2018 Worldwide Survey of Health-Care Providers Caring for Patients with Narcolepsy

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Abstract

Background: There are limited data available on regional differences in the diagnosis and management of narcolepsy. In order to better understand worldwide trends in clinical assessment and management of narcolepsy, a survey of health-care providers was conducted by the World Sleep Society Narcolepsy task force.

Methods: A total of 146 surveys that included items on the diagnosis and management of narcolepsy were completed by practitioners representing 37 countries.

Results: Most of the participants were from Europe, North America, Oceania, Asia and Latin America. A consistent approach to applying the diagnostic criteria of Narcolepsy was documented with the exception of measurement of CSF hypocretin-1, which has limited availability. While the majority of practitioners (58%) reported not using the test, 1% indicated always evaluating CSF hypocretin-1 levels. There was much variability in the availability of currently recommended medications such as sodium oxybate and pitolisant; modafinil and antidepressants were the most commonly used medications. Amphetamines were unavailable in some countries.

Conclusion: The results of the study highlight clinical and therapeutic realities confronted by worldwide physicians in the management of narcolepsy. While the diagnostic criteria of narcolepsy rely in part on the quantification of CSF hypocretin-1, few physicians reported having incorporated this test into their routine assessment of the condition. Regional differences in the management of narcolepsy appeared to be related to geographic availability and expense of the therapeutic agents.

Introduction

The management of patients with symptoms of excessive daytime sleepiness (EDS) represents one of the core clinical activities in the practice of sleep medicine. Significant advances in the understanding of the pathophysiology of narcolepsy type 1 and the increasing availability of effective pharmacological agents have occurred in the last 10 years. While there are available consensus papers on the diagnosis and management of narcolepsy [1, 2, 3], actual clinical practice is determined by access to care, availability of resources and affordability of available therapies, which differ around the world and have not been characterized. The World Sleep Society [WSS] Narcolepsy Task Force surveyed clinicians around the world, in an effort to advance the understanding of regional differences in the diagnosis and management of narcolepsy.

Methods

Individuals connected to the WSS database were contacted on four occasions via e-mail between October 24 and November 15, 2018 asking them for their participation on a web-based survey. At the time, 2715 individuals were listed on the database. Note that no information was available about these individuals; they had a connection to the WSS but were not necessarily members of the society and thus it is not possible to ascertain the actual number of health providers among the potential participants. One hundred and forty-six practitioners from 37 countries, who reported providing clinical care for sleep disorders patients completed the survey. Participants were asked to report on the characteristics of their practice, preferred diagnostic tools, provide estimates of the number (and clinical characteristics) of narcoleptic patients and the available/preferred therapeutic agents to treat narcolepsy. Due to the diagnostic relevance of cataplexy, the survey asked practitioners to estimate the percent of narcolepsy type 1 patients in their practice; also, in a different section of the survey, they were asked to provide an estimate of the percent of patients with cataplexy. In regards to available therapies, limited or no availability of the newer agents Solriamfetol and Pitolisant at the time of the survey might have impacted reported therapeutic preferences. Unless indicated, the data provided reflect the answers of all participants.

Results

The participants' average years in practice was 21 (standard deviation ± 12 years). The majority reported being members of an academic institution [83%]. The geographic distribution of the participants includes those in all continents with over 50% from Europe and North America (Figure 1).

