Narcolepsy is a chronic neurological disorder that disrupts sleep and wake cycles due to irregular functioning of various neurophysiological pathways. Not only does this effect a persons ability to sleep at night but also impairs daytime wakefulness. Obstructive sleep apnea (OSA) is a condition that causes intermittent airway blockage during sleep. Both of these disorders can cause excessive sleepiness (ES) which can lead to decreased productivity, cognitive functioning, and quality of life, as well as, an increased risk of motor vehicle accidents. The prevalence of narcolepsy ranges from 25-50 per 100,000 individuals, and OSA is prevalent in 9%-38% of adults. Pharmacological treatments for narcolepsy primarily involve symptomatic control through medication classes such as stimulants, like amphetamines and methylphenidate, and the wake-promoting agents armodafinil and modafinil. However, most of these treatments are not well tolerated, have abuse potential, can build tolerance, or may not have adequate response. The primary treatment for OSA is through positive airway pressure (PAP), however 12%-65% of individuals treated with PAP still complain of ES. The use of armodafinil and modafinil to improve wakefulness can be added to PAP therapy if needed.

On March 20, 2018, Sunosi® (Solriamfetol), was approved by the FDA to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or OSA. It is a wake-promoting medication that selectively inhibits the reuptake of dopamine and norepinephrine. Solriamfetol is distinguished from other stimulants in that it has lower binding affinity to dopamine and norepinephrine transporters, and does not have the monoamine-releasing effects of amphetamines at usual therapeutic doses, thereby reducing abuse potential in comparison to the other currently FDA approved options. The purpose of this article is to review the pharmacology, pharmacokinetics, clinical trials, adverse events and the dosing of Sunosi® (solriamfetol) for the improvement of wakefulness in patients with narcolepsy or OSA.
er mean value is associated with a better ability to remain awake. Values range from 0-40 min. The ESS is a measure for assessing patient-reported sleepiness through a self administered 8 item questionnaire, scored between 0-3, where scores ≤10 are considered within the normal range.2 Therefore, lower values are associated with less sleepiness, and values range from 0-24. A summary of the trial results can be found in Table 2.

Thorpy et al

Thorpy et al. conducted a phase III double-blind, randomized, placebo-controlled, parallel-group study to demonstrate the safety and efficacy of solriamfetol for the treatment of ES and impaired wakefulness in patients with narcolepsy.1 Inclusion criteria were age 18 to 75 years, diagnosed with narcolepsy type 1 or type 2 based on either the International Classification of Sleep Disorders, 3rd edition (ICSD-3) or Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Additional inclusion criteria were baseline mean sleep latency <25 minutes during the first four trials of a five-trial, 40-minute MWT, baseline ESS score ≥10, self-reported usual nightly total sleep time ≥6 hours, and a body mass index between 18 and 45 kg/m². Exclusion criteria were any clinically relevant untreated medical, psychiatric, or behavioral disorder or medical condition other than narcolepsy that is associated with ES (ie, night-time or variable shift work), and a presence or history of any acutely unstable medical or psychiatric disorder, or surgical history that could affect the safety of the patient; female patients that were pregnant or lactating were excluded as well. Although use of medications that could affect the evaluation of ES or cataplexy was another reason for exclusion, patients may be enrolled if prior use had terminated for >5 half-lives of the drug and the patient had returned to baseline level of daytime sleepiness ≥7 days before baseline visit.

Patients who met criteria were randomly allocated 1:1:1:1 to placebo (n=58) or oral solriamfetol 75 mg (n=59), 150 mg (n=55), or 300 mg (n=59) once daily for 12 weeks. Patients in the 150 and 300 mg dose groups received 75 and 150 mg on days 1-3 of the first week, respectively, followed by the full dose starting on day 4. The co-primary endpoints were change from baseline to week 12 on MWT mean sleep latency on the first four trials of the MWT and ESS score.

For the primary outcome, change from baseline at week 12 on MWT, sleep latency increased by 9.8 (±1.3) minutes (min) in the 150 mg group and 12.3 (±1.4) min in the 300 mg solriamfetol group. This compared to a 2.1 (±1.3) min increase for placebo (p < 0.0001 for both 150 mg and 300 mg groups compared to placebo). The 75 mg solriamfetol group increased MWT by 4.7 (±1.3) minutes but was not a significant difference compared to placebo (p=0.1595).1 For the changes in the ESS score, the change from baseline at week 12 was −6.4 (±0.7) in the 300 mg group, −5.4 (±0.7) in the 150 mg group, and −3.8 (±0.7) for the 75 mg group. This was significant when compared with −1.6 (±0.7) for placebo (300 mg and 150 mg p < 0.0001, 75 mg p=0.0211).1

