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From: Name & Insurance Details

To: Appeals and Grievances
CareFirst BlueCross BlueShield

RE: **URGENT EXPEDITED APPEAL**
Sent through Web Portal

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Introduction

(contact info here)

URGENT APPEAL

Dear Sir or Madam,

I am a 40-year-old woman who has been diagnosed with idiopathic hypersomnia. My primary symptoms of severe, disabling sleepiness and cognitive dysfunction have been mostly refractory to treatment.

There is one therapy for my rare, disabling, treatment-resistant sleep disorder that has been uniquely helpful for restoring me to a functional state of wakefulness and cognitive function: Xyrem, aka sodium oxybate, a salt of gamma hydroxybutyric acid. I know exactly how well Xyrem works for me, because I was a participant in a clinical trial for JZP-258, a low-sodium reformulation of Xyrem, which has now been approved to market as Xywav. As active moieties, these drugs are identical.¹

Delayed Diagnosis

Idiopathic hypersomnia (IH) is one of the central primary hypersomnias, along with its better-known sister disease, narcolepsy. These hypersomnias are all rare diseases characterized mainly by constant overwhelming sleepiness. My sleepiness includes severe morning sleep inertia (an inability to transition fully from sleep to wake), the need for prolonged nocturnal sleep, and unavoidable napping. I suffer cognitive dysfunction typical of sleep deprivation, such as attention and memory deficits, as well as apparent dysautonomias in orthostasis and temperature regulation.

I have experienced an excessive requirement for sleep (needing 9+ hours) and disordered REM behaviors since at least early adolescence. The sleepiness began to get slowly and

¹ Xyrem and Xywav are equivalent drugs for the purpose of mechanism and effects. They are both salts of gamma hydroxybutyric acid. They thus have the same active moiety, and the same function. They are administered and dosed in exactly the same way, 4.5-9 grams in oral solution divided in two doses nightly. While they are considered different drugs for the purpose of FDA approval, they are considered the same drug for the purpose of FDA orphan designation—a reformulation of the active moiety that is simply conjugated to different ions. For the remainder of this appeal, I will refer Xyrem when discussing to my experience with Xywav, for the sake of simplicity.

progressively worse after a bout of infectious mononucleosis in my late twenties, in 2008. I regularly reported my fatigue and sudden sleep attacks to my doctors, but with no obvious problems on routine bloodwork, they failed to offer any meaningful further investigation or therapy.

In the fall of 2014, my sleepiness suddenly went from troubling to all-consuming. Over the span of a few months, my condition deteriorated until I was unable to stay awake more than a few hours at a time, sleeping 11 hours on my best days and as much as 21 on my worst. I also developed orthostatic symptoms, and became unable to stand for more than 10 minutes without becoming faint.

It felt exactly like my previous round of mononucleosis, so I was sure I was the rare case that had caught it second time. However, the mono test came back negative.

Many other negative tests followed.

Yet, even as my symptoms threatened my job and caused me to abandon all other pursuits, my CareFirst doctors seemed unable to believe my hypersomnia was something real.

- A CareFirst endocrinologist dismissed me outright, refusing to even run a simple cortisol test to rule out Addison disease.
- A CareFirst cardiologist checked for heart abnormalities on ultrasound, but was uninterested in my orthostatic symptoms, and had no suggestions for what might be causing my exhaustion except “some inflammatory process.”
- When I tested negative for lupus or rheumatoid arthritis markers, a CareFirst rheumatologist was so skeptical and rude to me that I left his office crying.

None of these doctors suggested I see a sleep specialist. They simply assumed I was exaggerating or perhaps even malingering, and treated me accordingly. Several of them unhelpfully suggested that maybe my tiredness was from sleeping too much.

The only reason I have a diagnosis today is because another patient recognized my symptoms. “That sounds just like me,” she said. “I have narcolepsy. You should see my doctor.” On the advice of this friend, I presented myself to the Center for Sleep and Wake Disorders, where knowledgeable sleep experts finally took my sleepiness seriously. I was diagnosed with idiopathic hypersomnia in 2016.

Treatment Failures

Unfortunately, central hypersomnias are notoriously difficult to treat. Since my diagnosis, I have tried numerous therapies with relatively little success. I am unable to tolerate modafinil or bupropion as stimulating agents. I am unable to tolerate trazodone, doxepin, or baclofen as sleep-consolidating agents. I saw no improvement on clarithromycin, a GABA antagonist. With the desperation of most rare disease patients, I have tried a long list of mostly ineffectual over-the-counter supplements, from mundane fish oil to obscure herbs, without any whisper of plausibility.

Lifestyle modifications such as maintaining a sleep schedule are important, but have had very limited effects. My daily and even hourly symptom severity continues to be unpredictable.

I have had moderate improvement of my symptoms using amphetamine stimulants. However, a known major drawback to amphetamines is the rapid development of patient tolerance to their stimulating effects. Increasing tolerance necessitated gradual increases of my amphetamine dose, which were accompanied by increasingly risky cardiac effects. At 40 mg dextroamphetamine daily, my sitting heart rate now runs between 110-120 beats per minute. My medical team and I are deeply concerned that we have reached my cardiac limits. This level of tachycardia does not pose an immediate risk, but it significantly elevates my long-term risk for cardiac hyperplasia and early death.

Unfortunately, this dose has been inadequate to manage my symptoms for quite some time. Although my workplace has accommodated me with telework and flexible hours, I still frequently miss work and deadlines due to extreme sleepiness, and constantly struggle to perform while in a constant haze of exhaustion, frequently unable to concentrate, plan, analyze, learn, or otherwise think.

Using all of my functional hours for work leaves me literally without the energy to perform basic self-maintenance such as preparing healthful meals and exercising. I have become overweight and deconditioned, which can only lead to further disability.

This inadequate and risky course of treatment is the compromise CareFirst would apparently have me continue to accept. Prior to Xyrem, this was my best available option. With a superior treatment available, this is obviously unacceptable.

Success with Xyrem

When I started the clinical trial for JZP-258, (now Xywav, a low-sodium reformulation of Xyrem) my hypersomnia symptoms were so severe and disabling that I was preparing an application for medical retirement. However, over the 8 months of the trial, my life was transformed.

I benefited from substantial improvements in my levels of daytime sleepiness almost immediately. I began to awake naturally with an internally regulated schedule, sometimes without the need for an alarm—an astonishing contrast to my previous severe morning sleep inertia. These changes were significant enough that I was able to reduce my dose of amphetamine stimulants.

My cognitive functions such as attention and memory improved so noticeably that my co-workers commented. I was able to propose and lead a new project at work.

Nothing I have tried for my hypersomnia has benefited me to the extent that Xyrem has.

Unfortunately, when the trial ended, my regression was swift. Within weeks, I deteriorated until I was once again struggling all day through a thick mental fog and overwhelming sleepiness.

At my next appointment, my sleep specialist immediately prescribed Xyrem so that I could resume treatment and return to my improved state. However, CareFirst denied coverage for Xyrem as quickly as my doctor had prescribed it.

A Careless Denial

CareFirst's denial letter offers two main reasons for this determination. The denial claims the use of Xyrem in idiopathic hypersomnia is not supported by "current Xyrem plan criteria" nor by "current medical literature."

Contrary to the claims in that denial, the use of Xyrem in my case is supported both by CareFirst medical policy and scientific evidence.

In this appeal, I will show that:

1. CareFirst's medical policy on orphan drugs has required coverage of Xyrem for idiopathic hypersomnia since July of 2019, when the FDA gave Xyrem an orphan drug designation specifically for the treatment of idiopathic hypersomnia.

2. Xyrem has been accepted as standard of care for over ten years by the relevant medical community. The peer-reviewed evidence proves the safety and efficacy of this treatment for cases like mine.
3. This is also demonstrated in the existence of prior precedents where Blue Cross Blue Shield and other US insurance companies have covered Xyrem for idiopathic hypersomnia.
4. The efficacy and medical necessity of Xyrem has been already established in my personal case with an extended clinical trial of JZP-258, a formulation of the same active moiety as Xyrem.
5. CareFirst has based its denial on diagnostic criteria that are unreliable and meaningless for treatment efficacy: the number of Sleep-Onset REM Periods (SOREMs or SOREMPs) during the Multiple Sleep Latency Test (MSLT). According to extensive peer-reviewed literature, SOREMs do not make any meaningful or reliable distinction between idiopathic hypersomnia and narcolepsy without cataplexy, for which Xyrem is FDA indicated. In fact, there is no scientifically-validated test or set of symptoms which can reliably categorize hypersomnolent patients into these two categories. Some experts doubt that these two diagnostic entities represent different diseases at all. SOREMs are an arbitrary basis on which to deny care.
6. CareFirst's SOREM-based diagnostic distinction is also systematically discriminatory. The literature clearly shows the MSLT SOREM criteria are biased against recognizing narcolepsy in women, patients diagnosed later in life, and patients who require REM-suppressing medications. I am all three of these. CareFirst thus creates a barrier to effective care that operates systematically against patients like me.

In short, I will show that CareFirst's denial of my treatment as "not medically necessary" is contrary to their own medical policy, prior precedent, and established scientific and clinical evidence.

Xyrem, or its reformulation Xywav, represent the only safe and efficacious treatment available to me for a rare, disabling disease. Without Xyrem, I require higher doses of amphetamines to achieve even part of the functionality that Xyrem bestowed. I incur more cardiac risk for an inadequate and ever-diminishing clinical benefit. Every day that I am denied care, I experience a greater risk to my health and a lower quality of life than if I were being treated appropriately with Xyrem.

Effective treatment is called for in my contract. Xyrem is the one effective treatment to manage my disease.

