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Diagnosis of central disorders of hypersomnolence: A reappraisal by European experts

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2 European experts.
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55 **Conflict of Interest**
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57 For all authors: there are no conflicts of interest related to this review
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104 **Keywords**
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106 Sleep, Classification, Diagnosis, Hypersomnolence, Hypersomnia, Excessive daytime

107 sleepiness, Narcolepsy, Cataplexy, Fatigue, MSLT

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158 **Abbreviations**
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161	AASM	American Academy of Sleep Medicine
162	ADHD	Attention deficit hyperactivity disorder
163	AHI	Apnea–Hypopnea Index
164	CPAP	Continuous positive airway pressure
165	CSF	Cerebrospinal fluid
166	EAN	European Academy of Neurology
167	EDS	Excessive Daytime Sleepiness
168	ELISA	Enzyme-Linked Immuno Sorbent Assay
169	ENS	Excessive need for sleep
170	ESRS	European Sleep Research Society
171	ESS	Epworth sleepiness scale
172	EU-NN	European Narcolepsy Network
173	HH	Hypnagogic hallucinations
174	HLA	Human leucocyte antigens
175	ICSD/ICSD3	International classification of sleep disorders / 3rd edition
176	IH	Idiopathic hypersomnia
177	MSLT	Multiple sleep latency test
178	NT1	Narcolepsy type 1
179	NT2	Narcolepsy type 2
180	OSA	Obstructive sleep apnea
181	PLMS/PLMD	Periodic limb movement syndrome / Periodic limb movement disorder
182	PSG	Polysomnography
183	PVT	Psychomotor vigilance test
184	RBD	REM sleep behaviour disorder
185	RIA	Radioimmunoassay
186	RLS	Restless legs syndrome
187	SART	Sustained attention to response task
188	SOREM	Sleep onset REM episode
189	SP	Sleep paralysis

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200 **Summary**
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203 The aim of this European initiative is to facilitate a structured discussion to improve the next

204 edition of the International Classification of Sleep Disorders (ICSD), particularly the chapter

205 on central disorders of hypersomnolence.

206 The ultimate goal for a sleep disorders classification is to be based on the underlying

207 neurobiological causes of the disorders with clear implication for treatment or, ideally,

208 prevention and or healing. The current ICSD classification, published in 2014, inevitably has

209 important shortcomings, largely reflecting the lack of knowledge about the precise

210 neurobiological mechanisms underlying the majority of sleep disorders we currently delineate.

211 Despite a clear rationale for the present structure, there remain important limitations that

212 make it difficult to apply in routine clinical practice. Moreover, there are indications that the

213 current structure may even prevent us from gaining relevant new knowledge to better

214 understand certain sleep disorders and their neurobiological causes.

215 We suggest the creation of a new consistent, complaint driven, hierarchical classification for

216 central disorders of hypersomnolence; containing levels of certainty, and giving diagnostic

217 tests, particularly the MSLT, a weighting based on its specificity and sensitivity in the

218 diagnostic context.

219 We propose and define three diagnostic categories (with levels of certainty):

220 1/ "Narcolepsy" 2/ "Idiopathic hypersomnia", 3/ "Idiopathic excessive sleepiness" (with

221 subtypes)

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231 **Introduction**

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233 <u>The goal of a classification</u>

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235 The ultimate goal for a sleep disorders classification is to be based on the underlying

236 neurobiological causes of the disorders with clear implication for treatment or, ideally,

237 prevention and healing.

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239 Currently, most sleep specialists refer to the International Classification of Sleep Disorders 3rd

240 edition (ICSD3), published in 2014 to diagnose and classify sleep disorders [1]. This

241 classification inevitably has important shortcomings, largely reflecting the lack of knowledge

242 about the precise neurological mechanisms underlying the majority of sleep disorders we

243 currently delineate. Despite a clear rationale for the present structure, there remain important

244 limitations that make it difficult to apply in routine clinical practice. Moreover, the current

245 structure may prevent us from gaining relevant new knowledge to better understand certain

246 sleep disorders and their neurobiological causes.

247

248 This "position paper" addresses sleep disorders in adults and discusses shortcomings in the

249 approach and structure of the ICSD3 in general with subsequent focus on the chapter:

250 "Central disorders of hypersomnolence". By dissecting the inconsistencies and shortcomings

251 of the current classification, and taking into account recently obtained knowledge, we produce

252 suggestions for an adjusted and updated section on hypersomnolence.

253 The aim of our "position paper" is primarily to facilitate discussions in order to:

254 1.   improve a new version of the classification for practical use

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255   2.   define a research agenda in this area, aiming to explore further neurobiological causes

256   and substrates for sleep-wake complaints and their underlying disorders

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259   General comments on the current ICSD3 classification

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261   *Some of our comments on the chapter "Central disorders of hypersomnolence" deal with the*

262   *general structure:*

263   -   For the classification of some disorders, such as insomnia and restless limb syndrome

264   (RLS), the diagnosis is based solely on subjective complaints whereas for others, such as

265   narcolepsy type 1, it presumes a precise pathophysiology. In others such as obstructive sleep

266   apnea (OSA), diagnosis can be solely defined by findings on ancillary investigations (i.e.

267   AHI).

268   -   There are no levels or grades of certainty defined for the various diagnoses.

269   -   There are hardly measures of severity for sleep-related symptoms included.

270   -   Several potentially important assessments that can be clinically useful and easy to

271   apply are not listed as mandatory in confirming or refuting diagnoses, largely due to problems

272   of reimbursement in many countries including the US. Examples include actigraphy,

273   hypocretin measurements, and HLA typing.

274

275   *Comments on the chapter "Central disorders of hypersomnolence"*

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277   *Terminology and consistency*

278   -   The chapter is titled "Central disorders of hypersomnolence" but contains a variety of

279   disorders such as "Insufficient Sleep syndrome" that generally have no "central" cause, but

280 are primarily related to behaviour or lifestyle. In contrast, OSA as one the most prevalent

281 causes of hypersomnolence is not listed although it may be argued that there is usually no

282 central origin for OSA.

