SEDATIVE HYPNOTICS

BACKGROUND

Insomnia can be defined as an inability to initiate or maintain sleep associated with daytime impairment that is not attributed to inadequate opportunities to sleep.[1,2] Insomnia is a common condition for which adults seek treatment with prevalence typically ranging from 10-30% of the population, with some estimates as high as 50-60%.[3,4] Sleep is essential for normal physiological and psychological functioning. Multiple factors (age, comorbid physical symptoms, comorbid psychiatric conditions, medication side effects, and poor sleep habits) can influence the amount and quality of sleep an individual receives.[5] The economic burden associated with insomnia has been estimated as high as $16 billion annually in direct costs and up to $75-100 billion annually in indirect costs.[6]

According to the International Classification of Sleep Disorders, Third Edition, insomnia can be classified as either short-term or chronic.[1] Short-term insomnia is the most common type of insomnia and usually lasts less than one month.[5] Chronic insomnia is defined as insomnia that persists for at least 3 months at a frequency of at least three times per week.[1] Chronic insomnia is associated with a significant impact on overall health and quality of life.

Treatment options for insomnia include both non-pharmacologic and pharmacologic therapies. Non-pharmacologic therapy centered around cognitive behavioral therapy (CBT) which includes psychological and behavioral interventions is often the initial recommended treatment.[7–10] CBT involves addressing root causes of insomnia and developing behaviors that promote sleep such as good sleep hygiene. Addressing comorbid conditions that commonly cause insomnia is also essential.

PHARMACOTHERAPY

Pharmacologic agents utilized in the treatment of insomnia can be broadly categorized into benzodiazepines (BZD) and nonbenzodiazepines (non-BZD). Under the current MS Medicaid Universal Preferred Drug List, agents for the treatment of insomnia are listed as “Sedative Hypnotics”. (Figure 1)

FIGURE 1: Medicaid Preferred Drug List – Sedative Hypnotics v.2020.3

THERAPEUTIC DRUG CLASS	PREFERRED AGENTS	NON-PREFERRED AGENTS	PA CRITERIA
SEDATIVE HYPNOTICS			
	BENZODIAZEPINES SmartPA		
	estazolam flurazepam temazepam (15mg and 30mg)	DALMANE (flurazepam) DAYVIGO (lemborexant)NR DORAL (quazepam) HALCION (triazolam) quazepam RESTORIL (temazepam) temazepam (7.5mg and 22.5mg) triazolam	Single source benzodiazepines and barbiturates are NOT covered – NO PA's will be issued for these drugs. **MS DOM Opioid Initiative** • Concomitant use of Opioids and Benzodiazepines Criteria details found here **Quantity Limit – CUMULATIVE**
			Quantity limit per rolling days for all strengths. *SmartPA will allow an early refill override for one dose or therapy change per year.* • **31 units/31 days** - all strengths **Triazolam – CUMULATIVE** Quantity limit per rolling days for all strengths • **10 units/31 days** • **60 units/365 days**
	OTHERS SmartPA		
	zaleplon zolpidem	AMBIEN (zolpidem) AMBIEN CR (zolpidem) BELSOMRA (suvorexant) doxepin EDLUAR (zolpidem) eszopiclone HETLIOZ (tasimelteon) INTERMEZZO (zolpidem) LUNESTA (eszopiclone) ramelteon ROZEREM (ramelteon) SILENOR (doxepin) SONATA (zaleplon) zolpidem ER zolpidem SL ZOLPIMIST (zolpidem)	**Quantity Limit – CUMULATIVE** Quantity limit per rolling days for all strengths. *SmartPA will allow an early refill override for one dose or therapy change per year.* • **31 units/31 days** • **1 canister/31 days** – Zolpimist & male • **1 canister/62 days –** Zolpimist & female **Gender and Dose Limit for zolpidem** • **Female** - Ambien 5mg, Ambien CR 6.25mg, Intermezzo 1.75 mg • **Male** – all zolpidem strengths **Non-Preferred Criteria** • Have tried 2 different preferred agents in the past 6 months **Hetlioz**

