



Determinants of substance use patterns in patients with narcolepsy type 1: A multi-center comparative cross-sectional study

Laure Peter-Derex^{a,b,*}, Emmanuel Fort^c, Benjamin Putois^{b,d}, Nora Martel^e, François Ricordeau^{a,b}, H el ene Bastuji^{a,b}, Isabelle Arnulf^f, Lucie Barateau^g, Patrice Bourgin^h, Yves Dauvilliers^g, Rachel Debsⁱ, Pauline Dodet^f, Benjamin Dudoignon^j, Patricia Franco^{k,b}, Sarah Hartley^l, Isabelle Lambert^m, Michel Lecendreux^j, Laurene Leclair-Visonneauⁿ, Damien L eger^o, Martine Lemesle-Martin^p, Antoine L eotard^l, Smaranda Leu-Semenescu^f, Nad ege Limousin^q, R egis Lopez^g, Nicole Meslier^r, Jean-Arthur Micoulaud-Franchi^s, Christelle Charley-Mocana^t, Marie-Pia d'Ortho^u, Pierre Philip^s, Elisabeth Ruppert^h, Sylvie de La Tullayeⁿ, Manon Brigandet^v, Barbara Charbotel^c, St ephanie Mazza^b, Benjamin Rolland^{w,b}

^a Centre for Sleep Medicine and Respiratory Diseases, National Reference Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, Croix-Rousse Hospital, Hospices Civils de Lyon, Lyon 1 University, Lyon, France

^b Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR 5292, Lyon, France

^c Transport Work and Environmental Epidemiology Research and Surveillance Unit – UMRESTTE (UMR T9405), University Lyon 1, Lyon, France

^d Swiss Distance Learning University, Faculty of Psychology, Brig, Switzerland

^e Clinical Research Center, Croix-Rousse Hospital, Hospices Civils de Lyon, Lyon, France

^f National Reference Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, Sleep Disorders Clinic, Piti -Salp etri re Hospital, APHP-Sorbonne University, Paris, France

^g National Reference Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, Sleep Unit, Department of Neurology, CHU Montpellier, Univ Montpellier, Montpellier, France

^h CIRCSom (International Research Center for ChronoSomnology), Sleep Disorders Center, National Competence Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, Strasbourg University Hospital, Strasbourg, France

ⁱ Sleep Unit, Department of Neurology, National Competence Centre for Orphan Diseases, Narcolepsy- Rare Hypersomnias, Pierre-Paul Riquet/Purpan University Hospital, Toulouse, France

^j Pediatric Sleep Disorders Center, National Reference Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, Robert Debre Hospital, APHP, Paris, France

^k Pediatric Sleep Unit and National Reference Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, Mother-Children's Hospital, Hospices Civils de Lyon, Lyon, France

^l Sleep Unit, Physiology Department, National Competence Centre for Orphan Diseases, Narcolepsy- Rare Hypersomnias, GHU Paris-Saclay, APHP, Raymond Poincar e Hospital, Garches, France

^m Sleep Unit, Epileptology and Cerebral Rhythmology, National Competence Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, Timone Hospital, APHM, Marseille, France

ⁿ Department of Clinical Neurophysiology, National Competence Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, CHU de Nantes, Nantes, France

^o APHP, H otel-Dieu, Centre Du Sommeil et de La Vigilance, National Reference Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, Universit  Paris Cit , VIFASOM, Paris, France

^p Department of Clinical Neurophysiology, National Competence Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, University Hospital of Dijon, Dijon, France

^q Department of Neurology and Clinical Neurophysiology, National Competence Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, University Hospital Bretonneau, Tours, France

^r Department of Respiratory and Sleep Medicine, National Competence Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias Angers University Hospital, Angers, France

^s Sleep Disorders Department, National Reference Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, CHU Bordeaux, Bordeaux, France

^t Neurophysiologie Clinique, National Competence Centre for Orphan Diseases, Narcolepsy-Rare Hypersomnias, H opital Roger Salengro, Lille, France

^u Service de Physiologie – Explorations Fonctionnelles, National Competence Centre for Orphan Diseases, Narcolepsy- Rare Hypersomnias, H opital Bichat, AP-HP, Universit  Paris Cit , Inserm, NeuroDiderot, Paris, France

^v ANC, Association for Patients with Narcolepsy Cataplexy and Rare Hypersomnias, France

^w Service Universitaire D'Addictologie de Lyon, Centre Hospitalier Le Vinatier, Hospices Civils de Lyon, Lyon 1 University, Lyon, France

* Corresponding author. Center for Sleep Medicine, Croix-Rousse Hospital, 103 Grande Rue de la Croix-Rousse, 69004, Lyon, France.

E-mail addresses: laure.peter-derex@chu-lyon.fr, laure.peter-derex@univ-lyon1.fr (L. Peter-Derex).

<https://doi.org/10.1016/j.sleep.2025.02.037>

Received 3 November 2024; Received in revised form 16 February 2025; Accepted 24 February 2025

Available online 26 February 2025

1389-9457/  2025 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

ARTICLE INFO

Keywords:

Narcolepsy type 1
 Substance use disorders
 Alcohol
 Cannabis
 Tobacco
 Rule breaking behavior
 Addiction

ABSTRACT

Objectives: In this multi-center cross-sectional study, we compared substance use patterns (SUPs) between patients with narcolepsy type 1 (NT1) and controls, and investigated, among patients, factors associated with the consumption of the main psychoactive substances.

Methods: Adult patients with NT1 and controls completed questionnaires about tobacco, alcohol, and cannabis use patterns. Unadjusted bivariable then multivariate analyses (adjusted for sex, age, education, family status, and depression) were performed to compare SUPs between controls and patients, and to explore socio-demographic, psycho-behavioral, and clinical determinants of consumptions.

Results: We included 235 patients (63.8 % women, 36.4 ± 14.7 years) and 166 controls (69.9 % women, 40.3 ± 14.4 years). Substances co-consumptions were frequent in both groups. Patients with NT1 were more frequently current smokers (32.3 % vs. 20.1 %, $p < 0.01$) or e-cigarettes users (12.1 % vs 2.4 %, $p < 0.001$) than controls, while no difference was observed for cannabis use and alcohol misuse. Only the increased likelihood of vaping remained significant in adjusted analysis. Among NT1 patients, smoking was associated with disrupted nighttime sleep (OR[95%CI] = 2.28[1.02–5.12], $p < 0.05$) and less obesity (OR = 0.24[0.09–0.59], $p < 0.05$). Alcohol misuse was associated with sleep paralysis (OR = 2.11[1.13–3.91], $p < 0.05$) and treatments (modafinil: OR = 2.14[1.15–4.01], $p < 0.05$; sodium oxybate: OR = 0.41[0.17–0.97], $p < 0.05$). Tobacco and cannabis consumptions were associated with lower physical activity (OR = 0.46 [0.24–0.87], $p < 0.05$ and OR = 0.25 [0.10–0.66], $p < 0.01$). Alcohol misuse and cannabis use were associated with rule breaking behaviors (OR = 5.89[1.61–21.60], $p < 0.05$ and OR = 8.52[1.79–40.48], $p = 0.01$).

Conclusion: Patients with NT1 do not seem less vulnerable to psychoactive substance use/misuse. Consumptions patterns are associated with multiple dimensions of the disease including sleep-related symptoms, comorbidities, treatments, and psycho-behavioral factors.

1. Introduction

Narcolepsy type 1 (NT1) is a neurological disease affecting 0.025–0.05 % of the population, caused by an acquired deficiency in orexin/hypocretin, a hypothalamic neurotransmitter involved in the regulation of sleep/wake states [1–3]. The main symptoms of NT1 are hypersomnolence, disrupted nighttime sleep, and manifestations related to rapid-eye-movement (REM) sleep dysregulation, i.e., cataplexy, sleep paralysis, and hallucinations [1,2]. Patients with NT1 also experience various comorbidities including sleep-related (REM sleep behavior disorder, sleep apnea, periodic limb movements and restless leg syndrome) and sleep-unrelated conditions [4] such as metabolic, digestive and cardiovascular diseases, along with neurocognitive and psychiatric disorders. These include anxiety, depression, attention deficit hyperactivity disorder (ADHD), emotional dysregulation, and executive dysfunction despite normal or high level global intellectual quotient [5–13]. The determinism of these psycho-cognitive-behavioral disorders is likely multifactorial, involving an indirect effect of sleep-related symptoms and the disability resulting from living with a chronic disease, as well as a direct effect of orexinergic pathways dysfunction [3, 14–16].

Among psychiatric comorbidities in patients with NT1, substance use disorders (SUDs) have received limited attention, despite extensive data from animal and human studies highlighting the role of orexin in motivation and reward system modulation [17–19]. Orexin neurons project not only on wake-promoting regions but also on reward-associated brain structures such as the nucleus accumbens and the ventral tegmental area [20,21]. Orexin signaling was described as a driver of “motivational activation” involved in situations of high motivational relevance [19,22], and it was proposed that orexin receptors 1 and 2 might be involved in different aspects of addictive behaviors, including “hedonic” motivation (positive reward-seeking) versus stress/arousal (negative relief-seeking) dimensions respectively, though there is clearly some overlap between these systems [23].

Sleep disorders and SUDs share a complex relationship, marked by multiple interconnections [24–26]. Psychoactive substances may provide temporary relief from sleep disturbances, while they tend to profoundly disrupt sleep quality and architecture on the long run. As a result, SUDs are highly prevalent in sleep disorders, such as insomnia [27]. Moreover, sleep disorders, particularly NT1, are strongly related to psychiatric conditions, including anxiety and mood disorders, which

may also pave the way for substance abuse and SUDs [28]. The direct role of the orexin system dysfunction has also been pointed out in the development of sleep disorders in SUDs, as the increased orexin activity observed in drug taking and withdrawal promotes stress-elicited drug-seeking, arousal and sleep disruption [29]. This makes orexin receptor antagonists, which aim to reduce orexin hypersignaling, a promising treatment approach for SUDs [29].

In NT1, reduced orexin signaling in the mesolimbic pathway could impact reward seeking behavior, and thus possibly affect the prevalence or clinical expression of SUDs [19,30]. However, Dimitrova et al. found no difference between patients with narcolepsy with (N = 30) vs without cataplexy (N = 15) vs 32 controls for the Alcohol Use Disorders Identification test, Consumption part (AUDIT-C). To note, the authors excluded participants with prior history of addiction, substance abuse, or psychiatric illness [31]. Accordingly, in a phone-interview survey, Ohayon et al. reported no difference in alcohol dependence between patients with narcolepsy (N = 320, 0.6 %) and controls matched on age, gender and body mass index (BMI) (N = 1464, 0.9 %) [32]. The largest study on the topic (N = 243 patients with NT1, 116 with narcolepsy type 2 (NT2), 91 with idiopathic hypersomnia (IH), and 710 controls) showed extremely rare abuse of amphetamine-like stimulants prescribed to alleviate sleepiness, a very low level of excessive illicit drug use or abuse, and a lower level of excessive alcohol consumption in NT1 vs controls after adjustment for age, gender, educational level, body-mass index (BMI) and depression score [33]. However, in this study, the prevalence of regular alcohol (>4 drinks/week) and tobacco (>10 cigarettes/day) use was higher in patients with NT1 than in controls (19.7 % vs 7.2 % and 22.7 % vs 4.2 % respectively, $p < 0.0001$). In total, 37.2 % NT1 vs 21.7 % controls were current smokers. The prevalence of tobacco consumption (>10 cigarettes/day) was also higher in NT1 (22.7 %) than in NT2 (8.7 %) and IH (10.0 %) ($p = 0.0004$), with the model described above plus additional adjustment for ESS and drugs intake at the evaluation. Interestingly, several other reports either based on clinical series or on large registry surveys, have consistently reported higher rates of tobacco consumption in patients with NT1. Thus, in a Czech series of 87 patients with NT1, 43.7 % were regular smokers (to note, the rate of active regular smokers in general population was 23.5 % in the Czech Republic at that time), 19.5 % were former smokers, and 72.2 % of smokers had started smoking prior to the first symptoms of narcolepsy [34]. In a study about nocturnal compulsive behaviors in 75 NT1 and 65 controls, Palaia et al. also reported increased prevalence of

smoking, reaching 46.2 % (vs 21.5 % of controls, $p = 0.003$) while no difference was observed for alcohol consumption. An increase in tobacco consumption was also found in the 437 patients with narcolepsy from the US National Health and Wellness Survey vs controls (current smokers: 32.3 % vs 17.9 %, $p < 0.001$) with no difference for alcohol consumption [35]. All in all, these data suggest that the relationship between orexin deficiency and addiction in NT1 is complex, especially regarding nicotine dependency, and might involve modulators (such as sleep-related symptoms or emotional dysregulation), as well as a possible individual vulnerability.

This question is of high interest, not only to understand the role of orexin in reward in humans but also to better assess, prevent, and manage SUDs in patients with NT1 as such disorders contribute to psychiatric and cardiovascular comorbidities [12,36]. The *NarcoScol NarcoVitae* is a national French multicenter cross-sectional study which aimed to investigate psychosocial and clinical characteristics as well as the academic and occupational paths of patients with NT1, compared to a population of matched healthy controls [37]. In this context, the patterns of use of the main psychoactive substances, i.e., tobacco, alcohol, and cannabis, were assessed. Here, we aimed to: (1) compare the substance use patterns of patients with NT1, relative to healthy controls; and (2) explore, within patients with NT1, the main socio-demographic and clinical features of individuals with a positive screening for tobacco or cannabis use, and alcohol misuse.

