Novel Drugs for Obstructive Sleep Apnea

Provider Quick Reference Guide

Overview

Positive airway pressure (PAP) therapy is first line with regard to management of Obstructive Sleep Apnea (OSA) with other options that include oral appliance therapy, hypoglossal nerve stimulation, upper airway surgical procedures, weight loss and positional therapy. Data from recent trials involving medications for weight loss have led to a renewed focus on pharmacotherapy for management of OSA and interest from providers and patients alike. This reference guide provides a brief summary of some of the medications used or proposed for management of OSA.

Table 1: Drugs that may be considered for use in OSA#

MEDICATION	PHARMACOLOGIC CATEGORY	MECHANISM OF ACTION
Tirzepatide	Glucagon-Like Peptide (GLP-1) receptor agonist and Glucose-Dependent Insulinotropic Polypeptide (GIP) receptor agonist	Promotes weight loss by central actions on satiety signaling and due to peripheral effects of increased pancreatic insulin secretion, and decrease in intestinal motility leading to delayed gastric emptying
Atomoxetine	Serotonin-norepinephrine reuptake inhibitor (SNRI)	Increase in upper airway dilator muscle tone by increasing norepinephrine availability in the central nervous system; may promote weight loss by decreasing appetite
Oxybutynin	Anticholinergic	Muscarinic blockade prevents the inhibitory effect of acetylcholine on upper airway muscle tone during REM sleep; may promote weight loss by decreasing appetite
Acetazolamide	Carbonic anhydrase inhibitor	Varying effects on chemosensitivity and loop gain; may promote weight loss by decreasing appetite
Dronabinol	Cannabinoid	May improve respiratory stability and attenuate apnea expression
Others – phentermine, topiramate, zonisamide, sulthiame		

#See Table 2 for additional details

ADVERSE EFFECTS AND CONTRAINDICATIONS (REFER TO TABLE 2)

Gastrointestinal side effects and thyroid cancer for the GLP-1 and GIP agonist agents, Stevens-Johnson syndrome and renal/electrolyte issues with acetazolamide, cardiovascular effects with the sympathomimetic agents and psychiatric concerns with several agents are among the significant adverse effects of these drugs.

WHAT ARE LIMITATIONS AND CHALLENGES TO USING THESE DRUGS FOR OSA?

Uncertainty regarding the level of efficacy especially when underlying pathophysiology is not obesity-related, managing adverse effects and adequate staff training are major considerations for the provider. Access to medications, limitations in coverage by health insurance companies and cost are the main barriers from the patient standpoint. Most commercial health insurance plans do not cover medications for weight loss, while some may cover the medications if the indication is diabetes treatment; linking drug coverage accordingly may help reduce costs. Medication coverage varies by the specific payer, the plan and may also vary by state. By law, Medicare cannot cover drugs used solely for weight loss, although Part D plans may provide coverage for the drugs when used for heart attack and stroke prevention. Medicaid coverage of weight loss drugs varies by state.

HOW DO I INCORPORATE THIS INTO MY PRACTICE?

When caring for the patient, acknowledge the interest and the potential for these medications in treating OSA, while reiterating that efficacy may be sub-par when compared to PAP therapy. Medications may be considered in patients with sub-optimal use of PAP therapy due to intolerance, and as adjunctive therapy. However, exercise caution in making a confident recommendation as data regarding use of novel drugs for OSA management is still evolving and more evidence is needed.

A discussion regarding the safety profile of these medications, especially the uncertain long-term effects and emphasizing need to incorporate lifestyle changes such as behavior modification, a balanced diet, physical activity and adequate sleep are imperative. Additionally, weight rebound on medication cessation and likely need for medication use indefinitely may be included in the discussion. Due to the evolving nature of this field, monitoring data from ongoing trials closely, while also sharing medication-related experiences among providers and reaching out to consultants (e.g. Endocrine and Obesity Medicine providers) are vital.

Pertinent trials and related links

1) SURMOUNT-OSA trials
2) Aroxybutynin and atomoxetine phase 3 trial (LunAIRo)
3) Aroxybutynin and atomoxetine phase 3 trial (SynAIRgy)
4) Triple–Hormone-Receptor Agonist Retatrutide
5) Dronabinol and acetazolamide phase 2/3 trial (RePOSA)
6) Phentermine and topiramate

Table 2: Summary of some of the medications under investigation for potential OSA pharmacotherapy

MEDICATION	TIRZEPATIDE	ATOMOXETINE	OXYBUTYNIN	ACETAZOLAMIDE	DRONABINOL	PHENTERMINE	TOPIRAMATE
Pharmacologic class/mechanism of action	Dual GIP and GLP-1 receptor agonist Others: semaglutide, liraglutide, retatrutride	SNRI	Anticholinergic (antimuscarinic)	Carbonic anhydrase inhibitor Others: zonisamide, topiramate, sulthiame (not available in USA)	Cannabinoid	Sympathomimetic	Anticonvulsant, carbonic anhydrase inhibitor
Dosage	10 mg, 15 mg	80 mg	5 mg	Wide dose range in trials (36-1000 mg/day, effect plateau at 500 mg)	2.5 mg, 10 mg	15 mg	92 mg extended release
Side effects (Refer to the manufacturer's package insert or FDA database for a complete list of side effects) **Serious side effects*	thyroid C cell tumor*, medullary thyroid Ca*, pancreatitis, nausea/emesis, anorexia, diarrhea, constipation, tachycardia	psychosis*, suicidal ideation*, headache, nausea/emesis, fatigue, insomnia	angioedema*, psychosis*, somnolence, nausea, headache, dry eyes/mucous membranes, confusion	metabolic acidosis*, Stevens-Johnson syndrome*, seizures, fatigue, malaise, nausea/emesis, confusion, drowsiness	dependency*, withdrawal*(if stopped abruptly), hyperemesis syndrome*, somnolence, euphoria, nausea/emesis, anxiety, paranoia	cardiovascular (hypertension, arrhythmias, MI, valvular heart disease, pulmonary hypertension), anxiety, delirium, mania, insomnia	suicidal ideation*, hyperthermia*, sedation, metabolic acidosis*, cognitive dysfunction, psychiatric disturbances, paresthesia, renal stones, vison changes*
Contraindications	hypersensitivity to drug, medullary thyroid carcinoma (including family history), MEN syndrome type 2	hypersensitivity to drug, recent use of MAO inhibitors, narrow-angle glaucoma, pheochromocytoma, severe cardiovascular disease	hypersensitivity to drug, narrow-angle glaucoma, urinary retention, impaired GI motility	hypersensitivity to acetazolamide and sulfonamides, electrolyte and acid-base derangements, liver disease, renal disease, adrenocortical insufficiency, glaucoma	hypersensitivity to drug, recent use of disulfiram or metronidazole	hypersensitivity to drug, hyperthyroidism, cardiovascular disease, glaucoma, agitation, drug abuse, recent use of MAO inhibitors	metabolic acidosis, alcohol use, significant drug interactions – consult database
FDA approval for weight management	Yes	No	No	No	No	Yes	Yes (in combination with phentermine)
FDA approval for OSA	Yes	No	No	No	No	No	No
AASM standard	AASM statement on Zepbound for OSA	No statement	No statement	No statement	No statement	No statement	No statement