	none	Selection from the Mayo Narcolepsy Research Center database	Review of the record, according to the judgment of 2 board-certified psychiatrists	14.6 % with comorbid psychotic disorder.
Different positron emission tomography findings in schizophrenia and narcolepsy type 1 in adolescents and young adults : a preliminary study	Prospective case-control study	Chin W-C. et al.	2021	n = 171	n = 171	/	none	Questionnaires, action graph, PSG and MSLT	Clinical interviews, DSM-5	10.5 % comorbid schizophrenia.
Psychotic symptoms in narcolepsy: phenomenology and a comparison with schizophrenia	Cross-sectional study	Fortuyn H. et al.	2008	n = 60	n = 60	/	n = 120	ICSD-2 + PSG and MSLT	Semistructured interview SCAN of which DSM-IV-TR diagnosis were derived. Clinical evaluation.	In both narcolepsy and control group, 2 people with psychotic disorder. No difference in prevalence between the two groups.
Narcolepsy and psychopathology: is there an association?	Case-control study	Vourdas A. et al.	2002	N = 45	?	?	N = 50	PSG + MSLT	Diagnosis made by a structured psychiatric diagnostic interview obtained by a psychiatrist	4/45 patients with comorbid psychotic disorder compared to none in the control group; statistically significant. But all related to amphetamine use.
Impact of Taiwan's 2021 COVID-19 lockdown on the symptom severity	Retrospective study	Chin, W-C. et al.	2023	n = 120	n = 80	n = 40	/	PSG, MSLT, HLA typing, actigraphy	Diagnosis based on records from the database	6 % of the narcolepsy

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Table 3 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
and quality of life of patients with narcolepsy Multiple sleep latency test in narcolepsy type 1 and narcolepsy type 2: A 5-year follow-up study	Cohort study	Huang, Y. et al.	2017	n = 157	n = 111	n = 46	/	PSG + MSLT	General clinical evaluation, diagnosis based on DSM-IV	patients had schizophrenia. 12 % of NT1 patients had comorbid schizophrenia but none of NT2 patients.
Schizophrenia, narcolepsy, and HLA-DR15, Dq6	Prospective cohort study	Douglass A. et al.	1993	n = 56	n = 56	SADS-RDC Structured diagnostic interview obtained by a clinician	SDQ questionnaire, HLA typing, PSG and MSLT	3.8 % comorbid narcolepsy.		
Exploring the presence of narcolepsy in patients with schizophrenia	Cohort study	Sansa G. et al.	2016	n = 366	none	SADS-RDC Clinical evaluation	Sequence: first a semi-structured questionnaire and collection of ESS, if ESS > 11 or cataplexy referred to a neurologist. Third stage: HLA typing. If positive, hypocretin-1 in CSV was determined. No PSG/ MSLT given irresponsible to pause medication long enough.	No patients with comorbid narcolepsy.		

Table 4
Overview of articles on narcolepsy and anxiety disorders.

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study	<i>Retrospective data-analysis</i>	Black, J. et al.	2017	n = 9312	n = 1890	n = 7422	n = 46,559	Medical claims data, diagnosis code for narcolepsy	Diagnosis code, clinical classification system	25.1 % “mental illness” in narcolepsy group versus 11.9 % in control group
Comorbidities in a community sample of narcolepsy	<i>Cohort study</i>	Cohen A. et al.	2018	n = 68	n = 28	n = 40	n = 272	PSG and MSLT	Clinical evaluation documented in the medical record	t0: 20.6 % anxiety disorder compared to 5.9 % of controls; statistically significant. t1 (follow-up): 25 % comorbid anxiety disorder compared to 15.1 % of controls; no longer statistically significant.
Associations between psychiatric comorbid disorders and executive dysfunctions in hypocretin-1 deficient pediatric narcolepsy type 1	<i>Cross-sectional study</i>	Hansen, B.H. et al.	2023	n = 59	n = 59	/	none	Actigraphy, PSG, MSLT and hypocretin-1 level in CSF	DSM 5 Semi-structured diagnostic interview obtained by a psychiatrist – clinical evaluation	22 % comorbid anxiety disorder.
Psychiatric Comorbidity and Cognitive Profile in Children with Narcolepsy with or without Association to the H1N1 Influenza Vaccination	<i>Cross-sectional study</i>	Szakács A. et al.	2015	n = 37	?	?	none	ICD-10 and ICSD (2005).	DAWBA, ASSQ, ADHDRS, PANNS Diagnostic interview consisting of structured interviews, questionnaires, and rating techniques. Final rating made by a psychiatrist – clinical evaluation	In the post-vaccination group, 3/30 with comorbid generalized anxiety disorder.
Central Disorders of Hypersomnolence: Association with Fatigue, Depression and Sleep Inertia Prevaling in Women	<i>Cross-sectional study</i>	Nevsimalova S. et al.	2022	n = 109	n = 87	n = 22	none	Actigraphy, PSG and MSLT	HADS, FSS and SIQ – self-report	22 % of NT1 patients with history of mixed anxiety-depressive disorder. HADS anxiety scale did not differ between groups.
Delayed Diagnosis, Range of Severity, and Multiple Sleep Comorbidities: A Clinical and Polysomnographic Analysis of 100 Patients of the Innsbruck Narcolepsy Cohort	<i>Cohort study</i>	Frauscher B. et al.	2013	n = 100	n = 87	n = 13	none	PSG, MSLT, HLA typing and level hypocretin-1 in CSF	Psychiatric comorbidity based on patient records and clinical interview	1/100 comorbid anxiety disorder.
Comorbid psychiatric disorders among patients with narcolepsy	<i>Cross-sectional study</i>	Alasim H. et al.	2020	n = 74	n = 30	n = 44	n = 265	ICSD-3, PSG and MSLT	MINI version 6 based on DSM-IV – clinical evaluation	4 % panic disorder in both control and narcolepsy groups. 1 % of controls had agoraphobia compared to 3 % of narcolepsy patients. 3 % social phobia in the control group compared to 4 % of the narcolepsy patients. 0.8 % of the controls had post-traumatic stress disorder compared to no one in

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Table 4 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
High rates of psychiatric comorbidity in narcolepsy	Cross-sectional study	Ruoff C.M. et al.	2017	n = 9312	?	?	n = 46 559	ICD-9	Diagnosis based on ICD-9 obtained from the database	in the narcolepsy group. 1 % of the control group had generalized anxiety disorder compared to 7 % of the narcolepsy group. None of these results were statistically significant. 25.1 % comorbid anxiety disorder compared to 11.9 % in controls; stat. significant.
Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population	Cross-sectional study	Ohayon M. et al.	2013	n = 320	?	?	n = 1464	ICSD-2 and DSM-IV-TR	Diagnosis based on DSM IV-TR obtained by clinical interview	8.5 % agoraphobia compared to 1.3 % in controls. 21.1 % social anxiety compared to 8.7 % of controls. 5.5 % generalized anxiety disorder compared to 1.7 % of controls and 5.2 % specific phobia compared to 1.3 % of controls. All results stat. significant. Panic disorder and post-traumatic stress disorder prevalent in > 10 % of narcolepsy patients; only significant in women.
Attention impairments and ADHD symptoms in adult narcoleptic patients with and without hypocretin deficiency	Case-control study	Filardi M. et al.	2017	n = 36	n = 21	n = 15	n = 22	ESS, PSG, MSLT and HLA typing	ANT, ASRS, OCIR, BDI and STAI – self-report	Non-significant trend for higher anxiety levels and OCD features in narcolepsy compared to controls.
Anxiety and mood disorders in narcolepsy: a case-control study	Case-control study	Fortuyn Droogleeveer, H. A. et al.	2010	n = 60	?	?	n = 120	ICSD-2	Semistructured interview SCAN (DSM-IV) – clinical evaluation	35 % comorbid anxiety disorder of which 20 % social phobia and 22 % panic disorder.
Burden of narcolepsy in Japan: A health claims database study evaluating direct medical costs and comorbidities	Retrospective cohort study	Kamada, Y. et al.	2024	n = 4594	?	?	n = 18,376 (schizophrenia) n = 18,376 (epilepsy) n = 4594 (ulcerative colitis)	ICD-10	ICD-10 Clinical evaluation	17.4 % comorbid anxiety disorder; not statistically significant.
Narcolepsy and psychopathology: is there an association?	Case-control study	Vourdas A. et al.	2002	N = 45	?	?	N = 50	PSG + MSLT	Diagnosis made by a structured psychiatric diagnostic interview obtained by a psychiatrist	2/45 patients and none of the controls met criteria for anxiety disorder NOS; not statistically significant.
Sex and age differences in the association between anxiety disorders and narcolepsy: A nationwide population-based case control study	Case-control study	Chen T-Y. et al.	2020	n = 478	?	?	n = 1912	ICD-9-CM	ICD-9-CM based on clinical evaluation.	14.23 % had any anxiety diagnosis compared to 4.29 % of the control group; statistically significant. This was before diagnosis of narcolepsy was made. No significant difference in anxiety diagnosis after diagnosis of narcolepsy was made. Also no differences in subtypes of anxiety