Blue Cross Blue Shield, my care team, and I all have the same goal—the appropriate treatment and the best outcome for me. Two out of three of us already agree that Xyrem is the only way to achieve that. I believe that Blue Cross Blue Shield will reach the same conclusion when they give a careful review to this urgent appeal.

All that I ask is the same consideration, coverage and effective treatment which has been granted to other Blue Cross Blue Shield enrollees with idiopathic hypersomnia who have benefited from this treatment.

I request that CareFirst Blue Cross Blue Shield act swiftly to approve my medically necessary treatment with Xyrem. I look forward to a timely resolution of this matter, so that I may resume my badly-needed treatment and restore the effective management of my disease.

Respectfully,

Name

Enclosures

- Physician's letter of medical necessity, March 2020
- Physician's letter of medical necessity, June 2020
- Patient record from the Center for Sleep and Wake Disorders
- Subject Information Sheet and Informed Consent Form and Authorization to Use and Disclose Protected Health Information for Research, Study Number
- Pharmacy Reconsideration Upheld Notice from CareFirst
- Notice of Adverse Benefit Determination from CareFirst

Abbreviations

- BC/BS – Blue Cross Blue Shield
- EDS – Excessive Daytime Sleepiness
- ESS – Epworth Sleepiness Scale
- IH – Idiopathic Hypersomnia
- N1 – Narcolepsy Type 1, aka Narcolepsy with Cataplexy
- N2 – Narcolepsy Type 2, aka Narcolepsy without Cataplexy
- OR – Odds Ratio

Xyrem is Medically Necessary, per CareFirst Definition

The CareFirst Medical Policy on Orphan Drugs Covers Xyrem for Idiopathic Hypersomnia

CareFirst's denial states "Your appeal for Xyrem for the diagnosis of idiopathic hypersomnia has been determined as not medically necessary." However, this denial directly contravenes CareFirst's own Medical Policy on orphan drug use for rare diseases.

The CareFirst *Medical Policy Reference Manual*, section 5.01.001, "Off-Label and Orphan Drug Use", explicitly and plainly states that the **use of an orphan drug is considered medically necessary to treat a rare disease for which the drug has received an FDA orphan designation.**

"The use of an orphan drug is considered medically necessary when used for the approved orphan indication and/**or an orphan designation by the FDA** if supported by the following source.

- <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>

Any **other** use of an FDA-approved drug is considered experimental/investigational, as it does not meet TEC criteria # 1 - 5."

Please observe that CareFirst's policy explicitly does not limit coverage to FDA-approved orphan *indications*, but specifically and intentionally extends coverage to any FDA orphan *designation* for that orphan drug. Xyrem has had FDA orphan drug designation for the treatment of idiopathic hypersomnia since 7/31/2019. This designation is listed in the FDA's Orphan Drug Product designation database as CareFirst requires. Thus, Xyrem is clearly defined as medically necessary for IH under this policy. Also note that this policy re-emphasizes that such use of an orphan drug under this policy is **not** experimental/investigational, directly contrasting it to uses that are considered experimental/investigational.

The relevant record from the FDA website is shown in Figure 1, and may be viewed online at: <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=20196946>

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Generic Name:	Gamma-hydroxybutyric acid
Date Designated:	07/31/2019
Orphan Designation:	Treatment of idiopathic hypersomnia
Orphan Designation Status:	Designated
FDA Orphan Approval Status:	Not FDA Approved for Orphan Indication
Sponsor:	Jazz Pharmaceuticals Ireland Limited 5th Floor Waterloo Exchange Waterloo Road Dublin Ireland

The sponsor address listed is the last reported by the sponsor to OOPD.

*Exclusivity Protected Indications are shown for approvals from Jan. 1, 2013, to the present.

Figure 1: Xyrem's orphan designation for IH from the FDA

Note that Xyrem's designation for IH is listed under its generic chemical synonym, gamma-hydroxybutyric acid. To avoid any contest over chemical names in this appeal, let me preemptively clarify that orphan drug designation is given to an "active moiety", not a single small molecule, so that the designated orphan drug actually includes a set of closely related chemicals that include the various salts of the base molecule, which in this case is gamma-hydroxybutyric acid.

"Gamma-hydroxybutyric acid", "sodium oxybate", "Xyrem", and any other chemical names and drug formulations that employ gamma-hydroxybutyric acid as the active moiety are considered equivalent for the purposes of orphan drug designation under Federal Regulations (unless a new formulation is specifically shown to be clinically superior from the originally designated drug). The relevant passages read:

(2) Active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

And:

(14) *Same drug* means:

(i) If it is a drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.

(Orphan Drugs Rule, 21 C.F.R. §316.3, 2020)

Xyrem, and very recently Xywav, are the only FDA approved formulations of GHB currently available. With this understanding, I expect that CareFirst will now honor their policy on orphan drug use and approve my coverage for Xyrem without further delay.

The CareFirst Plan Criteria for Xyrem Prior Authorization Are Outdated, Inadequate, and Not Compatible with Medical Necessity

The rationale given by CareFirst for the denial of coverage fails to refer to the orphan drug policy at all. Did CareFirst's reviewer not bother consulting this policy, or did they deliberately ignore it? Was this anonymous board-certified sleep expert somehow unaware that Xyrem is an orphan drug or unaware that idiopathic hypersomnia is an orphan disease, and simply too careless to check the orphan designation?

I suspect this reviewer consulted nothing but the Prior Authorization Criteria for Xyrem, which were last reviewed by CareFirst in 2017. Xyrem had not yet received orphan drug designation for the treatment of idiopathic hypersomnia at that time. I assume that CareFirst does not intend for their orphan drug policy to apply to "all orphan designations except the ones for Xyrem."

Additionally, these Prior Authorization criteria are based on a scant six references. A quick examination reveals these to be irrelevant, inadequate, and/or outdated for addressing the use of Xyrem for idiopathic hypersomnia:

1. Xyrem [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; July 2017

2. Krahn, L, Hershner S, et al. Quality Measures for the Care of Patients with Narcolepsy; Journal of Clinical Sleep Medicine; 2015; 11(3): 335-55.
-

Irrelevant. These two references do not include IH in their scope, and so cannot possibly exclude IH as a treatment indication. The Xyrem package insert by legal definition can only include information related to on-label uses. Similarly, the practice recommendation deals exclusively with narcolepsy. You can't use a recipe for cake to claim that no one cooks chicken.

3. American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic and Coding Manual. 3rd edition. Westchester, IL: American Academy of Sleep Medicine; 2014.
-

Inadequate. Since this does not contain any data or recommendations for therapies, it is presumably included simply for its much-criticized and invalidated diagnostic criteria for the central hypersomnias. I have already provided extensive evidence that the MSLT SOREM criteria from the ISCD-3 are invalidated, unreliable, and discriminatory.

4. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc. Accessed November 2017.3.
 5. Micromedex Healthcare Series [database online]. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc. Accessed November 2017.
-

Inadequate and Outdated. A 2019 study has confirmed long-standing physician complaints that these two commercially-supplied drug compendias are frequently inconsistent with each other, outdated, and incomplete, especially for rare disease indications. Less than a third of a cross-sectional sample of 273 established treatments were included in either compendia, and roughly half of the diseases examined had 1 or fewer treatment options (45% in DRUGDEX; 68% in AHFS). The authors conclude:

“These shortcomings mean that patients with rare but treatable diseases may not be able to access necessary, evidence-based therapies when these compendia are used to make coverage determinations....Policies to reduce the reliance on these compendia for coverage determinations should be developed....It is likely that there must always be an option to use supplementary

evidence to support necessary treatments for patients with rare diseases and special conditions.”

(Barbieri et al. 2019)

I investigated the MicroMedex coverage of Xyrem, hypersomnias, and cataplexy and can confirm that the problems found above are relevant here. Micromedex coverage of these topics is rife with easily identifiable errors and omissions, as well as extremely outdated references.

For example:

- Micromedex includes no consult record nor any treatment recommendations for idiopathic hypersomnia at all, and it makes no distinction between narcolepsy with or without cataplexy.
- The consult record for narcolepsy cites no reference later than 2007, and includes a citation for "Recent findings in the diagnosis and treatment of disturbed sleep" from 1974.
- Two lists of cataplexy treatments—the treatments for cataplexy listed on the consult record for narcolepsy versus the treatments listed in the record "drugs that treat cataplexy"—are completely different lists with no drugs in common.

Clearly, Micromedex has no quality control for internal consistency, let alone evidence syntheses that are thorough and current.

I was unable to access AHFS-DI to compare, but I do note that it was found to be even less comprehensive than MicroMedex in the study cited above.

Obviously, the absence of a treatment indication in these two drug compendia does not indicate that such a treatment indication doesn't exist. These compendia are utterly, recklessly inadequate as the main resources on which to base drug coverage and denials.

6. Morgenthaler TI, Vishesh KK, Brown T, et al. Practice Parameters for the Treatment of Narcolepsy and Other Hypersomnias of Central Origin. *Sleep* 2007; 30(12):1705-11.

Inadequate and outdated. This practice recommendation, which does not mention the use of Xyrem for IH, is over a decade old. One can practically hear it creaking when it cites a 1988 study as evidence for modafinil. CareFirst ignores numerous more recent reviews and recommendations that include the recommendation of Xyrem for treatment-refractory IH.

In summary, the CareFirst Plan Criteria for Xyrem Prior Authorization are outdated, inadequate, and not compatible with CareFirst’s own definition of medical necessity. I expect they will correct the oversight this has created in my case, by swiftly approving my coverage for Xyrem.

Precedents in Xyrem for the Treatment of Idiopathic Hypersomnia

During the preparation of this document, I have put out a call for help to idiopathic hypersomnia support groups. Other patients and patient guardians have shared their information with me so that I may be covered for the same successful treatment with Xyrem that they have had.