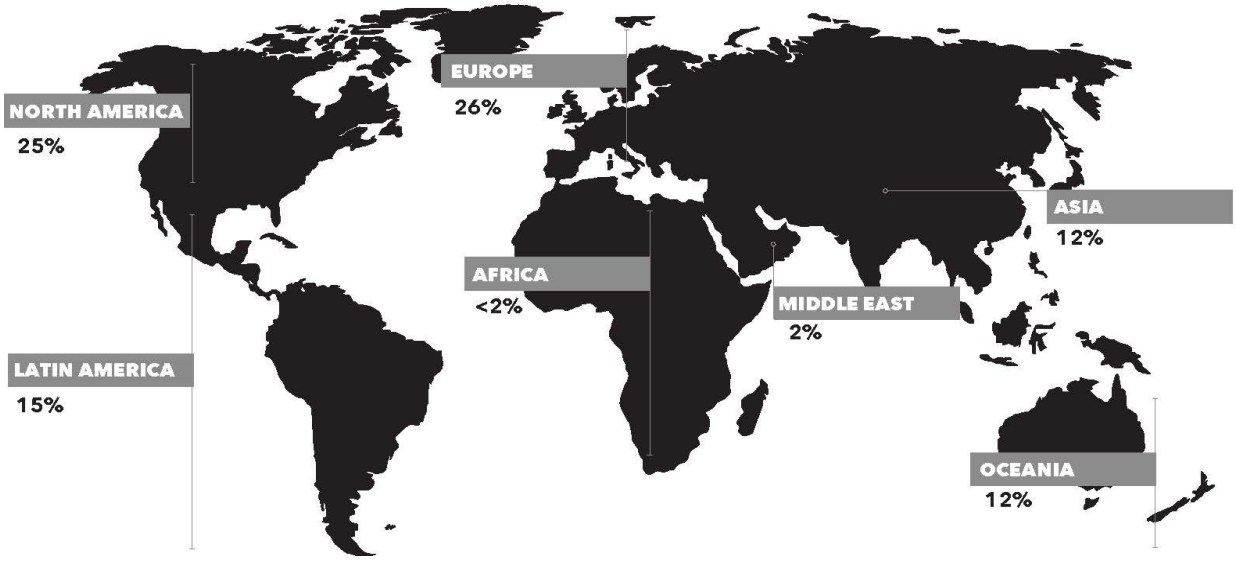

Figure 1: Geographic distribution of survey participants. The number of participants per country/continent: Asia [China (1), Hong Kong (1), India (2), Japan (8), South Korea (3), Taiwan (2), Thailand (1)], Africa [Nigeria (1), South Africa (1)], Europe [Austria (1), Belgium (1), Czech Republic (2), Finland (1), France (13), Germany (1), Italy (2), Poland (1), Portugal (2), Romania (1), Serbia (1), Slovakia (1), Spain (7), Switzerland (1), the Netherlands (1), UK (2)], Latin-America [Argentina (1), Brazil (4), Chile (2), Mexico (12), Peru (2), Venezuela (1)], Middle-East [Iran (1), Kuwait (1), Turkey (1)], North America [Canada (10), USA (27)] and Oceania [Australia (24), New Zealand (2)].

The primary specialties of the participants were neurologists [38%] and pulmonologists [21%]. Psychiatrists and various pediatric specialties represented 10% (respectively). The different medical specialties showed regional differences in that most neurologists were European [43%] followed by participants from North America & Latin America [18% each]. Most pulmonologists were from Oceania [60%]. Participants identifying their specialty solely as sleep medicine represented 15% and were mostly from North America [59%].

Over half of the participants reported spending more than 45 minutes evaluating new patients and 20-45 minutes on follow-up visits. Most reported follow up visits at 6 to 12 month intervals (Table 1). No significant differences in time spent by the different clinical specialties were documented. A trend for shorter evaluation periods was noted among practitioners in Asia where 39% reported

spending less than 30 minutes on an initial evaluation and 78% reported spending less than 20 minutes on follow-up visits. Fifty percent of practitioners indicated having followed narcolepsy patients during a pregnancy.

