Obstructive Sleep Apnea

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Overview
Obstructive sleep apnea (OSA) is common among all age groups and evidence shows that rates are increasing—likely due to increasing obesity rates (1). Repeated cessation or reduction of breathing while sleeping characterizes OSA and may be the result of repetitive complete or partial obstruction of the airway (2). Such disruptions prevent restful sleep, as they often wake those who experience OSA. As a result, affected persons may experience daytime fatigue and somnolence.

The first-line diagnostic test for OSA is a polysomnography performed overnight in a sleep lab. A split-night study or a follow-up night then occurs in order to titrate positive airway pressure (2). After diagnosis, treatment begins. Continuous positive airway pressure (CPAP) during sleep is the initial treatment for those diagnosed with OSA, accompanied by weight loss for overweight or obese patients (1). Other interventions include oral appliance therapy, such as mandibular advancement devices, and surgical options.

While a variety of pharmacologic approaches have been proposed based on the four phenotypic traits of OSA (pharyngeal anatomy, upper airway responsiveness, respiratory arousal threshold and loop gain), thus far the only pharmacologic agents approved to treat OSA are those that treat residual daytime sleepiness which occurs in approximately 15% of patients (3, 4). Prior to pharmacologic treatment for residual daytime sleepiness other causes must be assessed (4). Causes that may contribute to residual daytime sleepiness are detailed in Figure 1 (5). Once these factors are ruled out, pharmacologic treatment with wakefulness promoting agents (WPAs) may progress (4).

The pharmacologic options for treating residual daytime sleepiness associated with OSA for patients on CPAP therapy are CNS stimulants and the recently approved norepinephrine/dopamine reuptake inhibitor (NDRI) solriamfetol.

CNS Stimulants: Modafinil and Armodafinil
The two CNS stimulants approved to treat residual sleepiness are modafinil and armodafinil (the R enantiomer of modafinil) (3) and both are C-IV scheduled medications. The mechanisms by which they promote wakefulness are unknown; however, they are similar in their wake-promoting actions to sympathomimetics (6, 7). Modafinil reduces the Epworth Sleepiness Scale (ESS) by an average of 2.96 points compared to placebo, and armodafinil reduces the ESS by an average of 2.63 points (8). While modafinil is indicated for use in patients with OSA in the United States, this indication has been removed in Europe (5).

Due to armodafinil being the R-enantiomer of modafinil, they share similarities in pharmacokinetics. Their peak plasma concentrations occur in 2-4 hours and may be delayed if taken with food, although the overall effect of food on bioavailability for both medications is negligible (6, 7). Protein binding is 60%, therefore interactions with highly protein bound medications are not expected to occur. Finally, the half-life is approximately 15 hours for both medications, and metabolism is primarily via CYP3A4. The metabolism of modafinil and armodafinil make interactions with other medications a possibility. Due to CYP3A4/5 metabolism, use of alternative or concurrent contraception is recommend while taking steroidal contraceptives at the same times as these medications. For this same reason, modafinil and armodafinil may reduce blood concentrations of cyclosporine. Both medications may inhibit CYP2C19 and prolong systemic exposure of medications such as phenytoin, propranolol, and omeprazole, therefore the dose of these medications may need reduced in patients using these medications concurrently (6, 7).
In addition to metabolic interactions, there are disease state and condition interactions that need to be considered with modafinil and armodafinil (6,7). Cardiovascular disease requires increased monitoring, as clinical studies have found a slight increase in in blood pressure and heart rate among patients taking these medications compared to placebo. Neither of these medications should be used in pregnancy, as animal studies have suggested that they may lead to fetal harm (6,7).

Where modafinil and armodafinil differ is their dosages and prevalence of adverse effects (6,7). For OSA, the recommended dose for modafinil is 200 mg once daily in the morning, whereas the recommended dose for armodafinil is 150-250 mg daily in the morning. Armodafinil has less adverse reactions that occur ≥5% compared to modafinil. Adverse reactions associated with both medications are detailed in Table 1. Both modafinil and armodafinil may cause serious reactions such as Stevens-Johnson syndrome, angioedema, anaphylactic reactions, and multi-organ hypersensitivity reaction. If any of the above are suspected, discontinue the medication (6,7).