There are five benzodiazepines that are only indicated for use as sedative hypnotics for the treatment of insomnia: estazolam, flurazepam (Dalmane®), quazepam (Doral®), temazepam (Restoril®), and triazolam (Halcion®). Temazepam and triazolam are **only** indicated for short-term treatment of insomnia (generally 7-10 days), however, short-term use is recommended for all benzodiazepines.[11–15] Additionally, benzodiazepines contain a warning related to the failure of insomnia to remit after 7 to 10 days of treatment and the potential presence of other illnesses that should be evaluated. (Figure 2)

Figure 2: Benzodiazepine Warning

Warnings

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. **The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.** Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative-hypnotic drugs. Because some of the important adverse effects of sedative-hypnotics appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose, especially in the elderly.

Nonbenzodiazepines approved for use in the treatment of insomnia include nonbenzodiazepine receptor agonists (BzRA or Z Drugs), melatonin agonists, low-dose form of sedating antidepressant (doxepin), and orexin receptor antagonists. In addition to those agents FDA-approved for use as sedative hypnotics, non-FDA approved agents have been utilized in the management of insomnia such as other BZDs, antidepressants, antipsychotics, and analgesics. Although not FDA-approved, there is evidence supporting the use of low-dose trazodone in the management of insomnia.[16] Figure 3 provides an overview of agents FDA-approved in the treatment of insomnia along with their duration of action.

Figure 3: Agents FDA-Approved for the Management of Insomnia[5,17]

Drug	Usual Adult Dose	Indication	Duration of Action
BENZODIAZEPINES:			
estazolam	1 to 2 mg	sleep onset or maintenance	intermediate
flurazepam (Dalmane)	15 to 30 mg	sleep onset or maintenance	long
quazepam (Doral)	7.5 to 15 mg	sleep onset or maintenance	long
temazepam (Restoril)	7.5 to 30 mg	sleep onset or maintenance	intermediate
triazolam (Halcion)	0.125 to 0.25 mg	sleep onset	short
NONBENZODIAZEPINES:			
Nonbenzodiazepine benzodiazepine receptor agonists (BzRAs or Z Drugs):			
eszopiclone (Lunesta)	1 to 3 mg	sleep onset or maintenance	intermediate
zaleplon (Sonata)	5 to 20 mg	sleep onset	short
zolpidem (Ambien, Edular, Zolpimist)	5 to 10 mg	sleep onset or maintenance	short
zolpidem extended release (Ambien CR)	6.25 to 12.5 mg	sleep onset or maintenance	intermediate
zolpidem middle of the night (Intermezzo)	1.75 to 3.5 mg	sleep maintenance	short
Melatonin receptor agonist:			
ramelteon (Rozerem)	8 mg	sleep onset	short
tasimelteon (Hetlioz)	20mg	non-24 hr sleep/wake cycle	short
Low-dose antidepressant:			
doxepin (Silenor)	3 to 6 mg	sleep maintenance	long
Orexin receptor antagonists:			
lemborexant (Dayvigo)	5 to 10 mg	sleep onset or maintenance	long
suvorexant (Belsomra)	10 to 20 mg	sleep onset or maintenance	intermediate

TREATMENT RECOMMENDATIONS

Short-term insomnia treatment involves identifying and addressing the stressor involved in sleep disturbance. When short-term insomnia is severe, a trial of a short or intermediate acting benzodiazepine receptor agonist for two to four weeks is often recommended.[5] When insomnia persists and transitions into chronic insomnia, a combination approach of CBT and pharmacologic therapy is the primary treatment approach recommended.[5,7,10]

In 2017 the American Academy of Sleep Medicine published the Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults.[10] The recommendations were rated from STRONG (one that clinicians should, under most circumstances, always be following when pharmacologic treatment is indicated) to WEAK (one that reflects a lower degree of certainty in the appropriateness of the patient-care strategy and requires that the clinician use his/her clinical knowledge and experience, and refer to the individual patient's values and preferences to determine the best course of action). Figure 4 displays a summary of the clinical practice recommendations.