Table 1: Time spent in the initial assessment, follow-up & follow-up intervals

Clinical Assessment of Sleep Disorders			
Initial Evaluation (mins)	**>45**	**30-45**	**<30**
	53%	37%	10%
Follow-Up (mins)	**>45**	**20-45**	**<20**
	6%	75%	19%
Follow-Up Interval (months)	**6-12**	**3-6**	**<=3**
	47%	34%	19%

Assessment of Sleep Disorders

Practitioners were asked to estimate the percent of their clinical practice devoted to the assessment and treatment of sleep disorders. Most (53%) reported spending >75% of their time devoted to sleep medicine; mainly in Europe and the US where 58 and 84% (respectively), had their practice dedicated to sleep medicine. Among the practitioners' sleep disordered patients, symptoms of EDS were identified as prevalent by 38% who reported >50% of their caseloads with relevant symptoms of EDS. Only 9% of the practitioners identified caseloads with relevant EDS in less than 10% of their patients.

Assessment of Narcolepsy

The primary clinical tool reported in the assessment of EDS was the Epworth Sleepiness Scale (96%); use of sleep logs was reported by 57% and actigraphy by 54%.

Patients with narcolepsy represented up to 10% of the case load for 84% of clinicians. Only 11 [8%] reported having patients with narcolepsy representing >20% of their sleep-disordered patient load [with 8 of them located in Europe]. Diagnosis of narcolepsy at ages <12 y/o was reported by 36% of practitioners (the highest proportion reported by Europeans and Asians where 50% of the participants reported caring for patients <12y/o); 22% reported caring for patients >70 years old.

Nocturnal polysomnography as part of the assessment was reported by 95% and 98% reported using the multiple sleep latency test (MSLT) for diagnostic purposes (only 3 practitioners from Africa, Asia & Latin America reported no use of the MSLT); 39% use the maintenance of wakefulness test (MWT) (mostly in Europe & Oceania where more than 50% of participants reported the use of the test). Even in cases with cataplexy, 84% reported frequent to 100% reliance on the polysomnographic diagnosis for narcolepsy; only 2% [mostly in Latin America] reported making a diagnosis of narcolepsy based on the clinical identification of cataplexy (without the use of polysomnographic testing).

Inclusion of HLA DQB1*0602 typing in the diagnostic assessment was reported as always (or usually) by 38% (79% of Europeans compared to 17 to 30% from the other continents); 27% never included this test in their diagnostic assessment (mostly Latin-American's) and 34% rarely (or sometimes) used the test (mostly North-Americans & from Oceania).

Measurement of CSF hypocretin-1 was reported as "always" by 2 providers (1.4%: 1 in Japan and 1 in Italy) and "usually" by 6% (mostly in Europe); "rarely" or "never" doing the test was reported by 18% and 58% respectively.

Forty-two percent reported narcolepsy type 1 (NT1) in less than 50% of their patients with narcolepsy, 36% reported between 50 and 70%, and 16% reported >70%. Clinicians in Latin America, Europe and Asia reported NT1 to be 50% or more of their patients with narcolepsy; Europe reported the highest ratio of NT1 with over 70% of their diagnosed patients. In contrast, providers in Oceania and North America reported lower ratios of NT1 among their patients with narcolepsy.

At the time of the survey, most participants reported caring for relatively small cohorts of narcoleptic patients as 62% of clinicians care for less than 30 narcolepsy patients in total, and 51% reported making a new diagnosis on less than 5 patients per year (see Table 2). Most practitioners (58%) reported subsequent identification of cataplexy in the follow-up among narcolepsy type 2 (NT2), but in less than 10% of patients. The ratio of NT1 to NT2 was independent of case load. CSF hypocretin is more often "sometimes" or "usually" measured [36% vs $\leq$ 20%; $\chi 2$ <0.05] by

those with >30 narcolepsy patients. They were also more likely to see patients <12 years of age who were more likely to have cataplexy (70%).