283 - It is presumed that introducing the word "Hypersomnolence" in ICSD3, after its

284 introduction in DSM-5 in 2013 [2], was intended to solve previous inconsistencies around

285 other similar terms such as "excessive daytime sleepiness", "hypersomnia", and "excessive

286 sleepiness". However, it has led to potential further confusion as "hypersomnolence" is used

287 to describe both the symptom of "excessive sleepiness" and to define a group of disorders:

288 "Central disorders of hypersomnolence". This chapter then documents disorders such as

289 "idiopathic hypersomnia" but not, for example, "idiopathic hypersomnolence" or "Idiopathic

290 excessive sleepiness". "Hypersomnolence" as defined in the DSM-5 is very similar to what

291 used to be the definition of "hypersomnia". Compared to ICSD3, it covers a larger variety of

292 possible expressions of daytime sleepiness including an increased need for sleep, but it is

293 confusing that it is used only to describe expressions of "Hypersomnolence disorders" and is

294 not meant to be applied to narcolepsy although narcolepsy may have largely overlapping

295 expressions.

296 - From their original meanings, excessive daytime sleepiness (EDS) and hypersomnia

297 are qualitatively different complaints [3-5]. This is not taken into account in ICSD3 and the

298 distinction is blurred by use of the term "Hypersomnolence". In this manuscript, we use

299 "hypersomnolence" as an overarching description for the presence of EDS and/or excessive

300 need of sleep (ENS) or an increased quantity of sleep (see also the definition section).

301 - Hypersomnolence is not just characterized by "daily episodes of an irrepressible need

302 to sleep or daytime lapses into sleep" as in the definition described by ICSD3. The term

303 usually harbours much more in the way of disabling symptoms. Accordingly, it often includes

304 impaired vigilance or sustained attention; automatic behaviours; cognitive complaints,

305 especially linked to poor memory; and it can be accompanied by increased need for sleep and

306 severe sleep inertia [6-8].

307 -   An increased need for sleep as a separable symptom is not defined. There is also no

308 clarification in distinguishing it from clinophilia: the tendency to remain in bed in a reclined

309 position without increased actual sleep time when objectively assessed.

310 -   There is no explicit statement about the difference between fatigue and

311 hypersomnolence. Fatigue may accompany EDS and hypersomnia, but it is a qualitatively

312 different complaint and never a (core) symptom of a disorder of hypersomnolence, although it

313 may accentuate the impairment caused by it [9].

314 -   As mentioned, attentional problems may be an expression of hypersomnolence.

315 However, there is no guidance as how to separate conditions considered to be "pure" attention

316 deficit disorders such as attention deficit hyperactivity disorder (ADHD) from complaints of

317 attention deficit as an expression of a disorder of hypersomnolence [10].

318

319 *Diagnostic criteria and tests*

320 - There are no clear criteria to assess or measure sleep deprivation and circadian rhythm

321 disturbances as potential causes for hypersomnolence although it is stated that they should be

322 excluded before making the diagnosis of idiopathic hypersomnia, for example.

323 - The current classification relies heavily on the MSLT result despite the test having low

324 sensitivity and specificity for diagnostic purposes [11-13]. Moreover, more recently, the

325 consistency of the MSLT result over time is suggested to be unreliable for several diagnoses

326 (see also below) [14-16].

327 - The ability of the MSLT to quantify sleepiness has only been validated in healthy volunteers

328 with different degrees of sleep deprivation [17-20]. It is, therefore, questionable whether it is

9

329   justified to base diagnostic categories heavily depending on MSLT results [17] and not taking

330   age effects into account [21].

331   - In clinical practice, it is not uncommon for a single patient to have multiple potential causes

332   or contributors of hypersomnolence, including sleep deprivation, OSA, and depressed mood

333   as common examples. It would be helpful to include a paragraph in the classification

334   regarding this issue. This highlights our lack of knowledge on the difficult question of

335   whether depression is a primary cause of hypersomnolence in individual patients, especially

336   given how in many, it fuels symptoms of insomnia [22-24].

337   - It is inconsistent that depression may be comorbid in narcolepsy type 1 but must be excluded

338   in type 2 and idiopathic hypersomnia.

339   - It is not clear why narcolepsy type 1 should be diagnosed only when the symptoms are

340   present for at least 3 months when within this period there is clear-cut cataplexy or

341   established hypocretin deficiency.

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343

344   Relevant new knowledge and remaining unsolved issues

345

346   *New knowledge*

347   - It is known for many years that the sensitivity and specificity of MSLT criteria as used in

348   ICSD3 are acceptable in narcolepsy type 1 and, importantly, appear relatively consistent over

349   time [14-16, 25]. In contrast, and assessed in more recent studies, the test's sensitivity,

350   specificity and particularly consistency over time are much less secure for the currently

351   defined disorders: narcolepsy type 2, IH and chronic sleep deprivation[14, 25, 26].

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352　- Recent studies indicate that the sequence of sleep stages as assessed during MSLT testing

353　may have diagnostic significance [26-28]. REM sleep occurring before stage 2 sleep is

354　indicative of narcolepsy type 1, for example.

355　-　It may be diagnostically very helpful to observe video footage of provoked cataplexy

356　although this approach is clearly labour intensive and only suitable for patients with frequent

357　cataplexy attacks [29, 30].

358　- There are indications that prolonged sleep recordings and observations may offer additional

359　diagnostic information and improve classification. However, the expense and labour intense

360　nature of prolonged recording is likely to limit overall acceptance and standardization of

361　results may be difficult [31].

362

363　*Issues to be solved in a new classification of Sleep-Wake disorders*

364　- It remains unclear how chronic sleep deprivation can reliably be assessed or excluded as a

365　relevant factor. Actigraphy may be helpful but criteria and protocols for assessing the effects

366　of sleep extension, for example, are lacking.

367　- It is also unclear how circadian disorders should be reliably assessed or ruled out as causes

368　for EDS in the absence of precise criteria and diagnostic protocols.

369　-　As currently defined, it is very likely that the currently defined disorder IH is a

370　heterogenous entity. It appears sensible to separate a phenotype with an increased need for

371　sleep from a phenotype without [3-5].

372　- It is unclear whether the currently defined disorders IH and narcolepsy type 2 are always

373　separable entities [32]. Moreover, it is not known if EDS in narcolepsy type 2 can be

374　distinguished reliably from expressions of chronic sleep deprivation and narcolepsy type 1 [14,

375　26, 33].

376   - We know that narcolepsy with cataplexy can start as narcolepsy without cataplexy but we

377   have poorly identified reliable predictors which might include HLA typing (DQB1*06:02).

378   Currently, only hypocretin deficiency is known to be associated with a risk of subsequent

379   cataplexy [34].

380   - Narcolepsy type 1 & 2, and IH are currently largely defined and separated by MSLT criteria.

