

Assessment of Clinical Response to Narcolepsy Treatment: Challenges and Best Practices

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Introduction and objectives

- Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness, cataplexy, other REM-dissociative features, and disrupted nighttime sleep^{1,2}
- Most patients with narcolepsy require lifelong pharmacologic treatment^{3,4}
- A key challenge for the treating clinician is determining patient response and altering treatment to maximize improvement
 - When to stay with the current regimen and evaluate over time
 - When to change dose, add another medication, or change medication in effort to achieve additional improvement
 - When to add behavioral interventions and possibly cognitive/supportive psychotherapy

1. Scammell TE. *N Engl J Med*. 2015;373(27):2654-2662. <https://doi.org/10.1056/NEJMra1500587>.
2. Bassetti CLA, et al. *Nat Rev Neurol*. 2019;15(9):519-539. <https://doi.org/10.1038/s41582-019-0226-9>.
3. Thorpy MJ, Bogan RK. *Sleep Med*. 2020;68:97-109. <https://doi.org/10.1016/j.sleep.2019.09.001>.
4. Maski K, et al. *J Clin Sleep Med*. 2021;17(9):1881-1893. <https://doi.org/10.5664/jcsm.9328>.



Objectives: to identify challenges confronted by clinicians in the assessment of response to narcolepsy treatment and to discuss approaches for optimizing evaluation of treatment response

Challenges of assessing a complex disorder under time constraints

- Assessment of treatment response requires evaluating multiple domains during the limited time available for follow-up visits

Areas for Assessment	Specific Aspects
Narcolepsy symptoms	Daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, vivid dreams, disrupted nighttime sleep
Comorbid psychiatric conditions	Anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), substance abuse
Other comorbid medical conditions	Endocrine disorders (e.g., diabetes), cardiovascular disorders (e.g., hypertension), gastrointestinal disorders, other sleep disorders (e.g., sleep apnea, restless legs syndrome, periodic limb movement disorder, REM sleep behavior disorder, parasomnias, circadian rhythm disorders), history of head injury
Environmental factors	Level of stimulation, time of day, poor sleep hygiene
School/job demands	Schedule, level of physical activity, cognitive demands
Patient functioning	Participation/performance in school/work/family/social activities, driving
Quality of life	Emotional well-being, satisfaction with functioning and daily life
Medication side effects	Specific to the prescribed medication(s)

Challenges related to assessment of daytime sleepiness

- Persistent, residual sleepiness may be underreported or improvement in wakefulness may be overreported by some patients
 - Because excessive daytime sleepiness is so chronic, patients lack a frame of reference for “normal” wakefulness
 - Patients may downplay symptoms out of a desire to please the treating clinician
 - Misreporting leads to inadequate treatment
- Sleepiness may be multifactorial, due to long-term narcolepsy symptoms and other disorders (e.g., mood disorders, other sleep disorders)
- Symptom variation throughout the day; time of office visit (morning vs. afternoon) can affect patient’s presentation and reported symptoms



Challenges related to assessment of cataplexy

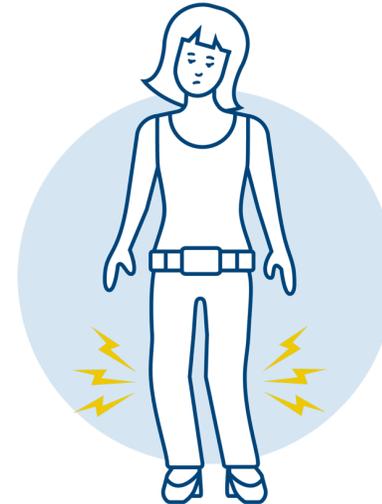
- Cataplexy (sudden involuntary muscle weakness or paralysis during wakefulness, typically triggered by strong emotions¹) is not well recognized
- Variability in symptom presentation
 - Head bobbing (due to neck muscle weakness), blurred vision, droopy eyelids, slurred speech, weakness of chin muscles with possible tongue protrusion, arm/hand weakness, dropping things frequently, shoulder weakness, leg weakness leading to clumsiness or buckling/complete collapse, ankle weakness leading to twisting and falls
- Patients may be unreliable reporters of cataplexy
 - Need for education and information about cataplexy for the patient, family, and friends
- Cataplexy may be masked by avoidance behaviors or REM sleep-suppressing medications such as antidepressants
- Cataplexy may be partial or subtle but still lead to avoidance behaviors



Neck weakness



Arm/hand weakness



Leg weakness/buckling



Collapse/fall

1. Dauvilliers Y. *Nat Rev Neurol*. 2014;10(7):386-395. <https://doi.org/10.1038/nrneurol.2014.97>.

Existing scales are insufficient for clinical assessment



Scales used in clinical practice: Epworth Sleepiness Scale (ESS),¹ Functional Outcomes of Sleep Questionnaire (FOSQ),² Narcolepsy Severity Scale³