Table 2. Narcolepsy caseload & measurement of CSF hypocretin-1

Practitioners' Narcolepsy Caseload				
	<30 patients	**<5 patients**	**>30 patients**	**New Dx <5/year**
	91 (62%)	22 (15%)	55 (38%)	75 (51%)
Measurement of CSF-hypocretin	20%* Sometimes or usually		36% * Sometimes or usually	
Have patients <12 years age			57% (30)	
*p <0.05				

Associated Symptoms and Features:

Most (67%) clinicians reported finding nocturnal sleep disruption in >50% of their caseloads and 32% reported finding this in more than 70% of patients. On the specific question of symptomatic Cataplexy (as a symptom and not as NT1 diagnosis), 43% reported it in >50% and 13% in more than 70% of patients with narcolepsy. Auxiliary symptoms in more than 70% of patients were as follows hypnagogic hallucinations (14%), sleep onset paralysis (2%) and automatic behaviors (5%). (See Table 3)

Table 3. Practitioners' estimates of symptoms and clinical features

	Associated Symptom and Features			
% of patients	*<=20%*	*>20 to 50%*	*>50% to 70%*	*>70%*
Cataplexy	25% (36)	32% (47)	30% (44)	13% (19)
Nocturnal sleep Disruption	5% (7)	28% (41)	35% (51)	32% (47)
Hypnagogic Hallucinations	20% (29)	47% (69)	19% (28)	14% (20)
Sleep Onset Paralysis	52% (76)	38% (55)	8% (11)	2% (3)
Automatic Behaviors	62% (90)	27% (39)	6% (9)	5% (8)
Obesity	26% (38)	47% (68)	20% (30)	7% (10)
Cognitive Problems	34% (49)	30% (43)	16% (29)	17% (25)

Sleep-Related and Psychiatric Comorbidities

The proportion of practitioners who reported the following sleep-related comorbidities in more than 10% of their patients was: obstructive sleep apnea (OSA) 81%, restless leg syndrome and periodic leg movements (RLS/PLMs) 62%, REM sleep behavior disorder (RBD) 45% and enuresis (10%). OSA was the most prevalent sleep comorbidity (see Table 4).

Table 4. Sleep-related comorbidities among narcoleptic patients

	Sleep-related comorbidities*		
	<10%	10%-30%	>30%
OSA	19% (27)	54% (78)	27% (39)
RLS/PLMs	38% (54)	43% (62)	19% (27)
RBD	55% (78)	28% (40)	17% (25)
Enuresis	90% (125)	8% (11)	2% (3)

*Proportion (number) of practitioners reporting on sleep-related comorbidities among their patients

Psychiatric comorbidities were surveyed including depression, attention deficit/hyperactivity disorder (AD/HD), schizophrenia and substance abuse. Depression was the most commonly found psychiatric disorder with 45% of clinicians reporting that more than 30% of their patients were depressed (see Table 5). Among the reported substances being abused, Cannabis was the most frequently reported.

Table 5. Psychiatric comorbidities as reported by the participants

	Psychiatric Comorbidities*		
	<10%	10%-30%	>30%
Depression	17% (24)	38% (55)	45% (66)
AD/HD	40% (56)	40% (57)	20% (28)
Schizophrenia	96% (132)	4% (5)	-
Substance abuse	86% (117)	13% (17)	1% (2)

AD/HD: attention deficit/hyperactivity disorder.

*Proportion (number) of practitioners reporting on psychiatric comorbidities among their patients

Pharmacological Management

Practitioners were asked to report on the availability of therapeutic agents by geographic region (see Table 6) and to identify their preferred agent in the management of the various symptoms associated with Narcolepsy. Table 7 summarizes the reported therapeutic preferences for symptoms of EDS and Cataplexy/other auxiliary symptoms.