381   We know that the result of the MSLT may change over time particularly in narcolepsy type 2

382   and IH. However, the contributory effects of different levels of sleep deprivation, including

383   night shifts, in the days and weeks before the individual test is performed are unknown. To

384   clarify if the MSLT is, indeed, a relatively inadequate test for accurately diagnosing central

385   disorders of hypersomnolence, we must first establish guidelines how to exclude sleep

386   deprivation in the week(s) before performing a MSLT.

387   - Given the current importance of the MSLT in defining whether a subject suffers from IH or

388   narcolepsy type 2, changes in MSLT results over time will effectively change a diagnosis,

389   even if the clinical picture is stable.

390   - Mindful that the sensitivity and specificity of the MSLT is low for IH and narcolepsy type 2,

391   we should allow a different approach in future classifications for patients who have genuine

392   complaints of hypersomnolence but fail to have diagnostic MSLT results.

393   - There is a need for an international standardization for measuring hypocretin levels.

394

395   In order to solve most of the issues raised, a new consistent, complaint driven, hierarchical

396   classification, containing levels of certainty, and giving diagnostic tests, particularly the

397   MSLT, a weighting based on its specificity and sensitivity in the diagnostic context is

398   proposed.

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Methods

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404 A European Task Force to develop an updated guideline for the treatment of narcolepsy,

405 endorsed by the European Neurological Association (EAN), the European Sleep Research

406 Society (ESRS) and the European Narcolepsy Network (EU-NN), was established in 2017.

407 Besides primary discussions concerning treatment and management of narcolepsy, issues

408 were raised concerning diagnostic uncertainties when applying the ICSD3 during initial

409 meetings in Lugano (2017), Montpellier (2018), Boston (2018), and Bern (2019). The current

410 paper summarizes these discussions and conclusions. Regarding the provided definitions and

411 recommendations: they are all ultimately based on consensus and expert opinion, but for all

412 PubMed searches (period 1979 – April 2019) have been performed first (by GJL, CB and YD),

413 using the respective appropriate searching terms. "Excessive sleepiness", "Daytime

414 sleepiness", "Hypersomnolence", "Hypersomnia", "Cataplexy", "Narcolepsy AND diagnostic

415 criteria", Idiopathic hypersomnia AND diagnostic criteria", "Multiple Sleep Latency Test",

416 "Sustained attention AND sleep ", "Fatigue", "Automatic behaviour", "Clinophilia", "Sleep

417 inertia", Sleep drunkenness", "Sleep attack", "Long sleeper", "Hypocretin", "Orexin", "HLA

418 narcolepsy", "Narcolepsy biomarkers", If recommendations are solely based on expert

419 opinion it is explicitly stated in the text. The three main authors (GJL, CB, YD) prepared a

420 first, second and third draft which were then sent for review and revised by the task force.

421 Consensus on all statements could be reached.

422

423 *The approach*

424 There is a focus on:

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425   - Expressions of hypersomnolence as a specific symptom, and on cataplexy as specific marker

426   for the only central disorder of hypersomnolence with an established cause, namely,

427   hypocretin deficient narcolepsy.

428   - Other symptoms such as hypnagogic hallucinations and sleep paralysis are not considered in

429   depth given their low diagnostic specificity for any particular cause of hypersomnolence.

430   - Adults.

431

432   <u>Principles:</u>

433   - *First:* we provide full definitions for the various concepts discussed.

434   - *Second:* the primary complaint of the patient is the starting point of any diagnostic

435   process.

436   - *Third:* the potential multiple dimensions of the complaint of hypersomnolence are

437   taken into account.

438   - *Fourth:* severity of complaints and degrees of certainty of a particular diagnosis are

439   taken into account.

440   - *Fifth*: relevant new knowledge obtained after the publication of the ICSD3 in 2014 is

441   taken into account, particularly regarding MSLT data

442   - *Sixth:* with the exception of narcolepsy type 1, we advocate a hierarchical approach to

443   the diagnostic process by first excluding sleep deprivation, then sleep apnea and

444   subsequently circadian rhythm disorders before considering a diagnosis of

445   hypersomnolence

446   - *Seventh:* a diagnosis may shift to different levels of certainty or categories over time,

447   depending on changes in symptoms or the results of additional diagnostic tests.

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14

450 **Definitions (alphabetical)**

451

452 **Problems of attention :** difficulties with sustaining a purposeful focus on stimuli.

453

454 **Automatic behaviours:** behaviours that are performed without conscious knowledge or full

455 voluntary control.

456

457 **Clinophilia / high levels of bed rest:** the tendency to spend prolonged amounts of time

458 reclined in bed without objective evidence for increased sleep time.

459

460 **Excessive daytime sleepiness (EDS)*:** the complaint of an inability to stay awake during the

461 normal wake period of the day.

462

463 **Excessive need for sleep (ENS)**:** the complaint of a need for an excessive quantity of sleep

464 over the full 24 hours period. At least 10 hours of sleep are needed over 24 hours of the day

465 with the nocturnal component providing at least 9 hours. The complaint for increased need for

466 sleep must be, associated with impairment and distress related primarily to deteriorated

467 quality of daytime wakefulness, and cannot be (fully) resolved by increasing the amount of

468 sleep.

469

470 **Fatigue:** the complaint of physical and/or mental exhaustion with difficulties in initiating or

471 sustaining voluntary activities that are not significantly improved by increased rest or sleep.

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473   **Hypersomnia**: the objectified complaint of ENS. An objective assessment of an excessive

474   quantity of sleep: at least 10 hours of sleep duration over 24 hours of the day with the

475   nocturnal component providing at least 9 hours of sleep duration.

476

477   **Hypersomnolence**: the presence of a complaint of EDS and/or ENS.

478

479   **Long sleeper***:** a person with a constitutional need for more sleep than average, reflected

480   in a habitual long nocturnal sleep period of up to 12 hours in the absence of daytime

481   complaints when this amount of sleep is fully achieved.

482

483   **Nap:** a short period of sleep during the wake period of the day

484

485   **Sleep attack:** a relatively sudden occurring unintended nap, not preceded by a feeling of

486   sleepiness.

487

488   **Sleep deprivation:** a situation in which a person is not achieving a sufficient amount of

489   nocturnal sleep as determined by their individual constitutional requirements.

490

491   **Sleep inertia and drunkenness:** the complaint of difficulty in achieving complete

492   wakefulness at the end of a sleep period, potentially accompanied by confusion, disorientation,

493   and poor motor coordination or even ataxia. Sleep drunkenness is considered as a severe

494   manifestation of this phenomenon [8].