- Not sensitive enough to capture changes in sleepiness or functional implications for many patients with narcolepsy
- Do not reflect the goals/priorities of individual patients, which vary based on age, employment, social/family situation
- Do not capture the social and lifestyle impacts of narcolepsy
- Do not give a sense of the dynamic and personalized nature of the changes that occur visit by visit



Assessment of cataplexy should include severity, not just number of events, and consider the impact of avoidance behaviors

1. Johns MW. *Sleep*. 1991;14(6):540-545. <https://doi.org/10.1093/sleep/14.6.540>.

2. Chasens ER, et al. *Sleep*. 2009;32(7):915-919. <https://doi.org/10.1093/sleep/32.7.915>.

3. Dauvilliers Y, et al. *Sleep*. 2020;15;43(6):zsaa009. <https://doi.org/10.1093/sleep/zsaa009>.



Assessment of clinical response to narcolepsy treatment

Clinical Considerations in the Assessment of Treatment Response

- Prior completion of thorough diagnostic workup
- Assessment of sleepiness
 - Daytime functioning (naps, head bobbing, ability to stay awake in more boring situations)
 - In addition to work/school functioning, consider patient functioning in the evening and the impact of sleepiness on family and social relationships
 - Sleepiness versus focus/concentration/memory versus mood
 - Routinely assess for confounding causes of sleepiness
- Assessment of the potential emergence of cataplexy in patients who have not previously identified this as a symptom
 - Cataplexy may worsen abruptly in highly emotional or stressful situations
 - Cataplexy may be masked by avoidance behaviors
 - Cataplexy may be masked by some antidepressants and other REM sleep-suppressing medications
- Assessment of situations patients try to avoid (as a compensatory strategy) and whether they are better able to participate in them
- Assessment of changes in comorbid psychiatric conditions (anxiety, depression, ADHD) and other health conditions

Need for comprehensive clinical assessment



- Clinical evaluation should be broad enough to cover multiple domains yet specific enough to address the issues/goals of the individual patient
 - Broad questions alone (e.g., “How are you doing?”) are insufficient

- Requires asking detailed questions and probing responses across a wide range of topics, including narcolepsy symptoms, mood, functioning, and quality of life



Potential questions about symptoms, mood, functioning, and quality of life



Naps: number?
duration?

Ability to focus?
Concentration?
Memory?

How is your
productivity/grades?

When do you
feel fully awake
(if at all)?

Sleepiness while
driving?

How does excessive
daytime sleepiness
affect your everyday
life?

Are you able to
stay awake during school
or work?

Are you late to work
or school because it's
hard to get up?

Are you able to stay awake
in more boring situations?

Is it easy or hard to wake
up in the morning?

How long
does your wakefulness/
energy last?

How is your sleep at night
(falling asleep, awakenings)?

■ Daytime sleepiness

■ Nighttime sleep

Potential questions about symptoms, mood, functioning, and quality of life



Have cataplexy episodes changed in any way?

Cataplexy?
Frequency?
Severity?

Sleep paralysis?

Visual or sensory hallucinations when going into or out of sleep?

How does cataplexy affect your everyday life?

Have you changed any medications?

In what ways have you noticed improvement?

Are you doing more activities with friends or family?

How is your mood (anxiety, depression)?

Has anyone around you mentioned improvement?

What situations or activities do you avoid?