Table 6. Reported Availability by Continent (when over 10 practitioners reporting per continent; [N%])

Drug	North America	Europe	Oceania	Latin America	Asia	Overall
Modafinil	37 (100%)	36 (95%)	26 (100%)	22 (100%)	18 (100%)	143 (98%)
Armodafinil	27 (73%)	4 (11%)	24 (92%)	16 (73%)	3 (17%)	75 (51%)
Sodium Oxybate	37 (100%)	33 (87%)	18 (69%))	2 (9%)	1 (6%)	93 (64%)
Pitolisant	4 (11%)	28 (74%)	0 (0%)	1 (5%)	1 (6%)	34 (23%)
Methylphenidate	37 (100%)	35 (9%)	24 (92%)	22 (100%)	16 (89%)	138 (95%)
Amphetamines	37 (100%)	25 (66%)	26 (100%)	15 (58%)	2 (11%)	108 (74%)
Ephedrine	8 (22%)	9 (24%)	6 (23%)	7 (32%)	1 (6%)	35 (24%)
Mazindol	0 (0%)	6 (16%)	1(4%)	7 (32%)	1 (6%)	15 (10%)
Pemoline	3 (8%)	4 (11%)	1 (4%)	4 (18%)	5 (28%)	17 (12%)
SSRIS	35 (95%)	37 (97%)	26 (100%)	21 (95%)	14 (78%)	138 (95%)
SNRI	35 (95%)	36 (95%)	26 100%)	21 (95%)	14 (78%)	136 (93%)
Tricyclics	35 (95%)	38 (100%)	25 (96%)	21 (95%)	16 (89%)	140 (96%)

SSRIs: Selective serotonin reuptake inhibitors. SNRI: Serotonin-norepinephrine reuptake inhibitors

Modafinil, methylphenidate, selective serotonine reuptake inhibitors (SSRIs), serotonine-norepinephrine reuptake inhibitors (SNRIs) and tricyclics were the most widely available pharmacological agents with reported availability by over 90% of the participants. Note that Pitolisant was only available in Europe at the time of this survey. Armodafinil was widely available in Oceania, North America and Latin America but not available in Europe or Asia. Amphetamines were limited or not available in Europe, Latin-America and Asia but were widely available in Oceania. Mazindol and Pemoline are by and large no longer available and thus it was surprising to see it reported albeit by a small number of practitioners.

Table 7. Reported Level of Preference for the Available Pharmacological Agents N (%)

	EDS				Cataplexy/Other Auxiliary Symptoms			
Drug	Preferred Agent	Secondary Agent	Prescribed if Others Fail	Do Not Rx or Rarely Rx	Preferred Agent	Secondary Agent	Prescribed if Others Fail	Do Not Rx or Rarely Rx
Modafinil	105 (72)	34 (23)	2 (1)	5 (3)	16 (11)	16 (11)	2 (2)	111 (76)
Armodafinil	46 (32)	18 (12)	2 (1)	71 (49)	6 (4)	8 (5)	1 (0.7)	131 (90)
Sodium Oxybate	19 (13)	16 (11)	30 (21)	81 (55)	41 (28)	17 (12)	23 (16)	65 (45)
Pitolisant	2 (1)	11 (8)	17 (12)	116 (79)	3 (2)	6 (4)	12 (8)	125 (86)
Methylphenidate	43 (29)	64 (44)	13 (9)	26 (18)	9 (6)	17 (12)	6 (4)	114 (78)
Amphetamines	19 (13)	42 (29)	20 (14)	65 (45)	4 (3)	13 (9)	4 (3)	125 (86)
Ephedrine	0 (0)	3 (2)	3 (2)	140 (96)	0 (0)	1 (1)	2 (1)	143 (98)
Mazindol	0 (0)	1 (1)	2 (1)	143 (98)	0 (0)	0 (0)	2 (1)	144 (99)
Pemoline	0 (0)	6 (4)	2 (1)	138 (95)	1 (1)	3 (2)	2 (1)	140 (96)
SSRIS	11 (8)	19 (13)	9 (6)	107 (73)	52 (36)	55 (38)	13 (9)	26 (18)
SNRI	14 (9)	17 (12)	11 (8)	104 (71)	69 (47)	36 (25)	11 (7)	30 (21)
Tricyclics	4 (3)	11 (7)	16 (11)	115 (79)	29 (20)	36 (25)	28 (19)	53 (36)

SSRIs: Selective serotonin reuptake inhibitors. SNRI: Serotonin-norepinephrine reuptake inhibitors

Management of Excessive Daytime Sleepiness

Modafinil was the most widely preferred agent for the treatment of EDS (72%); it was preferred mainly in North America (89%), Europe (79%), Latin America (73%), Asia (61%) and Oceania (46%). As a secondary agent, Modafinil was favored by 23%. Geographic preferences were Oceania (50%), Asia (28%), Latin America (27%), Europe (13%) and North American (11%).