2. Methods

2.1. Type of study

NarcoScol NarcoVitae is a national multicenter comparative cross-sectional study conducted in 18 Reference and Competence Centers for Orphan Diseases, Narcolepsy and Rare Hypersomnia Network in France, between Feb 2020 and Feb 2023. Details on the recruitment process are provided [37]. Briefly, patients with NT1 were notified about the study via letter by the sleep physician from the Center where they were usually followed up. They were encouraged to complete online questionnaires and to identify individuals among their close relations and invite them directly to participate in the study as controls.

2.2. Study population

Patients with NT1 consisted of 235 individuals regularly followed up in participating centers, who met the following inclusion criteria: (1) being aged of 18 years or more, and (2) meeting the international diagnostic criteria for NT1 at the time of the study (ICSD3-2014), that is, an excessive daytime time sleepiness over the last 3 months + either (cataplexy + a positive multiple sleep latency test [i.e., sleep latency ≤ 8 min and >1 REM sleep period within 15 min of sleep onset]), OR a low orexin-A cerebrospinal fluid level (<110 pg/mL) [38]. The diagnosis of narcolepsy was conducted by physicians specialist in sleep medicine in Rare Disease Reference and Competence Centers in France. These centers, established under the National Plan for Rare Diseases, combine national expertise with localized care to enhance diagnosis, treatment access, and research through coordinated efforts. We focused on narcolepsy type 1 to ensure a homogeneous population, as its diagnosis is notably clearer and more consistent over time compared to narcolepsy type 2 or idiopathic hypersomnia [39]. Exclusion criteria were as follows: insufficient knowledge of the French language, cognitive impairment inconsistent with questionnaire completion, and refusal to participate.

The control group consisted of 166 individuals selected by NT1 participants from within their close circle, who were acquaintances (but no relatives) of the same sex and age (± 5 years) willing to complete the same questionnaires than the NT1 participants, except for those specific to narcolepsy.

2.3. Measurements and data preprocessing

The following characteristics were collected in both groups with online questionnaires: (1) sociodemographic measures, i.e., age (in years), gender (male or female), occupational status (employed, unemployed, retired, or student), socio-professional category, level of study according to the international standard classification of education (ISCED [40]), marital status (married or in couple, single, separated, divorced, or widowed), and having children (yes or no); (2) sleep and/or NT1 features, i.e., age at NT1 onset and at diagnosis, previous episodes of cataplexy (yes or no), current episodes of (yes or no for each) cataplexy, sleep paralysis, hallucinations, night awakening or insomnia, morning sleep inertia, irresistible daytime sleep attacks, preventive naps (yes or no) and number of naps per day (less than daily, regular napping (>1 /day)), Epworth sleepiness scale (ESS [41]); Narcolepsy Severity Scale (NSS [42]); (3) substance use and misuse, using the past-month tobacco smoking status (current smoker, past smoker, or never smoker, and quantification of nicotine dependence with the Heaviness of Smoking Index (HSI) [43], a score ranging from 0 i.e. no dependence to 6, i.e. high dependence), past-month e-cigarette vaping status (yes or no), cannabis use over the past six month (yes or no, and quantification of the frequency of consumption from never (score 0), ≤ 1 time/month (score 1), 2–4 times/month (score 2), 2–3 times/week (score 3) and ≥ 4 times/week (score 4)), and the AUDIT-C [44,45]; and (4) other clinical parameters, that is, the BMI, previous depressive episode requiring pharmacotherapy or psychotherapy (yes or no), current physical activity (yes or no), Beck Depression Inventory version 2 (BDI-II [46]) questionnaire, the Euro Quality of Life 5 dimensions Y (EQ-5D-Y [47]) questionnaire, and the Adult Self Report (ASR), a component of the Achenbach System of Empirically Based Assessment designed to evaluate behavioral, psychosocial and adaptive functioning in adults [48]. In addition, data about current medications used for NT1, either as wake-promoting or anti-cataplectic drugs were collected (yes or no), within the following list: modafinil, methylphenidate, pitolisant, dexamphetamine, clomipramine, venlafaxine, fluoxetine, and sodium oxybate (note that solriamfetol was not available in France at the time of the study).

Data were pre-processed as follows. Age, as a continuous variable, was transformed into a 5-category variable, that is, 24 years or less, 25–34 years, 35–44 years, 45–50 years, and 55+ years. Marital status was transformed into a binary variable, consisting of either in couple (i.e., married, or having a partner), or not in couple (i.e., single, separated or divorced, or widowed). BMI was transformed into a 3-category variable, i.e., normal or subnormal (less than 25 kg/m^2), overweight (25 or more but less than 30 kg/m^2) and obesity (more than 30 kg/m^2). Narcolepsy onset and diagnosis age were considered as two variables and also compiled into three groups, that is, (1) NT1 onset and diagnosis <18 years, (2) NT1 onset <18 and diagnosis ≥ 18 years, and (3) NT1 onset ≥ 18 years). The ESS was considered as a continuous variable and transformed into a binary variable, i.e., normal (score of ≤ 10), or excessive sleepiness (score >10). The NSS score was also considered as a continuous and as a 4-item categorical variable (0–14; 15–28, 29–42; and 43–57 [49]). The AUDIT-C score was transformed into a binary variable, i.e., (1) alcohol misuse (abnormal threshold ≥ 4 for men, and ≥ 3 for women), and (2) no alcohol misuse (below these cut-offs). Alcohol, tobacco and cannabis consumption were considered as binary variables (use vs no or former use) and as quantitative variables (score AUDIT-C for alcohol, score HIS for tobacco and frequency of consumption score for cannabis). The BDI-II score was compiled into a four-item variable, i.e., no depression (score of 9 or less), minor depression (score between 10 and 18), moderate depression (score between 19 and 29), and severe depression (score of 30 or more). Syndromes scales and DSM IV oriented scale derived from the ASR questionnaire were classified in three groups (clinical range, limit range, normal range). Treatments were considered either individually, or as a group for psychostimulant medications (including modafinil, methylphenidate, mazindol and

dexamphetamine).

2.4. Statistical analyses

Descriptive statistics were presented as frequency and percentage for categorical variables and as mean ± std, median, Q1, Q3 for continuous variables.

Comparison between patients with NT1 and healthy controls were performed with Chi-squared test for ≥2 modality nominal variables or Fisher test if chi squared test was not applicable and with T-test test for quantitative variable or Wilcoxon when T-test was not applicable (small group size). Logistic regressions were performed in order to calculate odds ratio. Univariate analyses were performed first. Then multivariable analyses were performed in order to adjust (1) first, for sex, age, educational level and family status (Model 1) (2) secondly, for the same demographics variables plus the BDI score and previous depressive episode requiring pharmacotherapy or psychotherapy (Model 2).

For the group of patients with NT1, further analyses were performed, aiming to analyze the relationships between the main sociodemographic and clinical as well as psychobehavioral features of individuals and a positive screening for tobacco or cannabis use, and alcohol misuse. Univariate and multivariable analyses were performed. Variables of adjustment were first sex, age, educational level and family status (Model 1), and secondly the same demographics variables plus the BDI score and previous depressive episode requiring pharmacotherapy or psychotherapy (Model 2). A p-value ≤0.05 was considered as statistically significant. Analyses were performed with SAS software (version

9.4).

2.5. Standard protocol approvals, registrations and patient consents

The study was performed in accordance with the principles of good clinical practice and the Declaration of Helsinki. The trial was approved by the Ethic Review Board (CPP Nord-Ouest I, N° 2018-A01586-49), and by the National Commission for Data Protection. All participants provided informed consent. The trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT 03765892).

3. Results

Descriptive variables of the two groups, and comparisons between patients with NT1 and controls are displayed in [Table 1](#) for consumption variables, [Table 2](#) for sociodemographic variables and [Supplementary Table 1](#) for psychobehavioral variables from ASR. A total of 235 patients with NT1 (63.8 % women) and 166 controls (69.9 % women, most controls being friends of the patients) completed the questionnaires. Patients were younger (36.4 ± 14.7 vs 40.3 ± 14.4 years, p < 0.01). The two groups differed also for marital status (less patients were in a couple, 37.8 % vs 61.5 %, p < 0.0001), physical activity (less frequent in patients: 55.2 % vs 67.1 %, p = 0.02), depression (BDI II score 13.1 ± 10.1 vs 8.3 ± 6.9, p < 0.0001), sleepiness (ESS: 16.3 ± 4.0 vs 8.3 ± 4.9, p < 0.0001) and quality of life (ED5Q: 69.6 ± 17.2 % vs 80.0 ± 13.6 %, p < 0.0001). Regarding psychobehavioral variables, patients rated higher for almost all of syndrome scales (anxious/depressed, withdrawn,

Table 1
Substance use in patients with narcolepsy type 1 and controls.

	Patients with NT1		Healthy controls		Model 1			Model 2			
	n	%	n	%	p-value ^a	Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
Alcohol misuse (AUDIT-C)					0.07			0.2			0.5
No (Score men <4 and Score women <3)	137	59.3	82	50.0		1	–		1	–	
Yes (Score men ≥4 and score women ≥3)	94	40.7	82	50.0		0.73	0.48–1.12		0.85	0.54–1.35	
Score Audit-C					0.2	0.93 ^a	0.84–1.03	0.2	0.95 ^a	0.86–1.06	0.4
Mean (std)	2.62	(2.25)	2.90	(2.19)							
Median (Q1-Q3)	2	(1–4)	3	(1–4)							
Tobacco smoking status (QP39Recode2Cat)					0.007			0.06			0.1
No smoker/Past smoker	157	67.7	131	79.9		1	–		1	–	
Current smoker	75	32.3	33	20.1		1.60	0.98–2.62		1.51	0.89–2.54	
HSI score					0.04	0.91 ^b	0.65–1.26	0.2	0.86 ^b	0.61–1.21	0.4
Mean (std)	0.49	(1.12)	0.28	(0.88)							
Median (Q1-Q3)	0	(0–0)	0	(0–0)							
Past-month vaping status					0.0005			0.0008			0.002
No	203	87.9	159	97.6		1	–		1	–	
Yes	28	12.1	4	2.4		6.51	2.17–19.49		5.81	1.89–17.90	
Cannabis use over the past six months					0.1			0.5			0.7
No	199	85.4	149	90.9		1	–		1	–	
Yes	34	14.6	15	9.1		1.23	0.62–2.44		1.17	0.53–2.54	
Cannabis consumption frequency					0.09	1.08 ^c	0.82–1.42	0.6	1.02 ^c	0.74–1.42	0.9
Mean (std)	0.30	(0.89)	0.19	(0.71)							
Median (Q1-Q3)	0	(0–0)	0	(0–0)							

Model 1: Adjusted for sex, age, level of graduation, marital status.

Model 2: Adjusted for sex, age, level of graduation, marital status, BDI score, previous depressive episode requiring pharmacotherapy or psychotherapy.

^aChi-squared or Fisher test/Student or Wilcoxon test.

^a OR associated to patients with NT1 for an increase of 1 point of AUDIT-C score.

^b OR associated to patients with NT1 for an increase of 1 point of the HSI score.

^c OR associated to patients with NT1 for an increase of cannabis consumption frequency.

Table 2
Description of factors used in adjusted models (sociodemographic characteristics, depression).

	Patients with NT1		Controls		p-value ^a	Patients with NT1										p-value ^a				
	n	%	n	%		Alcohol misuse (n = 94)		No alcohol misuse (n = 137)		p-value ^a	Current smoker (n = 75)		No smoker/Past smoker (n = 157)		Cannabis use (n = 34)		No cannabis use (n = 199)		p-value ^a	
						n	%	n	%		n	%	n	%	n		%	n		%
Sex					0.2					0.06					0.09					0.03
Men	85	36.2	50	30.1		40	42.5	42	30.7		33	44.0	51	32.5		18	52.9	66	33.2	
Women	150	63.8	116	69.9		54	57.5	95	69.3		42	56.0	106	67.5		16	47.1	133	66.8	
Age					0.03					0.2					0.1					0.2
≤24 years	61	26.0	27	16.3		24	25.5	37	27.0		12	16.0	49	31.2		7	20.6	54	27.1	
25–34 years	63	26.8	37	22.3		30	31.9	31	22.6		21	28.0	41	26.1		9	26.5	53	26.6	
35–44 years	46	19.6	33	19.9		19	20.2	26	19.0		20	26.7	26	16.6		11	32.3	35	17.6	
45–54 years	40	17.0	45	27.1		10	10.6	30	21.9		14	18.7	25	15.9		6	17.7	34	17.1	
≥55 years	25	10.6	24	14.4		11	11.7	13	9.5		8	10.6	16	10.2		1	2.9	23	11.6	
Marital status					<0.0001					0.5					0.9					0.01
Single	145	62.2	64	38.5		60	64.5	82	60.3		46	62.2	98	62.8		27	81.8	117	59.1	
Couple	88	37.8	102	61.5		33	35.5	54	39.7		28	37.8	58	37.2		6	18.2	81	40.9	
Level of graduation (Isced)					0.4					0.01					0.06					0.8
Level 2	37	16.2	18	11.0		10	10.6	27	20.1		18	24.7	18	11.6		6	17.7	31	15.9	
Level 3	58	25.4	35	21.3		17	18.1	41	30.6		12	16.4	46	29.7		6	17.7	52	26.7	
Level 5	35	15.4	25	15.2		17	18.1	18	13.4		12	16.4	23	14.8		6	17.7	29	14.9	
Level 6	41	18.0	34	20.7		18	19.2	23	17.2		13	17.8	28	18.1		6	17.7	35	17.9	
Level 7–8	57	25.0	52	31.7		32	34.0	25	18.7		18	24.7	40	25.8		10	29.4	48	24.6	
Score BDI					<0.0001					0.5					0.3					0.9
Mean (std)	13.07 (10.20)		8.13 (6.90)			12.29 (9.40)		13.35 (10.59)			11.89 (8.80)		13.54 (10.78)			13.15 (8.14)		12.99 (10.48)		
Median (Q1-Q3)	11 (6–18)		7 (2–12)			10 (6–18)		10 (6–18)			11 (5–17)		10 (6–18.5)			12.5 (6–19)		10 (5.5–17.5)		
Previous depressive episode requiring pharmacotherapy or psychotherapy					0.1					0.1					0.1					0.3
No	173	74.9	136	81.9		75	79.8	96	71.1		61	81.3	112	72.3		28	82.4	145	73.6	
Yes	58	25.1	30	18.1		19	20.2	39	28.9		14	18.7	43	27.7		6	17.6	52	26.4	