I have gathered cases where insurers have approved and fully funded this drug for the treatment of idiopathic hypersomnia, including Blue Cross Blue Shield companies.

These insurers understand that there is no benefit in denying access to the most effective drug for a given individual with a rare, poorly-understood disease who requires individualized treatment. They recognize that the clinical standard of care for idiopathic hypersomnia includes sodium oxybate as an option for patients who have treatment-refractory hypersomnia.

All that I ask is the same treatment that Blue Cross Blue Shield has granted to subscribers like (Redacted) and (Redacted).

Table 1: Precedent for Insurance Approval for Xyrem to Treat Idiopathic Hypersomnia

IH Patient or Patient Guardian	Insurance Provider	Prescribing Doctor	Treatment First Approved
(Redacted)*	BC/BS of Alabama	Dr. James Roy	2009
(Redacted)*	Humana Employers Health Plan of Georgia	Dr. Lynn Marie Trotti	2014
(Redacted)*	Cigna HealthCare of North Carolina	Dr. Jeannie Gingras	2019
(Redacted)*	BC/BS of North Carolina	Dr. Jeannie Gingras	2020
(Redacted)	United HealthCare of Arizona	Dr. Paul Barnard	2017
(Redacted)	North Carolina Medicaid	Dr. Steve Thomas Kirk	2018
(Redacted)	Virginia Premier	Dr. Neil Crowe	2018

(Redacted)	Group Health Incorporated (EmblemHealth)	Dr. Micheal Thorpy	2016
(Redacted)	Aetna (Washington state)	Dr. Oneil S. Bains	2019
(Redacted)	United Health Care (Anthem)	Dr. Charu Sabharwal	2019

*Patient was approved for Xyrem treatment under multiple insurers on separate occasions.

The Evidence for Xyrem

Xyrem has Demonstrated Efficacy for this Patient

Clinical Trial Success

I know exactly how well Xyrem works for me, because I was a participant in a clinical trial for JZP-258, a low-sodium reformulation of Xyrem, which has now been approved to market as Xywav.

I enrolled in the clinical trial in May 2019. I took medication through the study from June 7th 2019 to March 12 2019, approximately 8 months.

I required a titration period of 12 weeks to reach my stable dosage of 5.25g, divided in two doses nightly. I had read that it takes months to reach the full benefits from Xyrem, so I was quite surprised to find my daytime sleepiness was dramatically improved almost immediately. Within just a few weeks, my Epworth Sleepiness Scale scores dropped from a very sleepy 15-16 to an 8-9—actually within “normal” range. As it turned out, that astonishing improvement was not the “full benefit.”

Over the course of months, I began to awake naturally with an internally regulated schedule, sometimes without the need for an alarm—an astonishing contrast to my previous severe morning sleep inertia. Getting up in the morning became a routine instead of a daily knock-down drag-out battle. These changes were so dramatic, I was able to decrease my amphetamine dose by 25% and still function better than I had before.

My absenteeism at work drastically declined. Previously, all of my sick leave and virtually all of my annual leave went to time off for exhaustion. Instead, I began to actually accumulate both. I thought I might someday go on a vacation again.

At home, I was able to start helping with housekeeping again. I started cooking healthful meals from scratch. I could walk my dogs again. I could work in my garden again. I was able to read for pleasure without falling asleep in my book.

I saw huge improvements to cognition. What patients refer to as “brain fog” gradually faded away. My train of thought stopped spontaneously dead-ending mid-sentence. I could focus for hours. I could remember things without writing them down. I could plan and coordinate. Analytical thought processes came back online. My work productivity skyrocketed.

Jazz Pharmaceuticals will not yet release my patient record from the trial. However, the specific instruments measuring my clinical improvement hardly capture the true extent of the benefits, despite my improvements on scales like the ESS. Nor are clinical phrases like “improved quality of life” and “cognitive function” are not very descriptive or specific. It is hard to quantify some parts of the extraordinary difference between my functionality and experience of life on Xyrem versus amphetamine stimulants alone.

Xyrem Corrects My Microarchitectural Sleep Abnormalities

I was not surprised that Xyrem was so effective for me. There are particular features of my case that logically made Xyrem more likely to help: namely, the abnormal features of my nighttime sleep, which are all perfect matches to the ways in which Xyrem affects sleep.

The supposedly “typical” description of IH sleep includes a very high sleep efficiency, few arousals, insensitivity to noise or other disturbances, a high slow-wave sleep percentage (“deep sleep”), and normal REM. My sleep is the opposite of this profile.

Aside from my lack of SOREMs, my sleep is characteristic of a “typical” narcolepsy patient. My sleep efficiency is normal, but moderate. My PSG shows hundreds of arousals and awakenings each night. I sleep shallowly and have never slept through an alarm. My slow-wave sleep percentage is around a third of what is normal, while my REM sleep is nearly double the normal amount. My sleep stage progression is highly disordered.

Almost nightly, I experience abnormal REM behaviors such as talking at length in my sleep, and frequently screaming, yelling, or even acting out my dream behaviors. This has been a life-long feature of my sleep, with onset in childhood long before antidepressants could increase the frequency of these occurrences. These behaviors are subclinical for REM sleep behavior diagnosis on my PSG, but such REM dysregulation is also generally characteristic of narcolepsy.

Xyrem promotes peaceful, uninterrupted sleep. Of particular benefit to me, it increases the slow-wave sleep I lack. It is one of only a handful of drugs known to do so. On Xyrem, my slow-wave sleep increased dramatically, according to the at-home single-channel EEG device I use to monitor my sleep. I slept through the night except when my alarm woke me for the mid-sleep dose. My REM behaviors stopped. In other words, Xyrem makes my sleep *normal*.

There Is No Alternative to Xyrem

Adding Xyrem is the only available course of treatment for me that is effective, and it is also safer than my current inadequate treatment. Without it, I have once again had to raise my dose of amphetamine, and with it, my risk of heart attack and stroke. I have significant genetic risk factors for heart disease. My function on amphetamines alone is a ghost of my functionality with Xyrem.

Xyrem Is the Standard of Care in the Scientific Literature and Clinical Community

Executive Summary

Xyrem is clearly included in the clinical standard of care for treatment-refractory idiopathic hypersomnia. Sodium oxybate has a documented history of use for the treatment of non-cataplectic hypersomnias of more than two decades. Xyrem was first FDA-approved for use in narcolepsy in 2002, and the peer-reviewed literature documents clinicians using it to treat idiopathic hypersomnia shortly thereafter (Ali et al. 2009). Numerous current literature reviews, practice guides, consensus statements, and clinical decision support tools confirm the recommendation of sodium oxybate for treatment-refractory idiopathic hypersomnia.

Current reviews and recommendations for the treatment of idiopathic hypersomnia consistently emphasize two important points:

1. Idiopathic hypersomnia requires carefully individualized treatment for each patient, because of the extreme variability seen in symptoms and treatment responses.
2. Xyrem is part of the clinically-accepted standard of care of treatment-refractory hypersomnia.

Major Consensus Treatment Guidelines

France's consensus treatment guidelines for the hypersomnias were updated in 2017, a decade more recent than the outdated American Association of Sleep Medicine guidelines from 2007:

The choice of treatment for IH patients resistant to modafinil and to methylphenidate requires the collective advice of the Narcolepsy-Hypersomnia Reference Centre....Recommendations: Sodium oxybate can be effective on EDS and sleep inertia in IH.

(Lopez, R et al. 2017. "French Consensus. Management of Patients with Hypersomnia: Which Strategy?" *Revue Neurologique* 173(1–2): 8–18.)

Of special note in the French consensus, the level of evidence for use of Xyrem is graded identically to the level of evidence for the use of dextroamphetamine—a drug widely used as a first- or second-line treatment strategy for IH. CareFirst approved dextroamphetamine to treat my hypersomnia with no difficulty.

Other Representative Literature Reviews and Practice Guides

"Studies illustrate the respective benefit of modafinil, sodium oxybate, pitolisant, mazindol, flumazenil, and clarithromycin in IH treatment."

(Arnulf, Isabelle, Smaranda Leu-Semenescu, and Pauline Dodet. 2019. "Precision Medicine for Idiopathic Hypersomnia." *Sleep Medicine Clinics* 14(3): 333–50.)

"Unlike modafinil and psychostimulants, [sodium oxybate] is not considered first or second line for IH treatment, but may be considered in individual, treatment-refractory cases."

(Saini, Prabhjot, and David B. Rye. 2017. "Hypersomnia: Evaluation, Treatment, and Social and Economic Aspects." *Sleep Medicine Clinics* 12(1): 47–60.)

"Treatment options for treatment-refractory IH [include] sodium oxybate, titrated up to 4.5 g twice nightly (separated by 2.5–4.0 h); mean dose in IH patients 4.3 g/night; lower than in patients with NT1"

(Trotti, Lynn Marie. 2017. "Idiopathic Hypersomnia." *Sleep Medicine Clinics* 12(3): 331–44.)

"Treatment for [non-cataplectic] hypersomnolence may have to be more aggressive (high-dose stimulants, sodium oxybate, etc.) on a case-by-case, empirical trial basis....

Sodium oxybate can help significantly, notably if sleep difficulties are present."

(Mignot, Emmanuel J.M. 2012. "A Practical Guide to the Therapy of Narcolepsy and Hypersomnia Syndromes." *Neurotherapeutics* 9(4): 739–52.)

Clinical Decision Support Tools

The literature I have cited is not obscure. The same recommendations are incorporated in the major evidence-based point-of-care tools, Dynamed and UpToDate. They reflect that same literature consensus, indicating the use of sodium oxybate as a therapy for IH in treatment-refractory cases.

