UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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Palliative Care Pharmacy Team:

Clinical Pharmacy Specialist:

Maria Felton Lowry, PharmD, BCPS, BCGP
Assistant Professor
University of Pittsburgh School of Pharmacy, Department of Pharmacy and Therapeutics
Palliative Care Clinical Pharmacy Specialist
UPMC Palliative and Supportive Institute

Cell: 412-627-8473
Office: 412-864-2899
Email: lowrymf@upmc.edu

If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

New Medication Review: Sunosi® (solriamfetol) for wakefulness in narcolepsy and obstructive sleep apnea (OSA)

Background:

Sunosi is a newly approved dopamine and norepinephrine reuptake inhibitor (DNRI) indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or OSA. It is available as 75mg (scored tablets, can be cut in half) and 150mg tablets.

- Dosing regimen is: once daily upon awakening, avoiding administration within 9 hours of planned bedtime
- Starting dose for patients with narcolepsy: 75mg PO daily
- Starting dose for patients with OSA: 37.5mg PO daily
- Dose can be increased every 3 days
- Maximum dose is 150mg PO daily

Importance:

Seriously ill patients have co-existing OSA or narcolepsy. It is important for palliative care clinicians to be aware of new potential treatment options and the evidence to support its use.

Pharmacology:

Mechanism of Action	Dopamine and norepinephrine reuptake inhibitor No appreciable binding to serotonin receptors/does not inhibit serotonin reuptake
Absorption	Oral bioavailability is 95%; steady state achieved within 3 days
Distribution	Moderate Vd (199 L), small amount protein bound (~13.3-19.4%)
Metabolism	Hepatic metabolism is minimal
Excretion	Half-life is ~7 hours Approximately 95% of the dose was recovered in urine as unchanged

Other Clinical Pearls:

Contraindications	Do not use with a monoamine oxidase inhibitor (MAOI) or use of an MAOI within the preceding 14 days
Warnings and Precautions	• Can increase blood pressure and heart rate. Monitor throughout treatment. Avoid use in patients with unstable cardiovascular disease and serious heart arrhythmias • Can induce psychiatric symptoms. Use caution in treating patients with a history of psychosis or bipolar disorders
Adverse Reactions	Headache, nausea, decreased appetite, insomnia, and anxiety
Drug Interactions	Avoid co-administration with medications that increase blood pressure and/or heart rate and dopaminergic medications
Dose Adjustments	Liver: none; drug is minimally metabolized by the liver Renal: • eGFR 30-59: Starting dose is 37.5mg once daily and may increase to 75mg once daily after at least 7 days • eGFR 15-29: Starting dose and maximum dose is 37.5 mg once daily • eGFR < 15: Use is not recommended
Other	Schedule IV Controlled Substance

The Literature:

Ann Neurol. 2019 Mar;85(3):359-370.

A randomized study of solriamfetol for excessive sleepiness in narcolepsy

Methods: phase 3, double-blind, randomized, placebo-controlled, parallel group study randomized 1:1:1 with solriamfetol 75, 150, or 300mg, or placebo once daily for 12 weeks

- Inclusion: Adults w/narcolepsy type 1 or 2 (ICSD-3/DSM-5) with baseline sleep latency < 25 minutes on first 4 trials of a 5-trial 40-minute Maintenance of Wakefulness Test (MWT), baseline Epworth Sleepiness Scale (ESS) score ≥ 10 (range from 0-24, scores of 16-24 with severe excessive sleepiness), usual nightly total sleep time ≥ 6 hours and BMI between 18-45
- Exclusion: Pregnancy or those with untreated medical, psychiatric, or behavioral disorder

Outcomes: *Primary*: Change from baseline to week 12 in MWT and ESS; *Secondary*: Improvement on the Patient Global Impression of Change (PGI-C): 7-point scale (1 = very much; improved to 7 = very much worse); *Safety*: adverse events reported by the patients, including blood pressure (BP) and heart rate (HR)

Results: n = 236, age: 36.2 +/- 13.2; 65.3% female

- MWT: mean differences versus placebo of 10.1 (95% CI = 6.4-13.9) mins for 300mg and 7.7 (95% CI 4-11.3) for 150mg. Insignificant increase for 75mg although not statistically significant
  - Improvements sustained throughout the 12-week period
- ESS: LS mean differences versus placebo of −4.7 (95% CI = −6.6 to −2.9) for 300 mg, −3.8 (95% CI = −5.6 to −2.0 for 150 mg, and −2.2 (95% CI = −4.0 to −0.3) for 75 mg
- PGI-C: percentage of patients with reported improvements in scores were higher in all solriamfetol groups compared to placebo across 12-week study period