^a Chi-deux or Fisher/Student or Wilcoxon.

somatic complaints, thought problems, attention problems, aggressive behaviors, rule-breaking behavior, and intrusive behaviors) and most items of DSM IV-oriented scales (depressive problems, anxiety problems, somatic problems, avoidant personality problems, attention disorders/hyperactivity-impulsivity problems) (Supplementary Table 1). In patients with NT1, the mean \pm sd NSS score was 27.4 ± 10.3 ; 69.8 % of patients reported cataplexy at the time of the survey, while 91.8 % had presented cataplexy in the past, 87.3 % had sleep attacks, 46.3 % had sleep paralysis, 52.4 % had hallucinations, 74.5 % had disrupted nighttime sleep, and 47.0 % had sleep inertia. Concurrent medications were as follows: Modafinil (40.4 %), Methylphenidate (30.9 %), Pitolisant (20.9 %), Dexamphetamine (0.9 %), Sodium oxybate (16.5 %), Venlafaxine (22.6 %), Fluoxetine (5.7 %) and Clomipramine (5.7 %), with 86.5 % of patients taking at least one wake-promoting and/or anti-cataplectic medication. Childhood onset of the disease was reported in 66.4 % of patients among whom 53.9 % were diagnosed before 18 years. The diagnosis delay was >5 years in 23.3 % of patients.

3.1. Comparisons of substance use between patients with NT1 and healthy controls

Unadjusted bivariable analyses found that, relative to healthy controls, patients with NT1 were more frequently current smokers (32.3 vs 20.1 %; $p < 0.01$, with overall increased HSI score: 0.49 ± 1.12 vs 0.28 ± 0.88 , $p = 0.04$) or users of e-cigarettes (12.1 vs 2.4 %; $p < 0.001$) (Table 1) (Fig. 1). Other comparisons were not found statistically different. In patients with NT1, the mean \pm sd AUDIT-C score was 2.62 ± 2.25 and in healthy controls 2.90 ± 2.19 . The difference in tobacco use tended to persist ($p = 0.06$) after adjustment for sociodemographic features, but not after adjustment for both sociodemographic and psychiatric features. By contrast, the likelihood of vaping was still found statistically higher in NT1 subjects in the most stringent model.

3.2. Factors associated with alcohol misuse among patients with NT1

In particular, after adjustment for sociodemographic and psychiatric features (Table 3), patients with vs without alcohol misuse were more likely to be current tobacco (OR 2.50; 95%CI[1.29–4.83], $p < 0.01$) and cannabis (OR 2.62; 95%CI[1.04–6.58], $p < 0.05$) smokers, to be retired (OR 15.61; 95%CI[2.58–94.47], $p < 0.05$), and to be currently treated

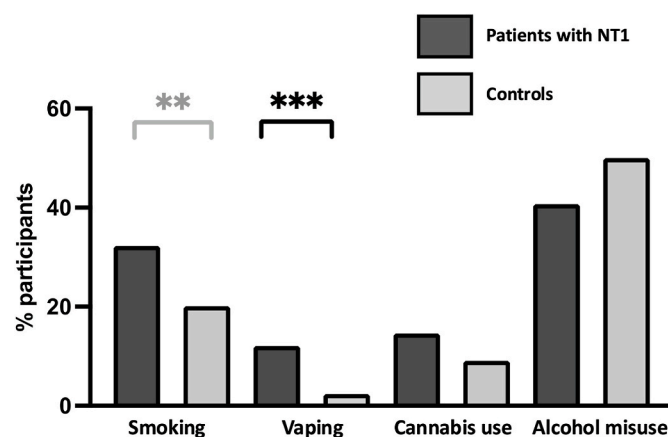


Figure. Prevalence of psychoactive substance consumptions in patients with narcolepsy type 1 (NT1) and controls

Prevalence of smoking (current vs past or never), vaping (past month), cannabis use (at least once over the 6 past months) and alcohol misuse (AUDIT-C score ≥ 4 for men and ≥ 3 for women) are presented in patients with NT1 and controls.

Smoking and vaping are increased in patients with NT1 but only vaping remains significant after adjustment for sociodemographic and psychiatric factors.

with modafinil (OR 2.14; 95%CI[1.15–4.01], $p < 0.05$). By contrast, they were less likely to have a current sodium oxybate treatment (OR 0.41; 95%CI[0.17–0.97], $p < 0.05$). Regarding sleep-related symptoms, alcohol misusers exhibited more sleep paralysis (OR 2.11; 95%CI [1.13–3.91], $p < 0.05$), and a trend was observed for hallucination ($p = 0.1$), sleep attacks ($p = 0.09$) and current cataplexy (0.08). Finally, they showed less withdrawn behavior (OR 0.52; 95%CI[0.19–1.43], $p < 0.05$), more attention disorders (OR 4.52; 95%CI[1.47–13.91], $p < 0.05$), and more rule breaking behaviors (OR 5.89; 95%CI[1.61–21.60], $p < 0.05$). No significant predictor was found in DSM IV oriented scales (Supplementary Table 2).

3.3. Factors associated with current tobacco smoking among patients with NT1

After adjustment for sociodemographic and psychiatric features (Table 4), patients with NT1 with current tobacco smoking were more likely to exhibit concurrent alcohol misuse (OR 2.50; 95%CI [1.29–4.83], $p = 0.007$), as well as concurrent e-cigarette (OR 5.61; 95% CI[2.03–15.52], and cannabis (OR 15.19; 95%CI[4.95–46.60], $p < 0.0001$) use. They were also more likely to have children (OR 3.74; 95% CI[1.37–10.16], $p < 0.01$), and less likely to have an obesity (OR 0.24; 95%CI[0.09–0.59], $p > 0.01$), compared to a normal BMI or an overweight. They reported a less frequent physical activity (OR 0.46; 95%CI [0.24–0.87], $p < 0.05$). Regarding the NT1 profile, current smokers had more disrupted nighttime sleep (OR 2.28; 95%CI[1.02–5.12], $p < 0.05$), and a trend toward a more frequent adult onset of symptoms (OR 3.24; 95%CI[1.21–8.67], $p = 0.07$) as well as a trend for more sleep attack (OR 2.29; 95%CI[0.95–5.55], $p = 0.07$). Tobacco users did not differ from non-users for psycho-behavioral features assessed by the ASR (Supplementary Table 2).

3.4. Factors associated with cannabis use among patients with NT1

After adjustment for sociodemographic and psychiatric features (Table 5), patients with NT1 with current cannabis use were more likely to exhibit concurrent alcohol misuse (OR 2.66 95%CI[1.04–6.82], $p > 0.05$), as well as concurrent tobacco (OR 15.36; 95%CI[4.99–47.22], $p < 0.0001$), and e-cigarette (OR 5.96; 95%CI[1.78–19.95], $p < 0.01$) use. They were also less likely to report regular physical activity (OR 0.25; 95%CI[0.10–0.66], $p < 0.01$). Regarding the NT1 profile, a trend toward more frequent sleep disruption (OR 3.57; 95%CI[0.94–13.57], $p = 0.06$) was observed. Finally, patients showed more rule breaking behavior (OR 8.52; 95%CI[1.79–40.48], $p = 0.01$). No significant predictor was found in DSM IV oriented scales (Supplementary Table 2).

3.5. Factors associated with SUDs in controls

Factors associated with substance use and abuse are presented in details in Supplementary Tables 3, 4, 5 and 6. Briefly, as in patients with NT1, co-consumptions were frequent with a significant association between alcohol misuse and tobacco (OR 3.42; 95 %CI[1.37–8.55], $p < 0.01$) and well as cannabis (OR 4.23; 95%CI[1.00–17.81], $p < 0.05$) smoking. Alcohol misusers had more pain issues (OR 3.43; 95%CI [1.43–8.20], $p < 0.01$), and a trend was observed for more sleepiness (mean ESS 8.77 ± 4.36 vs 7.23 ± 4.48 , $p = 0.051$) and less unemployment (OR 0.19; 95%CI[0.05–0.69], $p = 0.06$). A younger age ($p < 0.001$), being single ($p < 0.01$), depression (mean BDI II 11.19 ± 8.03 vs 7.4 ± 6.38 , $p < 0.01$) and practicing less physical activity (OR 0.41; 95% CI[0.17–1.03], trend: $p = 0.06$) were associated with smoking. A younger age (mean age 29.33 ± 9.49 vs 41.27 ± 14.37 , $p < 0.01$), being single ($p < 0.01$), and having less children ($p < 0.05$) were associated with cannabis consumption. After adjustment, no psycho-behavioral feature assessed by the ASR remained significantly associated with SUDs in controls.

Table 3
Factors associated with alcohol misuse in patients with narcolepsy type 1.

	Alcohol misuse (n = 94)		No alcohol misuse (n = 137)		Model 1			Model 2			
	n	%	n	%	p-value ^a	Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
Tobacco smoking status (QP39Recode2Cat)											
No smoker/Past smoker	53	56.4	103	75.7	0.002	1	–	0.001	1	–	0.007
Current smoker	41	43.6	33	24.3		2.85	1.53–5.33		2.50	1.29–4.83	
HSI score											
Mean (std)	0.53 (1.08)		0.44 (1.11)		0.5	1.18 ^b	0.89–1.55	0.3	1.14 ^b	0.84–1.55	0.4
Median (Q1–Q3)	0 (0–0)		0 (0–0)								
Past-month vaping status											
No	82	87.2	119	88.2	0.8	1	–	0.6	1	–	0.7
Yes	12	12.8	16	11.8		1.30	0.54–3.10		1.21	0.46–3.17	
Cannabis use over the past six months											
No	72	76.6	125	91.2	0.002	1	–	0.007	1	–	0.04
Yes	22	23.4	12	8.8		3.16	1.38–7.23		2.62	1.04–6.58	
Cannabis consumption Frequency											
Mean (std)	0.44 (1.03)		0.21 (0.77)		0.005	1.35 ^c	0.97–1.88	0.08	1.22 ^c	0.86–1.73	0.5
Median (Q1–Q3)	0 (0–0)		0 (0–0)								
Body-mass index (BMI)											
Underweight or Normal range (≤ 24.9)	46	48.9	44	33.1	0.005	1	–	0.06	1	–	0.03
Overweight (25.0–29.9)	33	35.1	43	32.3		0.70	0.36–1.35		0.74	0.37–1.48	
Obese (≥ 30)	15	16.0	46	34.6		0.40	0.19–0.86		0.33	0.15–0.75	
Current sport activity											
No	41	43.6	63	46.0	0.7	1	–	0.5	1	–	0.5
Yes	53	56.4	74	54.0		0.82	0.46–1.46		0.80	0.44–1.46	
Occupational status											
Employed	63	70.0	90	69.8	0.4	1	–	0.04	1	–	0.03
Unemployed	9	10.0	17	13.2		1.01	0.39–2.62		0.85	0.31–2.32	
Retired	9	10.0	6	4.6		9.68	1.94–48.40		15.61	2.58–94.47	
Student	9	10.0	16	12.4		0.52	0.17–1.58		0.59	0.19–1.87	
Sleep and/or NT1 features											
Age at NT1 diagnosis											
<10 years	5	5.3	12	8.8	0.2	0.77	0.19–3.06	0.6	1.02	0.24–4.36	0.8
11–14 years	10	10.6	14	10.2		0.82	0.24–2.79		0.89	0.24–3.38	
15–18 years	17	18.1	25	18.2		1.08	0.40–2.93		1.29	0.43–3.88	
18–25 years	37	39.4	36	26.3		1.53	0.69–3.42		1.57	0.66–3.73	
>25 years	25	26.6	50	36.5		1	–		1	–	
Age at NT1 onset											
<10 years	12	12.8	26	19.0	0.5	0.63	0.22–1.83	0.6	0.97	–	0.2
11–14 years	29	30.8	30	21.9		1.23	0.46–3.33		1.39	–	
15–18 years	22	23.4	34	24.8		0.87	0.34–2.24		1.06	–	
18–25 years	15	16.0	19	13.9		1.26	0.46–3.46		1.52	–	
>25 years	16	17.0	28	20.4		1	–		1	–	
Delay between NT1 onset and diagnosis											
<1 year	36	38.3	44	32.1	0.4	1	–	0.4	1	–	0.7
1–5 years	35	37.2	62	45.3		0.73	0.37–1.42		0.72	0.35–1.45	
5–10 years	16	17.0	17	12.4		1.30	0.54–3.15		1.16	0.46–2.94	
>10 years	7	7.5	14	10.2		0.54	0.17–1.66		0.71	0.22–2.31	
Age at NT1 onset and age at diagnosis											
NT1 onset and diagnosis <18 years	32	34.0	51	37.2	0.8	1	–	0.6	1	–	0.8
NT1 onset <18 and a diagnosis onset ≥ 18 years	31	33.0	39	28.5		1.40	0.65–3.00		1.24	0.55–2.83	
NT1 onset and diagnosis ≥ 18 years	31	33.0	47	34.3		1.55	0.66–3.63		1.29	0.52–3.24	
Previous episodes of cataplexy (Yes vs. No)											
	86	91.5	126	92.0	0.9	0.94	0.34–2.63	0.9	0.98	0.33–2.90	0.9