Figure 4: Summary of Clinical Practice Recommendations[10]

Treatment	Recommendation	Direction and Strength of Recommendation	Quality of Evidence	Benefits and Harms Assessment	Patients' Values and Preferences Assessment
Orexin receptor agonists					
Suvorexant This recommendation is based on trials of 10, 15/20, and 20 mg doses of suvorexant.	We suggest that clinicians use suvorexant as a treatment for sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Low	Benefits outweigh harms	The majority of patients would use this treatment (over no treatment), but many would not.
BZD receptor agonists					
Eszopiclone This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.	We suggest that clinicians use eszopiclone as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Very low	Benefits outweigh harms	The majority of patients would use this treatment (over no treatment), but many would not.
Zaleplon This recommendation is based on trials of 10 mg doses of zaleplon.	We suggest that clinicians use zaleplon as a treatment for sleep onset insomnia (versus no treatment) in adults.	WEAK	Low	Benefits outweigh harms	The majority of patients would use this treatment (over no treatment), but many would not.
Zolpidem This recommendation is based on trials of 10 mg doses of zolpidem.	We suggest that clinicians use zolpidem as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Very low	Benefits outweigh harms	The majority of patients would use this treatment (over no treatment), but many would not.
Benzodiazepines					
Triazolam This recommendation is based on trials of 0.25 mg doses of triazolam.	We suggest that clinicians use triazolam as a treatment for sleep onset insomnia (versus no treatment) in adults.	WEAK	High	Benefits approx equal to harms	The majority of patients would use this treatment (over no treatment), but many would not.
Temazepam This recommendation is based on trials of 15 mg doses of temazepam.	We suggest that clinicians use temazepam as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Moderate	Benefits outweigh harms	The majority of patients would use this treatment (over no treatment), but many would not.
Melatonin agonists					
Ramelteon This recommendation is based on trials of 8 mg doses of ramelteon.	We suggest that clinicians use ramelteon as a treatment for sleep onset insomnia (versus no treatment) in adults.	WEAK	Very low	Benefits outweigh harms	The majority of patients would use this treatment (over no treatment), but many would not.
Heterocyclics					
Doxepin This recommendation is based on trials of 3 mg and 6 mg doses of doxepin.	We suggest that clinicians use doxepin as a treatment for sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Low	Benefits outweigh harms	The majority of patients would use this treatment (over no treatment), but many would not.
Trazodone This recommendation is based on trials of 50 mg doses of trazodone.	We suggest that clinicians not use trazodone as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Moderate	Harms outweigh benefits	The majority of patients would use this treatment (over no treatment), but many would not.
Anticonvulsants					
Tiagabine This recommendation is based on trials of 4 mg doses of tiagabine.	We suggest that clinicians not use tiagabine as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Very low	Harms outweigh benefits	The majority of patients would not use this treatment (over no treatment), but many would.
Over-the-counter preparations					
Diphenhydramine This recommendation is based on trials of 50 mg doses of diphenhydramine.	We suggest that clinicians not use diphenhydramine as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Low	Benefits approx equal to harms	The majority of patients would not use this treatment (over no treatment), but many would.
Melatonin This recommendation is based on trials of 2 mg doses of melatonin.	We suggest that clinicians not use melatonin as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Very low	Benefits approx equal to harms	The majority of patients would use this treatment (over no treatment), but many would not.
L-tryptophan This recommendation is based on trials of 250 mg doses of tryptophan.	We suggest that clinicians not use tryptophan as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.	WEAK	High	Harms outweigh benefits	The majority of patients would use this treatment (over no treatment), but many would not.
Valerian This recommendation is based on trials of variable dosages of valerian and valerian-hops combination.	We suggest that clinicians not use valerian as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.	WEAK	Low	Benefits approx equal to harms	The majority of patients would not use this treatment (over no treatment), but many would.

approx = approximately.

