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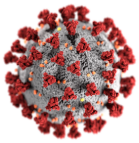
vACCine covid-19  monitoring readinESS

EVENT DEFINITION FORM

Event: Narcolepsy
Outcome/covariate: Outcome
Version: **1.0**
Status: **final**

Contributing authors

authors	**Role**	**Date**
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Miriam Sturkenboom	Review codes	14-08-2020
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Miriam Sturkenboom	Final update after group discussion	25-08-2020
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Miriam Sturkenboom	Finalization of codes base on project	16-7-2021

1. Event definition

Narcolepsy is a sleep disorder primarily characterized by excessive daytime sleepiness and cataplexy- episodes of muscle weakness brought on by emotions. Additional symptoms may comprise hypnagogic hallucinations, sleep paralysis, fragmented nocturnal sleep, as well as impaired ability for sustained attention and non-sleep symptoms such as obesity, anxiety, cognitive and emotional disturbances, and behavioural problems and precocious puberty in children.[1]
The Brighton collaboration defines narcolepsy cases as follows:

Table 1.Event definition by Brighton collaboration.[1]

Level 1
In the presence of:
Excessive daytime sleepiness[a] OR
Unambiguous cataplexy[c]
AND
CSF hypocretin-1 deficiency[b]

Level 2
In the presence of:
Excessive daytime sleepiness[a]
AND
Unambiguous cataplexy[c]
AND
MSLT[d] mean sleep latency
≤8 min in adults OR
MSLT[d] mean sleep latency
≤12 min in children and adolescents OR
MSLT[d] SOREMP≥2

Level 3
In the presence of:
Excessive daytime sleepiness[a]
AND
MSLT[d] mean sleep latency
≤8 min in adults OR
MSLT[d] mean sleep latency
≤12 min in children and adolescents
AND
MSLT[d] SOREMP ≥2

All levels
AND in the absence of other mimicking disorders, see[e]

[a] **Excessive daytime sleepiness**
In adults (≥16 years):
- unintended sleep episodes during the day
AND
- present almost daily for at least one month
In children and adolescents (<16 years):
- an increase in daytime sleep episodes
AND

- present almost daily for at least one month
Note: usually in combination with feelings of subjective sleepiness and impaired concentration. Sleepiness may also be manifested as irritability
or hyperactivity.

[b] **CSF hypocretin-1 deficiency**
- hypocretin-1 concentration below 110 pg/ml in crude, unextracted CSF.
AND
- measured by the Phoenix radioimmunoassay
AND
- performed in a laboratory according to published guidelines and by using the Stanford reference sample.[2]

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[c] **Unambiguous cataplexy**
In adults (≥16 years):
- sudden AND unexpected onset of episodes
AND
- presence of all of the following criteria during episodes (before initiation of treatment):
- partial or generalized muscle weakness
- preserved consciousness
- clear emotional trigger in
≥2 episodes
- duration of <30 s
OR
- episodes with documented, reversible areflexia AND
- duration of <30 s
NOT
- partial or generalized seizure OR
- neuromuscular disorders
In children and adolescents (<16 years):
- episodes of cataplexy that fulfil the criteria for adult cataplexy
OR
- the following criteria of paediatric cataplexy:

Paediatric Cataplexy
- sudden AND unexpected onset of episodes
AND
- loss of muscle tone, e.g., falling during routine activity (i.e. while walking or running), wide-based gait, head droops, prominent facial involvement
resulting in “cataplectic facies,” eyelid ptosis, mouth opening, tongue
protrusion, facial weakness, facial grimacing, abnormal postures, swaying
of the head and trunk, stereotypic movements or chorea-like patterns.
Hypotonia and wide-based gait may also be disclosed at neurological examination
AND
- preserved consciousness
AND
- duration of episodes is a few seconds to several minutes (sometimes present in protracted clusters if emotional triggers continue)
Note: cataplexy in children may or may not be triggered by ‘emotional’
circumstances (e.g., watching funny cartoons, eating certain foods, playing games or video-games)
NOT
- partial or generalized seizure OR
- neuromuscular disorders
- any other known explanation