UpToDate, similar to the French consensus, specifically treats sodium oxybate and amphetamines as second-line therapies which can be tried if treatment with modafinil fails. (Chervin, Ronald D. 2020. "Idiopathic Hypersomnia." In *UpToDate*, eds. Thomas E Scammell and April F Eichler. Waltham, MA: UpToDate)

"Treatment [for idiopathic hypersomnia] may include modafinil, armodafinil, methylphenidate, amphetamines, sodium oxybate, clarithromycin, flumazenil, or pitolisant....

Sodium oxybate may be considered in individual, treatment-refractory cases - consider dosing as in treatment for narcolepsy".

(DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T921449, Central Disorders of Hypersomnolence; [updated 2018 Nov 30, accessed 2020 Sep 4].)

Benefits for IH Are Unique to Xyrem

For IH patients who benefit from Xyrem, the effects are downright astonishing. The most important study released to date on Xyrem for IH compared 49 patients with either IH or N1 using sodium oxybate. It found that Xyrem is just as effective for daytime sleepiness in IH as it is in N1, even in patients who were refractory to stimulants. In addition, it found that Xyrem provides other major benefits to IH patients unique to this treatment, especially the reduction in disabling sleep inertia.

“The drug improved daytime sleepiness to the same degree as in patients with narcolepsy type 1. This improvement was observed despite the fact that SXB was used at a lower dose in IH than in NT1 and after patients had tried other stimulants.

In addition, the treatment reduced the severe morning inertia, facilitated sleep onset at night, and shortened the prolonged nighttime sleep of patients with IH.

A prominent result here is the clear benefit of SXB treatment on severe sleep inertia in patients with IH. **The drug improved severe sleep inertia in 71% of the hypersomnia patients.**

Severe sleep inertia is one of the most disabling symptoms in IH. To date, **no [other] drug has been shown to specifically improve this symptom.”** (*emphasis mine*)

(Leu-Semenescu, Smaranda, Pauline Louis, and Isabelle Arnulf. 2016. “Benefits and Risk of Sodium Oxybate in Idiopathic Hypersomnia versus Narcolepsy Type 1: A Chart Review.” *Sleep Medicine* 17: 38–44.)

CareFirst’s Denial Is Based on Invalidated and Irrelevant Diagnostic Criteria Executive Summary

“There is no pathognomonic sign or symptom that is diagnostic of IH.”

(Saini, Prabhjyot, and David B. Rye. 2017. "Hypersomnia: Evaluation, Treatment, and Social and Economic Aspects." *Sleep Medicine Clinics* 12(1): 47–60.)

The MSLT is the least discriminating test of daytime sleepiness.

(Johns, Murray W. 2000. "Sensitivity and Specificity of the Multiple Sleep Latency Test (MSLT), the Maintenance of Wakefulness Test and the Epworth Sleepiness Scale: Failure of the MSLT as a Gold Standard." *Journal of Sleep Research* 9(1): 5–11.)

The basis on which CareFirst separates patients into "narcolepsy" patients, who may be approved for Xyrem, and "idiopathic hypersomnia" patients, who may be denied, is the appearance of multiple sleep onset REM periods on the MSLT.

However, the SOREM test is extremely unreliable for making this categorization. It is also irrelevant to clinical management of the patient.

In the following sections I will demonstrate:

1. Multiple SOREMs cannot reliably categorize patients into the categories N2 and IH. The categorization is little better than chance.
2. Categories based on SOREMs are irrelevant to treatment, by both evidence and logic.
3. Multiple SOREMs are not an accurate biomarker for narcolepsy and have no meaning on an individual MSLT.

The following sections will show how the SOREM test and the MSLT have been proven by multiple studies to be unreliable for sorting any given patient into N2 and IH. In the largest study to date, they perform little better than chance. SOREMs are so poor a marker for narcolepsy that they do not even perform very well for diagnosing N1. SOREMs are an invalidated, arbitrary basis on which to deny care.

In fact, there is no set of symptoms or tests that can separate these entities reliably, there is no substantial knowledge of the etiology or pathophysiology of either entity, and multiple authors have made the obvious suggestion that they may not be separate disease entities at all.

Certainly there is no basis on which to treat them as separate for clinical management. There is no evidence that any drugs used to treat narcolepsy have a different effect in idiopathic

hypersomnia—and there is no plausible reason they *would*. All drugs tested work the same without regard for SOREMs, because SOREMs are not a meaningful marker for any pathology specific to narcolepsy. SOREMs are an irrelevant basis on which to deny care.

In other words, an idiopathic hypersomnia diagnosis is a narcolepsy diagnosis, by any and all measures that matter clinically. I know CareFirst would not want to deny me coverage for a necessary treatment based only on an invalidated and irrelevant “diagnostic” marker.

We should consider the current findings as a wakeup call...Moreover, we might consider focusing more on tests that can separate sleep disorders from life style disorders, **instead of trying to stick to unclear categories such as narcolepsy without cataplexy, which may only exist because of the existence of the MSLT.**

(Mayer, Geert, and Gert Jan Lammers. 2014. “The MSLT: More Objections than Benefits as a Diagnostic Gold Standard?” *Sleep* 37(6): 1027–28.)

The MSLT and SOREMs Do Not Reliably Categorize Patients into IH or N2

An accurate test should be reliable: it should give the same diagnosis to a given patient each time they take the test. Unfortunately, the only reliable thing about the MSLT is its incredibly poor performance. The SOREM criteria used on the MSLT to separate N2 and IH are particularly unreliable.

There is widespread agreement in the scientific community that this test is unacceptable for making a diagnostic distinction between N2 and IH.

The odds the test will yield the same results on repeat testing have been shown to be little better than chance. Surely CareFirst would not deny my care based on the outcome of a coin flip.

The continued use of SOREMs to distinguish narcolepsy without cataplexy from idiopathic hypersomnia is not justified.

The distinction between narcolepsy without cataplexy and idiopathic hypersomnia based on MSLT testing alone does not appear justified.

It is possible that idiopathic hypersomnia and narcolepsy without cataplexy are manifestations of the same underlying pathology or exist along a spectrum with overlapping features. Family studies of narcolepsy (with and without cataplexy) support this assertion, as family members of narcoleptics have higher rates of narcolepsy, but also of idiopathic hypersomnia, excessive daytime sleepiness, and abnormal multiple sleep latency tests."

(Trotti, Lynn Marie, Beth A. Staab, and David B. Rye. 2013. "Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia." *Journal of Clinical Sleep Medicine* 09(08): 789–95.)

The presented results suggest that **a positive MSLT is not a trait marker of narcolepsy without cataplexy**...What is the value of performing an MSLT in subjects without cataplexy when only 10% to 20% of those who have a positive initial MSLT show it four years later, as in this study?

(Mayer, Geert, and Gert Jan Lammers. 2014. "The MSLT: More Objections than Benefits as a Diagnostic Gold Standard?" *Sleep* 37(6): 1027–28.)

This finding is mirrored in the general population, in which the finding of multiple SOREMs has a kappa of only 0.1, that is, **repeatability is only minimally higher than expected by chance alone.**

(Trotti, Lynn Marie. 2017. "Idiopathic Hypersomnia." *Sleep Medicine Clinics* 12(3): 331–44.) referring to

The concordance for a positive MSLT [in N2] was quite low and not significantly different than controls.

[N2 and IH] are essentially diagnoses of exclusion that have relied upon a test prior to completion of proper validation studies. Diagnoses are therefore frequently rendered without regard to accumulating evidence that...test-retest reliability of the MSLT outside the context of NT1 appears poor.

A single positive MSLT as defined by ICSD-3 has little diagnostic value as currently defined...The continued use of the MSLT as per ICSD-3 to differentiate NT2 from IH should be reevaluated.

(Ruoff, Chad et al. 2018. "The MSLT Is Repeatable in Narcolepsy Type 1 But Not Narcolepsy Type 2: A Retrospective Patient Study." *Journal of Clinical Sleep Medicine* 14(01): 65–74.)

The PSG–MSLT measures and classification are not stable in patients with noncataplectic central disorders of hypersomnolence, with frequent diagnostic changes, particularly for NT2 and IH.

(Lopez, Régis et al. 2017. "Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence." *Sleep* 40(12).)

The MSLT was developed and validated as an aid in the diagnosis of narcolepsy [with cataplexy], and since then it has been shown to possess significant flaws of accuracy and precision....

Test-retest reliability outside of the context of NT1 appears poor.

(Saini, Prabhjot, and David B. Rye. 2017. "Hypersomnia: Evaluation, Treatment, and Social and Economic Aspects." *Sleep Medicine Clinics* 12(1): 47–60.)

These weaknesses result in low test-retest reliability of the MSLT.

(Baumann, Christian R. et al. 2014. "Challenges in Diagnosing Narcolepsy without Cataplexy: A Consensus Statement." *Sleep* 37(6): 1035–42.)

The lesson learned about the MSLT...is that we cannot continue to rely on "sleepability" as our most fundamental measure of the complex and multifaceted experience of hypersomnolence.

(Trotti, Lynn Marie. 2016. "Another Strike Against Sleepability." *Journal of Clinical Sleep Medicine* 12(04): 467–68.)

These results challenge generally accepted knowledge regarding the prevalence of narcolepsy without cataplexy and MSLT SOREMPs. Our results suggest...the need for re-evaluating the MSLT as a diagnostic tool for narcolepsy.

(Mignot, Emmanuel et al. 2006. "Correlates of Sleep-Onset REM Periods during the Multiple Sleep Latency Test in Community Adults." *Brain* 129(6): 1609–23.)

Mindful that the sensitivity and specificity of the MSLT is low for IH and narcolepsy type 2, we should allow a different approach in future classifications for patients who have genuine complaints of hypersomnolence but fail to have diagnostic MSLT results.