The guideline noted multiple difficulties and limitations related to the development of meaningful clinical guidelines. These limitations lead to a relatively low level in quality of evidence for the vast majority of recommendations. With the significant risks of sedation and related complications associated with the use of hypnotic agents, clinicians are encouraged to prescribe the lowest dose

for the shortest duration possible, conduct appropriate patient counseling and maintain diligent monitoring of individuals prescribed hypnotic agents.[10]

DOM and MS-DUR have undertaken multiple initiatives involving sedative hypnotics in recent years. Based on recommendations from the DUR Board in 2015, DOM implemented quantity limits for triazolam as indicated on the current UPDL. (Figure 1) At the September 2016 DUR Board meeting, MS-DUR recommended the implementation of further quantity limits on temazepam (quantity limit of 10 day supply per month, cumulative quantity limit of 60 days within a 365-day period). No action was taken at that time due to a lack of therapeutic alternatives available. Additionally, as part of the DOM's Opioid Initiative that was implemented in 2019, concomitant use of opioids and benzodiazepines was restricted.

Recently the Centers for Medicare and Medicaid Services (CMS) released proposed rule changes to the minimum standards for Medicaid State Drug Utilization Review. Included as part of the proposed rule changes is the following language around concomitant use of opioids and sedatives, " *We also would like to remind states that section 1927(g)(1) of the Act also currently supports including other potentially harmful opioid interactions as* ***additional prospective or retrospective reviews in state DUR programs, such as opioids and central nervous system (CNS) depressants, including alcohol or sedatives. We fully support states including such additional opioid interactions or contraindications in prospective or retrospective reviews as part of a comprehensive DUR program***."[18] In conjunction with this proposed rule change, the CMS Medicaid DUR Annual Report for Federal Fiscal Year (FFY) 2019 included for the first time a question related to DUR activities involving the monitoring of concomitant use of opioids and sedatives.

With the changing landscape in the treatment of insomnia, the approval of new therapeutic agents, and updated CMS guidance around sedatives hypnotics, MS-DUR conducted an updated review of the utilization of sedative hypnotics in the treatment of insomnia.

METHODS

A retrospective analysis was conducted using Mississippi Medicaid pharmacy claims for sedative hypnotics and opioids during the study period June 2019 – May 2020. The analysis included data from the Fee-for-Service (FFS) program and the coordinated care organizations (CCOs) which include Magnolia Health (MAG), Molina Healthcare (MOL), and UnitedHealthcare (UHC). Sedative hypnotics were classified into benzodiazepines indicated for insomnia (estazolam, flurazepam, quazepam, temazepam, and triazolam) and non-benzodiazepines (based on MS-UPDL v2020.3). Low-dose formulations of doxepin (3/6/10 mg) and trazodone (50 and 100 mg) were also evaluated.

Beneficiaries were included if they had at least one pharmacy claim for any sedative hypnotic during the study period. Maximum duration of continuous sedative-hypnotic therapy was evaluated as date of first fill to date of last fill, including days' supply of last fill, allowing for a 15-day refill gap. Concomitant use of sedative hypnotic therapy and opioids was evaluated if a beneficiary had at least one day of overlap between two therapies with duration of concomitant therapy assessed. Demographic characteristics including age at first fill of sedative-hypnotic therapy, gender, race, and health plan at first fill were evaluated. Beneficiaries prescribed both non-benzodiazepines and benzodiazepines were classified based on the drug type of first sedative hypnotic prescribed. Concomitant treatment episodes of sedative hypnotics and opioids were evaluated for physician characteristics. Provider specialty of the second prescribing physician (for either a sedative-hypnotic or an opioid) resulting in a concomitant treatment episode is reported.

RESULTS

Table 1 displays an overall utilization summary of sedative hypnotics by drug type. Of the benzodiazepine agents, temazepam accounted for the vast majority of use (97.9%) among beneficiaries. Low-dose trazodone and zolpidem accounted for 94.8% of non-benzodiazepine use.