Armodafinil was the next most preferred agent for the treatment of EDS by 32%; it was preferred in North America (57%), Oceania (46%) and Latin America (45%). It was identified as a secondary agent by 12% (in Oceania by 35% and in North America by 14%).

Methylphenidate as a preferred agent for EDS was reported by 29% of the practitioners. The higher preference was in Europe (39%), Latin America (36%) and North America (27%). As a secondary agent, it was favored by 44%; geographically North America (57%), Latin America (50%), Asia (44%), Europe (37%) and Oceania (31%).

Amphetamines were limited or not available in Europe, Latin-America and Asia, and few clinicians identified them as the preferred agent for EDS (13%). They were

most commonly preferred in Oceania. As a secondary agent they were favored by 29%, mostly in North America (59%) and Oceania (46%).

Sodium oxybate was not available in Asia and Latin America and was only identified as a preferred agent for EDS by 13%; mainly in Europe and North America.

Management of Cataplexy and other Auxiliary Symptoms

The most widely preferred agents for the treatment of cataplexy and other auxiliary symptoms were serotonin-norepinephrine reuptake inhibitors (SNRIs: 47%) and Selective serotonin reuptake inhibitors (SSRIs: 36%). SNRIs were favored in Europe (61%), Oceania (58%), North America (41%), Asia (39%) and Latin America (32%). SSRIs were favored in Latin America (41%), North America (35%), Europe (34%), Oceania (31%) and Asia (28%).
SSRIs were the most favored secondary agents in the treatment of Cataplexy and other auxiliary symptoms (38%); they were most favored in Oceania (46%), Europe (45%), and North America (43%). SNRIs as secondary agents were favored by 25%, mostly in Latin America (32%).
Sodium Oxybate was the preferred agent for 28%, mostly in Europe (50%) and in North America (49%). As a secondary agent was favored by 12%.
Tricyclics as the preferred agents were identified by 20% and as secondary agents by 25%; they were most favored in Asia (44%). As secondary agents, they were identified by 25%, mostly in Europe (34%) and North America (30%).

Discussion

The results of the study reflect the worldwide experience of some health providers caring for patients with narcolepsy. While the number of completed surveys is small and mostly derived from practitioners at academic institutions (limiting the generalizability of these results), participants reported respectable clinical experience as reflected by the number of years in practice. The study shows that the care of narcolepsy involves physicians of different medical specialties with regional differences in the assessment and management of patients. A consistent approach to the diagnosis indicates almost complete reliance on the diagnostic use of nocturnal polysomnography and MSLT. Regional differences in clinical phenotypes were suggested by providers in Europe and Asia reporting the highest proportion of cases with NT1. There was a low rate of progression reported (i.e. less than 10%) from narcolepsy without cataplexy to narcolepsy with cataplexy

