

## Stimulant Use in Excessive Somnolence Disorders

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Excessive daytime sleepiness (EDS), that interferes with an individual's daily activities has a direct impact on the quality of life of patients, as it can affect social aspects, occupation, education, and functional status (i.e. increased risk of traffic accidents while driving).<sup>1</sup> Approximately 20% of the general population is afflicted with EDS, although consistency in defining, measuring, and evaluating daytime sleepiness has not been clearly defined.<sup>2</sup> Funded conditions associated with EDS include sleep apnea, narcolepsy and cataplexy. General hypersomnia is unfunded by the Oregon Health Authority (OHA) as primary first line therapies for hypersomnia often rely on treatment of the underlying comorbid condition, lifestyle changes, and non-pharmacological interventions. The purpose of this newsletter is to explore and compare pharmacologic treatment options for EDS associated with narcolepsy or obstructive sleep apnea (OSA) unresponsive to sleep hygiene or nonpharmacological therapies.

EDS is evaluated by a variety of metrics including the maintenance of wakefulness test (MWT), which examines a patient's capacity to combat sleepiness in a calming and neutral laboratory setting, and Epworth Sleepiness Scale (ESS), which is a patient-rated subjective score of theoretical scenarios measuring the likelihood the patient would fall asleep.<sup>3,4</sup> There is no evidence to suggest changes in MWT correlate with improvement in patient outcomes. Changes in ESS are considered clinically meaningful with a reduction of at least 25%.<sup>5,6</sup> Both of these metrics are commonly used as endpoints in clinical trials, though it is uncertain if either endpoint correlates with realistic improvements in quality of life. The goal of therapy is to increase alertness during "normal" waking hours to allow a better coordination for work, school, driving, and other social and behavioral activities.

### Pharmacologic Treatments for Excessive Daytime Sleepiness

Commonly used drugs for EDS include dopamine reuptake inhibitors (modafinil, armodafinil), sympathomimetic agents (methylphenidate, mixed amphetamine salts), dopamine and norepinephrine reuptake inhibitor (solriamfetol), and central nervous system depressant (sodium oxybate). All of these therapies have the potential for abuse and are controlled substances: methylphenidate (CII), amphetamine salts (CII), sodium oxybate (CIII), modafinil (CIV), armodafinil (CIV) and solriamfetol (CIV).

Modafinil has demonstrated effectiveness in treating daytime sleepiness due to narcolepsy at a recommended dose of 200

mg once daily.<sup>1</sup> Increases in MWT ranged from 8.1 to 8.9 minutes compared to 5.1 minutes for placebo ( $p < 0.05$ ) and changes in ESS score decreases were 13.0 to 14.4 versus placebo increase of 17 ( $p < 0.001$ ). There is no evidence to suggest that doses beyond 200 mg confer additional benefit.<sup>7</sup>

Armodafinil, is the R-enantiomer of modafinil, Changes in MWT from baseline to 12 weeks for armodafinil was an increase of 1.3, 2.6, and 1.9 minutes in the 150 mg, 250 mg, and combined groups, respectively, compared with a decrease of 1.9 minutes for placebo ( $p < 0.01$  for all three active treatments vs. placebo comparisons).<sup>7</sup> A head-to-head comparison of both drugs showed similar efficacy in the treatment of excessive sleepiness due to sleep work disorder (SWD).<sup>8</sup>

Methylphenidate has had a long history of use in EDS with success in reducing sleepiness symptoms by inhibiting reuptake of dopamine and norepinephrine into presynaptic nerve terminals. However, doses required to obtain therapeutic levels and desired outcomes are correlated with an increased risk of adverse events, including abuse and dependence.<sup>9</sup> Methylphenidate is associated with more side effects compared to other EDS treatments, which include adverse cardiovascular events (i.e. hypertension, arrhythmias), psychoses, and diminished seizure threshold.<sup>10</sup>

Amphetamines such as mixed amphetamine salts (dextroamphetamine/amphetamine) and dextroamphetamine (Dexedrine) are also used as EDS agents, though typically considered second-line due to adverse effects and risk of abuse.<sup>11</sup> Amphetamine salts act primarily by promoting release of dopamine and norepinephrine from presynaptic nerve terminals. This drug class has a history of success and efficacy for EDS; however, high dose requirements promote development of significant adverse effects similar to methylphenidate (cardiovascular effects, psychoses, and dependency).<sup>9</sup>