Safety (n=236)

- Incidence of adverse events was higher with solriamfetol than with placebo; headache (21.5%), nausea (10.7%), decreased appetite (10.7%), nasopharyngitis (9%), dry mouth (7.3%), anxiety (5.1%)
- Minimal effects on blood pressure seen

Conclusion: "Once-daily oral dosing of solriamfetol 150 and 300 mg resulted in major improvements in wake-fulness and reductions in ES associated with narcolepsy together with patient- and clinician-reported global improvements"

Am J Respir Crit Care Med. 2019 Jun 1;199(11):1421-1431.

Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3). A randomized controlled trial

Methods: double-blind, randomized, placebo-controlled, parallel-group, 12-week trial

- 1:1:2:2:2 solriamfetol, 37.5, 75, 150, and 300 mg, with placebo x 12 weeks
- Inclusions: Adults w/OSA (ICSD-3) w/ current or prior use of primary OSA therapy including PAP, mandibular advancement device, or surgery with ESS ≥ 10 at baseline, baseline sleep latency ≤ 30 mins for first 4 of a 5 trial, 40- minute MWT, nightly sleep time ≥ 6 hours
- Exclusions: OTC/Rx medications affecting evaluation of ES, diagnosis of substance use disorder, nicotine dependence, or other clinically relevant medical, behavioral, psychiatric disorder associated with ES

Outcomes: *Primary*: change from baseline to week 12 in MWT and ESS; *Secondary*: percentage of participants at week 12 reporting PGI-C, functional outcomes, productivity, QOL ; *Safety*: adverse events, vital signs, ECG, lab tests

CLINICAL PEARL: Solriamfetol (Sunosi®) is a newly approved dopamine and norepinephrine reuptake inhibitor (DNRI) that has demonstrated benefit for OSA and narcolepsy. It is unclear how this data would translate for off-label use in a palliative care population.

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Results: n = 404; age ~53 years old and ~60% male across groups

- Dose-dependent effects observed at week 1 and maintained across 12-week study period for MWT and ESS
- MWT: LS mean differences were statistically significant from placebo were 4.5 (1.2-7.9), 8.9 (5.6-12.1), 10.7 (8.1-13.4) and 12.8 (10-15.6) in 37.5mg, 75mg, 150mg, 300mg groups respectively
- ESS: LS mean differences were statistically significant from placebo were -1.9 (-3.4 to -0.3), -1.7 (-3.2 to -0.2), -4.5 (-5.7 to -3.2) and -4.7 (-5.9 to -3.4) in 37.5mg, 75mg, 150mg, 300mg groups respectively
- PGI-C: significantly higher percentage of participants (ranges 23.3-39.6%) on solriamfetol (75mg, 150mg, 300mg) reported overall improvement relative to placebo

Safety (n=474)

- Higher overall incidence of adverse effects in solriamfetol group; most were dose-dependent: headache (10.1%), nausea (7.9%), decreased appetite (7.6%), anxiety (7%), nasopharyngitis (5.1%)
- Small changes in BP: ~2.5mmHg for systolic and 1.5mmHg for diastolic

Conclusion: "Solriamfetol significantly increased wakefulness and reduced sleepiness in participants with obstructive sleep apnea and excessive sleepiness; most adverse events were mild or moderate in severity."

Other studies with patient-reported outcomes such as quality of life, work productivity, Functional outcomes can be found here:

- J Clin Sleep Med. 2021 Oct 1;17(10):1995-2007.
- Sleep Med. 2020 Mar;67:128-136.

Discussion:

- Lack of active comparator, especially in OSA, makes it difficult to draw conclusions between these results and other therapies although seems to be effective for increased wakefulness in OSA and narcolepsy based on data available
- Given the mechanism, I wonder if the benefit of wakefulness could translate to our seriously ill patients with fatigue… although given side effect profile (headaches, nausea, decreased appetite) might limit off-label use in a palliative care population
- Data is limited to a 12-week period, long term safety being evaluated in a separate 1-year extension study
- Side effects of nausea, headache, reduced appetite would be problematic for our palliative care patients
- Simple, once daily regimen to be taken ~9 hours before bedtime
- Wholesale Acquisition Cost: $37 per tablet (either 75mg or 150mg)
    - At UPMC, solriamfetol is formulary-restricted to continuation of home therapy

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