(i.e. from NT2 to NT1). In this context, the reliance on the polysomnographic diagnosis of narcolepsy warrants caution [4]. In particular, studies of the test re-test reliability of the polysomnographic diagnosis of narcolepsy have identified variability in the consistency of the MSLT findings [5, 6, 7 and 8]. While adequate stability in MSLT findings has been documented for NT1, frequent diagnostic changes have been encountered for NT2 and Idiopathic Hypersomnia (IH). The identification of CSF hypocretin-1 represents a major advancement in sleep medicine, which has been incorporated into the diagnostic criteria [9] but has been slow to be integrated into clinical practice, as reflected in the present results. The survey results and the available literature on the spectrum of NT1, NT2 and IH highlight the importance of the differential diagnosis, the limitations of the polysomnographic/MSLT criteria and the need for further integration of biologic markers in the diagnosis of these patients. These considerations may need to be integrated in the next revision of the diagnostic criteria [10]. On the other hand, these results may also indicate that a clear clinical history of EDS and cataplexy, in association with typical MSLT, is sufficient in most cases to reach the NT1 diagnosis, with no further requirement to perform an invasive test.

Consistent with previous reports [11], there was a high comorbidity of depression among patients cared by participating health-care providers. The complexity of the relationship between symptoms of EDS, psychiatric and sleep disorders has been well documented [12, 13] but remains poorly understood. The chronicity of the condition and added comorbidities have been shown to have negative effects on the quality of life of these patients [14], which highlights the importance of ongoing care and clinical monitoring. In this context the availability of additional tools to help monitor specific symptoms of narcolepsy patients represents a welcome development. The Narcolepsy Severity Scale (NSS), a 15-item scale to assess the frequency and severity of excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and disrupted nighttime sleep has been shown to be a reliable and valid tool which can assist in the monitoring of the patients' symptomatic status [15].

Another aim of the study was to characterize geographic trends in the treatment of narcolepsy but the small sample size of the cohort limits the generalizability of the results. Nevertheless, regional differences were evident and national controls were often put on clinicians with regard to prescribing as illustrated by the following comment: "In Australia, the Pharmaceutical Benefits Schedule dictates that all patients must be started on Amphetamines and Modafinil and Armodafinil are only funded if patient is shown to be intolerant or have contraindications. Sodium

Oxybate is an unregistered product and needs special access application to the Therapeutics Good Administration making this treatment option difficult to access." Clearly a variety of administrative and fiscal restrictions peculiar to different geographic areas impacts the availability of therapeutic agents.

It was evident that some therapeutic agents are not available in certain countries, particularly pitolisant, amphetamines and sodium oxybate. However, modafinil was clearly the medication most often used (95% of practitioners) around the world for narcolepsy. Armodafinil was less commonly available (44% of practitioners) and amphetamines, although not available in some countries, was still widely used (42% of practitioners). SSRIs and SNRIs were the most prevalent agents used in the treatment of cataplexy [and other auxiliary symptoms] as 74% and 72% of practitioners reported their use as preferred or secondary agents. These preferences are remarkable despite the absence of an approved indication for their use in this clinical context by most regulatory agencies around the world. This preferential use may indicate that these experienced clinicians consider SSRIs and SNRIs as safe and beneficial (and probably cheaper than sodium oxybate). Sodium oxybate was a preferred or secondary agent in the treatment of cataplexy by 40%. Although rarely used in some countries, tricyclics were reported as the preferred or secondary agent by 45% of the practitioners in the management of cataplexy [or other auxiliary symptoms].

The introduction of a dual-acting dopamine and norepinephrine reuptake inhibitor (DNRI: Solriamfetol) agent [16] and the wider availability of Pitolisant (a potent and highly selective histamine 3 receptor antagonist/inverse agonist [17]) will likely impact the practitioners' preferences. This will be driven by clinical expertise with a particular therapeutic drug, geographic availability of specific agents and the expense associated with their use.

Beyond the clinician's control is the designation of preferred therapeutic agents by insurance companies and/or governmental agencies that frequently determine what is available in the clinician's armamentarium. Nevertheless, more concerted efforts by Sleep Medicine Organizations are required in order to engage insurance and/or government decision makers and facilitate timely and adequate availability of newer therapeutic agents for patients with narcolepsy and narcolepsy spectrum conditions, as these agents have not only been proven to provide clear clinical benefit but have the potential to decrease the high utilization and expense of medical services that are typically rendered to these patients [18].

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