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Table 4 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Impact of Taiwan's 2021 COVID-19 lockdown on the symptom severity and quality of life of patients with narcolepsy	Retrospective study	Chin, W.-C. et al.	2023	n = 120	n = 80	n = 40	/	PSG, MSLT, HLA typing, actigraphy	Diagnosis based on records from the database	disorders between two groups. 7 % of the narcolepsy patients had anxiety.
Long-term follow-up of symptom and quality of life changes in patients with narcolepsy during and after the COVID-19 pandemic	Retro- and prospective cohort study	Chin, W.-C. et al.	2024	n = 100	n = 67	n = 33	/	PSG, MSLT, HLA typing, actigraphy	Diagnosis based on records from the database	8 % of the narcolepsy patients had comorbid anxiety

patients with narcolepsy were diagnosed with a comorbid anxiety disorder (Hansen et al., 2023). Similarly, Nevsimalova et al. stated that 22 % of NT1 patients had a history of a mixed anxiety-depressive disorder (Nevsimalova et al., 2022). In two other cross-sectional studies, however, this percentage was much lower, between 1 % and 10 % (Frauscher et al., 2013; Szakacs et al., 2015). Similarly, in two retrospective studies of the same author this percentage was between 7 % and 8 % (Chin et al., 2023, 2024). All these studies lacked a control group, which was a limitation.

In the study of Hansen et al. psychiatric diagnosis was based on a semi-structured interview obtained by a psychiatrist, however Nevsimalova et al. used self-report questionnaires which theoretically may have led to an overrepresentation of anxiety diagnoses in this study (Hansen et al., 2023; Nevsimalova et al., 2022).

In a study by Fortuyn et al. up to 35 % of patients with narcolepsy had a comorbid anxiety disorder, with social phobia (20 %) and panic disorder (22 %) being the most common. Diagnoses were made based on a semi-structured interview obtained by a psychiatrist (Fortuyn et al., 2010).

One cohort study and two cross-sectional studies showed similar results, each of which was found to be statistically significant (Cohen et al., 2018; Ohayon, 2013; Ruoff et al., 2017). The study by Ruoff et al. showed comorbid anxiety disorder (extracted from information in a database) in 25.1 % of patients with narcolepsy, compared with 11.9 % in the control group (Ruoff et al., 2017). Cohen et al. found comorbid anxiety disorder based on medical records in 20.6 % of patients with narcolepsy, compared with 5.9 % in controls. However, this result was no longer significant after follow-up (Cohen et al., 2018). Ohayon et al. also reported a significant result for all subgroups regarding anxiety disorders; diagnosis was obtained from a clinical interview (Ohayon, 2013).

A study from 2020 stated that patients with anxiety disorders had a 2.7 fold risk of developing narcolepsy compared to controls (Chen et al., 2020). A large study based on medical claims data similarly found a 2.5 fold risk for anxiety disorders in patients with narcolepsy versus controls (25.1 % versus 11.9 %) (Black et al., 2017).

In contrast, a case-control study by Filardi et al. showed no significant increase in anxiety levels and features of OCD in patients with narcolepsy versus the control group (Filardi et al., 2017). Neither Alasim et al. Kamada et al. nor Vourdas et al. found a statistically significant increase in anxiety disorders in patients with narcolepsy compared to a control group (Alasim et al., 2020; Kamada et al., 2024; Vourdas et al., 2002). It is possible that these mixed results are partly due to very small study populations in 2 studies (Filardi et al., 2017; Vourdas et al., 2002), and a control group consisting of people with schizophrenia in which anxiety disorders are often comorbid in another study (Kamada et al., 2024).

Eating disorders

Patients with narcolepsy could have an increased risk of developing an eating disorder (Fortuyn et al., 2011; Morse & Sanjeev, 2018; Rocca et al., 2015). A 2018 review (Morse & Sanjeev, 2018) included three case-control studies that were also included in this paper. For example, 17.3 % of patients with narcolepsy had a comorbid eating disorder compared to 8.4 % of the controls according to a 2017 study by Black et al. Fortuyn et al. found similar results, with 23.3 % of patients with narcolepsy meeting criteria for a comorbid eating disorder, compared with 0 % in the control group (Fortuyn et al., 2008; Morse & Sanjeev, 2018). According to Chabas et al. patients with narcolepsy had double the EAT-40 scores of controls. They also found that bulimia occurred in approximately 46 % of patients with narcolepsy versus 11 % in the control group (Chabas et al., 2007; Morse & Sanjeev, 2018). Similarly, Baldini et al. reported a higher risk of developing an eating concern in the narcolepsy group than in controls. For example, patients with narcolepsy had higher EDE-Q scores, but this was only statistically

significant for the eating concern subscale. Unlike other studies, no significant differences were noted between the two groups for the bulimia-eating score. In general, patients with NT1 did have more severe eating concerns (Baldini et al., 2024b). The studies of Chabas et al. and Baldini et al. made use of self-report questionnaires which might have influenced the results leading to an overrepresentation of eating concerns in those studies (Chabas et al., 2007; Baldini et al., 2024b).

Another review confirms that bulimia appears to be more common in patients with narcolepsy. However, three case-control studies found no increased prevalence of anorexia, bulimia or binge eating disorder (Alasim et al., 2020; Dahmen et al., 2008; Fortuyn et al., 2011). Similarly, the cross-sectional study by Szakács et al. reported a comorbid eating disorder in only one of 37 included patients with narcolepsy (Szakacs et al., 2015). Those studies made use of clinical evaluation in obtaining a psychiatric diagnosis, except for Dahmen et al. where self-report questionnaires were used. These studies were also all cross-sectional studies, which means diagnosis later in life will not be included, thus potentially leading to an underrepresentation of comorbidity.

The above data is summarized in Table 5.

Addiction disorders

Several studies show that addiction problems are not significantly more prevalent in narcolepsy than in the general population. Four relatively recent studies all show similar results. A first study found comorbid alcohol dependence problems in 7.5 % of patients with narcolepsy, compared with 15.2 % of subjects in the control group (Morse & Sanjeev, 2018). A second study reported a rate of 1.9 % for patients with narcolepsy versus 1.3 % in the control group (Ruoff et al., 2017), while a third study showed that 0.6 % of patients with narcolepsy had an alcohol dependence problem, compared with 0.9 % in the control group (Ohayon, 2013). In a fourth study by Feketeova et al. only two subjects were diagnosed with a comorbid alcohol dependence disorder (2/61) (Feketeova et al., 2020).

In the study by Frauscher et al. only two patients with narcolepsy had a comorbid substance abuse problem (2/100), although a control group was missing (Frauscher et al., 2013). In the study by Barateau et al. no difference was found between the two groups in the incidence of illicit substance use (Barateau et al., 2016) and another study neither could retain people with substance dependence problems (Alasim et al., 2020).

Only Ruoff et al., the largest study, could retain a statistically significant outcome between both groups regarding substance abuse, with 4 % of people in the narcolepsy group versus 1.2 % in controls (Ruoff et al., 2017).

The above data can be found in detail in Table 6.

Neurodegenerative disorders

The probability of narcolepsy co-occurring with Parkinson's disease or Alzheimer's disease is estimated at 4.75/ 1000 000 and 24/ 1000 000, respectively (Economou et al., 2012). Thus, this seems to be a rare comorbidity.

In a study by Ruoff et al. 4.6 % of patients with narcolepsy were found to have a comorbid neurocognitive disorder compared to 1.5 % in the control group. A result that was statistically significant although they did not distinguish between other cognitive disorders and neurodegenerative disorders (Ruoff et al., 2017). In another study by Scammell et al., 12 patients with narcolepsy were examined postmortem for amyloid deposition. 4 of the 12 patients were found to exhibit typical amyloid depositions pointing to the comorbid diagnosis of Alzheimer's disease. However, this percentage is compatible with the prevalence in the general population (Scammell et al., 2012).

Furthermore, another case report was included in which two cases were explored, one with comorbid Parkinson's disease and the other with comorbid Alzheimer's dementia (Economou et al., 2012).