TONES 3

The TONES 3 trial was a 12-week phase III, placebo-controlled, parallel-group trial that aimed to evaluate the efficacy and safety of solriamfetol in adults with OSA and ES.2 Included in the study were patients age 18-75 years diagnosed with OSA according to the International Classification of Sleep Disorders-3 (ICSD-3) criteria and with current or prior use of a primary OSA therapy including PAP, mandibular advancement device, or surgical intervention. Participants without current primary OSA therapy use or a history of a surgical intervention to treat the underlying obstruction were required to have tried to use a primary OSA therapy for at least one month with at least one documented adjustment to the therapy (e.g., change in PAP pressure, change in mask, change in modality). Additional inclusion criteria were baseline ESS score ≥10; baseline sleep latency <30 minutes for the average of the first four of a five-trial, 40-minute Maintenance of Wakefulness Test (MWT); and typical nightly sleep time ≥6 hours. Patients were excluded that did not have a typical nightly total sleep time of at least 6 hours or if they had a typical bedtime later than 1 AM; an occupation that required nighttime shift work or variable shift work; use of any over-the-counter (OTC) or prescription medications that may affect the evaluation of excessive sleepiness; current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria; nicotine dependence affecting sleep (e.g., a subject who routinely awakens at night to smoke); or any other medical, behavioral, or psychiatric disorder other than OSA that is clinically relevant and associated with excessive sleepiness.

Individuals who met criteria were randomly allocated (1:1:2:2:2) to 12 weeks of oral solriamfetol 37.5 mg (n=56), 75 mg (n=58), 150 mg (n=116), 300 mg (n=115), or placebo (n=114) once daily by mouth. Solriamfetol or placebo was taken within 30 min of awaking at night to smoke); or any other medical, behavioral, or psychiatric disorder other than OSA that is clinically relevant and associated with excessive sleepiness.

For the primary outcome, change from baseline at week 12 on MWT, increased in sleep latency by 13.0 (±1.2) min in the 150 mg solriamfetol group, 11.0-12.2 min in the 150 mg group, compared to 0.2-1.2 min for placebo (p < 0.05 for both comparisons to placebo).2 The times for the 37.5 mg and 75 mg groups were not reported in the article. However, the authors state that a dose dependent increases in sleep latency from the 37.5 mg to 300 mg

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 hours</td>
</tr>
<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>~199 L</td>
</tr>
<tr>
<td>Protein binding</td>
<td>13.3-19.4%</td>
</tr>
<tr>
<td>First-order elimination</td>
<td>Minimal (&lt;1%)</td>
</tr>
<tr>
<td>Renal</td>
<td>95% unchanged in the urine</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.1 hours</td>
</tr>
</tbody>
</table>

<sup>a</sup>Time to maximum concentration; <sup>b</sup>Volume of distribution; <sup>c</sup>Half-life
group was seen at week one and maintained through 12 weeks of the study. For changes in the ESS score, the change from baseline at week 12 was a decrease of >7 points in the 150 mg and 300 mg groups, compared to a decrease of 3.3 points for placebo (p < 0.0001 for both comparisons to placebo). Once again, changes in the 37.5 mg and 75 mg groups were not reported. The article states that stable dose dependent decreases in ESS score were seen in all treatments groups relative to placebo over the course of the 12 weeks.²

**TONES 4**

The TONES 4 trial was a 6-week phase III, double-blind, placebo-controlled withdrawal trial that was designed to demonstrate maintenance of solriamfetol efficacy and safety.⁴ Inclusion criteria consisted of adults (age range, 18-75 years) with OSA diagnosed according to ICSD-3 criteria who had current or prior primary OSA therapy including CPAP, oral appliance, or surgical intervention. Additional inclusion criteria were BMI 18 to < 45 kg/m²; baseline ESS score ≥10 and mean sleep latency < 30 minutes on the first four trials of a five trial, 40-minute MWT; and usual nightly sleep time ≥6 hours. Key exclusion criteria were any disorder other than OSA associated with ES; an occupation requiring nighttime shift work or variable shift work; excessive caffeine use one week prior to the study or nicotine dependence with a reported effect on sleep; presence of any acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect participant safety or interfere with study assessments; and use of any over-the-counter or prescription medications that could affect ES evaluation within a period corresponding to at least 5 half-lives of the drug. Pregnant, breastfeeding, or lactating women were excluded.