(continued on next page)

Table 3 (continued)

	Alcohol misuse (n = 94)		No alcohol misuse (n = 137)		p-value ^a	Model 1		Model 2			
	n	%	n	%		Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
Current episodes of cataplexy (Yes vs. No)	65	73.9	85	67.5	0.3	1.63	0.85–3.14	0.1	1.89	0.93–3.85	0.08
Sleep paralysis	54	57.5	52	38.2	0.004	2.17	1.23–3.83	0.008	2.11	1.13–3.91	0.02
Hallucinations	56	59.6	64	47.1	0.06	1.70	0.97–2.99	0.07	1.61	0.88–2.96	0.1
Disrupted nighttime sleep insomnia	68	72.3	103	75.7	0.6	0.94	0.49–1.82	0.9	0.81	0.40–1.64	0.6
Sleep inertia	41	43.6	66	48.9	0.4	0.75	0.42–1.32	0.3	0.81	0.42–1.55	0.5
Sleep attack	81	86.2	105	77.8	0.1	1.85	0.86–4.01	0.1	2.06	0.90–4.69	0.09
Regular napping (>1/day)	60	63.8	91	66.9	0.6	0.93	0.52–1.68	0.8	1.04	0.55–1.95	0.9
Preventive naps	72	81.8	94	71.2	0.07	1.93	0.96–3.87	0.06	1.90	0.92–3.92	0.1
Epworth											
Excessive sleepiness (ESS>10) sommeil≤10	86	94.5	113	90.4	0.3	2.24	0.71–7.08	0.2	2.18	0.67–7.09	0.2
Score Epworth					0.9	1.02 ^d	0.95–1.09	0.6	1.02 ^d	0.94–1.11	0.6
Mean (std)	16.11		16.14								
	(3.75)		(4.13)								
Median (Q1-Q3)	17 (14–19)		16 (13–20)								
NSS score					0.8			0.7			0.7
0–14	8	9.5	13	11.6		1	–		1	–	
15–28	35	41.7	53	47.3		1.70	0.58–4.93		1.67	0.57–4.91	
29–42	35	41.7	39	34.8		1.84	0.64–5.32		1.91	0.64–5.70	
43–57	6	7.1	7	6.3		2.24	0.49–10.31		2.37	0.46–12.08	
NSS score					0.1	1.02 ^e	0.99–1.05	0.2	1.02 ^e	0.99–1.05	0.2
Mean (std)	27.88		26.53								
	(9.60)		(10.82)								
Median (Q1-Q3)	28		25								
	(21.5–35.5)		(18–35.5)								
Total number of NT1 symptoms					0.1	1.24 ^f	0.92–1.67	0.2	1.27 ^f	0.93–1.75	0.1
Mean (std)	4.17 (0.98)		3.94 (1.04)								
Median (Q1-Q3)	4 (4–5)		4 (3–5)								
Current medications used for NT1											
<i>Wake-promoting drugs</i>											
Modafinil#	47	50.0	46	34.1	0.01	2.32	1.23–4.04	0.008	2.14	1.15–4.01	0.02
Methylphenidate#	22	23.4	48	35.6	0.04	0.54	0.28–1.02	0.06	0.52	0.26–1.03	0.06
Pitolisant	21	22.3	27	20.0	0.7	1.06	0.52–2.12	0.9	1.14	0.55–2.37	0.7
Dexamphetamin#	0	0	2	1.2	NA			NA			NA
Psychostimulant (present) #	67	71.3	94	69.6	0.8	1.23	0.58–2.62	0.6	1.19	0.55–2.58	0.7
Psychostimulant (past) #	74	79.6	121	89.6	0.04	0.45	0.17–1.19	0.6	0.6	0.16–1.11	0.08
<i>Anti-cataplectic drugs treatments</i>											
Clomipramine	6	6.4	7	5.2	0.7	1.14	0.35–3.77	0.8	1.12	0.35–3.83	0.8
Venlafaxine	20	21.3	32	23.7	0.7	0.90	0.45–1.80	0.8	0.89	0.43–1.88	0.8
Fluoxetine	4	4.3	4	3.0	0.7	2.20	0.48–10.02	0.3	1.96	0.41–9.26	0.4
Sodium oxybate	9	9.6	29	21.5	0.02	0.43	0.18–0.99	0.04	0.41	0.17–0.97	0.04
Any of 3 treatments Clomipramine/Venlafaxine/Fluoxetine	30	31.9	43	31.8	0.9	1.09	0.58–2.03	0.8	1.08	0.55–2.09	0.8
EQ-5D-Y dimension											
Mobility: At least one problem	10	12.3	22	21.4	0.1	0.64	0.27–1.52	0.3	0.60	0.22–1.64	0.3
Self-Care: At least one problem	2	2.5	6	5.8	0.5	0.40	0.07–2.30	0.3	0.37	0.05–2.53	0.3
Usual Activities: At least one problem	46	56.8	57	55.3	0.8	1.16	0.62–2.17	0.6	1.39	0.69–2.78	0.4
Pain/Discomfort: At least one problem	38	46.9	58	56.3	0.2	0.83	0.44–1.58	0.6	0.92	0.47–1.80	0.8
Anxiety/Depression: At least one problem	54	66.7	73	70.9	0.5	0.94	0.47–1.86	0.8	0.99	0.45–2.19	0.9
Adult Self Report - Syndromes Scales											
Anxious-Depressed					0.2			0.2			0.1
Clinical range	14	19.7	24	23.5		1.18	0.51–2.73		1.42	0.46–4.45	
Limit range	16	22.5	13	12.8		2.36	0.96–5.81		2.63	0.99–7.00	
Normal range	41	57.8	65	63.7		1	–		1	–	
Withdrawn					0.01			0.05			0.03

(continued on next page)

Table 3 (continued)

	Alcohol misuse (n = 94)		No alcohol misuse (n = 137)		Model 1			Model 2			
	n	%	n	%	p-value ^a	Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
Clinical range	11	15.5	20	19.6		0.68	0.28–1.67		0.52	0.19–1.43	
Limit range	9	12.7	30	29.4		0.33	0.14–0.81		0.27	0.10–0.72	
Normal range	51	71.8	52	51.0		1	–		1	–	
Somatic complaints					0.8			0.3			0.3
Clinical range	15	21.1	26	25.5		1.21	0.51–2.87		1.25	0.46–3.39	
Limit range	21	29.6	27	26.5		1.95	0.84–4.52		1.97	0.82–4.75	
Normal range	35	49.3	49	48.0		1	–		1	–	
Thought problems					0.6			0.6			0.5
Clinical range	3	4.2	6	5.9		0.99	0.22–4.39		0.8	0.15–4.21	
Limit range	9	12.7	18	17.6		0.62	0.25–1.56		0.55	0.20–1.51	
Normal range	59	83.1	78	76.5		1	–		1	–	
Attention problems					0.1			0.06			0.03
Clinical range	18	25.7	14	13.7		2.91	1.20–7.08		4.52	1.47–13.91	
Limit range	10	14.3	14	13.7		1.61	0.61–4.20		2.15	0.76–6.07	
Normal range	42	60.0	74	72.6		1	–		1	–	
Aggressive behavior					0.4			0.4			0.3
Clinical range	2	2.8	7	6.9		0.6	0.11–3.15		0.54	0.09–3.26	
Limit range	7	9.9	7	6.9		2.09	0.65–6.39		2.13	0.63–7.18	
Normal range	62	87.3	88	86.2		1	–		1	–	
Rule-breaking behavior					0.03			0.01			0.006
Clinical range	10	14.1	4	3.9		5.89	1.61–21.60		7.22	1.87–27.86	
Limit range	6	8.4	5	4.9		3.23	0.81–12.94		3.85	0.93–15.93	
Normal range	55	77.5	93	91.2		1	–		1	–	
Intrusive					0.5			0.4			0.4
Clinical range	4	5.6	2	1.9		3.78	0.59–24.46		3.90	0.59–25.59	
Limit range	10	14.1	17	16.7		1.02	0.40–2.59		1.08	0.42–2.76	
Normal range	57	80.3	83	84.4		1	–		1	–	
Adult Self Report – Critical items					0.9			0.7			0.8
Clinical range	8	11.3	14	13.7		0.91	0.33–2.52		0.81	0.21–3.06	
Limit range	11	15.5	14	13.7		1.50	0.59–3.78		1.28	0.45–3.64	
Normal range	52	73.2	74	82.6		1	–		1	–	

Model 1: adjusted for sex, age, level of graduation, marital status.

Model 2: adjusted for sex, age, level of graduation, marital status, BDI score, past depression requiring pharmacotherapy or psychotherapy.

NA: Model not applicable.

^a Chi-squared or Fisher test/Student or Wilcoxon test.

^b OR associated to alcohol misuse for an increase of 1 point of the HSI score.

^c OR associated to alcohol misuse for an increase of cannabis consumption frequency.

^d OR associated to alcohol misuse for an increase of 1 point of the Epworth score.

^e OR associated to alcohol misuse for an increase of 1 point of the NSS score.

^f OR associated to alcohol misuse for an increase of 1 NT1 symptom.

4. Discussion

The main objectives of this prospective comparative cross-sectional study were to compare the substance use patterns of patients with NT1, relative to healthy controls, and to explore, within the NT1 population, the main features of individuals with a positive screening for tobacco, alcohol misuse, or cannabis use. We found that smoking and vaping were increased in patients with NT1, but only vaping remained significant after adjustment for sociodemographic and psychiatric factors. Variables associated with substance use/misuse in patients involved demographic (sex), habits (physical activity), cognitive-behavioral (withdrawal, attention disorders, rule breaking behaviors), social (graduation, marital, employment status), and clinical (BMI, age at narcolepsy onset, sleep-related symptoms, narcolepsy treatments) dimensions.

4.1. An increased prevalence of smoking and vaping in patients with NT1

Our findings regarding the prevalence of smoking in patients with NT1 (32.3 %) are in line with data from previous literature ranging from 22.7 to 46.2 % [33–35,50]. However, the difference for tobacco use between patients and controls did not remain significant after adjustment for demographic factors and depression, which is consistent with high rates of depression in narcolepsy [5,51], and with factors associated with smoking in the general population, in whom tobacco consumption is associated with lower socioeconomic status, as well as depression [52,53]. Interestingly, the prevalence of vaping remained higher in patients in all models. An inverse relationship between vaping and smoking has been reported in young populations [54]. This could also apply to patients with NT1 whose regular medical follow-up includes smoking prevention measures, and who could therefore adopt or

Table 4
Factors associated with current tobacco smoking in patients with narcolepsy type 1.

	Current smoker (n = 94)		No smoker/ Past smoker (n = 137)		Model 1		Model 2				
	n	%	n	%	p-value ^a	Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
Alcohol misuse (AUDIT-C)					0.002			0.001			0.007
No (Score men <4 and Score women <3)	33	44.6	103	66.0		1	–		1	–	
Yes (Score men ≥4 and score women ≥3)	41	55.4	53	34.0		2.83	1.52–5.28		2.48	1.28–4.81	
Score Audit-C					0.2	1.33^b	1.15–1.54	0.0002	1.31^a	1.11–1.54	0.001
Mean (std)	3.43 (2.38)	2.26 (2.08)									
Median (Q1-Q3)	3 (2–5)	2 (0.5–3.5)									
Cannabis use over the past six months					<0.0001			<0.0001			<0.0001
No	47	62.7	151	96.2		1	–		1	–	
Yes	28	37.3	6	3.8		16.56	6.14–44.67		15.19	4.95–46.60	
Cannabis consumption frequency					<0.0001	4.20^c	2.07–8.50	<0.0001	3.53^c	1.81–6.87	0.0002
Mean (std)	0.83 (1.34)	0.06 (0.36)									
Median (Q1-Q3)	0 (0–1)	0 (0–0)									
Body-mass index (BMI)					0.06			0.02			0.004
Underweight or Normal range (<=24.9)	36	49.3	53	34.2		1	–		1	–	
Overweight (25.0–29.9)	23	31.5	54	34.8		0.52	0.26–1.05		0.40	0.19–0.86	
Obese (>=30)	14	19.2	48	31.0		0.31	0.13–0.72		0.24	0.09–0.59	
Current sport activity					0.01			0.02			0.02
No	42	56.8	61	38.8		1	–		1	–	
Yes	32	43.2	96	61.2		0.48	0.26–0.88		0.46	0.24–0.87	
Occupational status					0.2			0.4			0.6
Employed	50	73.5	102	67.5		1	–		1	–	
Unemployed	10	14.7	17	11.3		1.18	0.48–2.87		1.20	0.44–3.22	
Retired	5	7.4	10	6.6		0.63	0.14–2.98		1.04	0.19–5.59	
Student	3	4.4	22	14.6		0.40	0.10–1.62		0.40	0.09–1.69	
Sleep and/or NT1 features											
Age at diagnosis					0.06			0.1			0.07
<10 years	2	2.7	15	9.6		0.12	0.02–0.69		0.11	0.02–0.65	
11–14 years	7	9.5	17	10.8		0.44	0.13–1.56		0.37	0.09–1.49	
15–18 years	10	13.5	32	20.4		0.33	0.11–0.95		0.20	0.06–0.70	
18–25 years	23	31.1	51	32.5		0.53	0.23–1.22		0.44	0.18–1.01	
>25 years	32	43.2	42	26.7		1	–		1	–	
Age at NT1 onset					0.01			0.08			0.1
<10 years	8	10.8	31	19.8		0.21	0.07–0.65		0.24	0.07–0.80	
11–14 years	16	21.6	43	27.4		0.32	0.11–0.88		0.22	0.07–0.71	
15–18 years	17	23.0	39	24.8		0.42	0.16–1.08		0.36	0.13–1.05	
18–25 years	10	13.5	24	15.3		0.35	0.12–1.00		0.36	0.12–1.08	
>25 years	23	31.1	20	12.7		1	–		1	–	
Delay between NT1 onset and diagnosis					0.2			0.2			0.6
<1 year	25	33.8	56	35.7		1	–		1	–	
1–5 years	30	40.5	66	42.0		0.97	0.48–1.94		1.09	0.52–2.28	
5–10 years	15	20.3	18	11.5		1.96	0.81–4.77		1.62	0.62–4.22	
>10 years	4	5.4	17	10.8		0.45	0.13–1.62		0.64	0.17–2.44	
Age at NT1 onset and age at diagnosis					0.03			0.1			0.07
NT1 onset and diagnosis <18 years	19	25.7	64	40.8		1	–		1	–	
NT1 onset <18 and a diagnosis onset ≥18 years	22	29.7	49	31.2		1.72	0.77–3.8		1.98	0.80–4.89	