Detailed results can be found in Tables 7 and 9.

OCD/ tic disorder/ Tourette syndrome

A recent study by Hansen et al. examined 59 patients with narcolepsy, of which 4 (6.8 %) were found to have comorbid obsessive-compulsive disorder (OCD) and 6 (10.2 %) were found to have comorbid Tourette syndrome (Hansen et al., 2023). Similarly, a cohort study by Huang et al. showed comorbid OCD diagnosis in 3 % of NT1 patients and 2 % of NT2 patients as well as a comorbid tic disorder in 3 % of NT1 patients and 4 % of NT2 patients (Huang et al., 2017). In another study by Filardi et al. comparing the results with a control group, there appeared to be a trend toward more OCD symptoms in people with narcolepsy, however this trend was not statistically significant (Filardi et al., 2017). Another study showed no significant difference from a control group, only one person had comorbid OCD compared to no one in the control group (Alasim et al., 2020). The studies by Hansen et al. and Alasim et al. were cross-sectional studies in which psychiatric diagnosis was obtained from clinical evaluation by a psychiatrist. The study by Hansen et al. only contained pediatric patients. Filardi et al. on the other hand made use of self-report questionnaires and excluded patients with a previous psychiatric disorder which may explain why the level of significance was not reached. Sample sizes of the studies conducted by Filardi et al. and Alasim et al. had only about half the sample size of the study by Hansen et al. possibly leading to an underdiagnosis of the comorbidity.

Some cases of comorbid OCD or tic disorder in patients with narcolepsy have also been described, but these cases also had an additional diagnosis of schizophrenia and autism, respectively, making this association difficult to interpret (Douglass et al., 1991; Prihodova et al., 2018).

All results can be found in Tables 7 and 9 below.

Personality disorders

Only one study from 1982 describes the comorbid presence of personality disorders in people with narcolepsy. Mainly obsessive-compulsive, passive-aggressive, histrionic and borderline personality disorders occurred (Kales et al., 1982). A detailed account can be found in Table 7.

Intellectual disability

In two controlled studies, intellectual disability was found to be comorbidly present in narcolepsy with a prevalence of 2.3 % (Lee et al., 2017) in one study and 14 % in the other (Feketeova et al., 2020). detailed description can be found in Table 7.

Autism spectrum disorder

A literature review by Posar et al. included seven cases in which narcolepsy co-occurred with autism spectrum disorder (ASD) (Posar et al., 2020). Four of these cases were also included in this study and can be found in Table 9 (3 others were excluded here because of diagnostic uncertainty). Two other cases described by Huang et al. had comorbid schizophrenia in addition to narcolepsy type 1 which could also explain the possible association with ASD (Huang et al., 2014; Posar et al., 2020).

In addition, the review of Posar et al. also included the study by Quaedackers et al. in which 53 children with NT1 were compared with 64 control subjects on social functioning. A T-score above 75 on the social response scale points to severely impaired social functioning, although no formal psychiatric diagnosis was established here. 11 of the 53 patients with narcolepsy showed this elevated T-score (20.8 %) compared to 1 patient in the control group (1.6 %) which was statistically significant (Quaedackers et al., 2019).

Table 5

Overview of articles on narcolepsy and eating disorders.

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
High Prevalence of Eating Disorders in Narcolepsy with Cataplexy: A Case-Control Study	Cross-sectional case-control study	Fortuyn et al.	2008	n = 60	n = 60	/	n = 120	PSG and MSLT, HLA typing. In some cases, hypocretin-1 level in CSF	Semi-structured interview SCAN (DSM-IV). Clinical evaluation.	23.3 % comorbid eating disorder compared with 0 % of controls. 15 % eating disorder not otherwise defined, 6.7 % bulimia nervosa and only 1/60 with anorexia nervosa.
Psychiatric Comorbidity and Cognitive Profile in Children with Narcolepsy with or without Association to the H1N1 Influenza Vaccination	Cross-sectional study	Szakács A. et al.	2015	n = 37	?	?	none	ICD-10 and ICSD (2005).	DAWBA, ASSQ, ADHDRS, PANNS Diagnostic interview consisting of structured interviews, questionnaires, and rating techniques. Final rating made by a psychiatrist – clinical evaluation	In the post-vaccination group consisting of 30 narcolepsy patients, one person showed a comorbid eating disorder not otherwise defined - type anorexia. No one had anorexia nervosa. 3 % had bulimia nervosa compared to no one in the control group; not statistically significant.
Comorbid psychiatric disorders among patients with narcolepsy	Cross-sectional study	Alasim H. et al.	2020	n = 74	n = 30	n = 44	n = 265	ICSD-3, PSG and MSLT	MINI version 6 based on DSM-IV – clinical evaluation	Twice as high EAT-40 scores as control patients. Based on CIDI-2: 46 % with bulimia nervosa compared to 11 % of controls. Only one with anorexia nervosa. Based on EDI-2: higher score for bulimia in narcolepsy. However, no official diagnosis.
Eating Disorder and Metabolism in Narcoleptic Patients	Case-control study	Chabas D. et al.	2007	n = 13	?	?	n = 9	Clinic, PSG, MSLT and HLA typing	CIDI-2 EAT-40 EDI-2 MADRS Combination of self-report and clinical evaluation	Higher EDE-Q scores in narcolepsy than in controls; only statistically significant for the eating concern subscale. For the BES score: no
Eating disorders in narcolepsy type 1: Evidence from a cross-sectional Italian study	Cross-sectional study	Baldini, V. et al.	2024b	n = 138	?	?	n = 162	ESS, NSS, PSG	DSM-5, EDE-Q, BES, NEQ Self-report questionnaires	Higher EDE-Q scores in narcolepsy than in controls; only statistically significant for the eating concern subscale. For the BES score: no

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Table 5 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Prevalence of eating disorders and eating attacks in narcolepsy	Case-control study	Dahmen, N. et al.	2008	n = 116	?	?	n = 80	Cataplexy or PSG	SIAB (DSM-IV) Self-report questionnaires and clinical evaluation	significant differences between both groups. Patients with narcolepsy type 1 did have more severe eating concerns than controls. No difference in prevalences of eating disorders.

In a 2020 controlled study, 6 out of 258 patients with narcolepsy were found to have comorbid ASD (2.3 %) compared to 6 out of 2580 subjects in the control group (0.2 %) (Yeh et al., 2020). Four other uncontrolled studies found similar results where the range of patients with narcolepsy with comorbid ASD was between 2.3 % to 8.1 % (Hansen et al., 2023; Nevsimalova et al., 2022; Szakacs et al., 2015; Huang et al., 2018). In contrast, the study by Kamada et al. examined 4594 patients with narcolepsy of whom 3.5 % were found to have comorbid autism, however, this result was not statistically significant compared to the control group. However, this wasn't a healthy control population, but people with schizophrenia, epilepsy or ulcerative colitis which can explain why comorbidity of ASD in these control groups were elevated since there is for example a known association between ASD and psychotic disorders (Kamada et al., 2024).

The above data are summarized in detail in Table 8.

Attention-deficit and hyperactivity disorder

According to two systematic reviews, the prevalence of ADHD symptoms in patients with narcolepsy is reported to be above 30 % (Bioulac et al., 2020; Kim et al., 2020). Another systematic review from 2024 gathered info from 10 articles with a total of 839 patients with narcolepsy whose pooled prevalence of ADHD was 25 %. However, patients with NT2 showed higher prevalence values for comorbid ADHD (46 %) compared to patients with NT1 (20 %) (Ren et al., 2024). Similarly, Rocca et al. (2015) and Morse et al. (Morse & Sanjeev, 2018) report a two times higher prevalence of ADHD symptoms in patients with narcolepsy compared to control subjects, and Thorpy & Krieger describe a significantly higher frequency of ADHD in narcolepsy than in control groups (Thorpy & Krieger, 2014).

Some controlled studies confirm these findings. For example, a cross-sectional study with 108 patients with narcolepsy showed a prevalence of 45 % comorbid ADHD symptoms compared with 5 to 6 % in the control group (Lecendreux et al., 2015). Similarly, a case-control study found that 33.33 % of patients with NT1 and 26.66 % of patients with NT2 had significantly elevated ADHD symptomatology scores compared with none in the control group (Krystal et al., 2022). Two other case-control studies reported similar results, where in one study 17.4 % of patients with narcolepsy were diagnosed with comorbid ADHD, while no one in the control group had ADHD (Huang et al., 2016). In the other study, up to 37.88 % of patients with narcolepsy showed ADHD symptoms, although the prevalence of a comorbid ADHD diagnosis was estimated between 8 and 15 % (Modestino & Winchester, 2013). Similarly, Kamada al. showed comorbid ADHD in 12 % of the patients with narcolepsy, a result that was statistically significant, although the control group did not consist of healthy individuals (Kamada et al., 2024).