The study consisted of three different phases. In the titration phase (weeks 1-2), 174 patients started with a once-daily oral dose of solriamfetol 75 mg and had the dose titrated up or down by one dose level every 3 days to 75 mg, 150 mg, or 300 mg to maximize efficacy and tolerability. This dose was then continued in these patients during the stable dose phase (weeks 3-4). A randomized double-blind withdrawal phase (weeks 5-6) followed the stable dose phase. For this phase, patients who reported “much” or “very much” improvement on the Patient Global Impression of Change (PGI-C) scale, which measures patient-reported improvement or decline in clinical status based on a seven point scale, and who had quantifiable improvement on the MWT and ESS after 4 weeks were randomly assigned 1:1 to receive either placebo (n=62) or continue on their stable solriamfetol dose (n=60). The co-primary efficacy endpoints were changes from week four to week six in mean sleep latency obtained from the first four weeks, 40-minute MWT, and ESS score.

The results showed that mean sleep latency on the MWT increased from 12-13 minutes to 30 minutes after 4 weeks in the mITT population. Additionally, the ES S was reduced from about 15 or 16 to about 6 (≤10 is considered normal). During the randomized withdrawal phase (weeks 4-6), patients that continued solriamfetol had maintained efficacy, with negligible changes on MWT and ESS, while patients that were switched to placebo had worsened scores in both measures from week four. The difference between treatments for these changes was statistically significant for both MWT and ESS. The change in MWT sleep latency from week 4 to week 6 was -12.1 (±1.3) minutes with placebo compared to -10.0 (±1.4) minutes with solriamfetol. The mean changes in ESS score from week four to week six were 4.5 (±0.7) for placebo and -0.1 (±0.7) for solriamfetol.⁴

**Adverse Effects and Precautions**

The most common adverse events of solriamfetol in Thorpy et al. included headache (21.5%), nausea (10.7%), decreased appetite (10.7%), nasopharyngitis (9.0%), dry mouth (7.3%) and anxiety (5.1%).¹ These events and occurrences were similar in the other two trials. In general, most of these adverse events were numerically higher in the treatment groups than placebo in all three studies.¹,³,⁴ There was also a dose dependent increase in the rates of the majority of these adverse effects, with the 300 mg group experiencing the most.¹ Solriamfetol dose-dependently increases systolic blood pressure, diastolic blood pressure, and heart rate.⁴ In Thorpy et al., 1-2 mmHg increases in baseline systolic and diastolic blood pressure, and 2-4 beats per minute increases in heart rate were seen in the 150 mg and 300 mg arms. Meanwhile, there were minimal changes in the placebo group (<1 mmHg or beats per minute).

Table 2 | Summary of Clinical Trial Results¹,²,⁴

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Outcome</th>
<th>Mean Change in MWT² (min)</th>
<th>Mean Change in ESSb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorpy et al¹</td>
<td>Change in MWT and ESS from baseline to week 12</td>
<td>Placebo: 2.1 ± 1.3   75 mg: 4.7 ± 1.3 (p=0.1595) 150 mg: 9.8 ± 1.3 (p &lt; 0.0001) 300 mg: 12.3 ± 1.4 (p &lt; 0.0001)</td>
<td>Placebo: -1.6 ± 0.7 75 mg: -3.8 ± 0.7 (p=0.0211) 150 mg: -5.4 ± 0.7 (p &lt; 0.0001) 300 mg: -6.4 ± 0.7 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>TONES 3²</td>
<td>Change in MWT and ESS from baseline to week 12</td>
<td>Placebo: 0.2-1.2 37.5 mg: not reported 75 mg: not reported 150 mg: 11.0-12.2 (p &lt; 0.05) 300 mg: 13.0-13.3 (p &lt; 0.05)</td>
<td>Placebo: -3.3 75 mg: not reported 150 mg: &lt; -7 (p &lt; 0.0001) 300 mg: &lt; -7 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>TONES 4⁴</td>
<td>Change in MWT and ESS (randomized withdrawal period)</td>
<td>Placebo: -12.1 ± 1.3 All doses: -1.0 ± 1.4</td>
<td>Placebo: 4.5 ± 0.7 All doses: -0.1 ± 0.7</td>
</tr>
</tbody>
</table>