(continued on next page)

Table 4 (continued)

	Current smoker (n = 94)		No smoker/ Past smoker (n = 137)		Model 1		Model 2				
	n	%	n	%	p-value ^a	Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
NT1 onset and diagnosis ≥18 years	33	44.6	44	28.0		2.64	1.09–6.37		3.24	1.21–8.67	
Previous cataplexy	67	90.5	145	92.4	0.6	0.78	0.28–2.17	0.6	0.87	0.29–2.60	0.8
Current cataplexy	44	64.7	105	71.9	0.3	0.75	0.39–1.43	0.4	0.9	0.44–1.86	0.8
Sleep paralysis	32	43.2	75	48.1	0.5	0.83	0.47–1.49	0.5	0.99	0.52–1.90	0.9
Hallucinations	40	54.1	80	51.3	0.7	1.17	0.65–2.08	0.6	1.20	0.64–2.27	0.6
Disrupted nighttime sleep	60	81.1	111	71.2	0.1	1.82	0.88–3.76	0.1	2.28	1.02–5.12	0.04
Sleep inertia	30	40.5	78	50.3	0.2	0.74	0.41–1.33	0.3	0.99	0.50–1.97	0.9
Sleep attack	64	86.5	122	78.7	0.2	1.81	0.81–4.06	0.1	2.29	0.95–5.55	0.07
Regular napping (>1/day)	49	66.2	101	64.7	0.8	0.99	0.53–1.82	0.9	1.11	0.57–2.16	0.8
Preventive naps	51	72.9	116	76.8	0.5	0.90	0.45–1.78	0.8	1.05	0.50–2.19	0.9
Current medications used for NT1											
<i>Wake-promoting drugs</i>											
Modafinil#	27	36.5	65	41.9	0.4	0.77	0.42–1.41	0.4	0.69	0.35–1.29	0.2
Methylphenidate#	24	32.4	47	30.3	0.7	1.12	0.59–2.13	0.7	1.24	0.62–2.47	0.5
Pitolisant#	20	27.0	28	18.1	0.1	1.41	0.70–2.84	0.3	1.62	0.76–3.44	0.2
Dexamphetamine	0	0	2	1.9	NA			NA			NA
Psychostimulant (present) #	50	67.6	111	71.6	0.5	0.79	0.42–1.48	0.5	0.76	0.38–1.53	0.4
Psychostimulant (past) #	65	89.0	129	83.2	0.3	1.60	0.66–3.87	0.3	1.38	0.55–3.47	0.5
<i>Anti-cataplectic drugs</i>											
Clomipramine	7	9.5	6	3.9	0.1	2.70	0.84–8.68	0.1	2.67	0.81–8.78	0.1
Venlafaxine	19	25.7	33	21.3	0.5	1.15	0.57–2.32	0.7	1.35	0.63–2.89	0.4
Fluoxetine	2	2.7	6	3.9	0.9	0.52	0.09–2.94	0.5	0.62	0.10–3.80	0.6
Sodium oxybate	12	16.2	26	16.8	0.9	0.77	0.34–1.74	0.5	0.78	0.33–1.81	0.6
Any of 3 treatments Clomipramine/ Venlafaxine/Fluoxetine	28	37.8	45	29.0	0.2	1.36	0.72–2.57	0.3	1.64	0.82–3.28	0.2
EQ-5D-Y dimension											
Mobility: At least one problem	9	15.0	23	18.4	0.6	0.58	0.22–1.50	0.3	0.75	0.25–2.21	0.6
Self-Care: At least one problem	1	1.7	7	5.6	0.4	0.24	0.03–2.25	0.2	0.35	0.03–3.94	0.4
Usual Activities: At least one problem	33	55.0	71	56.8	0.8	0.91	0.47–1.77	0.8	1.19	0.57–2.50	0.6
Pain/Discomfort: At least one problem	32	53.3	65	52.0	0.9	0.92	0.46–1.84	0.8	1.06	0.51–2.19	0.9
Anxiety/Depression: At least one problem	40	66.7	88	70.4	0.6	0.92	0.45–1.90	0.8	1.30	0.55–3.04	0.6
Epworth											
Excessive sleepiness (ESS>10) sommeil ≤10	67	94.4	132	91.0	0.4	1.64	0.49–5.44	0.4	1.74	0.50–6.06	0.4
Score Epworth											
Mean (std)	16.14 (3.85)	16.12 (4.03)				1.01 ^d	0.93–1.08	0.9	1.03 ^d	0.95–1.12	0.5
Median (Q1-Q3)	16 (13–19)	17 (14–19)									
Score NSS											
0–14	6	9.2	15	11.4							0.8
15–28	31	47.7	57	43.2		1	–		1	–	
29–42	24	36.9	51	38.6		1.60	0.53–4.87		1.64	0.53–5.09	
43–57	4	6.2	9	6.8		1.33	0.44–4.04		1.58	0.50–5.04	
						0.94	0.18–4.85		1.37	0.24–7.83	
Score NSS											
Mean (std)	27.35 (9.87)	27.05 (10.55)			0.8	1.01 ^e	0.97–1.03	0.9	1.01	0.98–1.05	0.4
Median (Q1-Q3)	26 (21–36)	27 (19–35)									
Total number of NT1 symptoms											
					0.4	1.11 ^f	0.81–1.51	0.5	1.24 ^f	0.89–1.73	0.2

(continued on next page)

Table 4 (continued)

	Current smoker (n = 94)		No smoker/ Past smoker (n = 137)		Model 1		Model 2					
	n	%	n	%	p-value ^a	Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value	
Mean (std)	4.12 (1.07)		4.00 (1.00)									
Median (Q1-Q3)	5 (3–5)		4 (3–5)									
Adult Self Report - Syndromes Scales												
Anxious-Depressed					0.1			0.04				0.1
Clinical range	7	13.0	32	26.7		0.31	0.11–0.85		0.31	0.08–1.18		
Limit range	11	20.4	18	15.0		1.26	0.51–3.11		1.29	0.48–3.48		
Normal range	36	66.7	70	58.3		1	–		1	–		
Withdrawn					0.4			0.5				0.8
Clinical range	9	16.7	23	19.2		0.69	0.26–1.80		0.86	0.30–2.50		
Limit range	9	16.7	30	25.0		0.6	0.24–1.48		0.74	0.28–1.96		
Normal range	36	66.6	67	55.8		1	–		1	–		
Somatic complaints					0.09			0.09				0.2
Clinical range	7	13.0	34	28.3		0.4	0.15–1.07		0.49	0.16–1.51		
Limit range	17	31.5	31	25.8		1.27	0.55–2.95		1.33	0.55–3.23		
Normal range	30	55.5	55	45.8		1	–		1	–		
Thought problems					0.3			0.1				0.3
Clinical range	3	5.5	7	5.8		0.52	0.09–3.00		0.64	0.09–4.29		
Limit range	5	9.3	22	18.3		0.35	0.12–1.05		0.41	0.12–1.33		
Normal range	46	85.2	91	75.8		1	–		1	–		
Attention problems					0.9			0.6				0.6
Clinical range	9	16.7	24	20.2		0.65	0.25–1.68		0.74	0.24–2.33		
Limit range	8	14.8	16	13.4		1.16	0.44–3.08		1.39	0.49–3.94		
Normal range	37	68.5	79	66.4		1	–		1	–		
Aggressive behavior					0.4			0.4				0.4
Clinical range	1	1.8	8	6.7		0.25	0.03–2.21		0.34	0.03–3.52		
Limit range	5	9.3	9	7.5		1.37	0.39–4.74		1.79	0.48–6.71		
Normal range	48	88.9	103	85.8		1	–		1	–		
Rule-breaking behavior					0.3			0.3				0.1
Clinical range	7	13.0	7	5.8		2.37	0.73–7.69		3.54	0.99–12.56		
Limit range	4	7.4	8	6.7		0.93	0.22–3.83		1.17	0.26–5.27		
Normal range	43	79.6	105	87.5		1	–		1	–		
Intrusive					0.9			0.6				0.5
Clinical range	2	3.7	4	3.3		1.80	0.30–10.75		2.07	0.34–12.76		
Limit range	8	14.8	19	15.8		1.49	0.56–3.96		1.65	0.61–4.46		
Normal range	44	81.5	97	80.8		1	–		1	–		
Adult Self Report – Critical items					0.8			0.5				0.9
Clinical range	6	11.1	17	14.2		0.50	0.16–1.55		0.71	0.17–2.96		
Limit range	7	13.0	18	15.0		0.93	0.33–2.59		0.95	0.29–3.05		
Normal range	41	75.9	85	70.8		1	–		1	–		

Model 1: Adjusted for sex, age, level of graduation, marital status.

Model 2: Adjusted for sex, age, level of graduation, marital status, BDI score, previous depression requiring pharmacotherapy or psychotherapy.

NA: Model not applicable.

^a Chi-squared or Fisher test/Student or Wilcoxon test.

^b OR associated to current tobacco smoking for an increase of 1 point of AUDIT-C score.

^c OR associated to current tobacco smoking for an increase of cannabis consumption frequency.

^d OR associated to current tobacco smoking for an increase of 1 point of the Epworth score.

^e OR associated to current tobacco smoking for an increase of 1 point of the NSS score.

^f OR associated to current tobacco smoking for an increase of 1 NT1 symptom.

convert to vaping. For alcohol misuse and cannabis use, no difference was found in our population, which echoes previous studies in the field [31–33]. Importantly, we observed frequent substances co-consumption both in patients and controls, which has already been highlighted in epidemiological studies and might be related not only to social and

psychiatric but also to neurobiological factors [55,56]. No difference between patients and controls was observed for cannabis use and alcohol misuse, for which prevalence was high in both groups. The scale used (AUDIT-C) was validated in French in its complete version, with no evidence of cultural specificity in the thresholds [57].

Table 5
Factors associated with cannabis use in patients with narcolepsy type 1.