Comparable rates are described in two cohort studies and one cross-

sectional study, in which 7.3 % to 8.9 % of patients with narcolepsy had a comorbid diagnosis of ADHD, compared with 0.9 % to 1.3 % in the control group (Lee et al., 2017; Ruoff et al., 2017; Yeh et al., 2020). Only one cross-sectional study found a statistically significant result exclusively in boys (Ohayon, 2013).

In seven uncontrolled studies, the prevalence of comorbid ADHD in patients with narcolepsy varied, with 2.7 % in one study (Nevsimalova et al., 2022), 13.6 % in another study (Hansen et al., 2023), 18 % in three other studies (Lopez et al., 2020; Chin et al., 2023, 2024), and around 25 % in another two studies (Qu et al., 2022; Szakacs et al., 2015). Similarly, a cohort study by Huang et al. found a comorbid ADHD diagnosis in 13 % of NT1 patients (n = 111) and 30 % of NT2 patients (n = 46) (Huang et al., 2018). A specific 2020 study by Hansen et al. examining post-influenza adolescents with NT1 found ADHD symptoms in 52 % (26/50). Reason for this increased prevalence could be due to the fact that these adolescents were not yet medicated so ADHD symptoms may be more pronounced given the fact that medication for narcolepsy simultaneously also treats ADHD symptoms (Hansen et al., 2020).

A detailed description of these results can be found in Table 8.

Discussion

Overall, we can state that psychiatric disorders are prevalent in people with narcolepsy, although prevalence rates vary, ranging from 4 % to 66.7 % (Black et al., 2017; Cohen et al., 2018; Feketeova et al., 2020; Frauscher et al., 2013; Haba-Rubio, 2005; Hansen et al., 2023; Jennum et al., 2013; Kales et al., 1982; Nevsimalova et al., 2022; Szakacs et al., 2015). Only three studies could withhold a statistically significant result compared to a control group with between 45 and 62 % of patients with narcolepsy having a comorbid psychiatric disorder (Alasim et al., 2020; Black et al., 2017; Cohen et al., 2018). In contrast, another study found no significant difference (4 % vs. 1.8 %) (Jennum et al., 2013).

Differences in cohort sizes and studies conducted in different countries, could partly explain the large variation in these prevalence rates. Another important reason for discrepancies in these rates could be the way psychiatric diagnoses were made (for example extensive interview by a psychiatrist versus a self-report questionnaire), as well as a potential overlap in symptoms that exists between narcolepsy and some psychiatric disorders (Frauscher et al., 2013; Jennum et al., 2013). For example, excessive sleepiness and fatigue is also a symptom of depression, night terrors may be misinterpreted as panic attacks, and hypnagogic or hypnopompic hallucinations may be reminiscent of psychosis (Modestino & Winchester, 2013). Moreover, the design of studies may be so that comorbidity is underestimated. For example, a cross-sectional designed study including mainly patients with narcolepsy in early

Table 6

Overview of articles on narcolepsy and addiction disorders.

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Delayed Diagnosis, Range of Severity, and Multiple Sleep Comorbidities: A Clinical and Polysomnographic Analysis of 100 Patients of the Innsbruck Narcolepsy Cohort	Cohort study	Frauscher B. et al.	2013	n = 100	n = 87	n = 13	none	Sleep history, PSG, MSLT, HLA typing and if necessary determination of hypocretin-1 in CSF	Patient records and clinical interview	2/100 with comorbid substance abuse problems.
Comorbid psychiatric disorders among patients with narcolepsy	Cross-sectional study	Alasim H. et al.	2020	n = 74	n = 30	n = 44	n = 265	ICSD-3, PSG ann MSLT	MINI version 6 based on DSM-IV – clinical evaluation	In both the group of narcolepsy and controls, no addiction problems.
Narcolepsy in Slovakia e Epidemiology, clinical and polysomnographic features, comorbid diagnoses: a case-control study	Case-control study	Feketeova E. et al.	2019	n = 61	n = 51	n = 10	n = 244	PSG, MSLT, HLA typing and determination of hypocretin-1 level in CSF	Medical history or telephone interview	5 % comorbid alcohol dependence problem.
High rates of psychiatric comorbidity in narcolepsy	Cross-sectional study	Ruoff C. M. et al.	2017	n = 9312	?	?	n = 46 559	ICD-9	Diagnosis based on ICD-9 obtained from the database	1.9 % with alcohol dependence versus 1.3 % of controls; not statistically significant. Significantly more people with substance dependence problem in narcolepsy (4 %) than in controls (1.2 %).
Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population	Cross-sectional study	Ohayon M. et al.	2013	n = 320	?	?	n = 1464	ICSD-2 and DSM-IV-TR	Diagnosis based on DSM IV-TR obtained by clinical interview	Alcohol dependence problem in 0.6 % compared to 0.9 % of controls. Not statistically significant.
Smoking, Alcohol, Drug Use, Abuse and Dependence in Narcolepsy and Idiopathic Hypersomnia: A Case Control Study	Case-control study	Barateau, L. et al.	2016	n = 359	n = 243	n = 116	n = 710	ICSD, MSLT, hypocretin in CSF	MINI Clinical evaluation	Increased proportion of both tobacco and heavy tobacco smokers was found in NT1 compared to controls and other hypersomniacs, increased regular and frequent alcohol drinking habit in NT1 versus controls but not compared to other hypersomniacs in adjusted models. Heavy drinkers were significantly reduced in NT1 versus controls but not compared to other hypersomniacs. The proportion of patients with excessive drug use (codeine, cocaine, and cannabis), substance dependence, or abuse was low in all subgroups,

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Table 6 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
										without significant differences between either hypersomnia disorder categories or compared with controls.

adolescence may largely miss psychiatric diagnoses that typically only occur later in life.

Nevertheless, there does seem to be an association between the presence of narcolepsy and the more frequent comorbid occurrence of psychiatric disorders. One hypothesis is that hypocretin deficiency plays a role in this. Hypocretin neurons project to several brain regions (including the amygdala, the nucleus accumbens, the ventral tegmental area and the prefrontal cortex) that regulate affect and mood, motivation and reward, stress sensitivity and cognition (Douglass et al., 1993; Ohayon, 2013). A deficiency of these could provide a direct link between NT1 and psychiatric disorders, but this may not provide sufficient explanation for people with NT2, suggesting that other factors, like sleep patterns, also may have an influence on the development of comorbid psychiatric disorders.

A study by B. Li et al. examined the genetic correlation among narcolepsy and three commonly associated psychiatric diseases, specifically depressive disorder, ADHD and psychotic disorders. They found a positive genetic correlation among narcolepsy and risk of psychotic disorder, but a negative correlation between major depressive disorder and risk for narcolepsy. No causal relationship was demonstrated with ADHD (Li et al., 2024).

Moving to specific categories of psychiatric disorders, depression and anxiety problems appear to be the most prevalent psychiatric disorders in patients with narcolepsy (Krahn et al., 2022; Morse & Sanjeev, 2018) with the prevalence of comorbid depressive/mood disorders ranging from 4.1 % to 37.9 % (Black et al., 2017; Cohen et al., 2018; Feketeova et al., 2020; Fortuyn et al., 2010; Hansen et al., 2023; Kales et al., 1982; Kamada et al., 2024; Szakacs et al., 2015; Chin et al., 2023, 2024; Huang et al., 2017) and that of anxiety disorder being between 1 % and 25.1 % (Black et al., 2017; Chabas et al., 2007; Cohen et al., 2018; Fortuyn et al., 2010; Frauscher et al., 2013; Hansen et al., 2023; Nevsimalova et al., 2022; Ruoff et al., 2017; Szakacs et al., 2015; Chin et al., 2023, 2024). The most common anxiety disorders are panic attacks and social anxiety disorder, but comorbid generalized anxiety disorder also occurs (Morse & Sanjeev, 2018; Rocca et al., 2015).

Quality of life is often impaired in people with narcolepsy and comorbid depression (Krahn et al., 2022). People with narcolepsy also have higher MADRS scores than control groups, with no link between this score and BMI or disease progression (Chabas et al., 2007).

Again, differences in comorbidity rate of these disorders across different studies could be due to the way psychiatric diagnoses were made. For instance, self-reporting questionnaires give a higher comorbidity than formal diagnostic instruments since there is a overlap in symptomatology between narcolepsy and depression (Fortuyn et al., 2010). Additionally cross-sectional design of studies may miss diagnoses.

