MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

Health Plan of San Joaquin

POLICY	Sleeping Disorders	**P&T DATE:**	5/14/19
THERAPEUTIC CLASS	Psychiatric Disorders	**REVIEW HISTORY:** (MONTH/YEAR)	2/18, 12/16, 2/16, 5/15, 2/12
LOB AFFECTED	Medi-Cal		

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the HPSJ Pharmacy and Therapeutic Advisory Committee.

BACKGROUND

In addition to their association with reduced quality and duration of life, sleep and wakefulness disorders are a growing public health concern due to motor vehicle accidents, occupation-related errors, and reduced productivity.[1] Sleep aids and anti-narcolepsy medications can be useful modalities to help patients improve daytime function by improving quantity and quality of sleep and decreasing excessive daytime sleepiness, respectively. Although these agents may offer benefit by improving symptoms, they should be used cautiously and sparingly due to potential risks of dependence, paradoxical insomnia, and next morning drowsiness. When possible, patients should use non-pharmacological techniques to achieve a restful night's sleep. The purpose of this coverage policy is to review the coverage criteria of HPSJ's formulary anti-narcolepsy agents and sleep aids *(Tables 1 & 2)*.

Table 1: Available Anti-Narcolepsy Agents

Class	Brand Name	Generic Name	Available Strengths	Fml Limits	Notes	Cost/Rx*
Wakefulness-Promoting Agents	Provigil	Modafinil	100 mg tablets	NF		$73.35
			200 mg tablets	PA	Reserved for treatment of narcolepsy, shift work sleep disorder or obstructive sleep apnea treated by a sleep specialist or pulmonologist. For apnea, reserved for inadequate response to compliant use of properly-fitting CPAP for at least 90 days.	$87.49
	Nuvigil	Armodafinil	50 mg, 150 mg, 200 mg, 250 mg tablets	NF		$325.86
Anti-Narcolepsy & Anti-Cataplexy, Sedative-Type Agents	Xyrem	Sodium oxybate	500 mg/ml solution	PA,QL	See Coverage Criteria	$11,326

PA = Prior Authorization; NF = Non-Formulary
*Cost/Rx based on HPSJ Medi-Cal utilization historical data

Table 2: Available Sleep Aids

Class	Brand Name	Generic Name	Available Strengths	Fml Limits	Notes	Cost/Rx *
Antidepressants	Desyrel	Trazodone	50 mg, 100 mg, 150 mg tablets	-		$5.95
			300 mg tablets	NF		--
	Remeron	Mirtazapine	7.5 mg, 15 mg, 30 mg, 45 mg tablets	QL	Limit 1 tablet per day	$33.41
			15 mg, 30 mg, 45 mg ODT	PA; QL	Reserved for patients with a documented inability to swallow tablets or capsules. Limit 1 tablet per day.	$42.97
	Silenor	Doxepin	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg capsules	-		$28.25
			10 mg/ml oral concentrate	-		$2.23
			Silenor 3 mg, 6 mg tablets	NF		--
Benzodiazepines	Restoril	Temazepam	15 mg, 30 mg capsules	QL	Limit 60 per 75 days	$2.49
			7.5 mg, 22.5 mg capsules	NF		$23.86
	Halcion	Triazolam	0.125 mg, 0.25 mg tablets	NF		$61.75
Non-Benzodiazepine Sedative Hypnotics	Ambien	Zolpidem	5 mg, 10 mg tablets	QL	Limit 60 per 75 days	$1.48
			6.25 mg, 12.5 mg XR tablets	NF		$25.08
			1.75 mg, 3.5 mg SL tablets	NF		--
	Sonata	Zaleplon	5 mg, 10 mg capsules	QL	Limit 60 per 75 days	$8.80
	Lunesta	Eszopiclone	1 mg, 2 mg, 3 mg tablets	QL	Limit 60 per 75 days	$7.96
	Rozerem	Ramelteon	8 mg tablets	NF		$193.11
	Hetlioz	Tasimelteon	20 mg capsules	NF		--
	Belsomra	Suvorexant	5 mg, 10 mg, 15 mg, 20 mg tablets	NF		$307.92
Pineal hormone agents	Circadin	Melatonin	1 mg, 3 mg, 5 mg tablets	-		$1.09
Antihistamines	Sominex, Benadryl	Diphenydramine	12.5 mg/5 ml liquid, 12.5 mg/5 ml elixir, 12.5 mg/5 ml syrup	-		$1.16
			12.5 mg ODT	-		--
			12.5 mg chewable tablets	-		--
			25 mg, 50 mg capsules	-		$0.62
			25 mg, 50 mg tablets	-		--
	Doxytex, Nitetime Sleep-Aid	Doxylamine	2.5 mg/2.5 ml liquid	NF		--
			25 mg tablet	NF		--