495

496   **Unintended nap:** an episode of irresistible sleep, which may occur at any time during the

497   wake period of the day, but most commonly associated with tedious or monotonous activities.

498

499

500 * This is the definition of the core problem. It must be acknowledged that EDS has multiple

501 dimensions as explained in chapter 1.1.1.

502

503 **The cut-offs of 9 respectively 10 hrs are based on expert opinion. They are supported by

504 several publications and the DSM-5 and the previous edition of the ICSD [2, 35, 36].

505 However, additional knowledge is needed. Large data sets such as the Database of the

506 European Narcolepsy Network that also includes information on other hypersomnolence

507 disorders may provide these data in the near future. Machine learning could support

508 delineation of cut-off scores [37].

509

510 *** The cut-off score is expert opinion. It is highly unlikely that a completely healthy person

511 will need more than 12 hrs of nocturnal sleep.

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Results

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526   The result of applying the first four principles is described below. The clinical phenotyping

527   results from history taking rather than from the use of questionnaires.

528

529   **1)   Hypersomnolence**

530

531   Hypersomnolence may present in two forms, EDS and ENS.

532

533   **1.1.1 Manifestations of excessive daytime sleepiness (EDS)**

534

535   Clinical symptoms/complaints:

536   1)   The presence of a feeling of daytime sleepiness throughout most of the day as

537   opposed to symptoms of fatigue

538   2)   Inability to stay awake in monotonous situations with unintended napping and

539   possibly sleep attacks

540   3)   Acquired need for scheduled napping during the day

541   4)   Difficulty with sustained attention and vigilance

542   5)   Automatic behaviours that can be attributed to EDS

543

544   EDS often is accompanied by cognitive difficulties, particularly memory complaints, and

545   emotional difficulties, including irritability and distractibility. Headache complaints are also

546   likely to be commoner.

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547

548 **Criteria for presence of EDS:**

549 There is a daily or near daily presence of symptom 2 OR there is the daily presence of

550 symptom 1 and at least one of the other symptoms listed.

551

552

553 **1.1.2 Manifestations of excessive need for sleep (ENS) in adults**

554

555 Clinical symptoms/complaints:

556   1)   An increased need for sleep in normal daily life. The need must comprise at least

557   10 hours of sleep per 24 hours and/or at least 9 hours of nocturnal sleep* AND

558   2)   The presence of at least one of the listed symptoms of EDS and/or the presence of

559   sleep inertia/sleep drunkenness, AND

560   3)   Sleep extension will not (fully) eliminate the symptoms/complaints of 2.

561

562 **Criteria for presence of ENS:**

563 There is a daily or near daily presence of all three listed symptoms/complaints.

564

565 * The defined cut-offs are based on expert opinion and in line with definition used in DSM-V.

566

567 **1.2.1 Severity of EDS**

568

569 Subjective assessment

570   1) For example the score on the Epworth Sleepiness Scale

571   2) Frequency of voluntary and involuntary naps (per day/per week)

572   3) Presence of complications that can be attributed to EDS (cognitive symptoms, lapses,

573   accidents)

574

575   Of note: the presence of co-morbid fatigue may increase the burden of EDS.

576

577   <u>Objective assessment</u>

578   1) Mean sleep latency by MSLT <2-5 min; 5-8 min; > 8 min)

579   2) Results of vigilance test (SART)

580

581

582   **1.2.2 Severity of ENS**

583

584   <u>Subjective assessment</u>

585   1) Total number of hours sleep needed over 24 hours when given the full opportunity to

586   sleep as compared to the amount of sleep normally obtained in the pre-symptomatic

587   period

588   2) frequency/duration of inertia/sleep drunkenness following a nocturnal sleep period and

589   a nap

590

591   <u>Objective assessment</u>

592   1) the amount of sleep per 24 hours as estimated with two weeks of actigraphy/sleep log

593   and confirmed by a ambulant PSG recording of at least 24 hours allowing ad libitum

594   sleep, or at least 24 hours clinical PSG recording in standardized conditions also

595   allowing ad libitum sleep [31].*

596

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597   * This recommendation is expert opinion supported by the referred study.

598

599   **2) Cataplexy**

600

601   **2.1.1 Presence of typical or unambiguous partial cataplexy (history taking*) [38-42]**

602   1. Bilateral loss of muscle tone in face, neck or legs (buckling knees), with or without

603   involvement of the arms, in the absence of falls or collapse

604   2. Events triggered by sudden emotions, particularly of a positive nature related to mirth.

605   Typical situations include laughing out loud or telling an amusing story/joke; making

606   a witty remark; or pleasant surprise when unexpectedly meeting a familiar

607   acquaintance. Other situations include weakness induced by orgasm or occasionally

608   anger. It is most reliably diagnosed if triggers other than laughter can be identified

609   given the significant number of healthy people who report a degree of generalised

610   weakness induced by laughter, particularly in the legs [40, 42].

611   3. Duration of episodes from about a second up to 1 minute for a single attack, typically

612   less than 30 seconds. Sequential attacks caused by a persisting precipitant trigger may

613   have a much longer duration.

614   4. Preserved level of consciousness

615   5. Abrupt return of muscle activity after the attack

616   6. It is very common to have a second attack in the months after an initial episode unless

617   treatment immediately started

618

619   **2.1.2 Presence of typical or unambiguous generalized cataplexy (history taking*)** [38-42]

620   1. Bilateral progressive loss of muscle tone generally starting in the face or neck and

621   building up over seconds, leading to a fall to the ground with buckling of the legs

21

622   2. Events triggered by sudden emotions, particularly of a positive nature related to mirth.

623   Typical situations include laughing out loud or telling an amusing story/joke; making

624   a witty remark; or pleasant surprise when unexpectedly meeting a familiar

625   acquaintance. Other situations include weakness induced by orgasm or occasionally

626   anger. It is most reliably diagnosed if triggers other than laughter can be identified

627   given the significant number of healthy people who report a degree of generalised

628   weakness induced by laughter, particularly in the legs [40, 42].

629   3. Duration of an episode typically lasts several seconds and up to 2 minutes. In

630   exceptional cases, sequential attacks may have a much longer duration.

631   4. Preserved level of consciousness

632   5. Abrupt return of muscle activity after the attack

633

634

635   Supportive criteria [40]:

636   - Quick clinical response to anti-cataplectic drugs, particularly antidepressants such as

637   clomipramine or venlafaxine

638   - Muscle tendon areflexia/H-reflex suppression, particularly during generalized

639   episodes [41-43].