For comorbid depression, one hypothesis assumes that increased daytime sleepiness as well as more interrupted sleep may lead to depressive symptoms. Another hypothesis assumes hypocretin deficiency. As described above, hypocretin neurons influence the amygdala. When hypocretin is deficient, changes in emotion regulation occur, disrupting emotional processes which can lead to depression. In addition, hypocretin normally excites serotonergic neurons. Consequently, a

hypocretin deficiency will also lead to a deficiency of serotonin which, as is known, plays a crucial role in the evolution of depressive symptoms and anxiety disorders (Nevsimalova et al., 2022). Furthermore, hypocretin neurons also affect nociception causing patients with narcolepsy to develop more pain symptoms which could also be a trigger for the development of depression or anxiety (Modestino & Winchester, 2013).

The prevalence of bipolar disorder in narcolepsy is around 2 % to 8 % and several studies have shown that this disorder is significantly more common in patients with narcolepsy than in the general population (Fortuyn et al., 2010; Frauscher et al., 2013; Ohayon, 2013; Ruoff et al., 2017) although more research is needed.

Results regarding the prevalence of psychotic disorders in narcolepsy vary considerably, ranging from 0 % to 14.6 % (Alasim et al., 2020; Auger et al., 2005; Chin et al., 2021; Dauvilliers et al., 2016; Feketeova et al., 2022, 2020; Fortuyn et al., 2009, 2011; Haba-Rubio, 2005; Hanin et al., 2021; Huang et al., 2014, 2016; Morse & Sanjeev, 2018; Nevsimalova et al., 2022; Ruoff et al., 2017; Szakacs et al., 2015). Four of the included clinical studies showed a significant difference in the comorbidity of psychotic disorders in narcolepsy compared to control groups, yet one other study found a statistically non-significant result (Fortuyn et al., 2009; Huang et al., 2016; Ruoff et al., 2017; Yeh et al., 2020). Overall, we can say that the comorbid occurrence of narcolepsy and a psychotic disorder is rather rare (Fortuyn et al., 2011; Haba-Rubio, 2005; Hanin et al., 2021; Morse & Sanjeev, 2018).

Some studies indicate that there is a possible pathophysiological overlap between narcolepsy and schizophrenia which would be immune-mediated. Another possibility is that dopaminergic dysfunction underlies this overlap (Feketeova et al., 2020). Hypocretin neurotransmission regulates dopaminergic activity in the ventral tegmental area, nucleus accumbens and prefrontal cortex which may clarify the common pathophysiology of psychotic features in both diseases (Cavalier & Kothare, 2018).

In the above studies some inconsistencies in findings may be explained by the study designs in which cross-sectional studies might miss a later diagnosis of psychotic disorder, certainly when the population consists of pediatric patients (Szakacs et al., 2015).

It can also not be excluded that medication like stimulants could exacerbate psychotic symptoms in some patients. Some of the included studies set strict criteria not to take any medication during the study, where others did not, which could theoretically also partly influence the variation in comorbidity rate (Auger et al., 2005; Huang et al., 2017; Chin et al., 2021; Dauvilliers et al., 2016).

There seem to be three possible explanations for the comorbid occurrence of narcolepsy and schizophrenia: (1) psychotic disorders present comorbidly with narcolepsy by chance, (2) there exists a psychotic variant of narcolepsy in which the psychotic elements are more strongly present than the normally described hypnagogic/hypnopompic hallucinations, (3) psychotic symptoms arise after treatment of narcolepsy with central stimulants (Chen et al., 2014; Hanin et al., 2021; Kishi et al., 2004). The distinction between psychotic symptoms as part of narcolepsy or a stand-alone psychotic disorder is not always clear, yet the hallucinations are different in both disorders. For example, patients with narcolepsy generally experience multisensory hallucinations

Table 7

Overview of articles on narcolepsy and other disorders.

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Associations between psychiatric comorbid disorders and executive dysfunctions in hypocretin-1 deficient pediatric narcolepsy type 1	Cross-sectional study	Hansen, B. H. et al.	2023	n = 59	n = 59	/	none	Actigraphy, PSG, MSLT and hypocretin-1 levels	DSM 5 Semi-structured diagnostic interview obtained by a psychiatrist – clinical evaluation	6.8 % comorbid OCD and 10.2 % comorbid Tourette.
Narcolepsy-Cataplexy II. Psychosocial Consequences and Associated Psychopathology	Cross-sectional study	Kales A. et al.	1982	n = 50	n = 50	/	n = 50	Patients selected from a clinical sleep center	Psychiatric interview, MMPI and SCL-90 – clinical evaluation	11/50 with comorbid personality disorder. Obsessive-compulsive, passive-aggressive, histrionic and borderline personality disorder.
Comorbid psychiatric disorders among patients with narcolepsy	Cross-sectional study	Alasim H. et al.	2020	n = 74	n = 30	n = 44	n = 265	ICSD-3, PSG and MSLT	MINI version 6 based on DSM-IV – clinical evaluation	Only one person with comorbid OCD compared to no one in the control group; not significant.
Narcolepsy in Slovakia e Epidemiology, clinical and polysomnographic features, comorbid diagnoses: a case-control study	Case-control study	Feketeova E. et al.	2019	n = 61	n = 51	n = 10	n = 244	PSG, MSLT, HLA typing and determination of hypocretin-1 in CSF	Medical history and telephone interviews	Mental retardation in 14 % of narcolepsy patients.
Comorbidity of narcolepsy and depressive disorders: a nationwide population-based study in Taiwan	Cohort study	Lee M.-J. et al.	2017	n = 258	?	?	n = 2580	ICD-9-CM	DSM-IV Diagnosis based on patient medical records	2.3 % with comorbid intellectual disability; significantly more than in the control group.
High rates of psychiatric comorbidity in narcolepsy	Cross-sectional study	Ruoff C.M. et al.	2017	n = 9312	?	?	n = 46 559	ICD-9	Diagnosis based on ICD-9 obtained from the database	4.6 % cognitive impairment compared to 1.5 % of controls; statistically significant
Attention impairments and ADHD symptoms in adult narcoleptic patients with and without hypocretin deficiency	Case-control study	Filardi M. et al.	2017	n = 36	n = 21	n = 15	n = 22	ESS, MSLT and HLA typing.	ANT, ASRS, OCIR, BDI and STAI – self-report	A non-significant trend of higher OCD symptoms in narcolepsy patients than in controls.
Coexistence of narcolepsy and Alzheimer's Disease	Case reports	Scammell, T.E. et al.	2012	n = 12	?	?	none	Clinical symptom of cataplexy	Postmortem analysis of amyloid deposits.	4 out of 12 cases had amyloid deposits typical of Alzheimer's disease. This amounts to a prevalence of 33 % which is similar to this in the

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Table 7 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Multiple sleep latency test in narcolepsy type 1 and narcolepsy type 2: A 5-year follow-up study	Cohort study	Huang, Y. et al.	2017	n = 157	n = 111	n = 46	/	PSG + MSLT	General clinical evaluation, diagnosis based on DSM-IV	general population. 3 % of NT1 patients had comorbid OCD and 2 % of NT2 patients. 3 % of NT1 patients had a comorbid tic disorder and 4 % of NT2 patients.

whereas the hallucinations in schizophrenia are more often verbal-auditory in nature and also often involve comorbid delusions (Chen et al., 2014). In studies of patients with schizophrenia, 4–7 % are reported to have a psychotic variant of narcolepsy. However, these are old studies from 1991 to 1993 with sample sizes around 60 patients (Bioulac et al., 2020; Douglass et al., 1993). Another difficult distinction concerns the development of bipolar disorder or psychotic problems after treatment of narcolepsy by central stimulants. The risk of psychostimulant-induced psychosis would be around 3 % and higher if a higher dose is used for treatment (Auger et al., 2005; Kishi et al., 2004).

If narcolepsy co-occurs with a psychotic disorder, treatment is often difficult and the prognosis poor since antipsychotics often exhibit sedative effects that exacerbate narcolepsy symptoms and psychostimulants may induce or exacerbate psychotic symptoms (Chen et al., 2014; Kishi et al., 2004).