(Lammers, Gert Jan et al. 2020. "Diagnosis of Central Disorders of Hypersomnolence: A Reappraisal by European Experts." *Sleep Medicine Reviews* 52: 101306.)

Specific Findings

Goldbart, Aviv et al. 2014. "Narcolepsy and Predictors of Positive MSLTs in the Wisconsin Sleep Cohort." *Sleep* 37(6): 1043–51.

Note: the Kappa coefficient (κ) is a measurement of reliability that accounts for the possibility of agreement by chance. In biomedicine, a κ between 0-0.2 should be interpreted as "no agreement", with 0-4% of the data being reliable (McHugh 2012).

- A population-based longitudinal study, with PSG-MSLT repeated in 590 adults.
- After controlling for age, sex, shift work, short sleep, and sleep apnea:
 - $\kappa = 0.1$ for having ≥ 2 SOREMs on the MSLT (i.e., no agreement between tests)
 - $\kappa = 0.1$ for having a positive MSLT (again, no agreement between tests)

Ruoff, Chad et al. 2018. "The MSLT Is Repeatable in Narcolepsy Type 1 But Not Narcolepsy Type 2: A Retrospective Patient Study." *Journal of Clinical Sleep Medicine* 14(01): 65–74.

- Multi-center retrospective study of patients with at least 2 clinical MSLTs where at least one was positive for N2 (n=54)
 - 83% of cases changed diagnosis on repeat MSLT testing
 - 30% changed SOREM category (between multiple or non-multiple SOREMs)
 - 70% of N2 cases had one MSLT with < 2 SOREMs
 - MSLT concordance for N2 (N2 on both tests) was 17%
 - 26% of N2 cases also had a positive test for IH (14 of 54)
- Normal controls with at least 2 MSLTs were drawn from the Wisconsin Sleep Cohort for comparison. To adjust for differences in selection bias between the disease and control groups, only the subset with positive results on the first MSLT was examined (In N2, n=30, In controls, n=13). Multivariate analyses also controlled for age, sex, and medication status.
 - Adjusted MSLT repeatability for N2 in this subset was still only 30%.
 - Repeatability was not significantly different for NT2 cases versus controls.

Lopez, Régis et al. 2017. "Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence." *Sleep* 40(12).

- Multi-center retrospective study of patients with a primary hypersomnolence complaint, without cataplexy, who had at least two clinical MSLT under drug-free conditions (n = 75).
- 61% of patients changed diagnosis on repeat MSLT testing
 - 33% changed SOREM category (between multiple or non-multiple SOREMs)
- 50% of N2 cases also had one MLST with <2 SOREMs (14 of 28)
 - MSLT concordance for N2 (N2 on both tests) was 29% (8 of 28 N2 positive tests)
 - MSLT concordance for IH (IH on both tests) was 17% (5 of 29 IH positive tests)
- 18% of N2 cases also had a positive test for IH (5 of 28)

Trotti, Lynn Marie, Beth A. Staab, and David B. Rye. 2013. "Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia." *Journal of Clinical Sleep Medicine* 09(08): 789–95.

- Multi-center retrospective study of patients with a primary hypersomnolence complaint, without cataplexy, who had at least two clinical MSLT (n = 36).
- 53% of patients changed diagnosis on MSLT retesting
 - 31% changed SOREM category (multiple or non-multiple SOREMs)
- 47% of N2 cases had one MLST with <2 SOREMs (8 of 17)
 - MSLT concordance for N2 (N2 on both tests) was 29% (5 of 17 N2 diagnoses)
 - MSLT concordance for IH (IH on both tests) was 42% (8 of 19 IH diagnoses)
- 14% of patients diagnosed with N2 or IH shifted between those diagnoses

Huang, Yu-Shu et al. 2018. "Multiple Sleep Latency Test in Narcolepsy Type 1 and Narcolepsy Type 2: A 5-Year Follow-up Study." *Journal of Sleep Research* 27(5): e12700.

- 46 teenagers and young adults diagnosed with N2 in Taiwan repeated the MSLT every year for five years.
- 24% had <2 SOREMPs on at least one MSLT.
 - 11% had <2 SOREMPs on *multiple* MSLTs.

SOREMs Are Clinically Irrelevant for Treatment

There is no evidence or even a plausible basis for clinically-significant differences between narcolepsy and IH for any drug therapy. Instead, all drugs tested so far have shown similar performance across narcolepsy and IH, including Xyrem. This is unsurprising given that IH and N2 are diagnostically indistinguishable.

There is no evidence that the pathophysiology or therapeutic response is substantially different for hypersomnia with or without SOREMPs on the MSLT.

(Mignot, Emmanuel J.M. 2012. "A Practical Guide to the Therapy of Narcolepsy and Hypersomnia Syndromes." *Neurotherapeutics* 9(4): 739–52.)

[Poor sensitivity and specificity] and **the absence of apparent therapeutic or biological significance to multiple SOREMs** argue that the continued use of SOREMs to distinguish narcolepsy without cataplexy from idiopathic hypersomnia is not justified.

(Trotti, Lynn Marie, Beth A. Staab, and David B. Rye. 2013. "Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia." *Journal of Clinical Sleep Medicine* 09(08): 789–95.)

There is literally not a single drug that has shown efficacy for sleepiness in narcolepsy that has not also been effective when tested for IH.

Direct comparisons of treatment responses between IH patients and narcolepsy patients have all shown modafinil, mazindol, and Xyrem have similar benefits and risks in both groups:

[Xyrem] improved daytime sleepiness [in IH] to the same degree as in patients with narcolepsy type 1. This improvement was observed despite the fact that SXB was used at a lower dose in IH than in NT1 and after patients had tried other stimulants.

(Leu-Semenescu, Smaranda, Pauline Louis, and Isabelle Arnulf. 2016. “Benefits and Risk of Sodium Oxybate in Idiopathic Hypersomnia versus Narcolepsy Type 1: A Chart Review.” *Sleep Medicine* 17: 38–44.)

Modafinil produced a similar ESS change in IH patients and in narcolepsy patients and a similar benefit as estimated by the patients and clinicians.

(Lavault, Sophie et al. 2011. “Benefit and Risk of Modafinil in Idiopathic Hypersomnia vs. Narcolepsy with Cataplexy.” *Sleep Medicine* 12(6): 550–56.)

The benefit of mazindol on sleepiness...was important and similar in both groups.

(Nittur, Nandini et al. 2013. “Mazindol in Narcolepsy and Idiopathic and Symptomatic Hypersomnia Refractory to Stimulants: A Long-Term Chart Review.” *Sleep Medicine* 14(1): 30–36.)

Additionally, studies of modafinil and pitolisant conducted in IH patients alone have yielded similar benefits and side effect profiles as recorded for IH and narcolepsy elsewhere (Leu-Semenescu et al. 2014; Mayer et al. 2015). Additional drugs, particularly the various amphetamines, lack formal publications for IH, but have a very long clinical history of use in both groups.

SOREMs Are Not Specific or Sensitive for Narcolepsy even in N1

When the MSLT was designed in the 1970s, multiple SOREMs were thought to be pathognomonic for narcolepsy—a highly *specific* marker that was only observed in narcolepsy, and a highly *sensitive* marker that was observed in nearly all cases of narcolepsy. It is on this basis that the SOREM criteria were created.

We now know neither is the case.

First, the presence of multiple SOREMs does not indicate the presence of narcolepsy: Multiple SOREMs occur on MSLTs of 4-7% of normal adults and much more frequently in many

sleep-disordered conditions (Goldbart et al. 2014; E. Mignot et al. 2006; Singh, Drake, and Roth 2006).

Second, the absence of multiple SOREMs does not indicate the absence of narcolepsy: SOREMs frequently fail to occur as expected on the MSLTs of narcoleptics. This should be abundantly clear from the data on N2 presented already, but it is also true for N1, as I will show below.

Why am I bothering to explain this about N1? Because it further demonstrates how extraordinarily badly the MSLT fails at detecting narcolepsy of any kind, and how utterly meaningless the presence or absence of SOREMs is to narcolepsy for any individual MSLT.

Allen notes that the SOREM test for narcolepsy is so bad that **as a single predictor, it is actually more likely to be wrong than right**, and even more so in women than for men:

[Multiple SOREMs] occur in 13% of males and 6% of females, making it only somewhat more specific for narcolepsy than is average MSLT ≤ 8 min.

This lack of specificity is particularly important for a test to diagnose an uncommon disorder since it translates into very poor positive predictive value for the diagnosis. For example, in this study more than half of the males and 80% of the females with two SOREMs had an average MSLT > 8 min; **that is, the SOREM test alone is more likely to be false than true for the diagnosis of narcolepsy, particularly for females.**

(Allen, Richard P. 2006. "When, If Ever, Can We Use REM-Onset Naps on the MSLT for the Diagnosis of Narcolepsy?")

In the absence of a spinal tap or visible cataplexy, SOREM-lacking narcoleptics will be diagnosed with "idiopathic hypersomnia," like myself. The best estimates indicate that around 10-20% cases of N1 go undiagnosed on the MSLT, mostly due to the SOREM criteria, even though this is the patient group for which the MSLT is the most reliable. The false negative rate for N2, which can't be directly measured, can be assumed to be at least this high, but is likely much, much higher.

Unlike N2 or IH, N1 has two laboratory tests considered “gold-standard” diagnostics to which we can compare the MSLT: orexin deficiency in the cerebrospinal fluid or the presence of the high-risk allele (HLA)–DQB1*06:02 plus confirmed cataplexy. **In “gold standard” N1 patients, the MSLT fails 7-21% of the time, usually because of SOREM failures.**

- In the largest study to date, the MSLT was falsely negative in 9.7% of 1099 gold-standard N1 cases in the European Narcolepsy Network database. This was almost always because of the SOREM criteria: 9.6% of N1 cases had fewer than the “required” 2 SOREMs on the MSLT, with 3.9% having none at all.
(Luca, Gianina et al. 2013. “Clinical, Polysomnographic and Genome-Wide Association Analyses of Narcolepsy with Cataplexy: A European Narcolepsy Network Study.” *Journal of Sleep Research* 22(5): 482–95.)