PA = Prior Authorization; QL = Quantity Limit; NF = Non-Formulary
*Cost/Rx based on HPSJ Medi-Cal utilization historical data

EVALUATION CRITERIA FOR APPROVAL/EXCEPTION CONSIDERATION

Below are the coverage criteria and required information for each agent. These coverage criteria have been reviewed approved by the HPSJ Pharmacy & Therapeutics (P&T) Advisory Committee. For conditions not covered under this Coverage Policy, HPSJ will make the determination based on Medical Necessity as described in HPSJ Medical Review Guidelines (UM06).

Wakefulness-Promoting Agents
Modafinil (Provigil), Armodafinil (Nuvigil)

Modafinil 200 mg tablets

- ❒ **Coverage Criteria:** Modafinil is reserved for treatment of narcolepsy, shift work sleep disorder or obstructive sleep apnea treated by a sleep specialist or pulmonologist. For apnea, reserved for inadequate response to compliant use of properly-fitting CPAP for at least 90 days.
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** For narcolepsy, clinic notes with diagnosis of narcolepsy as determined by sleep study. For obstructive sleep apnea, clinic notes or fill history indicating patient has tried CPAP for at least 90 days.
- ❒ **Other Notes:** Must be prescribed by sleep specialist or pulmonologist.
- ❒ **Non-Formulary:** Modafinil 100 mg tablets, Armodafinil tablets

Anti-Narcolepsy & Anti-Cataplexy, Sedative-Type Agents
Sodium Oxybate (Xyrem)

- ❒ **Coverage Criteria:** Xyrem is reserved for use in narcolepsy with cataplexy who meet all of the following criteria:
    a. Treated by a sleep specialist or pulmonologist
    b. Treatment failure to 4 weeks of ALL of the following:
        i. Fluoxetine
        ii. Venlafaxine
        iii. Tricyclic Antidepressant
- ❒ **Limits:** 540ml per 30 days
- ❒ **Required Information for Approval:** Clinic notes with diagnosis of narcolepsy with cataplexy and fill history of Fluoxetine, Venlafaxine, and TCA.
- ❒ **Other Notes:** Must be prescribed by sleep specialist or pulmonologist. The FDA requires a REMS program for this medication.

Antidepressants
Trazodone (Desyrel), Mirtazapine (Remeron), Doxepin (Silenor)

Trazodone (Desyrel) 50 mg, 100 mg, 150 mg tablets

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** Consider use in patients with comorbid depression. Sleep Aid quantity limits do not apply to antidepressants. Side effects may limit use of high doses of these medications.
- ❒ **Non-Formulary:** Trazodone 300 mg tablets

Mirtazapine (Remeron)

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** 1 tablet per day
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** Mirtazapine oral-disintegrating tablets (ODT) are reserved for patients with a documented inability to swallow tablets or capsules. Limit 1 tablet per day. Consider use in patients with comorbid depression. Side effects may limit use of high doses of these medications.

Doxepin (Silenor) capsules, oral concentrate

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** Consider use in patients with comorbid depression. Sleep Aid quantity limits do not apply to antidepressants. Side effects may limit use of high doses of these medications.
- ❒ **Non-Formulary:** Silenor tablets

Benzodiazepines
Temazepam (Restoril), Triazolam (Halcion)

Temazepam (Restoril) 15 mg, 30 mg capsules

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** 60 capsules per 75 days
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** Restricted to 60 Capsules per 75 days for members with uncomplicated Insomnia. Please submit PA for members with "activating" psychiatric disorders such as Bipolar Disorder, or for patients in Skilled Nursing Facilities.
- ❒ **Non-Formulary:** Temazepam 7.5 mg, 22.5 mg capsules; Triazolam

Non-Benzodiazepine Sedative Hypnotics
Zolpidem (Ambien), Zaleplon (Sonata), Eszopiclone (Lunesta), Ramelteon (Rozerem), Tasimelteon (Hetlioz), Suvorexant (Belsomra)