Furthermore, there is evidence that people with narcolepsy have an increased risk of developing an eating disorder, but the prevalence varies from 2.7 % to 46 % (Chabas et al., 2007; Fortuyn et al., 2008; Morse & Sanjeev, 2018; Szakacs et al., 2015). Overall, the prevalence seems rather low given that often the criteria for a formal diagnosis are not met (Frauscher et al., 2013). In the included studies, mainly eating disorder NAO and bulimia seem to be prevalent and more common in narcolepsy than in the general population (Chabas et al., 2007; Morse & Sanjeev, 2018), but a case-control study by Dahmen et al. could not confirm this (Dahmen et al., 2008). However, several of these studies used self-reporting instruments which might have influenced the results (Dahmen et al., 2008; Chabas et al., 2007; Baldini et al., 2024b).

There are several hypotheses that attempt to explain the relation between narcolepsy and a comorbid eating disorder. Patients with narcolepsy often have a higher BMI, which is partly linked to the deficiency of hypocretin neurons. This is because hypocretin, in addition to stimulating food intake, also has metabolic and endocrine regulation as its purpose. Patients with narcolepsy are less stimulated in food intake (hypocretin deficiency causes a less efficient reward system) but still have an increased BMI. This can be explained by the metabolic and endocrine function performed by hypocretin, which causes patients with narcolepsy to exhibit less spontaneous physical activity and lowers their basal metabolism (Frauscher et al., 2013; Krahn et al., 2022; Modestino & Winchester, 2013). Another hypothesis is that they develop eating disordered behavior by adjusting their eating patterns. Given food affects sleepiness, they start to adjust their eating habits accordingly, but in doing so, they eventually develop an eating disorder (Krahn et al., 2022).

In contrast to previous arguments, a third hypothesis states that patients with narcolepsy still experience an irresistible craving for food resulting in binge-eating and loss of control. One will then take restrictive actions to control weight in compensation; thus developing

an eating disorder. Patients taking concomitant antidepressants, which is not uncommon in the treatment of narcolepsy, also experience more craving (Frauscher et al., 2013).

Addiction disorders, on the other hand, do not seem to be significantly more prevalent in narcolepsy than in the general population. In terms of comorbid alcohol dependence problems, results vary, ranging from 0.6 % to 7.5 %, but were not significant when compared with a control group (Feketeova et al., 2020; Morse & Sanjeev, 2018; Ohayon, 2013; Ruoff et al., 2017). The prevalence of comorbid substance abuse ranged from 0 % to 4 % with one study showing significant results compared to the control group (Ruoff et al., 2017), but other studies did not (Alasim et al., 2020; Frauscher et al., 2013; Morse & Sanjeev, 2018). The reason that drug use is more present in one study (Ruoff et al., 2017) may have to do with the large size of the cohort studied.

The comorbid occurrence of narcolepsy with neurodegenerative disorders appears to be rare with an estimate of 24/ 1000 000 for Alzheimer's disease (Economou et al., 2012). A postmortem study found that the comorbid occurrence of Alzheimer's disease in narcolepsy was in the same range as the prevalence of Alzheimer's disease in the general population (Scammell et al., 2012). In very late onset of narcolepsy some symptoms (like hallucinations) may mimic neurodegenerative disorders (like Lewy body dementia) (Martens & Van Den Bossche, 2025). However, studies in older populations are scarce.

The comorbidity of OCD or Tourette syndrome with narcolepsy has not been widely reported, but a study by Hansen et al. found 6.8 % to have comorbid OCD and 10.2 % to have comorbid Tourette syndrome (Hansen et al., 2023). Similarly, a cohort study by Huang et al. showed comorbid OCD diagnosis in 3 % of NT1 patients and 2 % of NT2 patients as well as a comorbid tic disorder in 3 % of NT1 patients and 4 % of NT2 patients (Huang et al., 2017). Yet another study only included one person compared to no one in the control group (Alasim et al., 2020). In a third study by Filardi et al. there appeared to be a trend toward more OCD symptoms in people with narcolepsy, however this trend was not statistically significant (Filardi et al., 2017). Filardi et al. made use of self-report questionnaires and excluded patients with a previous psychiatric disorder which may explain why the level of significance was not reached. Sample sizes of the studies conducted by Filardi et al. and Alasim et al. were also only half the sample size of the study by Hansen et al. possibly leading to an underdiagnosis of the comorbidity in these studies.

Similarly, there is only one study available on the comorbid presence of personality disorders in narcolepsy (Kales et al., 1982) and two controlled studies regarding the presence of comorbid intellectual disability (Feketeova et al., 2020; Lee et al., 2017), which did not provide conclusive results.

The included studies show that an autism spectrum disorder (ASD) is comorbidly present in narcolepsy in 2.3 % to 8.1 % of cases (Hansen

Table 8
Overview of articles on narcolepsy and developmental disorders.

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Comorbidity of Narcolepsy and Psychotic Disorders: A Nationwide Population-Based Study in Taiwan	<i>Retrospective cohort study</i>	Yeh J-Y. et al.	2020	n = 258	?	?	n = 2580	ICD-9	Patient records were screened to find a psychiatric diagnosis based on ICD-9 criteria.	2.3 % comorbid ASD compared with 0.2 % in controls. 8.9 % comorbid ADHD compared with 0.9 % in control group. 6.8 % comorbid ASD. 13.6 % comorbid ADHD.
Associations between psychiatric comorbid disorders and executive dysfunctions in hypocretin-1 deficient pediatric narcolepsy type 1	<i>Cross-sectional study</i>	Hansen, B.H. et al.	2023	n = 59	n = 59	/	none	Actigraphy, PSG, MSLT and determination of hypocretin-1 in CSF in some	DSM 5 Semi-structured diagnostic interview obtained by a psychiatrist – clinical evaluation	
Psychiatric Comorbidity and Cognitive Profile in Children with Narcolepsy with or without Association to the H1N1 Influenza Vaccination	<i>Cross-sectional study</i>	Szakács A. et al.	2015	n = 37	?	?	none	ICD-10 and ICSD (2005).	DAWBA, ASSQ, ADHDRS, PANNS questionnaire Diagnostic interview consisting of structured interviews, questionnaires, and rating techniques. Final rating made by a psychiatrist – clinical evaluation	Only in the post-vaccination group 1/30 had pervasive developmental disorder NOS (i.e., atypical autism) In the post-vaccination group, 8/28 narcolepsy patients had comorbid ADHD diagnosis of the inanimate type as well as 1/7 in the unvaccinated group. About 1/4 of the narcolepsy patients had comorbid ADHD.
Central Disorders of Hypersomnolence: Association with Fatigue, Depression and Sleep Inertia Prevailing in Women	<i>Cross-sectional study</i>	Nevsimalova S. et al.	2022	n = 109	n = 87	n = 22	none	Actigraphy, PSG, MSLT	HADS, FSS and SIQ – self-report	2 of 87 NT1 patients and none of NT2 patients had comorbid ASD. 4 of the patients studied (2 in the NT1 group and 2 in the NT2 group) had a comorbid diagnosis of ADHD, representing a rate of 2.7 %.
Comorbidity of narcolepsy and depressive disorders: a	<i>Cohort study</i>	Lee M-J. et al.	2017	n = 258	?	?	n = 2580	ICD-9-CM	DSM-IV-TR Diagnosis based on patient medical records	8.8 % had comorbid ADHD; significantly

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Table 8 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
nationwide population-based study in Taiwan										higher than in the control group (0.9 %).
High rates of psychiatric comorbidity in narcolepsy	Cross-sectional study	Ruoff C.M. et al.	2017	n = 9312	?	?	n = 46 559	ICD-9	Diagnosis based on ICD-9 obtained from the database	7.3 % with ADHD compared to 1.3 % in the control group; statistically significant.
Brain imaging and cognition in young narcoleptic patients	Case-control study	Huang Y-S. et al.	2016	n = 71	?	?	n = 20	ICSD-3 criteria + clinical interview, actigraphy, PSG, MSLT and HLA typing. In some, hypocretin-1 level in CSF	Clinical interview	17.4 % of narcolepsy patients had a comorbid ADHD diagnosis compared with no one in the control group.
Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population	Cross-sectional study	Ohayon M. et al.	2013	n = 320	?	?	n = 1464	ICSD-2 criteria and DSM-IV-TR	Diagnosis based on DSM IV-TR obtained by clinical interview	5.4 % with comorbid ADHD versus 2.5 % in the control group. Only statistically significant in boys.
Attention impairments and ADHD symptoms in adult narcoleptic patients with and without hypocretin deficiency	Case-control study	Filardi M. et al.	2017	n = 36	n = 21	n = 15	n = 22	ESS, PSG, MSLT and HLA typing	ANT, ASRS, OCIR, BDI and STAI – self-report	33.33 % of the NT1 group had significantly increased scores on the ADHD tests as well as 26.66 % of the N2 group compared to 0 % in the control population.
Burden of narcolepsy in Japan: A health claims database study evaluating direct medical costs and comorbidities	Retrospective cohort study	Kamada, Y. et al.	2024	n = 4594	?	?	n = 18,376 (schizophrenia) n = 18,376 (epilepsy) n = 4594 (ulcerative colitis)	ICD-10	ICD-10 Clinical evaluation	3.5 % had comorbid autism spectrum disorder and 12 % ADHD. Only ADHD was significant.
Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms in Pediatric Narcolepsy: A Cross-Sectional Study	Cross-sectional study	Lecendreux M. et al.	2015	n = 108	?	?	n = 67	PSG, MSLT, HLA typing and sometimes determination of hypocretin-1 level in CSF	ADHD-RS based on DSM-IV-TR. Self-report.	In 45 % of patients with narcolepsy, ADHD scores were significantly increased compared to 5–6 % in the control group.
A Retrospective Survey of Childhood ADHD	Retrospective study	Modestino E. J. et al.	2013	n = 161	?	?	n = 117	PSG + MSLT and HLA typing	WURS Self-report questionnaire	37.88 % showed ADHD symptoms;