This is in line with the false negative rates in other smaller “gold standard” based studies:

- Gabryelska et al. found the MSLT was falsely negative in 21% of 19 gold-standard N1 patients. SOREM criteria failed in 10.5%.
(Gabryelska, Agata et al. 2020. “Utility of Measuring CSF Hypocretin-1 Level in Patients with Suspected Narcolepsy.” *Sleep Medicine* 71: 48–51.)
- Mignot et al. found the MSLT was falsely negative in 14% of 90 gold-standard N1. SOREM criteria failed in all of these cases (14%).
(Mignot, Emmanuel et al. 2002. “The Role of Cerebrospinal Fluid Hypocretin Measurement in the Diagnosis of Narcolepsy and Other Hypersomnias.” *Archives of Neurology* 59(10): 1553–62.)
- Lopez et al found the MSLT was falsely negative in 27% of 22 gold-standard N1 patients. SOREM criteria failed in 5%.
(Lopez, Régis et al. 2017. “Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence.” *Sleep* 40(12).)
- Andlauer et al. found the MSLT was falsely negative in 7.1% of 516 gold-standard N1 patients. The number due to SOREM failure was not broken out in this study, but it was mentioned explicitly as occurring.
(Andlauer, Olivier et al. 2013. “Nocturnal Rapid Eye Movement Sleep Latency for Identifying Patients with Narcolepsy/Hypocretin Deficiency.” *JAMA Neurology* 70(7): 891–902.)

Studies still reach similar estimates for the false negative rates of the MSLT and SOREM criteria when using slightly less stringent criteria for the N1 “gold standard”, such as confirmed cataplexy plus abnormal scores on the Epworth Sleepiness Scale:

- Aldrich et al. found the MSLT failed in 29% of 106 N1 patients. SOREM criteria failed in 26%, with 13% displaying no SOREMs at all.
(Aldrich, Michael S., Ronald D. Chervin, and Beth A. Malow. 1997. “Value of the Multiple Sleep Latency Test (MSLT) for the Diagnosis of Narcolepsy.” *Sleep* 20(8): 620–29.)

Studies of test-retest reliability for N1, with patients taking the MSLT twice, also confirm similar false negative rates:

- Lopez et al found the MSLTs failed in 19% in 16 N1 cases. SOREM criteria failed in 6%.
(Lopez, Régis et al. 2017.)
- Ruoff et al. found the MSLTs failed in 28% of 60 N1 cases. SOREM criteria failed in 23%.
(Ruoff, Chad et al. 2018.)

Allen supplies the inescapable community-wide conclusion with an almost humorous understatement:

Overall the results are not very supportive of SOREMs as a specific test for narcolepsy....

Massive under-diagnosis certainly seems possible.

(Allen, Richard P. 2006.)

SOREM Criteria Discriminate Based on Sex, Age, and Medication Status

Executive Summary

Using SOREMs as the sole diagnostic criteria to separate patients into N2 and IH isn't simply arbitrary: it is also discriminatory. Certain groups of people are far more likely to experience SOREMs, *independent* of narcolepsy.

In this part of my appeal, I will explain how the SOREM criteria are biased based for sex, age, and medication status. This makes SOREMs an inherently discriminatory method of diagnosis—and thus an inherently discriminatory barrier to effective care for women, older adults, and patients who rely on REM-suppressing medications.

This section provides a summary. The sections that follow provide the evidence base from the scientific literature.

SOREM frequency is inherently age- and sex-dependent, across healthy people as well as sleep disordered populations. Older adults and women are each dramatically less likely to experience SOREMs on the MSLT due to **intrinsically** lower REM-propensity with age and with female sex, unrelated to narcolepsy pathology.

Similarly, patients who rely on REM-suppressing medications obviously have a lower REM propensity than patients who are not using such medications. They are less likely to display SOREMs, for reasons that are unavoidable for practical purposes.

Many common neurological medications are REM-suppressing, such as SSRI and SNRI antidepressants. It is unreasonable and irresponsible to expect patients with disorders like depression, anxiety, bipolar disorder, chronic pain, or epilepsy to risk dangerous and painful relapses by discontinuing their medication for weeks prior to the MSLT.

Furthermore, if they were to relapse, many of these patients would become ineligible for *any* primary hypersomnia diagnosis: a positive MSLT during such a relapse would be considered invalid. The ICSD-3 diagnostic criteria for primary hypersomnias require first ruling out other possible causes of sleepiness, like uncontrolled depression or epilepsy. With both the original disorder and the treatment as potential confounding factors, the SOREM criteria arbitrarily reduce the chance these patients will receive a narcolepsy diagnosis, *no matter what they chose to do*.

Despite this knowledge, the diagnostic criteria for narcolepsy and IH are not adjusted for age, sex, or medication status. CareFirst also does not adjust for age, sex, or medication status in the Prior Authorization Criteria for Xyrem, to compensate for this bias in the diagnostic criteria. This means that women, older adults, and patients reliant on REM-suppressing medication are more likely to be denied coverage for Xyrem, based on a measure inherent to these population groups, not a measure inherent in their actual disease pathology, symptoms, clinical needs, or clinical response to Xyrem.

I am a member of all three of these groups unfairly disadvantaged by SOREM criteria:

- I am a woman.
- I am a patient reliant on REM-suppressing antidepressants to control depression that is otherwise severe, and pain that otherwise disturbs my sleep.
- I was first tested for hypersomnia at the age of 35, well past the mean for adult SOREM propensity. If I were to retake the test now, my chance of exhibiting SOREMs would be even lower.

My odds of being diagnosed with narcolepsy rather than idiopathic hypersomnia were reduced many times over for reasons utterly unrelated to disease pathology.

Surely CareFirst does not want to deny women, older adults, and patients with depression equal access to effective treatments, based solely on criteria that the published scientific literature has criticized and rejected so thoroughly. I request that CareFirst adjust appropriately for my sex, age at diagnosis, and required medications, and approve my treatment with Xyrem without regard to SOREMs.

Age: The MSLT Discriminates Based on Age

Reduced incidence of SOREMs is an intrinsic feature of age, across both healthy and sleep-disordered populations. Across both healthy and sleep-disordered populations, age has been confirmed as a highly predictive and highly significant variable for SOREMs. Incidence of SOREMs appears to decrease beginning in the late 20s.

This means that the later in adulthood that patients are tested, the less likely they are to be diagnosed with narcolepsy and more likely to be diagnosed with IH--not because narcolepsy magically disappears with age, but because older adults intrinsically have fewer SOREMs than younger adults.

The progressive decrease in the number of SOREMP and increase in the mean sleep latency on the MSLT as a function of age suggest that the current criteria used for diagnosis may be too stringent in older patients. **The major influence of age on MSLT results should therefore be taken into account when diagnosing a narcoleptic patient.**

(Dauvilliers, Y. et al. 2004. "Effect of Age on MSLT Results in Patients with Narcolepsy-Cataplexy." *Neurology* 62(1): 46–50.)

[Our study] highlights the reduced sensitivity of the MSLT in detecting narcolepsy in older individuals. This conclusion is based on the growing literature substantiating age-related decline in nocturnal and diurnal REM amount.

(Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." *Sleep Medicine* 55: 115–23.)

Age-related changes in MSLT outcomes, including a decrease in the number of SOREMPs and increase in the mean sleep latency with increasing age, as well as poor reliability and lack of adequate normative data in children and adolescents, reduce interpretability of the MSLT.

(Ruoff, Chad, and David Rye. 2016. "The ICSD-3 and DSM-5 Guidelines for Diagnosing Narcolepsy: Clinical Relevance and Practicality." *Current Medical Research and Opinion* 32(10): 1611–22.)

Findings in General or Healthy Populations:

Goldbart, Aviv et al. 2014. "Narcolepsy and Predictors of Positive MSLTs in the Wisconsin Sleep Cohort." *Sleep* 37(6): 1043–51.

-
- Population-based longitudinal study
 - 1,135 randomly-invited subjects completing at least 1 PSG-MSLT
 - Strongly confirmed prevalence of multiple SOREMPs decreases with age, with variable significance of $p = 0.005$

Findings in Hypersomnolent Patients:

Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." *Sleep Medicine* 55: 115–23.

- Multi-center retrospective analysis of 2,498 cases evaluated for hypersomnolence.
- Age was a strong predictor for SOREMs frequency, with older age correlated to fewer SOREMs.
- Patients over the age of 21, compared to patients age 13-21, had less chance of displaying any SOREMs on the MSLT overall, and for each nap individually. See Figures 2 and 3.