640

641   Compatible with typical cataplexy (if criteria above are also met) [39, 40]:

642   - Occasionally spontaneous episodes

643   - Facial twitching

644   - Prolonged episodes after discontinuation of anti-cataplectic drugs (except sodium

645   oxybate)

646   - Attacks experienced as asymmetrical but not strictly unilateral

22

647   -   A generalized attack may occasionally result in a full-blown sleep episode

648

649   * There is debate whether cataplectic attacks always start in the neck and face, and also if

650   muscle jerking or twitches are part of the typical clinical picture of cataplexy although

651   observations made by experts lend support to this view. However, since we rely on history

652   taking and not all patients experience these observations, these elements are not part of the

653   mandatory criteria.

654

655   **2.2 Severity of cataplexy**

656   By history

657   1) Frequency of cataplexy episodes with ranges typically quantified as less than 1 per

658   month to more than 5 per day [44]

659   2) Typical duration of episodes

660   3) Presence or absence of generalized attacks (e.g. associated with falls)

661   4) Subjective levels of disability caused by episodes of cataplexy, taking into account the

662   typical situations in which they occur (e.g. at workplace)

663

664   **2.3 Certainty of typical cataplexy**

665   - The optimal method for confirming the presence of cataplexy relies on direct observation by

666   an experienced clinician in real life or, more typically, from recorded video material [29, 30].

667

668   - Unfortunately, direct or recorded observations are rare to witness in adult patients and

669   reliance is placed on accurate history taking. Only descriptions fulfilling all characteristics

670   above can be considered as **typical cataplexy**.

671

672 Cataplexy should still be considered, but as **atypical**, if the patient reports one of the

673 following features during history taking:

674 - attacks are purely unilateral or unusually prolonged in the absence of the precipitant (> 3

675 min)

676 - no clear precipitants for episodes or if only negative emotions act as triggers

677 - it is uncertain whether consciousness is fully preserved

678 - hyperacute generalised muscle weakness without build-up over seconds, leading to falls and

679 injuries.

680 - only generalized attacks

681 - it takes minutes or longer to recover after a single attack

682

683 -If more than one of the above listed characteristics is present the attacks must be considered

684 to be "**cataplexy-like**" attacks. In all such cases, the measurement of hypocretin-1 in CSF

685 may be helpful, as presence of low hypocretin favours presence of cataplexy and high levels

686 of hypocretin decreases probability of cataplexy.

687

688 - Cataplexy is generally excluded if there is no doubt that loss of consciousness or awareness

689 occurs at the onset of episodes.

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700 **3) Proposal for a new classification of central disorders of hypersomnolence in adults**

701

702 We believe the current ISCD3 guidelines on central causes of hypersomnolence have created

703 a degree of diagnostic confusion by:

704 - not consistently taking the symptomatic complaint of the patient as a starting point

705 - not emphasising the importance or impact of chronic sleep deprivation in the clinical

706 assessment of hypersomnolence and its influence on the results of ancillary investigations

707 - incorporating the detailed results of the MSLT as primary diagnostic criteria for certain

708 categories of hypersomnolence

709

710 The exaggerated and arguably unjustified central role for MSLT results to influence diagnosis

711 has over-shadowed the importance and relevance of detailed clinical characteristics in

712 disorders causing hypersomnolence. Moreover, it has stifled the search for updated and more

713 accurate diagnostic strategies.

714 We argue that progress will depend on more descriptive diagnostic categories that permit

715 changes in MSLT results over time without necessarily producing differing diagnostic labels.

716 We would also advocate the introduction of "probable" diagnoses when the MSLT result is

717 intermediate and potentially alternative explanations or diagnoses such as chronic sleep

718 deprivation, OSA and circadian disorders after these have been adequately addressed.

719 However, we advocate to avoid the use of "possible" diagnosis to prevent confusion for

720 patients and health insurance companies (a diagnosis labelled as "possible" might be interpret

721 to be uncertain or unclear). Finally, it should be acknowledged that problems of sustained

722 attention or vigilance may be the most disabling aspects of patients with hypersomnolence, as

723 opposed to sleepiness per se.

724 With the previous discussions in mind, we now propose a new classification for disorders of

725 hypersomnolence that is aimed to improve diagnostic clarity and our understanding of

726 disorders causing hypersomnolence. Moreover, it will facilitate treatment pathways for those

727 who suffer from complaints of hypersomnolence in whom MSLT results have not necessarily

728 fulfilled strict diagnostic criteria and in whom sleep deprivation has been satisfactorily

729 excluded.

730

731 When OSA, chronic sleep deprivation and circadian rhythm disorders have been effectively

732 excluded, we suggest the creation of three diagnostic categories, with levels of certainty, for

733 central disorders of hypersomnolence :

734

735   1   "Narcolepsy" replacing NT1 and NT2

736   2   "Idiopathic hypersomnia"

737   3   "Idiopathic excessive sleepiness"

738

739 Only for narcolepsy are there criteria proposed for primary (idiopathic), familial, secondary

740 (symptomatic), and narcolepsy plus (hereditary forms with additional neurological symptoms)

741 forms [45]. We suggest discontinuing entities such as "hypersomnia due to medical disorder",

742 "hypersomnia due to substance abuse", or "hypersomnia associated with a psychiatric

743 disorder", because in most cases it is generally unknown if the relationship is truly causal or

744 simply co-morbid [22, 24]. Instead, medical disorders and psychiatric disorders including

745 substance abuse are considered and listed as possible co-morbidities. This is in line with the

26

746 decision made in ICSD3 to allow to diagnose insomnia independently from the presence of a

747 mental disorder, a medical condition, or drug or substance intake.

748 We suggest no changes to the diagnostic criteria for Kleine-Levin syndrome because we focus

749 on chronic disorders characterized by persistent and not remittent hypersomnolence.

750 **3.1 Diagnostic criteria for narcolepsy**

751

752 Level 1   A.
753 Definite   EDS and or typical cataplexy and CSF hypocretin deficiency*

754

755   B.
756   EDS <u>with</u> typical cataplexy and MSLT**: SL < 8 min and > 1 SOREM
757   (including nocturnal sleep)

758

759 Level 2   A.
760 Probable   EDS <u>with</u> typical cataplexy and MSLT**: either SL < 8 min or > 1
761   SOREM (including nocturnal sleep)

762

763   B.
764   EDS without typical cataplexy, but with HH and or SP and or disturbed
765   nocturnal sleep; MSLT**: SL < 5 min and > 1 SOREM or SL < 8 min
766   and > 2 SOREMs (including nocturnal sleep) & HLA DQB1*0602
767   positive*; other causes of EDS need to be excluded¶.