Zolpidem (Ambien) 5 mg, 10 mg tablets; Zaleplon (Sonata), Eszopiclone (Lunesta)

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** 60 tablets per 75 days
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** Restricted to 60 tablets per 75 days for members with uncomplicated Insomnia. Please submit PA for members with "activating" psychiatric disorders such as Bipolar Disorder, or for patients in Skilled Nursing Facilities.
- ❒ **Non-Formulary:** Zolpidem XR, SL tablets; Ramelteon; Tasimelteon; Suvorexant

Pineal hormone agents
Melatonin (Circadin)

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** None

Antihistamines
Diphenhydramine (Sominex, Benadryl)

Diphenhydramine (Sominex, Benadryl)

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** Anticholinergic; May increase risk of falls in patients greater than 65 years old.
- ❒ **Non-Formulary:** Doxylamine

CLINICAL JUSTIFICATION

HPSJ's sleep and wakefulness medication management policy is based on recommendations by the *American Academy of Sleep Medicine (AASM)* and *European Federation of Neurological Societies (EFNS).* In general, the recommended general sequence of pharmacological therapy trials for insomnia is: (1) short-intermediate-acting benzodiazepine (BZD) receptor agonists (BzRAs) [benzodiazepines or non-benzodiazepine agents (e.g., zolpidem, eszopiclone, zaleplon, temazepam)] or ramelteon; (2) alternate

short-intermediate-acting BzRAs or ramelteon; (3) sedating antidepressants (e.g., trazodone, amitriptyline, doxepin, mirtazapine); (4) combined BzRAs or ramelteon + sedating antidepressant; other sedating agents, such as anti-epilepsy medications (e.g., gabapentin, tiagabine) and atypical antipsychotics (e.g., quetiapine, olanzapine).[2] Historically, traditional stimulants (i.e., amphetamine derivatives) were used to treat narcolepsy while tricyclic antidepressants were used to treat cataplexy symptoms. Since 2000, practice parameters have included other therapies: wakefulness promoting medications (e.g., modafinil) and sodium oxybate for excessive daytime sleepiness and sodium oxybate, SSRIs, and SNRIs for cataplexy.[3]

Quantity Limit for Sleep Aids:

It is important that patients do not become dependent on sleep medications. Overuse of sleep medications is not benign. There is evidence that use of sleep aids may reduce the quality of sleep and increase the risk of next-morning sedation. Non-benzodiazepines are not free from abuse potential. Taking excessively high doses of non-benzodiazepine sleep medications, such as zolpidem, can act in the same way as benzodiazepines, causing a sense of euphoria. It is also possible that insomnia may be related to an underlying undiagnosed condition including but not limited to, obstructive sleep apnea, anxiety, chronic pain, and adrenal carcinoma. Treatment of the underlying condition can improve patient quality of life significantly, and reduce the potential exposure to side effects from medication overuse.

Considerations for Exceeding Quantity Limits:

Medications for insomnia do not require prior authorization for coverage in the case of uncomplicated insomnia. However, they do require prior authorization in special circumstances that require more than the quantity limit (60 doses per 75 day period). Some examples that may be approved on a case-by-case basis include skilled nursing facility placement and mental health disorder leading to disturbed sleep.

Non-Pharmacological Measures:

All patients with insomnia should attempt to use non-pharmacological measures before starting a sleep aid.

Avoid:

- Smoking (Especially in the evening)
- Caffeine after 2pm
- Alcohol near bed time
- Going to bed hungry
- Drinking too much fluid before bedtime
- Napping excessively
- Watching TV or Reading in bed
- Staying in bed when not sleepy

Do:

- Keep a regular sleeping schedule (including weekends)
- Use the bedroom only for sleep and sex
- Adjust the bedroom so that it's a quiet, dark, and comfortable environment
- Exercise at least 20 minutes daily (but not immediately before bedtime)

Special Situations:

In all special situations, the underlying condition should be treated first to see if that alleviates sleep issues. Only if sleep issues persist after treatment, then should pharmacological therapy be considered.

Obstructive Sleep Apnea (OSA):

Patients with OSA should use Continuous Positive Airway Pressure (CPAP) or Bi-level Positive Airway Pressure (BiPAP). Obese patients with OSA should be encouraged to lose weight, as it may be contributing to their sleep issues, among other things. Avoid agents that will cause respiratory depression, such as benzodiazepines and non-benzodiazepine such as zaleplon or zolpidem.