**NDR1: Soliriamfetol**

Like modafinil and armodafinil, soliriamfetol is a C-IV scheduled medication, and the exact mechanism through which it improves wakefulness in patients with residual daytime sleepiness is unclear. Soliriamfetol is an NDR1, and therefore it is theorized that it could affect wakefulness through increased dopamine availability (9). Soliriamfetol decreases the ESS by an average of 3.13 points (10).

Peak plasma concentration of soliriamfetol occurs in approximately 2 hours; although it may be delayed an hour when taken with a high fat meal (9). Soliriamfetol binds 33-19.4% of protein and has an elimination half-life of around 7 hours. Minimal metabolism of soliriamfetol occurs, and clearance largely occurs renal—therefore dose adjustments are necessary when used in patients with renal impairment. With minimal metabolism comes minimal drug interactions, although there are a few potential interactions. Soliriamfetol should not be taken with monoamine oxidase inhibitors (MAOIs) or within 14 days after stopping MAOIs. Concurrent use has demonstrated an increased risk of hypertensive reactions. Studies have not been performed with other medications that increase blood pressure or heart rate, and therefore soliriamfetol should be used cautiously with such medications. Likewise, interactions with dopaminergic drugs have not been evaluated. In general, dopaminergic drugs that increase levels of dopamine or directly bind dopamine receptors may interact with soliriamfetol, and should be used cautiously (9).

Disease state and condition precautions include patients with unstable cardiovascular disease, serious heart arrhythmias, or other serious health problems as soliriamfetol may increase blood pressure and heart rate (9). Soliriamfetol should be used cautiously in patients with a history of psychosis or bipolar disorders due to its modification of dopamine. Dose reduction or discontinuation of soliriamfetol should occur if psychiatric symptoms develop. Insufficient data exists concerning the use of soliriamfetol in pregnant patients, and a pregnancy exposure registry is available through the manufacturer, Jazz Pharmaceuticals, at www.SunesisPregnancyRegistry.com (9).

Soliriamfetol is administered once daily in the morning after waking up at a starting dose of 37.5 mg for the treatment of residual drowsiness in OSA (9). Doses may be increased in three-day intervals until optimized, with a maximum dose of 150 mg daily. In patients with moderate and severe renal impairment, the max daily doses are 75 mg and 37.5 mg respectively. It is not recommended to use soliriamfetol in patients with end stage renal disease. The most common adverse reactions of soliriamfetol are headache (16%), decreased appetite (9%), nausea (7%), anxiety (6%), and insomnia (5%) (9).

**Considerations**

Thus far, no head-to-head comparisons of soliriamfetol, modafinil, and armodafinil have occurred. All medication starting doses, ESS reduction, and adverse effects are compared in Table 1. A modest decrease in CPAP use after treatment with modafinil and armodafinil has been demonstrated, although it did not appear to be clinically relevant in the setting of the trials conducted (11). This trend is likely to be more significant with wider population use, and the effect of reduced CPAP use on wakefulness and cognitive function may be masked by WPA (11). CPAP compliance is important due to the fact that it has been associated with a decreased risk of cardiovascular events (12). More trials, and longer trials, need to occur to assess CPAP compliance in relation to WPA (10).

Use of pharmacologic agents for residual daytime somnolence should be used only after other factors have been ruled out, and CPAP use has been optimized. CPAP use has been associated with less cardiovascular deaths due to OSA while WPA have shown no association to cardiovascular death. Therefore, CPAP adherence during treatment with WPA should be continuously assessed.

**References:**

P&T Committee Meeting Update
The P&T Committee met for its quarterly business meeting on May 14, 2020.

Highlights of this meeting include:

COVID-19 updates:
- Hydroxychloroquine was limited to diagnosis and 90-day fills are allowed for a wider variety of medications.
- Telemedicine is greatly expanding as a result of COVID. Over 300 primary care providers and more than 500 mental health providers are now enrolled.
- Medicaid client copays were lifted for COVID-19 testing, diagnosis and treatment.

With no evidence of a difference in safety or efficacy compared to other agents in their respective classes, Vumerity, Reyvow, Ubrelvy, Nurtec, Caplyta and Nexletol were referred to the Department of Health for cost analysis and PDL placement. Valtoco will be limited to indication.

The proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewist13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to July 31, 2020.

The next P&T Committee meeting will be held August 13, 2020 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.
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