*Maintenance and Wakefulness Test; *Epworth Sleepiness Scale
Solriamfetol has shown significant improvements in the co-primary outcomes in all three phase III trials in comparison to placebo. Between the trials, it has been shown to increase sleep latency by about 4-12 minutes, and reduced ESS by about 4-6 points depending on the dose. However, the clinical significance of these findings may need to be evaluated on case-by-case basis. For example, if treatment can delay an individual from falling asleep between 4 and 12 minutes, it may reduce chances of them periodically falling asleep during the daytime. Additionally, solriamfetol has less cardiovascular effects than amphetamines, and may be a better option for hypertensive patients. Adderall® and Ritalin® can cause an average increase in blood pressure between 2-4 mmHg, and an average increase in heart rate of 3-6 beats per minute. These effects are double than that of solriamfetol, which increases blood pressure between 1-2 mmHg and increase heart rate by 2-4 beats per minute. However, direct comparison studies have not been done. Solriamfetol is also limited by the fact that no abuse potential was measured in the clinical trials, and there is no long term safety data. Also, despite trials not providing results for lower doses in publications, the FDA has approved these lower doses. The true effect of these lower doses are unknown based on the information provided in the publications.

**Conclusion**

Solriamfetol is a new FDA approved drug indicated to improve the wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea. In clinical trials, solriamfetol has shown dose-dependent improvement in wakefulness over placebo with minimal serious adverse effects. Overall, solriamfetol is an alternative option to conventional treatment for excessive sleepiness in patients with narcolepsy or OSA, however, additional studies should be done to assess long term safety effects.

**Table 3 | Change in Vital Signs from Baseline to Last Assessment**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Systolic Blood Pressure (mmHg)</th>
<th>Diastolic Blood Pressure (mmHg)</th>
<th>Heart Rate (BPM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo: 0.6±8.1</td>
<td>Placebo: −0.6±5.2</td>
<td>Placebo: 0.5±6.7</td>
</tr>
<tr>
<td></td>
<td>75 mg: 0.3±6.8</td>
<td>75 mg: 1.0±4.4</td>
<td>75 mg: 0.6±6.6</td>
</tr>
<tr>
<td></td>
<td>150 mg: 1.2±7.4</td>
<td>150 mg: 1.4±4.9</td>
<td>150 mg: 2.5±4.7</td>
</tr>
<tr>
<td></td>
<td>300 mg: 2.0±7.4</td>
<td>300 mg: 2.1±5.0</td>
<td>300 mg: 4.3±7.6</td>
</tr>
<tr>
<td>Thorpy et al¹</td>
<td>Placebo: −0.2 (−1.7, 1.4)</td>
<td>Placebo: 0.0 (−0.9, 1.0)</td>
<td>Placebo: 0.1 (−0.9, 1.1)</td>
</tr>
<tr>
<td></td>
<td>37.5 mg: 1.8 (−0.6, 4.1)</td>
<td>37.5 mg: 0.6 (−0.7, 2.0)</td>
<td>37.5 mg: 0.7 (−1.3, 2.7)</td>
</tr>
<tr>
<td></td>
<td>75 mg: 0.5 (−1.8, 2.8)</td>
<td>75 mg: −0.2 (−2.0, 1.5)</td>
<td>75 mg: 0.8 (−0.8, 2.3)</td>
</tr>
<tr>
<td></td>
<td>150 mg: 0.7 (−0.8, 2.1)</td>
<td>150 mg: 0.5 (−0.5, 1.6)</td>
<td>150 mg: 2.2 (1.0, 3.4)</td>
</tr>
<tr>
<td>TONES 3²</td>
<td>300 mg: 2.5 (0.4, 4.6)</td>
<td>300 mg: 1.5 (0.3, 2.7)</td>
<td>300 mg: 2.9 (1.7, 4.1)</td>
</tr>
<tr>
<td>TONES 4⁴</td>
<td>All doses: 1.6±8.7</td>
<td>All doses: 0.8±5.3</td>
<td>All doses: 1.0±6.1</td>
</tr>
</tbody>
</table>

¹Millimeter of Mercury; ²Beats per minute

A summary of the changes in vital signs among the three trials can be found in Table 3. Blood pressure should be assessed and hypertension should be controlled before treatment is initiated, and should be continually monitored through the course of therapy. If side effects develop in association with the start of solriamfetol administration, dose reduction or discontinuation of therapy should be considered. Solriamfetol is contraindicated in patients who are being concomitantly treated with monoamine oxidase (MAO) inhibitors, or within 14 days after discontinuation of a MAO inhibitor, due to risk of hypertensive reaction.