[d] 4 or 5 nap MSLT performed according to the American Academy of Sleep Medicine (AASM) protocol.[3]

[e] Exclusion of other conditions

The following conditions must be clinically/instrumentally assessed, since they could either mimic one or more narcolepsy symptoms (mainly excessive daytime sleepiness) or constitute co-morbidities with narcolepsy:

- other sleep disorders, according to ICSD-2 criteria:
- sleep related disorder breathing
- behaviorally induced insufficient sleep
- circadian rhythm disorders
- recurrent hypersomnias secondary to medical or psychiatric conditions
- use of sedating medication and antidepressants
- focal cerebral lesions, indicated by neurological examination and/or brain imaging

Note: Clinical assessment should be performed after adequate treatment of the co-morbid conditions, to show that they are not the primary cause of the symptoms.

2. Synonyms / lay terms for the event

- Paroxysmal Sleep
- Sleep, Paroxysmal
- Narcoleptic Syndrome
- Narcoleptic Syndromes
- Syndrome, Narcoleptic
- Syndromes, Narcoleptic
- Gelineau Syndrome
- Syndrome, Gelineau
- Gelineau's Syndrome
- Gelineau's Syndromes
- Gelineaus Syndrome
- Syndrome, Gelineau's
- Syndromes, Gelineau's
- Narcolepsy-Cataplexy Syndrome
- Narcolepsy Cataplexy Syndrome
- Narcolepsy-Cataplexy Syndromes
- Syndrome, Narcolepsy-Cataplexy
- Syndromes, Narcolepsy-Cataplexy
- Excessive day time sleepiness

3. Laboratory tests that are specific for event

- Genetic testing for HLA-DQB1*06:02 positivity adds little to the reliability of the diagnosis of narcolepsy with cataplexy.
- Hypocretin-1 (orexin A). A concentration below 110 pg/ml in crude, unextracted cerebrospinal fluid (CSF).[1] Hypocretin-1 levels in CSF are usually measured using radioimmunoassay with polyclonal antibodies against hypocretin-1. A cut-off of 110 pg/ml defines abnormally low levels when the essay is standardised using Stanford reference sample. Nonetheless, if a laboratory includes its own control sample, the cut-off is defined either as a level less than one-third the mean of normal healthy controls, or two or more standard deviations from the mean.

4. Diagnostic tests that are specific for event

- **Polysomnographic test.** The main polysomnographic test is the Multiple Sleep Latency Test (MSLT), typically showing a short mean sleep latency (SL, ≤ 8 min) and ≥2 Sleep Onset Rapid Eye Movement Periods (SOREMPs).[1] Video polysomnography. SOREMPs can be identified during nocturnal video polysomnography. This test seems to be more specific but less sensitive than the MSLT for the diagnosis of narcolepsy.[4]
- Neuroimaging.
- **Questionnaires.** Patients with narcolepsy normally score ~18 (range 14–20 out of a possible 24) points on the nonspecific Epworth sleepiness scale. The Swiss Narcolepsy Scale was found to have the best sensitivity and specificity (both ~90%) for the diagnosis of narcolepsy with cataplexy in three separate populations.[4]
- **Lumbar puncture** in the cerebrospinal fluid to obtain the neuropeptide hypocretin-1.[1]
- **Radioimmunoassay** with polyclonal antibodies against hypocretin-1.