	Cannabis misuse (n = 34)		No cannabis misuse (n = 137)		Model 1			Model 2			
	n	%	n	%	p-value ^a	Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
Alcohol misuse (AUDIT-C) (auditpositif)					0.002			0.006			0.04
No (Score men <4 and Score women <3)	12	35.3	125	63.5		1	–		1	–	
Yes (Score men ≥4 and score women ≥3)	22	64.7	72	36.5		3.31	1.42–7.72		2.66	1.04–6.82	
Score Audit-C					<0.0001	1.37^a	1.14–1.63	0.0006	1.31^a	1.07–1.60	0.008
Mean (std)	4.09		2.37	(2.11)							
	(2.52)										
Median (Q1–Q3)	4	(2–6)	2	(1–4)							
Tobacco smoking status (QP39Recode2Cat)					<0.0001			<0.0001			<0.0001
No smoker/Past smoker	6	17.6	151	76.3		1	–		1	–	
Current smoker	28	82.4	47	23.7		17.31	6.31–47.49		15.36	4.99–47.22	
HSI score					<0.0001	2.06^b	1.44–2.94	<0.0001	1.78^b	1.20–2.63	0.004
Mean (std)	1.38		0.44	(0.94)							
	(1.58)										
Median (Q1–Q3)	1	(0–2)	0	(0–0)							
Past-month vaping status					0.0004			0.0002			0.004
No	22	66.7	181	91.4		1	–		1	–	
Yes	11	33.3	17	8.6		7.05	2.50–19.87		5.96	1.78–19.95	
Body-mass index (BMI)					0.4			0.4			0.3
Underweight or Normal range (<=24.9)	13	39.4	77	39.3		1	–		1	–	
Overweight (25.0–29.9)	14	42.4	63	32.1		1.48	0.61–3.61		1.55	0.57–4.24	
Obese (≥30)	6	18.2	56	28.6		0.77	0.25–2.32		0.59	0.16–2.18	
Current sport activity					0.01			0.003			0.005
No	22	64.7	82	41.4		1	–		1	–	
Yes	12	35.3	116	58.6		0.28	0.12–0.66		0.25	0.10–0.66	
Occupational status^b					0.3			0.1			0.1
Employed. Student	23	74.2	155	82.0		1	–		1	–	
Unemployed. Retired	8	25.8	34	18.0		2.31	0.81–6.52		2.59	0.80–8.42	
Sleep and/or NT1 features											
Age at diagnosis					0.3			0.4			0.2
<10 years	1	2.9	16	8.1		0.24	0.02–2.51		0.20	0.02–2.75	
11–14 years	6	17.7	18	9.1		1.32	0.29–6.08		1.15	0.20–6.72	
15–18 years	4	11.8	38	19.2		0.45	0.10–2.05		0.17	0.02–1.26	
18–25 years	13	38.2	61	30.8		1.16	0.37–3.62		0.80	0.21–3.02	
>25 years	10	29.4	65	32.8		1	–		1	–	
Age at NT1 onset					0.2			0.3			0.06
<10 years	5	14.7	34	17.2		1.14	0.24–5.44		3.06	0.41–22.99	
11–14 years	10	29.4	49	24.8		1.55	0.36–6.71		2.44	0.35–17.05	
15–18 years	6	17.6	50	25.2		1.25	0.28–5.48		1.38	0.17–11.31	
18–25 year	9	26.5	25	12.6		3.70	0.89–15.46		9.43	1.42–62.40	
>25 years	4	11.8	40	20.2		1	–		1	–	
Delay between NT1 onset and diagnosis					0.2			0.2			0.4
<1 year	9	26.5	72	36.4		1	–		1	–	
1–5 years	17	50.0	80	40.4		2.04	0.80–5.23		2.14	0.75–6.11	
5–10 years	7	20.6	26	13.1		2.93	0.91–9.45		2.62	0.69–10.00	
>10 years	1	2.9	20	10.1		0.56	0.06–5.18		0.98	0.10–9.82	
Age at NT1 onset and age at diagnosis					0.8			0.4			0.3
NT1 onset and diagnosis <18 years	11	32.4	72	36.4		1	–		1	–	
NT1 onset <18 and diagnosis ≥18 years	10	29.4	61	30.8		1.62	0.58–4.54		1.61	0.48–5.38	
NT1 onset and diagnosis ≥18 years	13	38.2	65	32.8		2.2	0.71–6.80		2.95	0.79–11.05	
Previous cataplexy	32	94.1	181	91.4	0.9	1.26	0.26–6.14	0.8	2.53	0.29–22.02	0.4

(continued on next page)

Table 5 (continued)

	Cannabis misuse (n = 34)		No cannabis misuse (n = 137)		p-value ^a	Model 1			Model 2		
	n	%	n	%		Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
Current cataplexy	25	75.8	125	68.7	0.4	1.38	0.56–3.39	0.5	2.35	0.73–7.61	0.2
Sleep paralysis	17	50.0	90	45.7	0.6	1.12	0.52–2.42	0.8	1.27	0.52–3.13	0.6
Hallucinations	21	61.8	100	50.8	0.2	1.66	0.75–3.68	0.2	1.8	0.71–4.57	0.2
Disrupted nighttime sleep	30	88.2	142	72.1	0.04	4.12	1.16–14.62	0.03	3.57	0.94–13.57	0.06
Sleep inertia	16	47.1	92	46.9	0.9	0.97	0.45–2.11	0.9	1.15	0.44–2.97	0.8
Sleep attack irrésistibles (QP72)	30	88.2	157	80.1	0.3	1.91	0.61–5.93	0.3	2.2	0.58–8.34	0.2
Regular napping (>1/day)	21	61.8	130	66.0	0.6	0.90	0.40–2.02	0.8	1.21	0.47–3.10	0.7
Preventive naps	22	73.3	145	75.9	0.8	0.89	0.35–2.25	0.8	1.43	0.46–4.41	0.5
Current medications used for NT1											
<u>Wake-promoting drugs</u>											
Modafinil ^b	12	35.3	81	41.3	0.5	0.82	0.36–1.86	0.6	0.81	0.32–2.06	0.7
Methylphenidate ^b	12	35.3	59	30.1	0.5	1.16	0.50–2.65	0.7	1.35	0.53–3.42	0.5
Pitolisant	11	32.3	37	18.9	0.07	1.79	0.75–4.24	0.2	2.08	0.80–5.42	0.1
Dexamphetamine ^b	0	0	2	1.0	NA			NA			NA
Psychostimulant (present) ^b	23	67.7	139	70.9	0.7	0.81	0.36–1.86	0.6	0.95	0.36–2.50	0.9
Psychostimulant (past) ^b	28	84.9	167	85.2	0.9	1.04	0.35–3.12	0.9	0.74	0.23–0.38	0.6
<u>Anti-cataplectic drugs</u>											
Clomipramine	3	8.8	10	5.1	0.4	2.34	0.55–9.95	0.2	3.3	0.72–15.16	0.1
Venlafaxine	9	26.5	43	21.9	0.6	1.16	0.47–2.87	0.8	1.62	0.59–4.46	0.3
Fluoxetine	0	0	8	4.1	0.6			NA			NA
Sodium oxybate	3	8.8	35	17.9	0.2	0.35	0.1–1.29	0.1	0.39	0.10–1.54	0.2
Any of 3 treatments Clomipramine/Venlafaxine/Fluoxetine	12	35.3	61	31.1	0.6	1.16	0.50–2.70	0.7	1.73	0.67–4.48	0.3
EQ-5D-Y dimension											
Mobility: At least one problem	3	12.0	29	18.1	0.6	0.76	0.20–2.91	0.7	0.58	0.11–3.03	0.5
Self-Care: At least one problem	1	4.0	7	4.4	0.9	62	0.07–5.81	0.7	0.40	0.03–5.67	0.5
Usual Activities: At least one problem	12	48.0	92	57.5	0.4	0.68	0.28–1.66	0.4	0.69	0.25–1.95	0.5
Pain/Discomfort: At least one problem	8	32.0	89	55.6	0.03	0.42	0.16–1.11	0.08	0.45	0.16–1.32	0.1
Anxiety/Depression: At least one problem	18	72.0	110	68.8	0.7	1.19	0.43–3.26	0.7	0.9	0.28–2.92	0.9
Epworth											
Excessive sleepines (ESS>10) sommeil≤10	30	96.8	170	91.4	0.5	3.05	0.38–24.74	0.3	2.45	0.29–20.84	0.4
Score Epworth					0.6	1.02 ^d	0.95–1.09	0.6	1.07 ^d	0.95–1.21	0.3
Mean (std)	16.45		16.09								
	(3.87)		(3.99)								
Median (Q1-Q3)	16 (13–20)		17 (13–19)								
Score NSS					0.01			NA			NA
0–14	0	0	21	12.1							
15–28	8	33.3	80	46.2							
29–42	16	66.7	59	34.1							
43–57	0	0	13	7.5							
Score NSS					0.07	1.03 ^e	0.99–1.08	0.2	1.04 ^e	0.99–1.09	0.1
Mean (std)	30.58		26.68								
	(6.92)		(10.62)								
Median (Q1-Q3)	31.5		26 (19–35)								
	(25.5–37)										
Total number of NT1 symptoms					0.3	1.25 ^f	0.77–2.01	0.4	1.41 ^f	0.82–2.42	0.2
Mean (std)	4.25		4.01 (1.03)								
	(0.94)										
Median (Q1-Q3)	5 (3.5–5)		4 (3–5)								
Adult Self Report - Syndromes Scales											
Anxious-Depressed					0.5			0.5			0.2
Clinical range	3	13.0	36	23.8		0.42	0.10–1.68		0.17	0.02–1.29	
Limit range	4	17.4	25	16.6		0.90	0.25–3.32		0.65	0.16–2.70	
Normal range	16	69.6	90	59.6		1	–		1	–	

(continued on next page)

Table 5 (continued)

	Cannabis misuse (n = 34)		No cannabis misuse (n = 137)		Model 1			Model 2			
	n	%	n	%	p-value ^a	Ajusted OR	95 % CI	p-value	Ajusted OR	95 % CI	p-value
Withdrawn					0.2			0.2			0.2
Clinical range	4	17.4	28	18.5		0.86	0.24–3.06		0.65	0.16–2.74	
Limit range	2	8.7	37	24.5		0.25	0.05–1.26		0.17	0.03–1.08	
Normal range	17	73.9	86	57.0		1	–		1	–	
Somatic complaints					0.4			0.2			0.1
Clinical range	3	13.0	38	25.2		0.88	0.21–3.74		1.06	0.19–5.78	
Limit range	8	34.8	40	26.5		2.59	0.79–8.48		3.26	0.89–11.94	
Normal range	12	52.2	73	48.3		1	–		1	–	
Thought problems					0.2			0.1			0.1
Clinical range	2	8.7	8	5.3		2.53	0.39–16.33		2.26	0.25–20.18	
Limit range	1	4.3	26	17.2		0.17	0.02–1.44		0.15	0.02–1.40	
Normal range	20	87.0	117	77.5		1	–		1	–	
Attention problems					0.7			0.6			0.7
Clinical range	5	21.7	28	18.7		1.45	0.43–4.92		1.01	0.20–5.01	
Limit range	4	17.4	20	13.3		1.80	0.48–6.70		1.74	0.44–6.94	
Normal range	14	60.9	102	68.0		1	–		1	–	
Aggressive behavior					0.8			NA			NA
Clinical range	0	0	9	6.0							
Limit range	2	8.7	12	7.9							
Normal range	21	91.3	130	86.1							
Rule-breaking behavior					0.01			0.01			0.01
Clinical range	5	21.7	9	6.0		6.28	1.54–25.52		8.52	1.79–40.48	
Limit range	3	13.1	9	6.0		4.28	0.84–21.88		5.19	0.94–28.63	
Normal range	15	65.2	133	88.0		1	–		1	–	
Intrusive					0.5			NA			NA
Clinical range	0	0	6	4.0							
Limit range	2	8.7	25	16.5							
Normal range	21	91.3	120	79.5							
Adult Self Report – Critical items					0.6			0.6			0.7
Clinical range	4	17.4	19	12.6		1.73	0.45–6.66		2.32	0.35–15.21	
Limit range	4	17.4	21	13.9		1.64	0.44–6.12		1.33	0.27–6.61	
Normal range	15	65.2	111	73.5		1	–		1	–	

Model 1: Ajusted for sex. Age. Level of graduation. Marital status.

Model 2: Ajusted for sex. Age. Level of graduation. Marital status. BDI score. Previous depression requiring pharmacotherapy or psychotherapy.

NA: Model not applicable.

^aChi-squared or Fisher test/Student or Wilcoxon test.

^bIn these analyses. Modalities of occupational status have been grouped in because of low frequencies: Employed/Student and Unemployed/Retired.

^a OR associated to cannabis use for an increase of 1 point of AUDIT-C score.

^bOR associated to cannabis use for an increase of 1 point of the HSI score.

^dOR associated to cannabis use for an increase of 1 point of the Epworth score.

^eOR associated to cannabis use for an increase of 1 point of the NSS score.

^fOR associated to cannabis use for an increase of 1 NT1 symptom.

Figure caption

4.2. Factors associated with alcohol misuse in patients with NT1

Regarding alcohol, NT1 patients with misuse had higher level of education, and were more often retired. The link between retirement and heavy drinking has previously been reported and is thought to be attributable to increased leisure time and decreased work-related constraints on drinking [58]. Interestingly, patients with alcohol misuse showed more symptoms related to REM-sleep dysregulation (sleep paralysis, with a trend for hallucinations and cataplexy). This might be associated with the disruptive effect of alcohol on sleep, with increased stage shifts following the short-term increase in sleep stability after ingestion, although this remains speculative as no information was

available on the relative timing between alcohol consumption and sleep symptoms in participants [59,60]. It is however interesting to note that hallucinations have been related to rebound of REM sleep during alcohol withdrawal [61]. Another explanation might be the lower use of sodium oxybate (an anti-cataplectic medication also known to increase sleep stability and decrease REM sleep related parasomnia [62]) in these patients, which may result from a prescription bias (such treatment may not be proposed to patients with alcohol consumption as it is a contra-indication) or from patients behavior (patients using sodium oxybate are forbidden to take alcohol). The lower use of methylphenidate and higher use of modafinil argue for a prescription bias; the conditions for prescribing, renewing and dispensing are much more

constraining for methylphenidate than for modafinil in France. Whilst there are many reasons for opting for a particular medication in a specific patient, the fact that both the physician and the patient believe that it may be difficult to manage the constraints and possible side effects of the treatment (which may be the case in people with alcohol abuse) are likely to favor the choice of certain drugs. We also observed a lower BMI in alcohol misusers; although alcohol-related calories might contribute to weight gain, epidemiological studies show conflicting results regarding the link between alcohol intake and obesity, suggesting the involvement of a behavioral and social modulation [63]. Finally, patients with alcohol misuse had more attention disorders and rule breaking behaviors. Such disorders might be associated with impulsivity which has been reported in NT1 and SUDs [31,64,65] but also with altered reward processing [66].