Sodium oxybate, a GABA derivative that acts as an inhibitory chemical transmitter in the brain, approved by the Food and Drug Administration (FDA) for the treatment of EDS due to narcolepsy in patients aged 7 years and older. Sodium oxybate is currently available only through the Xyrem<sup>®</sup> REMS Program due to risk of central nervous system depression and potential for abuse/misuse.<sup>12</sup>

Concomitant use of modafinil with sodium oxybate has shown additive effects and subsequent improvement from baseline in EDS outcomes compared to sodium oxybate monotherapy or placebo: MWT +2.68, +0.58, and -2.72 minutes, respectively ( $p < 0.001$  for combined therapy vs monotherapy and combined therapy vs placebo) and ESS -4.0, -3.0 and 0.0 minutes, respectively ( $p < 0.001$  for combined therapy vs monotherapy and combined therapy vs placebo).<sup>13</sup>

Solriamfetol was approved in 2019 and has demonstrated improved MWT and ESS compared to placebo for patients with OSA or narcolepsy.<sup>14</sup> Clinical trial data for solriamfetol for treatment of narcolepsy is displayed in **Table 1**. Similar efficacy was noted in patients with OSA. The currently FDA-approved maximum dose is 150 mg daily as higher doses were associated with no difference in efficacy and more frequent adverse events. There is insufficient evidence comparing solriamfetol to other therapies used in the treatment of EDS. Long-term safety and efficacy, in addition to mechanism of action, remain unclear.

**Table 1. Efficacy of Solriamfetol Compared to Placebo in Narcolepsy<sup>14</sup>**

Endpoint	Dose Strength	Mean Difference
Maintenance of Wakefulness Test (minutes)	150 mg daily	7.65 (95% CI, 3.99 to 11.31) $p < 0.0001$
	75 mg daily	2.26 (95% CI, -1.04 to 6.28) $p = 0.1595$
Epworth Sleepiness Scale (range 0-24)	150 mg daily	-3.8 (95% CI, -5.6 to -2.0) $p < 0.0001$
	75 mg daily	-2.2 (95% CI, -4.0 to -0.3) $p = 0.0211$

Abbreviations: CI = confidence interval

There is insufficient evidence for off-label use of other medications for the treatment symptoms related to EDS including selegiline, tricyclic antidepressants, and selective serotonin reuptake inhibitors.<sup>1,13</sup>

**Adverse Events**

The most common adverse events associated with EDS therapy include: headache, nausea, vomiting, diarrhea, insomnia, dizziness, anxiety, diminished appetite, weight loss, and tachycardia.<sup>10,15-19</sup> Armodafinil has a longer half-life compared to modafinil and a subsequent longer duration of action, which has been associated with a higher risk of developing adverse reactions. Though uncommon, use of modafinil or armodafinil can increase the risk of emergent psychiatric symptoms, including suicidal ideation, at any dose, and DRESS (drug

reaction with eosinophilia and systemic symptoms), also known as multi-organ hypersensitivity.<sup>7</sup> Solriamfetol use was associated with increases in blood pressure and heart rate during clinical trials, and use in patients with uncontrolled blood pressure is not recommended.<sup>19</sup> Because patients with any acute, uncontrolled medical condition were excluded from clinical trials of solriamfetol, the risk of long-term cardiovascular events is unknown. Black box warnings exist for the following EDS treatments: sodium oxybate (central nervous system depression and misuse/abuse), methylphenidate (abuse and dependence), and mixed amphetamine salts (potential for abuse).<sup>10,17,18</sup>

**Cost**

Thirty-day cost comparisons of EDS treatments are detailed in **Table 2**. There is no established benefit of newer therapies that are associated with a much higher cost.

**Table 2. Comparative Costs for EDS Treatments**

Medication	Initial Dose	30-Day Supply Cost
Methylphenidate	5 mg twice daily	\$3.59
Dextroamphetamine/amphetamine	10 mg daily	\$7.28
Modafinil	200 mg daily	\$12.25
Armodafinil	150 mg daily	\$16.20
Sodium oxybate (Xyrem®)	2.25 g twice daily	\$9720
Solriamfetol (Sunosi™)	75 mg daily	\$690

Oregon Health Authority Average Acquisition Costs (7/31/19) and drugs.com

EDS due to shift-work and unspecified hypersomnia are not funded by the Oregon Health Plan (OHA). Modafinil and armodafinil are available with prior authorization approval.

**Conclusion**

- There is insufficient comparative evidence for EDS treatments to inform strong conclusions on place in therapy.
- Newer EDS treatments are substantially more costly than established therapies.
- Careful differential diagnosis of sleep symptom origin is critical to safe and effective treatment of sleep disorders.

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