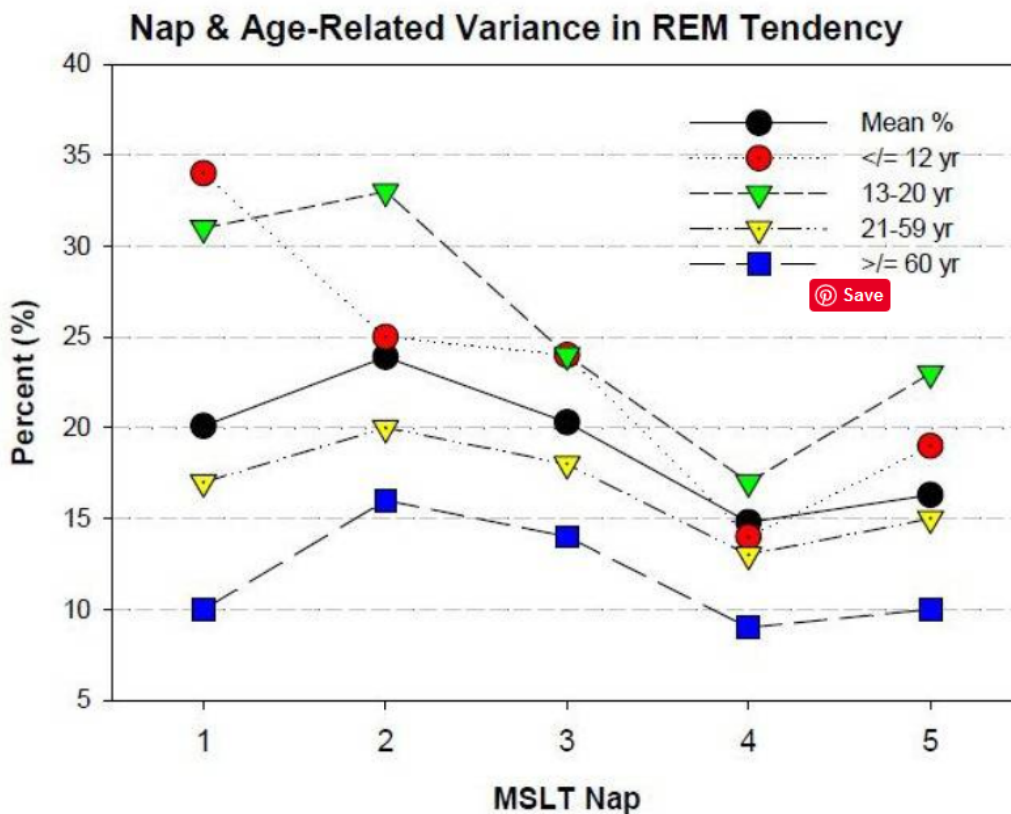


Figure 2: Nap and Age-Related Variance in SOREM (from Cairns et al.)

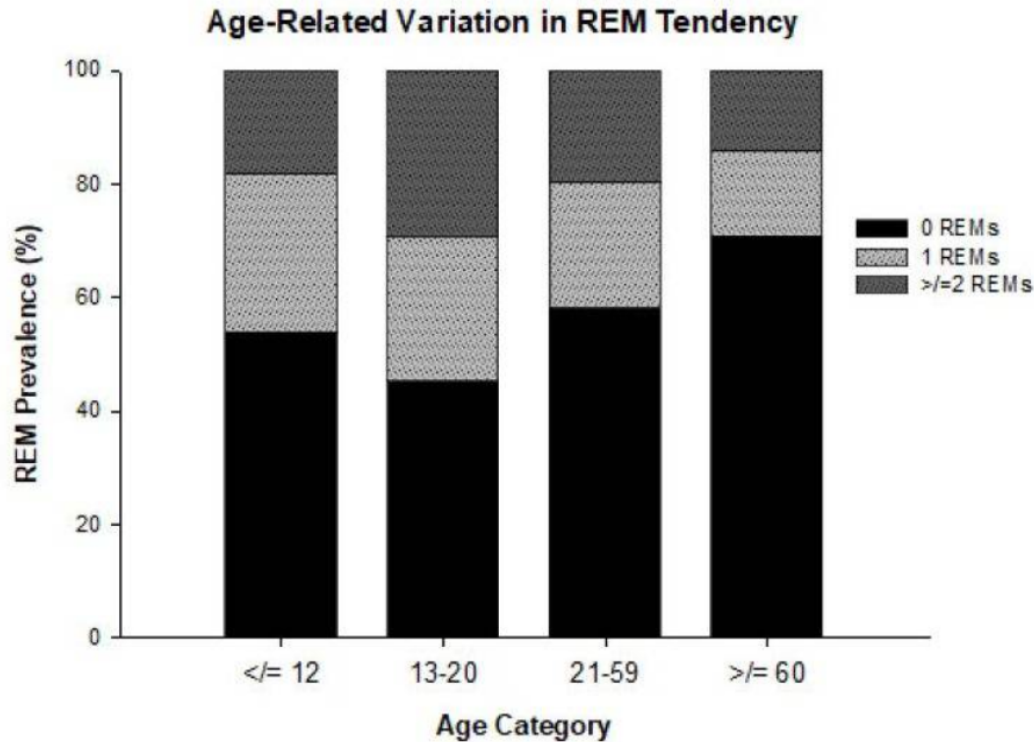


Figure 3: Age-Related Variation in SOREM (from Cairns et al)

Sansa, Gemma et al. 2014. "Non-Random Temporal Distribution of Sleep Onset REM Periods in the MSLT in Narcolepsy." *Journal of the Neurological Sciences* 341(1-2): 136-38.

- Single-center study of PSG-MSLTs from 129 patients with N1 or N2.
- Patients older than 29 years had fewer SOREMs than patients age 11-28 (p 0.045).

Sex: the MSLT discriminates against women

Men display more SOREMs than women, across healthy and sleep-disordered populations. This is one of the strongest predictors of SOREMs, and is understood to be due to an intrinsic sex-based difference in REM sleep regulation.

Thus, men are more likely than women to receive narcolepsy diagnoses because of differences in SOREM propensity that are sex-based, not narcolepsy-based. Men are thus more likely than women to be authorized for Xyrem and other "narcolepsy-only" drugs from CareFirst, simply because they are *male*. By the same effect, women like me are more likely to receive an idiopathic hypersomnia diagnosis instead, and thus less likely to be covered for the same range of effective therapies as hypersomnolent men.

Findings in General or Healthy Populations:

Goldbart, Aviv et al. 2014. "Narcolepsy and Predictors of Positive MSLTs in the Wisconsin Sleep Cohort." *Sleep* 37(6): 1043–51.

- Population-based longitudinal study
- 1,135 randomly-invited subjects completing at least 1 PSG-MSLT
- Strongly confirmed prevalence of multiple SOREMs decreases with age
- Men were nearly 3 times more likely than women to have multiple SOREMs on the MSLT controlled for age, shift work, and short sleep (OR 2.75, $p = < 0.0001$)

These results confirmed earlier smaller samples from this cohort. The authors at that time concluded:

The occurrence of SOREM is strongly sex-dependent.

None of the parameters found to be significant in males with SOREM predicted SOREMs in females, **suggesting fundamental differences in REM sleep regulation between the sexes.**

(Mignot, Emmanuel et al. 2006. "Correlates of Sleep-Onset REM Periods during the Multiple Sleep Latency Test in Community Adults." *Brain* 129(6): 1609–23.)

Bishop, Christopher et al. 1996. "The Frequency of Multiple Sleep Onset REM Periods among Subjects with No Excessive Daytime Sleepiness." *Sleep* 19(9): 727–30.

- Single-center study of PSG-MSLTs in 139 healthy, drug-free volunteers
- PSG indicated no sleep apnea and adequate TST (total sleep time)
- Men were 3 times as likely as women to display multiple SOREMPs

Findings in Sleep Apnea Patients:

Chervin, Ronald D., and Michael S. Aldrich. 2000. "Sleep Onset REM Periods during Multiple Sleep Latency Tests in Patients Evaluated for Sleep Apnea." *American Journal of Respiratory and Critical Care Medicine* 161(2 I): 426–31.

- Single-center retrospective analysis of PSG-MSLTs of 1,145 patients evaluated for suspected sleep apnea and not suspected of central hypersomnias, and free from psychoactive drugs
- Men were nearly 4.4 times more likely than women to have multiple SOREMs on the MSLT, in a study of patients with sleep apnea (OR 4.380, $p = 0.0002$)
- This difference was not related severity or frequency of apnea events or REM pressure as shown on PSG
- Male sex was the strongest predictor of having ≥ 2 SOREMs out of any predictive variables

Findings in Hypersomnolent Patients:

Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." *Sleep Medicine* 55: 115–23.

- Multicenter retrospective analysis of PSG-MSLTs of 2,498 patients evaluated for suspected hypersomnias.
- The largest database of clinical PSG-MSLTs published to date.
- Men were 1.5 times more likely than women to have multiple SOREMs on the MSLT (OR: 1.49).
- Women and men were equally likely to meet the diagnostic threshold for sleep latency.
- This allowed men to qualify for a narcolepsy diagnosis about 1.5 times more often than women (OR: 1.55), while women were more likely to get an IH diagnosis instead (Male OR: 0.58).
- Results were controlled for age, race, and the use of REM-suppressing medications.

The authors concluded:

Because the diagnostic criteria for N2 and IH differ only in number of MSLT SOREMPs, an underlying gender difference in REM propensity would tend to systematically increase the percentage of sleepy women, relative to men, diagnosed with idiopathic hypersomnia.

Medication Status: The MSLT Discriminates Against People Who Require REM-Suppressing Medications

REM-suppressing medications have been shown to reduce SOREMs in multiple large studies, in the general population as well as sleep-disordered patients. See findings subsections below.

Sleepy patients who rely on REM-suppressing medication have two choices on their MSLT: bad and worse. Do they keep the psychiatric disorder under stable control but accept a greatly reduced chance of a narcolepsy diagnosis and medication access? Or do they risk a (dangerous, painful) relapse that may actually prevent a receiving sleep diagnosis *at all*?

Prior to my MSLT, I was not even informed my medication could affect my results, let alone instructed to discontinue it. However, even if it had been recommended, I could not have safely done so. I am not alone:

Despite the recommendation that patients should “ideally” stop REM suppressants for at least two weeks prior to testing, only 5.9% of patients taking ≥ 1 REM suppressant agent suggested that they refrained from said compound(s) prior to the MSLT.

(Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. “Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance.” *Sleep Medicine* 55: 115–23.)