**Dosing and Administration**

Solriamfetol is available in 75 mg and 150 mg tablets and can be taken by mouth with or without food.³ It should be taken orally upon awakening and avoided within 9 hours of planned bedtime. For narcolepsy, solriamfetol should be initiated at 75 mg once daily. The recommended dosing range is 75 mg-150 mg daily. For OSA, solriamfetol should be initiated at 37.5 mg once daily. The recommended dosing range is 37.5 mg-150 mg daily. Dosing may be doubled at 3-day intervals based on efficacy and tolerability for both narcolepsy and OSA. The maximum dose for both indications is 150 mg daily. The benefits of solriamfetol for doses over 150 mg do not outweigh the increased incidence of adverse effects, according to the package insert. For patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m²), dosing should be initiated at 37.5 mg once daily and can be titrated up to 75 mg daily after seven days considering efficacy and tolerability. However, in patients with severe renal impairment (eGFR 15-29mL/min/1.73 m²), initial and maximum daily dose is 37.5 mg. Solriamfetol is not recommended for patients with ESRD (eGFR <15 mL/min/1.73 m²).³

**Clinical Implications**

Solriamfetol has shown significant improvements in the co-primary outcomes in all three phase III trials in comparison to placebo. Between the trials, it has been shown to increase sleep latency by about 4-12 minutes, and reduced ESS by about 4-6

References


http://pharmacy.ufl.edu/pharmanote/
used to induce liver tumorigenesis. It is therefore anticipated to
NDEA is thought to affect DNA integrity via alkylation and thus
for industry materials.
used as a gasoline and lubricant additive, antioxidant and stabilizer
decrease in function of the kidney, liver and lungs. The Environ-
fever, nausea and abdominal cramps whereas the more serious
Overexposure to NDMA can lead to a variety of symptoms rang-
mers but which is currently used only for research purposes.
chemical processes.
either environmental contaminants or the results of industrial
agents are known to be potential human carcinogens, occurring as
identified as impurities in the affected medications. They are N-
leave many with questions over how to adjust therapy.
There are three nitrosamine compounds that have been iden-
tォン class have been named including losartan, valsartan and irbesar-
tensive medications in the angiotensin receptor blocker (ARB)
place to respond to the Food and Drug Administration (FDA)
medications. Pharmacies and retail distributors have processes in
portant steps taken to prevent any patient harm from affected
pharmacies and, if necessary, affected patients are contacted.9 This
second medication such as ranitidine are often removed from
pharmacies have control over their ordering process and detailed
This is
also be a human carcinogen. NMBA is another nitrosamine that
has been typically identified in various types of tobacco such as
pipe tobacco, cigars and cigarettes.4 The FDA has estimated that
the cancer risk for NMBA exposure is similar to that of NDMA,
but less than that of NDEA.5
In response to these concerns, the FDA has published interim
limits for NDMA, NDEA and NMBA in order to allow pa-
tient access to these medications.6 These limits represent the ac-
ceptable daily exposure that approximates a 1:100,000 cancer risk
after 70 years of exposure. Losartan being the primary ARB af-
fected, the FDA has included a statement that it is temporarilly
objecting to losartan with NMBA levels below 9.82 ppm remain-
ing on the market. In regards to over the counter ranitidine, which
patients commonly use for symptoms of gastroesophageal reflux
disease (also referred to as heartburn), the FDA has not yet called
for individuals to stop taking it and voluntary recalls by the manu-
facturers are the only issuances at this time.7 However, other
agents in the same class do exist and are available over the coun-
ter. Pepcid Complete/AC (famotidine), Tagamet HB (cimetidine),
and Axid AR (nizatidine) are other potential options for consum-
ers that do not have impurity concerns at this time.8
When impurities such as these are discovered, there are im-
portant steps taken to prevent any patient harm from affected
medications. Pharmacies and retail distributors have processes in
place to respond to the Food and Drug Administration (FDA)
and manufacturer recalls. Affected stock is removed from phar-
macies and manufacturer recalls. Affected stock is removed from phar-
macies and, if necessary, affected patients are contacted.9 This
is most effective for prescription medications (primarily ARB's in
this article although prescription forms of ranitidine do exist) as
pharmacies have control over their ordering process and detailed
dispensing records to identify those affected. While over the
counter medications such as ranitidine are often removed from the
shelves in response to recalls, anyone can have purchased
these medications prior to removal and records for those affected
may not exist.
In conclusion, while the nitrosamine impurities found in
several ARB's and ranitidine are concerning, patient impact can be
significantly limited. The FDA constantly updates its pubic drug
recall information for patient and physician awareness. Physicians
can still prescribe these medications as pharmacies will have re-
moved the affected manufacturer's stock. Over the counter
ranitidine products should have been removed as well in response
to voluntary recalls, but patients may still take ranitidine at this
time per the FDA and therapeutic class alternatives are available.

References:
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2) US Environmental Protection Agency. Technical Fact Sheet –
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