5. Drugs that are used to treat event

Drugs used to treat narcolepsy are stimulants, antidepressants, sodium oxybate, intravenous immunoglobulins and others.
In table 2 symptomatic narcolepsy treatment is listed.
Excessive day sleepiness (EDS) is usually managed with psychostimulants.
Modafinil and armodafinil, increasing the extracellular concentration of dopamine by inhibiting its transporter.[5]
For cataplexy and other symptoms related to deregulation of REM sleep such as sleep paralysis, sodium oxybate and antidepressant agents are effective.[5]

Table 2| Symptomatic narcolepsy treatment (modified from [4])

Drugs	Daily dosage	Indication
Modafinil	100–400mg	First-line treatment for EDS
Armodafinil	l 100–250mg	First-line treatment for EDS
Pitolisant	4.5–36.0mg	First-line treatment for EDS and cataplexy
Sodium oxybate	4.5–9.0g	First-line treatment for cataplexy, disturbed night-time sleep and EDS
Solriamferol	75–150mg	First-line treatment for EDS
Antidepressants	Venlafaxine 37.5–300.0mg Fluoxetine 20–60mg Clomipramine 10–50mg Citalopram 10–75mg	First-line and second-line treatment for cataplexy and third-line treatment for EDS
Methylphenidate	10–60mg	Second-line treatment for EDS
Amphetamines	Amphetamine mixed salts[a] 10–60mg Dexamphetamine 10–60mg	Second-line treatment for EDS

These recommendations apply only to adults. The presence of comorbidities (and other medications) might also alter the choice
of pharmacological approach. EDS, excessive daytime sleepiness; EMA, European Medicines Agency.
[a]A mixture of four salts of the two enantiomers of amphetamine with dexamphetamine.

- **Treatment in children.** Stimulants, modafinil, sodium oxybate and antidepressants improve narcoleptic symptoms in children.[4]

6. Procedures used specific for event treatment

Non-pharmacological treatment strategies include self-care, behavioural therapy such as scheduled napping and regular night sleep, self-help groups and psychotherapy.[4]

7. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

The condition will be most reliably diagnosed in outpatient specialist or in-hospital.

8. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA

- **Black et al.**[6]

Diagnosis code of narcolepsy with or without cataplexy (International Classification of Diseases (ICD)-9, 347.0,347.00, 347.01, 347.1, 347.10, or 347.11).
IC9-9
347.0 Narcolepsy
347.00 Narcolepsy, without cataplexy
347.01 Narcolepsy, with cataplexy
347.10 Narcolepsy in conditions classified elsewhere, without cataplexy
347.11 Narcolepsy in conditions classified elsewhere, with cataplexy

- **Tzeng et al.**[7]

ICD-CM: 347.

- **Yang et al.**[8]

ICD-9-CM: 347

- **Nohynek et al.**[9]

ICD10 code: G47.4

- **Duffy et al.**[10]

ICD-9 : narcolepsy diagnosis code (347.00 – 347.11)

- **Scheer et al.**[11]

Narcolepsy without cataplexy ICD-9-CM 347.00 or 347.10
Narcolepsy with cataplexy ICD-9-CM 347.01 or 347.11
polysomnography(PSG) (CPT 95808, 95810, 95811, or ICD-9-CM 89.17)
multiple sleep latency test (MSLT) (CPT 95805 or ICD-9-CM
89.18)

- **SOMNIA Wijnans et al./Dodd et al.**[12]

- READ CPRD: F27..00, F270.00, F271.00, F27z.00
- ICD-9: 347

- ICD-10: G47.4
- ICPC: no code but search based on free text

Validation studies conducted in primary databases show very low PPV<10% (Weibel/Dodd et al.)