4.3. Factors associated with smoking in patients with NT1

Regarding tobacco, NT1 users showed more disrupted nighttime sleep and a trend toward more sleep attacks. Nicotine exerts a wake-promoting effect, and it is possible that some patients may use it as a contra-measure to sleepiness (although data about the efficacy of this measure in narcolepsy are inconsistent), with sleep disruption as a side effect [67–73]. The increase in sleep attacks among smokers was previously reported in a series of 105 patients with narcolepsy (87 with cataplexy); the authors also reported that smoking was associated with hallucinations, which was not the case in our cohort, but might also reflect sleep disruption [74]. Tobacco users were older at narcolepsy onset; one can hypothesize that tobacco use had started before the disease (and thus before orexin deficiency, as emphasized in a previous study [34]), and was maybe amplified by the sleepiness at disease onset before diagnosis. Given the stimulating effect of nicotine on orexin neurons, it is possible that smoking might even delay or mitigate the onset of narcolepsy symptoms [75]. For patients whose disease began in childhood, early medical management might be accompanied by preventive measures regarding the use of substances, particularly tobacco, given the cardiovascular risk associated with this disease [36]. We also observed the well-known association between nicotine consumption and a lower BMI as well as less physical activity [76,77].

4.4. Factors associated with cannabis use in patients with NT1

Regarding cannabis, NT1 users showed more disrupted night sleep. It is possible that some patients may use cannabis to alleviate insomnia symptoms although data regarding the efficacy of cannabis in sleep disturbances remains conflicting, except in the context of associated pain [78,79]; in our cohort, pain level was indeed lower in cannabis users. Interestingly, some studies in animals suggest that CBD might reduce excessive daytime sleepiness and that THC might inhibit REM sleep [80,81], which may be relevant in narcolepsy; no published study on the topic in patients with narcolepsy is available to our knowledge. Patients with NT1 who used cannabis were less often in a couple, suggesting a reduction in substance use associated with social expectation of marital role as previously reported [82]. This was also found in the our control group. As for alcohol, rule breaking behaviors were associated with cannabis consumption. In addition, a lower physical activity level was found in cannabis users; this may be related to tobacco co-consumption, as data about cannabis intake and physical activity is inconsistent [83,84].

4.5. Relationship between substance use patterns and NT1: a multidimensional equation

Our findings highlight the complexity of the relationship between substance use patterns and NT1: 1) Orexin deficiency should theoretically protect patients from SUDs, but age at onset is probably a crucial factor; notably in adult-onset, SUDs may develop before orexin

deficiency occurs whereas in childhood-onset, reward brain networks may reorganize during neurodevelopment and become partly orexin-independent [85] 2) several symptoms of narcolepsy, especially disrupted nighttime sleep and sleepiness, are likely to favor the use of substances that promote sleep (alcohol, cannabis) or wake (nicotine), which in turn can aggravate sleep disturbances. Interestingly, sleepiness is associated with impulsivity and the frequent comorbidity between ADHD and narcolepsy may play a key role in substance use [86,87] 3) the frequent co-morbidities of narcolepsy (depression, anxiety or other psycho-behavioral disorders) can indeed influence substance use either with the aim to alleviate some symptoms [88] or as a result of behavioral disturbances such as emotional dysregulation [89] or impulsivity [31,64,65,90] although we did not identify impulsivity as a significant determinant of substance use, probably due to lack of power as few patients were in the clinical range 4) therapeutic approaches including preventive advice regarding substances and the prescription of treatments contraindicated with alcohol may also influence substance use and misuse.

4.6. Limitations and strengths of the study

We have to acknowledge several limitations to our study. Firstly, the limited size of our sample of patients and controls hindered subgroup analyses, and the low proportion of patients who participated in the study among those approached probably led to the selection of the least severe patients, given the length of the questionnaire [37]. To note, this bias likely also applied to the control subjects. However, our results regarding the prevalence of SUDs are consistent with those published to date, and we did not find that disease severity, as assessed by the NSS, was a major determinant of substance use. Second, although the sex ratio of the disease is around 1:1, almost two third of participants were women, as expected in health research surveys where women are usually more willing to participate [91]. We adjusted our analyses for this factor which was indeed associated with cannabis consumption. Third, a more detailed investigation of the type of use, particularly problematic use for cannabis, would have provided additional insights into its consequences (e.g., cognitive, social, etc.). In addition, a more systematic assessment of all substances, including psychostimulants and opioids, which patients might use to alleviate certain symptoms [33,92,93], would have contributed to a more comprehensive understanding of substance use in narcolepsy type 1. This would warrant further research and could potentially lead to the exploration of innovative therapeutic options. Finally, we cannot exclude a possible deliberate under-report, although the anonymous online questionnaire probably limited this bias. The strength of our study lies in a well-defined NT1 population and the presence of a socio-demographically matched control group (controls were selected from the patients' environment) which is crucial in studies on SUDs. Detailed questionnaires including narcolepsy symptoms, drug use, academic and occupational data and psycho-behavioral symptoms enabled us to provide an in-depth and comprehensive investigation of the determinants of substance use in NT1s and to adjust for numerous confounding factors.

5. Conclusion

The relationship between sleep-related symptoms, comorbidities, treatments, and SUDs is complex in patients with NT1, who does not seem less vulnerable to addictive behaviors. One cannot disentangle the specific effect of orexin deficit from other factors involved in SUDs; it might be hypothesized that, given the symptoms and comorbidities observed in patients with NT1, as well as the prescription of psychostimulants, an even higher prevalence of addiction would have been expected, that might be mitigated by orexin deficit. However, another study reported that patients with NT1 do not differ from patients with NT2 and IH in this respect [33]. This strongly suggests adaptive mechanisms within reward networks. In clinical practice, although the

issue of SUDs may be overshadowed by the many other disabling symptoms reported by patients, considering substance use and misuse is crucial as such consumptions are likely to worsen sleep disturbances, psychiatric symptoms and the cardiovascular risk. This may involve 1) specifically addressing substance use during medical follow-ups for narcolepsy, 2) promoting psychoeducation to increase awareness among patients about the impact of substance use on physical and mental health, and their interaction with narcolepsy symptoms and treatments, and 3) offering specialized care and withdrawal support when needed. Such strategies may improve patient outcomes by addressing an often-overlooked aspect of narcolepsy care.

CRediT authorship contribution statement

Laure Peter-Derex: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Emmanuel Fort:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Benjamin Putois:** Writing – review & editing, Validation, Conceptualization. **Nora Martel:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **François Ricordeau:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Hélène Bastuji:** Writing – review & editing, Validation, Investigation, Conceptualization. **Isabelle Arnulf:** Writing – review & editing, Validation, Investigation, Conceptualization. **Lucie Barateau:** Writing – review & editing, Validation, Investigation, Conceptualization. **Patrice Bourgin:** Writing – review & editing, Validation, Investigation, Conceptualization. **Yves Dauvilliers:** Writing – review & editing, Validation, Investigation, Conceptualization. **Rachel Debs:** Writing – review & editing, Validation, Investigation, Conceptualization. **Pauline Dodet:** Writing – review & editing, Validation, Investigation, Conceptualization. **Benjamin Dudoignon:** Writing – review & editing, Validation, Investigation, Conceptualization. **Patricia Franco:** Writing – review & editing, Validation, Investigation, Conceptualization. **Sarah Hartley:** Writing – review & editing, Validation, Investigation, Conceptualization. **Isabelle Lambert:** Writing – review & editing, Validation, Investigation, Conceptualization. **Michel Lecendreux:** Writing – review & editing, Validation, Investigation, Conceptualization. **Laurene Leclair-Visonneau:** Writing – review & editing, Validation, Investigation, Conceptualization. **Damien Léger:** Writing – review & editing, Validation, Investigation, Conceptualization. **Martine Lemesle-Martin:** Writing – review & editing, Validation, Investigation, Conceptualization. **Antoine Léotard:** Writing – review & editing, Validation, Investigation, Conceptualization. **Smaranda Leu-Semenescu:** Writing – review & editing, Validation, Investigation, Conceptualization. **Nadège Limousin:** Writing – review & editing, Validation, Investigation, Conceptualization. **Régis Lopez:** Writing – review & editing, Validation, Investigation, Conceptualization. **Nicole Meslier:** Writing – review & editing, Validation, Investigation, Conceptualization. **Jean-Arthur Micoulaud-Franchi:** Writing – review & editing, Validation, Investigation, Conceptualization. **Christelle Charley-Mocana:** Writing – review & editing, Validation, Investigation, Conceptualization. **Marie-Pia d'Ortho:** Writing – review & editing, Validation, Investigation, Conceptualization. **Pierre Philip:** Writing – review & editing, Validation, Investigation, Conceptualization. **Elisabeth Ruppert:** Writing – review & editing, Validation, Investigation, Conceptualization. **Sylvie de La Tullaye:** Writing – review & editing, Validation, Investigation, Conceptualization. **Manon Brigandet:** Writing – review & editing, Validation, Funding acquisition, Conceptualization. **Barbara Charbotel:** Writing – review & editing, Validation, Methodology, Conceptualization. **Stéphanie Mazza:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Benjamin Rolland:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation,

Formal analysis, Conceptualization.

Disclosure statement

The project was funded by a research grant from the Rare Disease Foundation (2017).

Data availability statement

The data supporting this study are available upon reasonable request to the corresponding author and in compliance with local ethical regulations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2025.02.037>.

References

- [1] Scammell TE. Narcolepsy. *N Engl J Med* 2015;373:2654–62.
- [2] Barateau L, Pizza F, Chenini S, Peter-Derex L, Dauvilliers Y. Narcolepsies, update in 2023. *Rev Neurol (Paris)* 2023.
- [3] Mahoney CE, Cogswell A, Koralnik LJ, Scammell TE. The neurobiological basis of narcolepsy. *Nat Rev Neurosci* 2019;20:83–93.
- [4] Gudka S, Haynes E, Scotney J, Mukherjee S, Frenkel S, Sivam S, et al. Narcolepsy: comorbidities, complexities and future directions. *Sleep Med Rev* 2022;65:101669.
- [5] Dauvilliers Y, Paquereau J, Bastuji H, Drouot X, Weil JS, Viot-Blanc V. Psychological health in central hypersomnias: the French Harmony study. *J Neurol Neurosurg Psychiatry* 2009;80:636–41.
- [6] Del Bianco C, Ulivi M, Liguori C, Pisani A, Mercuri NB, Placidi F, et al. Alexithymia, impulsiveness, emotion, and eating dyscontrol: similarities and differences between narcolepsy type 1 and type 2. *Sleep Biol Rhythm* 2023;21:39–50.
- [7] Filardi M, D'Anselmo A, Agnoli S, Rubaltelli E, Mastris S, Mangiaruga A, et al. Cognitive dysfunction in central disorders of hypersomnolence: a systematic review. *Sleep Med Rev* 2021;59:101510.
- [8] Kapella MC, Berger BE, Vern BA, Vispute S, Prasad B, Carley DW. Health-related stigma as a determinant of functioning in young adults with narcolepsy. *PLoS One* 2015;10:e0122478.
- [9] Maski K, Steinhart E, Williams D, Scammell T, Flygare J, McCleary K, et al. Listening to the patient voice in narcolepsy: diagnostic delay, disease burden, and treatment efficacy. *J Clin Sleep Med* 2017;13:419–25.
- [10] Nordstrand SEH, Hansen BH, Rootwelt T, Karlsen TI, Swanson D, Nilsen KB, et al. Psychiatric symptoms in patients with post-H1N1 narcolepsy type 1 in Norway. *Sleep* 2019;42.
- [11] Rocca FL, Finotti E, Pizza F, Ingravallo F, Gatta M, Bruni O, et al. Psychosocial profile and quality of life in children with type 1 narcolepsy: a case-control study. *Sleep* 2016;39:1389–98.
- [12] Ruoff CM, Reaven NL, Funk SE, McGaughey KJ, Ohayon MM, Guilleminault C, et al. High rates of psychiatric comorbidity in narcolepsy: findings from the burden of narcolepsy disease (BOND) study of 9,312 patients in the United States. *J Clin Psychiatry* 2017;78:171–6.
- [13] Thieux M, Zhang M, Marcastel A, Herbillon V, Guignard-Perret A, Seugnet L, et al. Intellectual abilities of children with narcolepsy. *J Clin Med* 2020;9.
- [14] Brundin L, Björkqvist M, Petersén A, Träskman-Bendz L. Reduced orexin levels in the cerebrospinal fluid of suicidal patients with major depressive disorder. *Eur Neuropsychopharmacol* 2007;17:573–9.
- [15] Jacobson LH, Hoyer D, de Lecea L. Hypocretins (orexins): the ultimate translational neuropeptides. *J Intern Med* 2022;291:533–56.
- [16] Sakurai T. The role of orexin in motivated behaviours. *Nat Rev Neurosci* 2014;15:719–31.
- [17] James MH, Mahler SV, Moorman DE, Aston-Jones G. A decade of orexin/hypocretin and addiction: where are we now? *Curr Top Behav Neurosci* 2017;33:247–81.
- [18] Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. *Nature* 2005;437:556–9.
- [19] Bjornson TE, Greene RW. Orexin-mediated motivated arousal and reward seeking. *Peptides* 2024;180:171280.
- [20] Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J Neurosci* 1998;18:9996–10015.