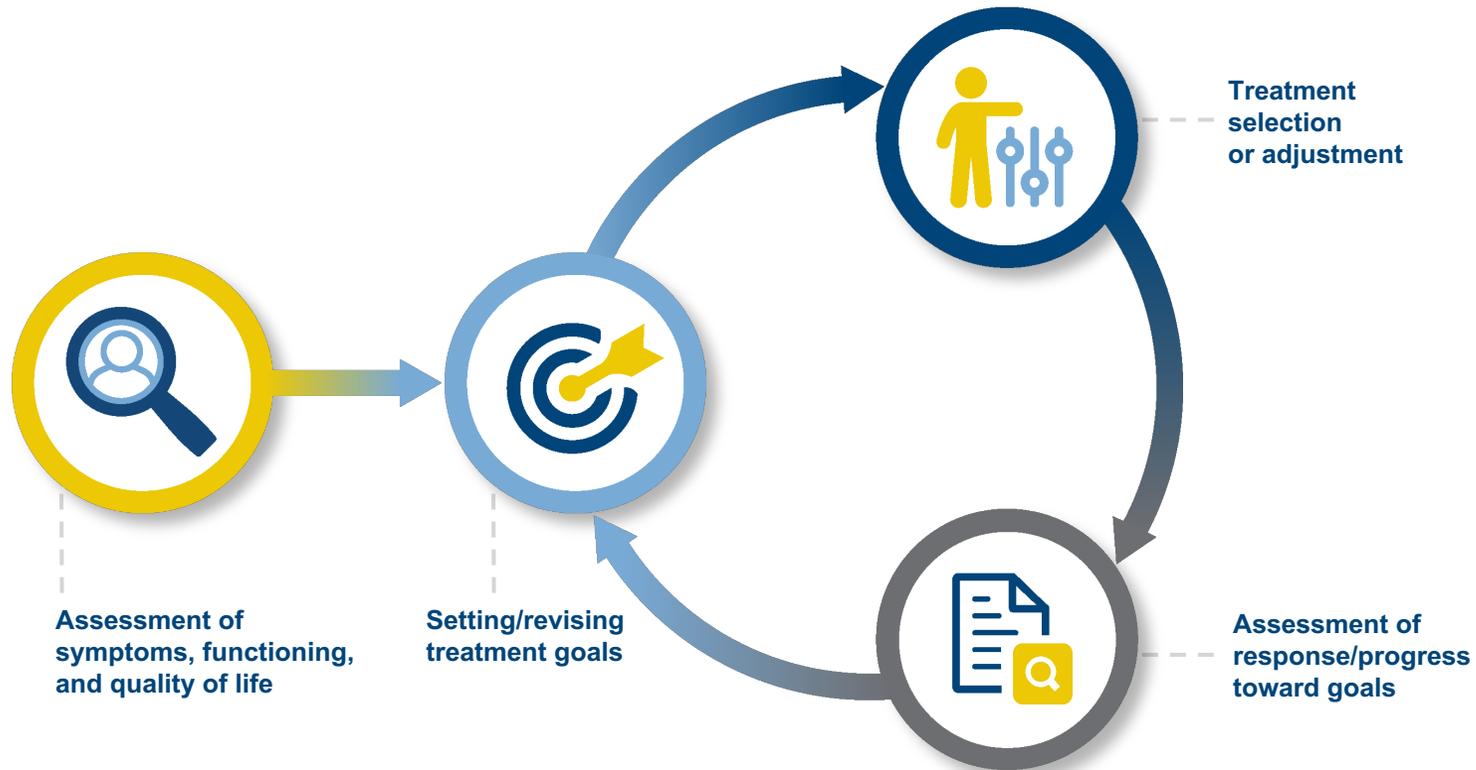
Are you getting out more?

Any changes in your other medical conditions?
Any new symptoms?

Medication side effects?

Individualized, patient-centered assessment of response

Iterative process that assesses symptoms, goals, functioning, and quality of life relative to previous visits



Wake up on my own and make it to class on time
[20-year-old college student with narcolepsy type 2]

Care for my toddler safely during the day
and awaken at night when needed
[30-year-old mother with narcolepsy type 1 (cataplexy)]

Identification of individualized patient goals and changes in those goals over time

Participate in evening family activities such as attending my daughter's sporting events and going out to dinner with my spouse without falling asleep
[A father with narcolepsy type 1]

Play games and other fun activities with my kids without worrying about cataplexy
[30-year-old mother with narcolepsy type 2]

Stay awake in the afternoon to do homework and then WANT to go to soccer practice, instead of sleep
[13-year-old boy with narcolepsy type 2]

Attend social events without embarrassment and interact freely with my work colleagues
[36-year-old woman with narcolepsy type 1 who avoids parties and leaves the room whenever anyone is joking, to prevent cataplexy]

Importance of patient education and involvement of family members

- Education to improve patients' recognition of symptoms and discernment of changes over the course of treatment
 - Improve patients' understanding of the potential benefits (and limitations) of treatment
- New use of technologies (perhaps app or smart-phone driven) may improve tracking of progress between office visits
- Input from family members may provide a more complete picture of patients' symptoms and functioning



Clinician and patient (and parents of pediatric patient) as a team working together to improve treatment outcomes

Summary



Clinicians treating patients with narcolepsy must assess clinical response across multiple domains to determine treatment selection and subsequent adjustments to the treatment regimen



Existing scales are practical for screening and useful for research, but less effective for assessment of response to treatment in clinical practice



Personalized assessment of treatment response should take into account the goals and functioning of each individual patient and track progress toward those goals over the course of treatment



There is an unmet need for a brief instrument that can be used efficiently in the clinic to improve the assessment of clinical response in patients with narcolepsy

Disclosures

- Dr. Herpel reports participating in clinical research for Apnimed, Avadel, Axsome Therapeutics, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, LivaNova/OSPNEY, NLS Pharmaceuticals, Oventus, Philips Respironics, Roche, Sanofi, Signifier Medical Technologies, Sommetrics, Suven Life Sciences, Takeda, and Vanda; serving as an advisor to Harmony Biosciences; and giving a presentation for Jazz Pharmaceuticals
- Dr. Kass reports serving on the speakers' bureau for Harmony Biosciences and Jazz Pharmaceuticals
- Dr. Stultz reports serving on the speakers' bureau for Axsome Therapeutics, Harmony Biosciences, and Jazz Pharmaceuticals; and serving on the advisory board for Harmony Biosciences

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