9. Codes used for extraction

Coding system	Code	Code name	Concept	Algorithm
ICD10/CM	G47.419	Narcolepsy NOS	C0027404	narrow
ICD10/CM	G47.41	Narcolepsy	C0027404	narrow
ICD10/CM	G47.4	Narcolepsy and cataplexy	C0751362	narrow
ICD10/CM	G47.411	Narcolepsy with cataplexy	C0751362	narrow
ICD10/CM	G47	Sleep disorders	C0851578	possible
ICD10/CM	G47.9	Sleep disorder, unspecified	C0851578	possible
ICD10/CM	G47.419	Narcolepsy without cataplexy	C1456240	narrow
ICD10/CM	G47.429	Narcolepsy in conditions classified elsewhere without cataplexy	C1456241	narrow
ICD10/CM	G47.421	Narcolepsy in conditions classified elsewhere with cataplexy	C1456242	narrow
ICD9CM	347.0	Narcolepsy	C0027404	narrow
ICD9CM	780.5	Sleep disturbances	C0037317	possible
ICD9CM	780.50	Sleep disturbance, unspecified	C0037317	possible
ICD9CM	89.17	Polysomnogram	C0162701	possible
ICD9CM	347	Cataplexy and narcolepsy	C0751362	narrow
ICD9CM	347.01	Narcolepsy, with cataplexy	C0751362	narrow
ICD9CM	347.00	Narcolepsy, without cataplexy	C1456240	narrow
ICD9CM	347.10	Narcolepsy in conditions classified elsewhere, without cataplexy	C1456241	narrow
ICD9CM	347.11	Narcolepsy in conditions classified elsewhere, with cataplexy	C1456242	narrow
ICD9CM	347.1	Narcolepsy in conditions classified elsewhere	C1456243	narrow
ICPC2P	N99013	Narcolepsy	C0027404	narrow
ICPC2P	P06010	Disturbed;sleep	C0037317	possible
ICPC2P	P06011	Disorder;sleep	C0851578	possible
ICPC2P	P06012	Problem;sleep	C0851578	possible
RCD2	F270.	Cataplexy	C0007384	narrow
RCD2	F271.	Narcolepsy	C0027404	narrow
RCD2	R005.	[D]Sleep disturbances	C0037317	possible
RCD2	Fy0..	Sleep disorders	C0037317	possible
RCD2	R0050	[D]Sleep disturbance, unspecif	C0037317	possible
RCD2	7P1B0	Polysomnography	C0162701	possible
RCD2	3148.	Sleep studies	C0162701	possible

RCD2	F27z.	Cataplexy or narcolepsy NOS	C0751362	narrow
RCD2	F27..	Cataplexy and narcolepsy	C0751362	narrow
RCD2	R005z	[D]Sleep dysfunction NOS	C0851578	possible
RCD2	Fy0..	Sleep disorders	C0851578	possible
SCTSPA	46263000	cataplexia	C0007384	narrow
SCTSPA	60380001	narcolepsia	C0027404	narrow
SCTSPA	206746001	[D]alteraciones del sueño	C0037317	possible
SCTSPA	206747005	[D]alteración del sueño, no especificada	C0037317	possible
SCTSPA	53888004	perturbación en la conducta durante el sueño	C0037317	possible
SCTSPA	164773008	estudios del sueño	C0162701	possible
SCTSPA	60554003	polisomnografía	C0162701	possible
SCTSPA	277180005	parálisis del sueño	C0456511	possible
SCTSPA	252731002	prueba múltiple de latencia del sueño	C0519186	possible
SCTSPA	193042000	cataplexia y narcolepsia	C0751362	narrow
SCTSPA	193043005	catalepsia o narcolepsia, SAI	C0751362	narrow
SCTSPA	206757006	[D]disfunción del sueño, SAI	C0851578	possible
SCTSPA	39898005	trastorno del sueño	C0851578	possible
SCTSPA	91521000119104	narcolepsia sin cataplexia	C1456240	narrow
SNOMEDCT_US	46263000	cataplexia		narrow
SNOMEDCT_US	60380001	narcolepsia		narrow
SNOMEDCT_US	193042000	narcolepsy and cataplexy		narrow
SNOMEDCT_US	193043005	narcolepsy or cataplexy		narrow

Based on Codemapper tool Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom MCJM, Kors JA; ADVANCE consortium. CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):998-1005. doi: 10.1002/pds.4245.

10. Algorithm proposal

Broad algorithm:

- Possible & narrow codes
- Index date: first occurrence of any of these concept sets

Narrow algorithm:

- Narrow codes
- Index date: first occurrence of any of these concept sets

11. Background rates published

The following search terms were used to extract the narcolepsy background rates from the literature:

(¨Narcolepsy¨[Mesh]) AND ("incidence"[tw]) NOT (Comment[ptyp] OR Editorial[ptyp] OR News[ptyp] OR Newspaper Article[ptyp]) NOT ("animals"[Mesh] NOT "humans"[Mesh]) AND English[lang]
Between 2010-2020

Table 3. References corresponding to the studies included in relation to the background rates.