- [21] Korotkova TM, Sergeeva OA, Eriksson KS, Haas HL, Brown RE. Excitation of ventral tegmental area dopaminergic and nondopaminergic neurons by orexins/hypocretins. *J Neurosci* 2003;23:7–11.
- [22] Mahler SV, Moorman DE, Smith RJ, James MH, Aston-Jones G. Motivational activation: a unifying hypothesis of orexin/hypocretin function. *Nat Neurosci* 2014;17:1298–303.
- [23] Hopf FW. Recent perspectives on orexin/hypocretin promotion of addiction-related behaviors. *Neuropharmacology* 2020;168:108013.
- [24] Valentino RJ, Volkow ND. Drugs, sleep, and the addicted brain. *Neuropsychopharmacology* 2020;45:3–5.
- [25] Roehrs T, Sibai M, Roth T. Sleep and alertness disturbance and substance use disorders: a bi-directional relation. *Pharmacol Biochem Behav* 2021;203:173153.
- [26] Hasler BP, Smith LJ, Cousins JC, Bootzin RR. Circadian rhythms, sleep, and substance abuse. *Sleep Med Rev* 2012;16:67–81.
- [27] Aernout E, Benradia I, Hazo JB, Sy A, Askevis-Leherpeux F, Sebbane D, et al. International study of the prevalence and factors associated with insomnia in the general population. *Sleep Med* 2021;82:186–92.
- [28] Lai HM, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: a systematic review and meta-analysis. *Drug Alcohol Depend* 2015;154:1–13.
- [29] Fragale JE, James MH, Avila JA, Spaeth AM, Aurora RN, Langleben D, et al. The insomnia-addiction positive feedback loop: role of the orexin system. *Front Neurol Neurosci* 2021;45:117–27.
- [30] Bayard S, Dauvilliers YA. Reward-based behaviors and emotional processing in human with narcolepsy-cataplexy. *Front Behav Neurosci* 2013;7:50.
- [31] Dimitrova A, Fronczek R, Van der Ploeg J, Scammell T, Gautam S, Pascual-Leone A, et al. Reward-seeking behavior in human narcolepsy. *J Clin Sleep Med* 2011;7:293–300.
- [32] Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. *Sleep Med* 2013;14:488–92.
- [33] Barateau L, Jaussent I, Lopez R, Boutrel B, Leu-Semenescu S, Arnulf I, et al. Smoking, alcohol, drug use, abuse and dependence in narcolepsy and idiopathic hypersomnia: a case-control study. *Sleep* 2016;39:573–80.
- [34] Peřinová P, Feketeová E, Kemlink D, Kovalská P, Chlebuřová K, Nepožitek J, et al. Smoking prevalence and its clinical correlations in patients with narcolepsy-cataplexy. *Prague Med Rep* 2016;117:81–9.
- [35] Flores NM, Villa KF, Black J, Chervin RD, Witt EA. The humanistic and economic burden of narcolepsy. *J Clin Sleep Med* 2016;12:401–7.
- [36] Ben-Joseph RH, Saad R, Black J, Dabrowski EC, Taylor B, Gallucci S, et al. Cardiovascular burden of narcolepsy disease (CV-bond): a real-world evidence study. *Sleep* 2023;46.
- [37] Peter-Derex L, Fort E., Putois B., Martel N., Ricordeau F., Bastuji H., et al. Effort/reward imbalance and comorbidities burden in academic and professional careers of patients with narcolepsy type 1. *J Clin Sleep Med*. 2025 Feb 13. doi: 10.5664/jcsm.11598. Epub ahead of print. PMID: 39943847.
- [38] American Academy of Sleep M. International classification of sleep disorders. third ed. 2014. IL: Darien.
- [39] Lopez R, Doukkali A, Barateau L, Evangelista E, Chenini S, Jaussent I, et al. Test-retest reliability of the multiple sleep latency test in central disorders of hypersomnolence. *Sleep* 2017;40.
- [40] Commission regulation (EU) No 317/2013 of 8 april 2013 amending the annexes to regulations (EC) No 1983/2003, (EC) No 1738/2005, (EC) No 698/2006, (EC) No 377/2008 and (EU) No 823/2010 as regards the international standard classification of education text with EEA relevance. 2013. p. 1–10.
- [41] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–5.
- [42] Dauvilliers Y, Beziat S, Pesenti C, Lopez R, Barateau L, Carlander B, et al. Measurement of narcolepsy symptoms: the narcolepsy severity scale. *Neurology* 2017;88:1358–65.
- [43] Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addict* 1989;84:791–9.
- [44] Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction* 1993;88:791–804.
- [45] Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). *Alcohol Use Disorders Identification Test*. *Arch Intern Med* 1998;158:1789–95.
- [46] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
- [47] Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337–43.
- [48] Achenbach TM, Rescorla L. Manual for the ASEBA adult forms & profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth 2003.
- [49] Dauvilliers Y, Barateau L, Lopez R, Rattu AL, Chenini S, Beziat S, et al. Narcolepsy Severity Scale: a reliable tool assessing symptom severity and consequences. *Sleep* 2020;43.
- [50] Palaja V, Poli F, Pizza F, Antelmi E, Franceschini C, Moghadam KK, et al. Narcolepsy with cataplexy associated with nocturnal compulsive behaviors: a case-control study. *Sleep* 2011;34:1365–71.
- [51] Cohen A, Mandrekar J, St Louis EK, Silber MH, Kotagal S. Comorbidities in a community sample of narcolepsy. *Sleep Med* 2018;43:14–8.
- [52] Hiscock R, Bauld L, Amos A, Fidler JA, Munafò M. Socioeconomic status and smoking: a review. *Ann N Y Acad Sci* 2012;1248:107–23.
- [53] Fluharty M, Taylor AE, Grabski M, Munafò MR. The association of cigarette smoking with depression and anxiety: a systematic review. *Nicotine Tob Res* 2017;19:3–13.
- [54] Levy DT, Warner KE, Cummings KM, Hammond D, Kuo C, Fong GT, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. *Tob Control* 2019;28:629–35.
- [55] Degenhardt L, Hall W, Lynskey M. Alcohol, cannabis and tobacco use among Australians: a comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis. *Addiction* 2001;96:1603–14.
- [56] Sharma R, Lodhi S, Sahota P, Thakkar MM. Nicotine administration in the wake-promoting basal forebrain attenuates sleep-promoting effects of alcohol. *J Neurochem* 2015;135:323–31.
- [57] Gache P, Michaud P, Landry U, Accietto C, Arfaoui S, Wenger O, et al. The Alcohol Use Disorders Identification Test (AUDIT) as a screening tool for excessive drinking in primary care: reliability and validity of a French version. *Alcohol Clin Exp Res* 2005;29:2001–7.
- [58] Zins M, Guéguen A, Kivimaki M, Singh-Manoux A, Leclerc A, Vahtera J, et al. Effect of retirement on alcohol consumption: longitudinal evidence from the French Gazel cohort study. *PLoS One* 2011;6:e26531.
- [59] Roehrs T, Roth T. Sleep, sleepiness, sleep disorders and alcohol use and abuse. *Sleep Med Rev* 2001;5:287–97.
- [60] Ebrahim IO, Shapiro CM, Williams AJ, Fenwick PB. Alcohol and sleep I: effects on normal sleep. *Alcohol Clin Exp Res* 2013;37:539–49.
- [61] Piazzi G, Montagna P, Meletti S, Lugaresi E. Polysomnographic study of sleeplessness and oneiricisms in the alcohol withdrawal syndrome. *Sleep Med* 2002;3:279–82.
- [62] Roth T, Dauvilliers Y, Bogan RK, Piazzi G, Black J. Effects of oxybate dose and regimen on disrupted nighttime sleep and sleep architecture. *Sleep Med* 2023;114:255–65.
- [63] Traversy G, Chaput JP. Alcohol consumption and obesity: an update. *Curr Obes Rep* 2015;4:122–30.
- [64] Bayard S, Langenier MC, Dauvilliers Y. Effect of psychostimulants on impulsivity and risk taking in narcolepsy with cataplexy. *Sleep* 2013;36:1335–40.
- [65] Adinoff B, Rilling LM, Williams MJ, Schreffler E, Schepis TS, Rosvall T, et al. Impulsivity, neural deficits, and the addictions: the "oops" factor in relapse. *J Addict Dis* 2007;26(Suppl 1):25–39.
- [66] Li G, Chen Y, Chaudhary S, Tang X, Li CR. Loss and frontal striatal reactivities characterize alcohol use severity and rule-breaking behavior in young adult drinkers. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2022;7:1007–16.
- [67] Catoire S, Nourredine M, Lefebvre S, Couraud S, Gronfier C, Rey R, et al. Tobacco-induced sleep disturbances: a systematic review and meta-analysis. *Sleep Med Rev* 2021;60:101544.
- [68] Saint-Mieux B, Eggermann E, Bisetti A, Bayer L, Machard D, Jones BE, et al. Nicotinic enhancement of the noradrenergic inhibition of sleep-promoting neurons in the ventrolateral preoptic area. *J Neurosci* 2004;24:63–7.
- [69] Boutrel B, Koob GF. What keeps us awake: the neuropharmacology of stimulants and wakefulness-promoting medications. *Sleep* 2004;27:1181–94.
- [70] Krahn LE, Martin KA, Silber MH. Narcoleptic patients' perceptions of nicotine. *J Clin Sleep Med* 2009;5:390.
- [71] Browman CP, Gujavarty KS, Mitler MM. Tobacco use by narcoleptics and daytime sleep tendency. *Drug Alcohol Depend* 1984;14:23–6.
- [72] Kirschbaum C, Wüst S, Strasburger CJ. 'Normal' cigarette smoking increases free cortisol in habitual smokers. *Life Sci* 1992;50:435–42.
- [73] Ebben MR, Krieger AC. Narcolepsy with cataplexy masked by the use of nicotine. *J Clin Sleep Med* 2012;8:195–6.
- [74] Nevsimalova S, Buskova J, Kemlink D, Sonka K, Skibova J. Does age at the onset of narcolepsy influence the course and severity of the disease? *Sleep Med* 2009;10:967–72.
- [75] Pasumarthi RK, Reznikov LR, Fadel J. Activation of orexin neurons by acute nicotine. *Eur J Pharmacol* 2006;535:172–6.
- [76] Piirtola M, Jelenkovic A, Latvala A, Sund R, Honda C, Inui F, et al. Association of current and former smoking with body mass index: a study of smoking discordant twin pairs from 21 twin cohorts. *PLoS One* 2018;13:e0200140.
- [77] Heydari G, Hosseini M, Yousefifard M, Asady H, Baikpour M, Barat A. Smoking and physical activity in healthy adults: a cross-sectional study in tehran. *Tanaffos* 2015;14:238–45.
- [78] AminiLari M, Wang L, Neumark S, Adli T, Couban RJ, Giangregorio A, et al. Medical cannabis and cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized clinical trials. *Sleep* 2022;45.
- [79] Suraev AS, Marshall NS, Vandrey R, McCartney D, Benson MJ, McGregor IS, et al. Cannabinoid therapies in the management of sleep disorders: a systematic review of preclinical and clinical studies. *Sleep Med Rev* 2020;53:101339.
- [80] Murillo-Rodríguez E, Millán-Aldaco D, Palomero-Rivero M, Morales-Lara D, Mechoulam R, Drucker-Colín R. Cannabidiol partially blocks the excessive sleepiness in hypocretindeficient rats: preliminary data. *CNS Neurol Disord: Drug Targets* 2019;18:705–12.
- [81] Calik MW, Carley DW. Effects of cannabinoid agonists and antagonists on sleep and breathing in sprague-dawley rats. *Sleep* 2017;40.
- [82] Salvatore JE, Gardner CO, Kendler KS. Marriage and reductions in men's alcohol, tobacco, and cannabis use. *Psychol Med* 2020;50:2634–40.
- [83] Ong IQ, Bellettiere J, Alvarado C, Chavez P, Berardi V. Cannabis use, sedentary behavior, and physical activity in a nationally representative sample of US adults. *Harm Reduct J* 2021;18:48.

- [84] Gibson LP, Skrzynski CJ, Giordano GR, Bryan AD. A daily diary investigation of cannabis use and its diet and exercise correlates. *Front Psychol* 2023;14:1217144.
- [85] Ponz A, Khatami R, Poryazova R, Werth E, Boesiger P, Bassetti CL, et al. Abnormal activity in reward brain circuits in human narcolepsy with cataplexy. *Ann Neurol* 2010;67:190–200.
- [86] Andrillon T, Burns A, Mackay T, Windt J, Tsuchiya N. Predicting lapses of attention with sleep-like slow waves. *Nat Commun* 2021;12:3657.
- [87] van Emmerik-van Oortmerssen K, van de Glind G, van den Brink W, Smit F, Crunelle CL, Swets M, et al. Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. *Drug Alcohol Depend* 2012;122:11–9.
- [88] Tizabi Y, Overstreet DH, Rezvani AH, Louis VA, Clark Jr E, Janowsky DS, et al. Antidepressant effects of nicotine in an animal model of depression. *Psychopharmacology (Berl)* 1999;142:193–9.
- [89] Varallo G, Musetti A, D'Anselmo A, Gori A, Giusti EM, Pizza F, et al. Exploring addictive online behaviors in patients with narcolepsy type 1. *Healthcare (Basel)* 2022;10.
- [90] Mombelli S, Ricordeau F, Gillard L, Lecca R, Vidal T, Pereira B, et al. Psychobehavioural profile in narcolepsy type 1 with and without REM sleep behaviour disorder. *J Sleep Res* 2023:e13925.
- [91] Glass DC, Kelsall HL, Slegers C, Forbes AB, Loff B, Zion D, et al. A telephone survey of factors affecting willingness to participate in health research surveys. *BMC Public Health* 2015;15:1017.
- [92] Gool JK, van Heese EM, Schinkelshoek MS, Remmerswaal A, Lammers GJ, van Dijk KD, et al. The therapeutic potential of opioids in narcolepsy type 1: a systematic literature review and questionnaire study. *Sleep Med* 2023;109:118–27.
- [93] Thannickal TC, John J, Shan L, Swaab DF, Wu MF, Ramanathan L, et al. Opiates increase the number of hypocretin-producing cells in human and mouse brain and reverse cataplexy in a mouse model of narcolepsy. *Sci Transl Med* 2018;10.