768

769

770 Familial***   - EDS with cataplexy or cataplexy-like episodes****; MSLT*: SL < 8
771   min and > 1 SOREMP, and or hypocretin deficiency; At least one first
772   degree family member with similar complaints including cataplexy.

773

774 Symptomatic or
775 secondary***   - EDS with cataplexy or cataplexy-like episodes****; the subject is
776   known to suffer from Niemann Pick type C, Prader-Willi syndrome, or

777   has a demonstrated lesion in the hypothalamus [45, 46]. MSLT*: SL <

778   8 min and > 1 SOREMP, or hypocretin deficiency

779

780

781   * Hypocretin deficiency is considered both the primary cause and most specific biological

782   marker for narcolepsy with cataplexy. The presence of hypocretin deficiency in an individual

783   is key to determining the level of certainty in this diagnostic classification. Category 1A is

784   therefore the most certain category. When applying the strict interpretation of typical

785   cataplexy which is mandatory, 98% of the category 1B patients will be hypocretin deficient

786   (familial en secondary cases excluded, see below).

787

788   Hypocretin-1 measurement in the CSF, by adjusted radio immune assay (RIA), is by far the

789   most specific and sensitive test to diagnose narcolepsy with (typical) cataplexy [47]. By

790   definition it is diagnostic for narcolepsy type 1 [1]. For the Stanford group, and those who

791   adjust to Stanford values by using Stanford reference samples, the cut off is 110 pg/ml. In a

792   clinical context, a value below this concentration is considered diagnostic. Intermediate

793   hypocretin-1 levels between 110-200 pg/ml cannot exclude the diagnosis but there are

794   currently not enough data to alter cut off levels to higher than 110 pg/ml. New methods of

795   measuring CSF-hypocretin for example by mass spectrometry are under development.

796   Currently, the mentioned cut-off points cannot be used in ELISA-based methods, which may

797   show abnormally low values, and hence falsely positive results.

798

799   In non-familial and non-secondary cases of narcolepsy type 1, 98% are HLA DQB1*0602

800   positive [48]. In narcolepsy type 2, this percentage is much lower, averaging 40 to 50%.

801   However, in the group of narcolepsy type 2, HLA DQB1*0602 positivity is nearly always

802   seen if there is subsequent hypocretin deficiency or symptoms of cataplexy [34]. In the

803   general population, the presence of HLA DQB1*0602 is 15 – 38% [48, 49]. Therefore, the

804   presence of HLA is not helpful as a primary diagnostic tool but can provide evidence to

805   exclude it and for predicting eventual hypocretin status.

806

807   Typical cataplexy is the clinical hallmark of narcolepsy type 1. It is therefore very important

808   to define typical cataplexy as precise as possible. For this reason chapter 2 was added.

809

810 *Additional support for hypocretin deficiency, beyond the presence of (typical) cataplexy:*

811 Subjective symptoms:

812 - ESS >14 [39, 45, 50]

813 - frequent daily naps that are typically short, refreshing and associated with dream content [38,

814 45]

815

816 Objective testing:

817 Considered to be "proven" support:

818 - MSLT: mean SL < 5 min [34, 51]

819 - at least 2 SOREMPs [34]

820 - sleep stage sequence[27, 52-54]

821 - Short REM sleep latency nocturnal sleep (< 15 min) [55]. The evidence is strong in one

822 study but there has never been an independent confirmation and the specificity for narcolepsy

823 type 1 was very high but much less for hypocretin deficiency. Moreover, the sensitivity of this

824 finding is low.

825 - Consistent abnormal MSLT findings when repeating the MSLT

826 Suggested support but needs better validation:

827 - absolute REM sleep latency MSLT < 6 min [27, 37]

828 - sleep stage sequence (REM sleep before occurrence stage 2 sleep or frequent transition

829 REM to stage 2) [27, 52, 53]

830 - Relevant findings on a group level that need replication and validation to be added as

831 diagnostic criteria are: sleep stage sequence/transitions in nocturnal sleep [53, 56] distribution

832 of eye movement during sleep stages [57], and power spectra analyses [58, 59].

833

834 ** For an accurate interpretation of the MSLT, age should be taken into account [15, 21]

835

836 *** In familial and secondary cases, both the presence of HLA DQB1*0602, and hypocretin

837 deficiency in the CSF are less prevalent when compared to the idiopathic cases [60, 61].

838

839 **** For definition, see 2.3

840

841 ¶ Diagnoses to be excluded are chronic sleep deficiency, circadian rhythm disorders and OSA.

842 It is important to realize that there is a hierarchy. First exclude sleep deprivation as cause of

843 the complaints. If the complaints disappear after sleep extension, the complaint is cured and

844 the diagnostic process is completed. If the complaint remains, circadian rhythm disorders and

845 OSA need to be excluded or treated when they might be responsible for the complaint. Only

846 after completing these steps, and a remaining complaint that qualifies for narcolepsy level 2B,

847 the diagnostic process to assess whether the diagnostic criteria for narcolepsy level 2B are met

848 can be started. Symptoms must be present daily for at least 3 months,

849

850 **Narcolepsy phenotype** [45]

851 - acute

852 - progressive

853 - chronic-stable

854 - chronic unstable

855 - other

856

857 **Narcolepsy aetiology** [45]

858 - idiopathic (sporadic)

859 - familial

860 - secondary (symptomatic)

861 - narcolepsy plus (hereditary forms with additional neurological symptoms)

862

863 **Severity of narcolepsy***

864 To be taken into account

865   -   severity score of EDS (see 2.1.2)

866   -   severity score of cataplexy (see 2.2)

867   -   severity score for disturbance nocturnal sleep including the severity of HH

868   and or SP

869   -   quality of life score

870   -   score for severity of comorbidity

871

872 * a severity score has been suggested which could be elaborated on [62].