(continued on next page)

Table 8 (continued)

Title	Study Design	Author	Year	Narcolepsy (n =)	NT1 (n =)	NT2 (n =)	Controls (n =)	D/ Narcolepsy	D/ Psychiatric comorbidity	Result
Symptomatology Among Adult Narcoleptics										significantly more than in the control group. It was estimated that 8 % to 15 % of the narcolepsy group had comorbid ADHD diagnosis
Association of Inattention, Hyperactivity, and Hypersomnolence in Two Clinic-Based Adult Cohorts	Cross-sectional study	Lopez R. et al.	2020	n = 60	n = 32	n = 28	none	PSG, MSLT and determination of hypocretin-1 in CSF	Structured clinical interview and self-report questionnaires (DSM 5)	11 of 60 patients met the diagnosis of comorbid ADHD (18.33 %).
A comparison of mood, quality of life and executive function among narcolepsy type 1 patients with or without ADHD symptoms in China	Cohort study	Qu S. et al.	2022	n = 267	n = 267	/	none	PSG, MSLT and HLA typing	MINI Kid and ADHD-RS based on DSM-IV, clinical evaluation	28.8 % with comorbid ADHD, mainly the inanimate type.
High prevalence of ADHD symptoms in unmedicated youths with post-H1N1 narcolepsy type 1	Cross-sectional study	Hansen, B. et al.	2020	n = 50	n = 50	/	none	ICSD-3 + clinical interview, PSG, MSLT, HLA typing and hypocretin-1 level in CSF	ADHD RS, DSM 5 Parent-rated (self-report)	52 % had levels of ADHD symptoms above the cut-off.
Impact of Taiwan's 2021 COVID-19 lockdown on the symptom severity and quality of life of patients with narcolepsy	Retrospective study	Chin, W.-C. et al.	2023	n = 120	n = 80	n = 40	/	PSG, MSLT, HLA typing, actigraphy	Diagnosis based on records from the database	18 % of the narcolepsy patients had ADHD.
Long-term follow-up of symptom and quality of life changes in patients with narcolepsy during and after the COVID-19 pandemic	Retro- and prospective cohort study	Chin, W.-C. et al.	2024	n = 100 zelfde cohort?	n = 67	n = 33	/	PSG, MSLT, HLA typing, actigraphy	Diagnosis based on records from the database	18 % of the narcolepsy patients had comorbid ADHD.
Multiple sleep latency test in narcolepsy type 1 and narcolepsy type 2: A 5-year follow-up study	Cohort study	Huang, Y. et al.	2017	n = 157	n = 111	n = 46	/	PSG + MSLT	General clinical evaluation, diagnosis based on DSM-IV	13 % of patients with NT1 had comorbid ADHD and 30 % of NT2. 5 % of NT1 patients had comorbid Asperger and 2 % of NT2 patients.

Table 9

Overview and description of the included case reports.

Title	Author	Year	Gender	Age	Clinical symptoms	Diagnosis
Dual Cases of Type 1 Narcolepsy with Schizophrenia and Other Psychotic Disorders	Canellas F. et al.	2014	F, <i>n</i> = 6 M, <i>n</i> = 4	12 - 74y	<i>n</i> = 10 Schizoaffective disorder, <i>n</i> = 1 Delusional disorder, <i>n</i> = 1 Schizophrenic disorder, <i>n</i> = 2 Schizophrenia, <i>n</i> = 6 Symptoms: auditory hallucinations, disorganization and delusions. All with hypnagogic hallucinations and vivid dreams. Onset of psychotic symptoms after diagnosis of narcolepsy. Delusions and auditory hallucinations did not improve provided treatment for narcolepsy. In one case clear relationship between start of treatment and increase in psychotic symptoms.	Narcolepsy based on PSG, MSLT, HLA typing and hypocretin-1 deficiency. Diagnosis of schizophrenia via a specialized questionnaire (DIGSAN) based on DSM-IV through clinical evaluation.
Comorbidity of narcolepsy and schizophrenia in an adolescent patient	Chen M-H. et al.	2014	M	13y	First onset of narcoleptic symptoms, then auditory hallucinations, delusions, misidentification. Psychotic symptoms arose before initiation of medication.	Narcolepsy based on PSG/MSLT after 3 w discontinuation of medication. After treatment for narcolepsy, psychotic symptoms persisted. Consequently, the diagnosis of comorbid narcolepsy and schizophrenia was made.
Narcolepsy and psychosis; case report	Dulcinea V-D. et al.	2020	F	25y	Diagnosis of narcolepsy at 17, subsequently symptoms of anorexia and boulemia but undiagnosed. At 23, onset of jealousy delusions, suspicion, identity delusions, erotic delusions and auditory hallucinations.	Narcolepsy based on PSG/MSLT (4 SOREM), undetectable hypocretin-1 and positive HLA-DQB1*0602 typing. This combined with the nature of psychotic symptoms led by the clinician to the conclusion of a comorbid psychotic disorder in patient with narcolepsy.
Schizophrenia and narcolepsy: A review with a case report	Kishi Y. et al.	2004	F	25y	At 13y onset of narcoleptic symptoms. Subsequently at 19y onset of auditory hallucinations, haunting delusions and involvement delusions.	Narcolepsy based on PSG/MSLT and positive for HLA DR2. Diagnosis of schizophrenia based on DSM-IV. Psychotic symptoms persisted even after treatment for narcolepsy causing comorbid schizophrenia.
Florid Refractory Schizophrenias that turn out to be treatable variants of HLA-associated narcolepsy	Douglass A. B. et al.	1991	F, <i>n</i> = 5	30 - 48y	<i>n</i> = 5 Case 1: described in another paper not accessible to us. Case 2: auditory hallucinations (hearing God's voice), multimodal vivid dreams, ideas of poisoning, sleep apnea. Case 3: depression, social anxiety, hearing voices since 6yrs of age, auditory, visual, olfactory and tactile hallucinations, catatonic features, paranoid delusions. Case 4: paranoid delusions, visual and auditory hallucinations, twice postpartum psychosis in history Case 5: auditory and visual hallucinations, cataplexy and sleep apnea, daydreaming, sleep attacks	Narcolepsy based on questionnaire, PSG/MSLT and HLA typing. Diagnosis of schizophrenia based on structured interview (DIS), SANS, SAPS and BPRS by a clinician. Based on DSM-III.
Diagnostic and Therapeutic Challenges in Narcolepsy-Related Psychosis	Kondziella D. et al.	2006	F	38y	Recurrent anxious and depressive symptoms with subsequent onset of haunting delusions, ideas of relationship (idea that radio and television are dictating things to her), poisoning delusions, zonaesthesia. Subsequent onset of narcoleptic symptoms as well.	Narcolepsy based on PSG and MSLT (but unclear whether medication was discontinued). Given psychotic symptoms persisted despite treatment for narcolepsy, comorbid diagnosis of schizophrenia-like disorder was made.
Missed diagnosis of long-standing narcolepsy	Chepke C. et al.	2023	M	31y	Excessive daytime sleepiness since childhood, only lessened by stimulants. Muscle weakness with anxiety. Dazed head. Hypnagogic and hypnopompic hallucinations.	Narcolepsy based on PSG and MSLT. ADHD diagnosed at age 9y and depression as a teenager (basis of diagnosis unclear).
Development of Parkinson and Alzheimer Diseases in Two Cases of Narcolepsy-Cataplexy	Economou N-T et al.	2011	M, <i>n</i> = 2	69y and 71y	Case 1: excessive daytime sleepiness, hallucinations, cataplexy and sleep apnea since age 17. At age 64, onset of resting tremor, micrographia and bradykinesia on the right and hyposmia. Case 2: Since adolescence suffered from sleep attacks, cataplexy, insomnia and hypnopompic hallucinations. At 65 years of age onset of cognitive decline with particular difficulties in spatial orientation, word fluency, short-term memory and impaired attention.	Case 1: diagnosis of narcolepsy based on MSLT, PSG, positive HLA DQB1*0602 and undetectable hypocretin-1. Diagnosis of Parkinson's based on UPDRS score and improvement with L-dopa. Case 2: diagnosis of narcolepsy based on PSG and MSLT, positive HLA DQB1*0602 and undetectable hypocretin-1. Diagnosis of Alzheimer's dementia based on MMSE and MRI brain.
Childhood narcolepsy and autism spectrum disorders: four case reports	Prihodova I. et al.	2018	M, <i>n</i> = 2 F, <i>n</i> = 2	10y - 13y	Case 1: diagnosis of ASD and ADHD in history with subsequent development of cataplexy, excessive daytime sleepiness, sleep attacks. Also more irritable and aggressive mood. Case 2: Learning disabilities in history. Progressively more sleepy, developing anxiety symptoms and depressive symptoms. Also, socially maladjusted behavior, little social interaction, communication problems, few skills, attached to structure, stereotyped interests, sensory hypersensitivity and emotional and behavioral problems. Additional also emergence of cataplexy. Case 3: Chronic tic disorder in	Narcolepsy diagnosed based on MSLT and diagnosis of ASD based on clinical symptoms, psychiatric assessment, ADOS, DNEPSY and WIS through clinical evaluation.