Chronic Pain:

Patients with chronic pain should have their pain managed before considering the addition of sleep aid pharmacological therapies. Chronic use of opiate medications can cause insomnia, restlessness, hyperalgesia, and in men, low testosterone. All of these issues can cause or worsen insomnia. In many cases,

cross-tapering opiates with non-opiate medications (depending on diagnosis) such as NSAIDs or neuropathic agents such as gabapentin or amitriptyline can greatly improve patients' abilities to sleep as well as their pain control.

Shift Work Sleep Disorder:

Patients who work graveyard or night shift have severely disturbed circadian rhythm. Studies have shown that patients who work rotating shifts are more likely to have disturbed sleep than those who work one shift consistently. These workers many times will revert to daytime wakefulness on their days off. Encouraging short naps (1-3 hours) on days off can improve wakefulness on work days. Use of short acting benzodiazepines or short-acting non-benzodiazepines can help workers maintain a proper sleep cycle.

Non-24-Hour Sleep Wake Disorder (Non-24):

Non-24 is most common in the totally blind patients and their circadian rhythms are not synchronized with the 24-hour day-night cycle due to lack of light information received from the eyes. As a result, their internal body clock reverts to a non-24hour period, causing fluctuating periods of good sleep followed by period of poor sleep and excessive daytime sleepiness. Circadian rhythms are generated by the suprachiasmatic nuclei (SCN) in the hypothalamus that houses receptors for the pineal hormone melatonin, MT_1 and MT_2. Treatment with synthetic pharmaceutical-grade melatonin was previously shown to entrain the circadian pacemaker in a small number of totally blind patients with non-24. The 2015 AASM guidelines suggests strategically timed melatonin for the treatment of N24SWD in blind adults. Alternative treatment options include dual receptor melatonin agonists: Ramelteon (Rozerem) and Tasimelteon (Hetlioz).

Restless Leg Syndrome:

It is unknown what causes restless leg syndrome (RLS), but it is believed to be related to an imbalance of neurotransmitters in the brain. The constant need to move one's legs can prevent patients from having a restful night of sleep. Several treatment options are available, including Gabapentin, and Ropinirole. Treating the underlying cause can lead to better outcomes, less polypharmacy, and less side effects.

Mental Health:

Many medications used for depression can also cause sedation. In patients with insomnia and depression, these "side effects" can be beneficial. Doses for sedation are generally much smaller than doses for treatment of depression. Examples include Trazodone and Mirtazapine. Refer to the package insert of the respective drug for additional information.

For patients with chronic anxiety, anti-anxiety medications such as SSRIs should be initiated. Sleep aids or benzodiazepines should not be used chronically, as this can lead to dependence and tolerance. Treat the underlying anxiety before attempting to resolve sleep issues.

Pregnancy:

Behavioral therapy is of the utmost importance in treating underlying insomnia in pregnant women. Practicing sleep hygiene should be first line, as it prevents exposing the fetus to pharmaceutical agents. Care should be taken when initiating agents for insomnia especially in the first trimester, as sedative-hypnotic agents can increase the risk of fetal malformations.

REFERENCES

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10. Morgenthaler TI, Kapur VK, Brown T, et al. Practice Parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007; 30:1705-1711.
11. Mignot E, Nishino S. Emerging therapies in narcolepsy-cataplexy. *Sleep*. 2005; 28:754-763.

REVIEW & EDIT HISTORY

Document Changes	Reference	Date	P&T Chairman
Creation of Policy	Hypnotics Review 9-06.doc	9/2006	Allen Shek PharmD BCPS
Update to Policy	HPSJ Coverage Policy - Psychiatric - Sleeping Disorders 2015-05.docx	05/2015	Jonathan Szkotk, PharmD, BCACP
Update to Policy	Wakefulness-Promoting Agent Class Review 2-2016.docx	02/2016	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy - Psychiatric - Sleeping Disorders 2016-12.docx	12/2016	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy - Psychiatric - Sleeping Disorders 2018-2.docx	02/2018	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy - Psychiatric - Sleeping Disorders 2019-5.docx	05/2019	Matthew Garrett, PharmD

Note: All changes are approved by the HPSJ P&T Committee before incorporation into the utilization policy