873

874 **Frequent co-morbidities of definite and probable narcolepsy in adults** [45]

875

876 - Sleep disorders/disturbances: sleep disordered breathing, RLS/PLMS, RBD, other
877 parasomnias
878 - Medical disorders/disturbances: obesity, diabetes mellitus type 2, autonomic instability and
879 cardiovascular disorders
880 - Psychiatric disorders/disturbances: anxiety, depression, psychosocial problems
881
882 **3.2 Diagnostic criteria for idiopathic hypersomnia**
883
884 By definition, sleep deprivation as primary cause is excluded. Sleep apnea as cause needs to
885 be excluded and in case of doubt, first be treated.
886
887 Level 1
888 Definite IH*
889
890   1. The presence of ENS
891   2. The ENS complaint is acquired**
892   3. There is objective evidence for increased sleep need using actigraphy and PSG***
893
894 Level 2
895 Probable IH*
896
897 1. The presence of ENS
898 2. The ENS complaint is acquired**
899 3. There is objective support for increased sleep need using actigraphy and PSG***
900
901
902
903 * The complaint must be present daily for at least 3 months and all 3 criteria must be fulfilled.
904 Fatigue may be present but the excessive need for sleep must be the most prominent
905 complaint. There should be no concomitant major systemic symptoms or factors such as fever
906 or severe pain as these may indicate chronic inflammatory conditions, infection, or auto-
907 immune disorders. It is uncommon that the disorder develops in or after middle-age.
908 Depression may be present and it is often appropriate to document it as a co-morbidity.

31

909

910   ** The point at which symptoms start or even if the disorder is truly acquired may be difficult

911   to establish when ENS is reported in (early) childhood [5, 63].

912

913   *** For level 1, the criteria for objective confirmation are (both must be fulfilled): 1.

914   Actigraphy with sleep logs (2 weeks): strongly supports > 9 hours sleep per night or > 10

915   hours sleep over 24 hrs on the majority of days, and 2. PSG recording (performed at end

916   actigraphy recording); preferably > 19 hrs of sleep in a 32-hrs clinical protocol with

917   standardized conditions [31], or, alternatively, a clinical or ambulant PSG performed for 32-

918   hrs (night 1 + daytime + night 2) allowing ad libitum sleep showing > 19 hrs of sleep.

919   For level 2: not fulfilling criteria for level 1, but: 1. Actigraphy with sleep logs (2 weeks):

920   strongly supports > 9 hours of sleep over 24 hrs on the majority of days, and 2. PSG

921   (performed at end actigraphy recording): result 32-hrs protocol supports but does not meet the

922   19 hrs criterium, or a PSG for 32-hrs allowing ad libitum sleep is supportive but the PSG does

923   not fully meet the 19 hrs criterium or is not performed as requested for level 1.

924   For both levels sleep efficiency for nocturnal sleep must be > 85% (at least when diagnostics

925   are applied up to middle ages). If CSF hypocretin-1 measurement is performed, the

926   hypocretin-1 concentration should be in the normal range.

927   These criteria are essentially expert opinion although particularly the 32 hours PSG protocol

928   is supported by a study.

929

930   **Severity criteria**

931   See severity criteria of ENS paragraph 1.2.2. An existing and recently published scale might

932   be useful [64].

933

934   **Comorbidities**

935   - Depression, anxiety, chronic fatigue, circadian disorders, attention disorders are relatively

936   frequently seen

937

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3.3 Diagnostic criteria for Idiopathic excessive sleepiness

947

948 The diagnosis can only be made after exclusion of sleep apnea, chronic sleep deprivation, and

949 circadian disorders as likely causes of the sleep-related complaints (see ¶ paragraph 3.1).

950 If the criteria for narcolepsy or IH are fulfilled, these diagnoses should be made.

951

952

953 Level 1   1. EDS complaint (as defined earlier)*

954 Definite*   2. Confirmed by PSG and MSLT: SL < 8 min**

955   3. Not fulfilling criteria for narcolepsy or IH

956

957 Level 2

958 Probable*:   1. EDS complaint (as defined earlier)*

959   2. MSLT: SL > 8 and < 12 min

960   3. Not fulfilling criteria for narcolepsy or IH

961

962 Subtype 1

963 "REM type"   1. ≥1 SOREM on PSG / MSLT

964   2. Findings on SART may be normal or abnormal

965

966 Subtype 2

967 "NREM type"   1. No SOREM on PSG / MSLT

968   2. Normal findings on SART

969

970 Subtype 3

971 "Attention type"   1. No SOREM on PSG / MSLT

972   2. Abnormal findings on SART

33

973

974

975   * The complaint is present for at least three months

976

977   ** Those with inconsistent MSLT results over time will qualify for one of these categories,

978   unless criteria for narcolepsy or IH are met.

979

980   *** The Sustained Attention to Response Task (SART) is a vigilance test to assess sustained

981   attention. It has been applied and validated in patients suffering from hypersomnolence,

982   ADHD and brain injury [7, 65, 66]. For the SART cut off values are defined : for the

983   instruction "prefer accuracy over speed", the cut-off is 6 [67]. The Psychomotor Vigilance

984   Test (PVT) might be a good alternative for the SART but there are no cut-off data validated

985   for patients with hypersomnolence [68].

986

987   **Severity criteria**

988   See severity criteria paragraph 1.2.1

989

990   **<u>Comorbidities</u>**

991   - Depression, anxiety, chronic fatigue, attention disorders are frequently seen.

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1007 **Discussion**

1008

1009 US clinicians were the first to create a classification of sleep and arousal disorders in 1979

1010 [69]. In 1990 the first edition of the International Classification of Sleep Disorders (ICSD)

1011 was published, again with US physicians in the lead but representatives of sleep disorders

1012 associations outside the US became involved. The same holds true for the current edition of

1013 the classification, the ICSD3, published in 2014. All subsequent editions provided

1014 improvements but nevertheless it is not uncommon to be difficult or even impossible to make

1015 a proper diagnosis, including in people consulting us because of convincing complaints of

1016 hypersomnolence. In the absence of a proper diagnosis people who might deserve treatment

1017 may remain untreated. Discussions evoked by these experiences ultimately resulted in this

1018 position paper.

1019 Clinicians, researchers, and particularly members of classification committees working in the

1020 field of hypersomnolence should acknowledge the lack of knowledge and understanding of

1021 the precise underlying neurobiological cause(s) of hypersomnolence and therefore the

1022 uncertainty if disorders we currently define are real disease entities. Moreover, the impact of

1023 lifestyle factors is often poorly characterised or appreciated. In such a situation a tendency to

1024 compensate the lack of knowledge by overemphasizing the qualities and properties of any

1025 biological markers we currently have should be resisted. It is our contention that the current

1026 classification system is unintentionally prone to this tendency. This is not only a problem for

1027 patient care but may also prevent us from identifying additional biomarkers for sleep

1028 disorders.