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Table 9 (continued)

Title	Author	Year	Gender	Age	Clinical symptoms	Diagnosis
The Association of Schizophrenia and Narcolepsy in Adolescents	Cavalier Y. et al	2018	F	15y	history. Excessive daytime sleepiness as well as cataplexy. Mood swings and depressive symptoms. Additional problems in social interaction, avoidance of play and social activities, difficulty understanding rules, resistance to physical contact. Case 4: History of ADHD. From 9y emergence of prolonged sleep, more sleepiness during the day, more tired, more emotional instability and irritability, emergence of cataplexy. Since age 3 also problems in social interaction, communication difficulties, monotone speech, decreased emotional expression, behavioral difficulties, no fantasy play, repetitive behaviors, limited interests, rigidity, difficulty coping with changes and hypersensitive to tastes and smells. History of excessive sleepiness, cataplexy, sleep paralysis, insomnia and auditory hallucinations. Hallucinations involved one voice whispering fearful things to her. Psychostimulants were given with subsequent disorganization, idea that people could read her mind, that people knew things about her, changing body perception. There were auditory as well as olfactory and tactile hallucinations.	Diagnosis of narcolepsy based on PSG and MSLT. The diagnosis of schizophrenia was based on clinical aspects, such as delusions and olfactory and tactile hallucinations which is not typical in narcolepsy.
Severe Mania Complicating Treatment of Narcolepsy with Cataplexy	Crosby M.I.	2011	M	22y	After treatment with Modafinil 300 mg and Venlafaxine 75 mg for narcolepsy: irresponsible behavior, spending large amounts of money, verbosity, hyperactivity, grandiosity and sexual disinhibition.	Narcolepsy based on MSLT (4.7 min) and REM sleep in all naps. Based on clinical symptoms assessed by a psychiatrist, diagnosis of narcolepsy and comorbid bipolar disorder was made.
Concurrent narcolepsy and bipolar affective disorder	Trzepacz, P.	1983	F	41y	Decreased sleep, rumination, religious delusions, flight of thought, flood of words, unstable mood, euphoria, increased energy level, grandiosity, hypersexuality, pregnancy delusion. In addition, sleep attacks, cataplexy, sleep apnea and hypnagogic hallucinations.	Narcolepsy based on PSG. In combination with clinical symptoms assessed by a psychiatrist, diagnosis of comorbid narcolepsy and bipolar disorder was made.
Narcolepsy, Paranoid Psychosis, Major Depression, and Tardive Dyskinesia	Schrader G. et al.	1984	M	67y	History of alcohol abuse. He reports daytime drowsiness, cataplexy, sleep apnea and sometimes hypnagogic hallucinations. After R/ with dextroamphetamine development of daytime visual hallucinations (small men and animals), subsequent delusional system involving idea that people were throwing things in his eyes, belief in black magic, that people were trying to sleep with his wife. Afterwards also developing depressed mood, loss of interest, insomnia, diurnal mood variation.	Narcolepsy based on symptoms, 3x EEG was negative. Cataplexy however pathognomonic. Diagnosis of psychotic disorder and major depressive disorder made on the basis of symptoms assessed by a psychiatrist.

et al., 2023; Nevsimanova et al., 2022; Szakacs et al., 2015; Yeh et al., 2020; Huang et al., 2017). However rates of developmental disorders may be underestimated in adult populations (like the populations studied by Nevsimanova et al., Yeh et al. and Huang et al.) certainly in mild cases.

Rates of a comorbid occurrence with ADHD are much more diverse, ranging from 2.7 % to 45 %

(Filardi et al., 2017; Hansen et al., 2023; Lecendreux et al., 2015; Lee et al., 2017; Lopez et al., 2020; Modestino & Winchester, 2013; Nevsimanova et al., 2022; Qu et al., 2022; Szakacs et al., 2015; Yeh et al., 2020; Chin et al., 2023, 2024; Huang et al., 2017). However, a comorbid occurrence of ADHD was significantly more frequent in patients with narcolepsy than in controls in all controlled studies (Filardi et al., 2017; Huang et al., 2016; Lecendreux et al., 2015; Lee et al., 2017; Ruoff et al., 2017; Yeh et al., 2020). Again, as with ASD, there may be underdiagnosis of comorbid ADHD in adult narcolepsy patients. The comorbid occurrence of ADHD and narcolepsy could, on the one hand, be due to the fact that disturbed sleep and increased daytime sleepiness in narcolepsy lead to disturbed attention (Nevsimanova et al., 2022), which is also verified by a cohort study revealing that patients with narcolepsy exhibit more severe ADHD features of the inattentive type (Qu et al., 2022). More hyperactive-impulsive symptoms occurred in NT1 patients potentially indicating that hypocretin also plays a role in the modulation

of impulsivity (Qu et al., 2022). In addition, patients with narcolepsy show changes in the activation of the executive system in the prefrontal cortex, which is also part of the attention system in ADHD (Nevsimanova et al., 2022). Additionally, there would be an overlap between the genetic risk for narcolepsy and that for ADHD, and neuronal inflammation is part of both the development of narcolepsy and ADHD. Neuroinflammation alters the levels of monoamine neurotransmitters such as dopamine and norepinephrine but also histamine and orexin (Bioulac et al., 2020).

In this literature review we attempted to provide an overview of the prevalence of psychiatric comorbidity in narcolepsy. Since we included many different psychiatric disorders and the included papers are overall heterogeneous, no additional statistics were applied which can be seen as a limitation of this review. In addition, uncontrolled studies and case reports were also included.

There is a need for future studies to resolve some of the discrepancies in the current literature. Ideally, these studies should have a longitudinal design and large cohorts should be meticulously diagnosed for both narcolepsy and psychiatric disorders.

For clinicians and patients it is important to be aware of the high comorbidity of psychiatric disorders and narcolepsy.

In this way first symptoms of psychiatric disorders can be detected earlier, potentially enabling faster treatment and thus leading to better

quality of life of patients with narcolepsy. Symptoms of narcolepsy and psychiatric disorders may overlap, so careful exploration is needed not to mistake one disorder for another. Comorbidity can also influence treatment in a bidirectional way. It can for example be important to monitor psychotic symptoms carefully when prescribing stimulants in patients with narcolepsy who have a specific vulnerability for psychosis. The other way around, clinicians should realize that pharmacological treatment of psychiatric disorders, like some antidepressants or antipsychotics, may worsen symptoms of fatigue and sleepiness in some patients with narcolepsy.

Conclusion

Overall psychiatric disorders are more prevalent in patients with narcolepsy, but prevalence rates vary widely across studies and disorders. Higher prevalence of comorbid depression, anxiety disorders and ADHD is reported in narcolepsy. For other psychiatric disorders, current evidence is less conclusive. For optimal patient care, it is important for clinicians and care organizations to be aware of this comorbidity between psychiatric disorders and narcolepsy.

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