Even if I had withdrawn from my medication, it is unclear when I would have needed to do so in order to have “valid” results. Timeframes for withdrawal are not standardized, let alone tested and validated.

There is also a lack of consensus on how long a patient should be free from psychoactive medications, most of which suppress REM sleep, before performing a PSG followed by MSLT. Moreover, in some clinical situations, it may not even be clinically feasible that medications be discontinued (e.g., antidepressant therapy).

(Ruoff, Chad, and David Rye. 2016. “The ICSD-3 and DSM-5 Guidelines for Diagnosing Narcolepsy: Clinical Relevance and Practicality.” *Current Medical Research and Opinion* 32(10): 1611–22.)

Medications such as antidepressants or other psychotropic drugs may significantly affect REM sleep for weeks or months after discontinuation, but management of these medications is not uniformly defined for MSLT protocols.

(Baumann, Christian R. et al. 2014. "Challenges in Diagnosing Narcolepsy without Cataplexy: A Consensus Statement." *Sleep* 37(6): 1035–42.)

Despite widespread understanding that patients on REM-suppressing medications are unlikely to display SOREMs, CareFirst has made no adjustment to the diagnostic interpretation for medication status nor any compensation for it in the Xyrem authorization criteria. I respectfully request that CareFirst take into consideration the known effects that my REM-suppressing medication would have on my diagnosis for hypersomnolence, consider the risks and inherent Catch-22 of discontinuing it, and reverse my denial of coverage for Xyrem.

Findings in General or Healthy Populations:

For REM suppressant antidepressants such as SSRI, decreased antidepressant intake was observed in volunteers with SOREMPs.

(Mignot, Emmanuel et al. 2006.)

Findings in Hypersomnolent Patients:

Kolla, Bhanu Prakash et al. 2020. "Advance Taper of Antidepressants Prior to Multiple Sleep Latency Testing Increases the Number of Sleep-Onset Rapid Eye Movement Periods and Reduces Mean Sleep Latency." *Journal of Clinical Sleep Medicine*.

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- Single-center study of PSG-MSLTs from 502 patients with suspected primary hypersomnolence, with 178 taking REM-suppressing antidepressants.
 - **Patients who tapered off their antidepressant before the MSLT were more than 12 times as likely to have ≥ 2 SOREMs compared to patients still taking their antidepressants during the MSLT (OR=12.20).**

- They were also more than 2 times as likely to have ≥ 2 SOREMs compared to patients who simply did not take antidepressants at all (OR=2.22), as well as shorter sleep latencies ($p > 0.009$).
- Regression analysis controlled for multiple confounders.

Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." *Sleep Medicine* 55: 115–23.

- Multi-center retrospective analysis of 2,498 cases evaluated for hypersomnolence
- REM-suppressant use was associated with reduced odds of ≥ 2 REMs (OR: .52, $p < .001$)
- And also reduced odds of MSLTs consistent with narcolepsy (OR: .60, $p = .008$)
- Results were controlled for age, gender, and race

The authors concluded:

We have now demonstrated a substantial association between REM suppressant use (specifically antidepressants and antipsychotics) and reduced MSLT SOREMPs/MSLT consistent with narcolepsy.

Conclusions

In conclusion, when considering this appeal, it behooves CareFirst to consider:

1. Coverage of Xyrem for idiopathic hypersomnia is considered medically necessary, according to CareFirst's medical policy on orphan drugs.
2. The efficacy and medical necessity of Xyrem has been established in my personal case with an extended clinical trial of JZP-258, a formulation of the same active moiety as Xyrem.
3. Xyrem has been accepted as standard of care for over ten years by the relevant medical community, with peer-reviewed evidence for the safety and efficacy of this treatment for cases like mine.
4. This standard of care is reflected in prior precedents for coverage of Xyrem for idiopathic hypersomnia.

5. CareFirst has based its previous denials on diagnostic criteria that I have demonstrated are:
 - a. Unreliable for differentiating between N2 and IH;
 - b. Unrelated to treatment efficacy;
 - c. Systematically discriminatory to patients like me who are women, diagnosed at an older age, and require REM-suppressing medications.

In this light, we can now reassess each of the claims made by CareFirst's anonymous reviewer in their denial letter:

"Your appeal for Xyrem for the diagnosis of idiopathic hypersomnia has been determined as not medically necessary. Per physician review, current Xyrem plan criteria and current medical literature do not support the use of Xyrem as medically necessary in this case."

CareFirst's current medical policy on orphan drug use clearly covers the use of Xyrem for idiopathic hypersomnia, because Xyrem is an FDA-approved drug that has an orphan drug designation for idiopathic hypersomnia. CareFirst's prior approval criteria for Xyrem have not been updated to reflect this recent designation. The prior approval criteria furthermore rely on a scant six references that are collectively irrelevant, outdated, incomplete, and unreliable. I have provided far more extensive, current, and comprehensive medical literature demonstrating that Xyrem is medically necessary for non-cataplectic hypersomnia.

In fact, I have supplied clinical evidence from my own treatment with Xyrem that it improves my severe disabling hypersomnia symptoms, that it does so more effectively than my current treatment with amphetamines or any alternatives available to me, and that it allows me to reduce the cardiac risk of my current treatment by reducing my amphetamine dosage. It would be literally impossible for me to provide better evidence that Xyrem is "medically necessary in this case," because I have already provided **direct clinical evidence of both need and efficacy for my specific case**.

"Xyrem has been approved by the Food and Drug Administration (FDA) for the management of patients with narcolepsy with or without cataplexy. The medical literature does not support the use of Xyrem in patients with other forms of daytime sleepiness, including patients with idiopathic hypersomnia."

The reviewer demonstrates a lack of familiarity with the medical literature on this subject, as well as a fundamental inability to synthesize what the evidence shows about the efficacy of the drug. Hundreds of articles support the use of Xyrem in numerous non-narcoleptic daytime sleepiness

disorders, including idiopathic hypersomnia. These include retrospective and prospective studies demonstrating efficacy for excessive daytime sleepiness in at least four other diseases, including large randomized controlled clinical trials for Parkinson's disease and fibromyalgia. The fact that Xyrem has shown efficacy for excessive daytime sleepiness in multiple diseases which do not share N1 pathophysiology indicates that its mechanism of action is not narcolepsy-dependent, and that its valid off-label uses are much broader than CareFirst acknowledges.

Moreover, I have provided extensive, compelling evidence that idiopathic hypersomnia is clinically indistinguishable from narcolepsy without cataplexy for the purposes of both diagnosis and treatment. This evidence from the literature only provides additional legitimacy to the efficacy that Xyrem has already demonstrated in my individual case.

“There is no evidence in terms of large randomized trials that supports the long-term effectiveness and safety of Xyrem in the management of patients suffering from idiopathic hypersomnia.”

CareFirst's orphan drug policy is designed to recognize that orphan disease patients may never have *any* treatment options that are supported by “large randomized trials.” Not only do drug companies lack the financial incentive to develop drugs specifically for small patient populations with poorly understood diseases, but it can be literally impossible to gather a large simultaneous cohort for something that is *definitionally rare*. Thankfully, this does not mean that there are no effective treatments available for rare disease patients. CareFirst's orphan drug policy is designed to give orphan disease patients like myself access to treatments where efficacy is supported by a level of evidence that is reasonable in relation to the rarity of these diseases. With this understanding of rare diseases, CareFirst relies instead on the evaluation that the FDA makes when designating an orphan drug: an evaluation of “a medically plausible basis” and “clinical experience with the drug in the rare disease.” (21 C.F.R. §316.20.) For the use of Xyrem in idiopathic hypersomnia, we are fortunate to have decades worth of such evidence.

Indeed, CareFirst did not apply this unreasonable standard for “large randomized trials” specific to my rare diagnosis to any other drugs it has approved for my hypersomnia treatments. There are no randomized trials for IH regarding mixed amphetamines, dextroamphetamine, clarithromycin, or bupropion. The randomized trial for modafinil has only 33 patients, because the trial failed to recruit its full target of *40 patients*. Clearly, the clinical community does not share the specious expectations of CareFirst's anonymous reviewer when treating rare diseases, because modafinil is consistently recommended as the first-line treatment for idiopathic hypersomnia. In fact, all of these drugs were approved by CareFirst for my treatment,

presumably based on the strength of the sleep medicine clinical community consensus. That consensus is based on other types of published clinical evidence in IH, plus accumulated clinical experience with IH patients in practice, plus a cautious assumption that drug efficacy demonstrated in narcolepsy was likely to apply across the spectrum of central hypersomnias. This assumption is particularly justified given that N2 and IH are so *very* similar that they have proven to be diagnostically indistinguishable.

“There is a lack of evidence that Xyrem can improve overall clinical condition in patients with idiopathic hypersomnia.”

On the contrary, the existing literature indicates that not only is Xyrem just as efficacious in IH as it is in narcolepsy for excessive daytime sleepiness, but it also alleviates the otherwise intractable and disabling symptom of severe morning sleep inertia—a benefit that is unique to Xyrem among IH treatments so far.

As I have already stated above, there is not only evidence that Xyrem benefits idiopathic hypersomnia patients generally, but also compelling evidence that it benefits *me* specifically, as I demonstrably benefited from my treatment with an equivalent drug over an extensive clinical trial period of nine months.

The hypersomnia literature repeatedly emphasizes that best practices for care require customizing treatment according to individual patient response. My documented treatment response would be considered strong evidence of the efficacy of Xyrem for my individual case by any remotely reasonable clinician, and the established standard of individualized care for hypersomnia treatment demands that it be a primary consideration here.

I hope this appeal has been helpful in demonstrating that CareFirst has a clear prerogative to overturn the errors of this anonymous reviewer. I appreciate CareFirst promptly reevaluating this case, and request that they act swiftly to approve my coverage for Xyrem.

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