1029 We therefore suggest a different approach. Differences between the current and our approach:

1030 - Our classification is much more complaint driven

1031 - We emphasize that excessive daytime sleepiness is a multidimensional complaint and

1032 qualitatively different from an increased need for sleep.

1033 - We use "hypersomnia" only to describe the presence of objectified ENS.

1034 - We acknowledge that attentional problems frequently accompany disorders of

1035 hypersomnolence and isolated attention disorders should be separated from sleep disorders.

1036 - Sleep deprivation, OSA and circadian disorders need to be initially excluded as primary

1037 causes of EDS. This allows the differentiation of true central disorders of hypersomnolence

1038 from disorders related to lifestyle disorders and sleep related breathing disorders. In case of

1039 doubt the effect of increased time in bed, a therapeutic test with CPAP, or circadian alignment

1040 must first be established. Guidelines from the National Sleep Foundation may help to identify

1041 the presence of sleep deprivation [70].

1042 - We exclude possible confounders for changes in MSLT results over time.

1043 - If MSLT results change over time we emphasise this should not necessarily have an

1044 immediate major impact on diagnostic categories and affect patients' access to treatments, for

1045 example.

1046 - Within our classification, patients can shift to more certain levels of diagnosis over time.

1047 This will potentially provide more insight in how disorders of hypersomnolence progress or

1048 develop and will help to guide future research agenda.

1049 - We allow and formalise a certain level of diagnostic uncertainty, reflecting clinical reality in

1050 daily medical practice.

1051   - There will be relatively few patients who will switch to a new diagnosis as a result of a new

1052   classification.

1053   We realize that implementation of our proposal will have much impact on the current

1054   practices around the world. Different insurance systems and availability of the recommended

1055   tests (i.e. CSF orexin measurement, HLA typing, actigraphy, long term PSG recording) may

1056   be an issue for clinicians in some countries. However, our proposal is to move forward the

1057   field to improve the knowledge and management of patients affected with hypersomnolence.

1058   The main objectives are 1.to diagnose homogeneous groups of patients affected with these

1059   different hypersomnolence disorders, 2. to better understand the precise underlying

1060   neurobiological of such conditions (i.e. other than narcolepsy type 1), and finally 3. to

1061   improve the management of these patients. A registry to validate and optimize our suggested

1062   approach already exists in Europe within the European Narcolepsy Network (EU-NN) and

1063   could be extended to a global registry. In addition, studies to further validate the proposed

1064   diagnostic tools in a prospective setting should be initiated in several sleep labs around the

1065   world in the next few years. We also call for an international task force to formulate

1066   guidelines for the proper application of our suggested approach, The topics to be at least

1067   included:

1068   - how to define, assess and treat chronic sleep deprivation in a practicable way

1069   - what is the best and still feasible way to objectify ENS

1070   For a better understanding of hypersomnolence disorders in general we must initiate studies to

1071   get insight in:

1072   - what determines an individual's sleep need and can we find biological markers to measure

1073   this need

1074   - what is the relation between hypersomnolence and depression and how does it relate to the

1075   more studied close association between insomnia and depression

37

1076   - what is the exact inter-relation between sleepiness, fatigue and disorders of attention

1077   We are hopeful that further discussion will lead to a more consistent, widely accepted and

1078   workable future classification of central disorders of hypersomnolence. We also argue it will

1079   guide and prioritise our research agenda. Finally, we expect that more detailed attention to the

1080   multidimensional aspects of hypersomnolence complaints will facilitate and optimise clinical

1081   care tailored to individual patients.

1082

1083   **<u>Conclusion</u>**

1084   We suggest the creation of a new consistent, complaint driven, hierarchical classification for

1085   central disorders of hypersomnolence; containing levels of certainty, and giving diagnostic

1086   tests, particularly the MSLT, a weighting based on its specificity and sensitivity in the

1087   diagnostic context.

1088   We propose and define three diagnostic categories (with levels of certainty):

1089   1.   "Narcolepsy"

1090   2.   "Idiopathic hypersomnia"

1091   3.   "Idiopathic excessive sleepiness"

1092   Except for narcolepsy, the diagnoses can only be made after excluding sleep apnea, sleep

1093   deprivation and circadian disorders as primary causes for hypersomnolence.

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1113 **Practice Points**

1114 1. "Hypersomnolence" is the overarching name for the presence of EDS and/or ENS.

1115 2. EDS and ENS are multidimensional and qualitatively different complaints.

1116 3. There are large gaps in our understanding of the precise underlying neurobiological

1117 cause(s) of hypersomnolence and its associated disorders except for narcolepsy type 1.

1118 Moreover, the impact of lifestyle factors is often poorly characterised or appreciated.

1119 4. Sleep deprivation, obstructive sleep apnea and circadian disorders need to be initially

1120 excluded as primary causes of hypersomnolence before considering a central disorder of

1121 hypersomnolence as cause of the complaint of excessive daytime sleepiness (except for

1122 narcolepsy with cataplexy / narcolepsy type 1).

1123 5. For a reliable diagnosis of narcolepsy type 1, clear and detailed criteria for the presence of

1124 typical cataplexy are required.

1125 6. The structure of a classification of sleep disorders, including the chapter on central

1126 disorders of hypersomnolence, must be complaint driven and not a mixture of complaint

1127   driven diagnoses and diagnoses solely based on results of ancillary investigations (i.e. AHI,

1128   MSLT results).

1129   7. We propose and define three diagnostic categories with different levels of certainty and

1130   subtypes: 1/ "Narcolepsy"; 2/ "Idiopathic hypersomnia", and 3/ "Idiopathic excessive

1131   sleepiness".

1132

1133

1134

1135   **Research Agenda**

1136   We need to:

1137   1. Understand what determines an individual's sleep need and identify biological markers for

1138   it, as for disorders characterised by EDS and ENS.

1139   2. Develop and validate a guideline to identify and treat chronic sleep deprivation as cause of

1140   excessive daytime sleepiness.

1141   3. Better understand how disorders of hypersomnolence progress / develop over years.

1142   4. Bridge the current gap between disorders of attention and disorders of hypersomnolence.

1143   5. Better define and understand the proposed association between depression and

1144   hypersomnolence.

1145   6. Better understand the inter-relation between sleepiness and fatigue.

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