Number	Study reference
1.[13]	Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. Vaccine 2013;31(8):1246–54.
2.[11]	Scheer D, Schwartz SW, Parr M, Zgibor J, Sanchez-Anguiano A, Rajaram L. Prevalence and incidence of narcolepsy in a US health care claims database, 2008-2010. Sleep 2019;42(7).
3.[14]	Partinen M, Saarenpää-Heikkilä O, Ilveskoski I, Hublin C, Linna M, Olsén P, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. PLoS ONE 2012;7(3):e33723.
4.[15]	Oberle D, Drechsel-Bäuerle U, Schmidtmann I, Mayer G, Keller-Stanislawski B. Incidence of Narcolepsy in Germany. Sleep 2015;38(10):1619–28.
5.[16]	Lee RU, Radin JM. A population-based epidemiologic study of adult-onset narcolepsy incidence and associated risk factors, 2004-2013. J Neurol Sci 2016;370:29–34.
6.[12]	Dodd CN, de Ridder M, Huang W-T, Weibel D, Giner-Soriano M, Perez-Vilar S, et al. Incidence rates of narcolepsy diagnoses in Taiwan, Canada, and Europe: The use of statistical simulation to evaluate methods for the rapid assessment of potential safety issues on a population level in the SOMNIA study. PLoS ONE 2018;13(10):e0204799.
7.[17]	Choe YJ, Bae G-R, Lee D. No association between influenza A(H1N1)pdm09 vaccination and narcolepsy in South Korea: an ecological study. Vaccine 2012;30(52):7439–42.

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1. Poli F, Overeem S, Lammers GJ, Plazzi G, Lecendreux M, Bassetti CL, et al. Narcolepsy as an adverse event following immunization: Case definition and guidelines for data collection, analysis and presentation. Vaccine 2013;31(6):994–1007.

2. Nevsimalova S, Vankova J, Stepanova I, Seemanova E, Mignot E, Nishino S. Hypocretin deficiency in Prader–Willi syndrome. European Journal of Neurology 2005;12(1):70–2.

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6. Black J, Reaven NL, Funk SE, McGaughey K, Ohayon MM, Guilleminault C, et al. Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study. Sleep Medicine 2017;33:13–8.

7. Tzeng N-S, Hsing S-C, Chung C-H, Chang H-A, Kao Y-C, Mao W-C, et al. The Risk of Hospitalization for Motor Vehicle Accident Injury in Narcolepsy and the Benefits of Stimulant Use: A Nationwide Cohort Study in Taiwan. Journal of Clinical Sleep Medicine 2019;15(06):881–9.

8. Yang C-P, Hsieh M-L, Chiang J-H, Chang H-Y, Hsieh VC-R. Migraine and risk of narcolepsy in children: A nationwide longitudinal study. PLoS ONE 2017;12(12):e0189231.

9. Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, et al. AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland. PLoS ONE 2012;7(3):e33536.

10. Duffy J, Weintraub E, Vellozzi C, DeStefano F. Narcolepsy and Influenza A(H1N1) Pandemic 2009 Vaccination in the United States. Neurology 2014;83(20):1823–30.

11. Scheer D, Schwartz SW, Parr M, Zgibor J, Sanchez-Anguiano A, Rajaram L. Prevalence and incidence of narcolepsy in a US health care claims database, 2008-2010. Sleep 2019;42(7).

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15. Oberle D, Drechsel-Bäuerle U, Schmidtmann I, Mayer G, Keller-Stanislawski B. Incidence of Narcolepsy in Germany. Sleep 2015;38(10):1619–28.

16. Lee RU, Radin JM. A population-based epidemiologic study of adult-onset narcolepsy incidence and associated risk factors, 2004-2013. J Neurol Sci 2016;370:29–34.

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