TABLE 1. Overall Summary of Medication Utilization by Drug and Drug Type (June 2019 - May 2020)

Benzodiazepines			
Drug	**# of fills**	**# of benes**	**Mean Days Supply**
Temazepam	1,868	510	29.1
Triazolam	10	8	12.9
Estazolam	2	2	30.0
Flurazepam	1	1	30.0
Non-Benzodiazepines			
Drug	**# of fills**	**# of benes**	**Mean Days Supply**
Trazodone*	28,985	7,962	33.0
Zolpidem	6,170	1,465	29.1
Doxepin**	1,057	342	29.7
Zaleplon	285	88	28.4
Eszopiclone	194	53	29.2
Suvorexant	141	22	30.0
Tasimelteon	15	3	30.0
Ramelteon	11	8	30.0

*Trazodone - 50mg and 100mg.
**Doxepin - 3mg, 6mg, and 10 mg

TABLE 2. Demographic Characteristics of Beneficiaries Prescribed Sedative Hypnotic Therapy by Drug Type* (June 2019 - May 2020)

Variable	Benzodiazepines**									Non-benzodiazepines***									Grand Total
	FFS		UHC		Magnolia		Molina		Total	FFS		UHC		Magnolia		Molina		Total	
Age Category (yrs)																			
0-12	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	69	3.5%	123	3.8%	43	1.2%	5	0.6%	240	**240**
13-20	0	0.0%	0	0.0%	2	1.1%	1	2.9%	3	216	10.8%	464	14.5%	255	7.0%	77	10.0%	1,012	**1,015**
21-30	9	8.0%	13	9.8%	15	8.1%	9	26.5%	46	266	13.3%	442	13.8%	561	15.5%	200	26.0%	1,469	**1,515**
31-40	19	16.8%	32	24.1%	40	21.6%	9	26.5%	100	329	16.5%	676	21.1%	867	24.0%	241	31.3%	2,113	**2,213**
41-50	23	20.4%	26	19.5%	39	21.1%	8	23.5%	96	281	14.1%	610	19.0%	705	19.5%	123	16.0%	1,719	**1,815**
51-64	58	51.3%	62	46.6%	88	47.6%	7	20.6%	215	806	40.4%	886	27.6%	1,183	32.7%	124	16.1%	2,999	**3,214**
65+	4	3.5%	0	0.0%	1	0.5%	0	0.0%	5	26	1.3%	7	0.2%	4	0.1%	0	0.0%	37	**42**
Total	***113***		***133***		***185***		***34***		***465***	***1,993***		***3,208***		***3,618***		***770***		***9,589***	***10,054***
Gender																			
Female	77	68.1%	98	73.7%	142	76.8%	26	76.5%	343	1,209	60.7%	2,159	67.3%	2,531	70.0%	570	74.0%	6,469	**6,812**
Male	36	31.9%	35	26.3%	43	23.2%	8	23.5%	122	784	39.3%	1,049	32.7%	1,087	30.0%	200	26.0%	3,120	**3,242**
Total	***113***		***133***		***185***		***34***		***465***	***1,993***		***3,208***		***3,618***		***770***		***9,589***	***10,054***
Race																			
Caucasian	60	53.1%	64	48.1%	82	44.3%	16	47.1%	222	962	48.3%	1,471	45.9%	1,469	40.6%	360	46.8%	4,262	**4,484**
African American	46	40.7%	48	36.1%	81	43.8%	13	38.2%	188	849	42.6%	1,364	42.5%	1,760	48.6%	316	41.0%	4,289	**4,477**
Hispanic	0	0.0%	3	2.3%	1	0.5%	0	0.0%	4	9	0.5%	25	0.8%	15	0.4%	7	0.9%	56	**60**
Other	7	6.2%	18	13.5%	21	11.4%	5	14.7%	51	173	8.7%	348	10.8%	374	10.3%	87	11.3%	982	**1,033**
Total	***113***		***133***		***185***		***34***		***465***	***1,993***		***3,208***		***3,618***		***770***		***9,589***	***10,054***

NOTE: Of the 10,054 beneficiaries, 111 (1.10%) were prescribed both, benzodiazepines and non-benzodiazepines during the study period. For these beneficiaries, date and type of first sedative hypnotic fill was used for classification.
Health plan was assessed at the time of first fill of the medication.
*Classification of drug type was based on Mississippi Universal Preferred Drug List (v2020.3)
** Benzodiazepines assessed included estazolam, flurazepam, triazolam, temazepam, and quazepam.
*** Two of the drugs classified under non-benzodiazepines were included based on their dose as follows:
Doxepin - 3mg, 6mg, and 10 mg
Trazodone - 50mg and 100mg.

Table 2 describes demographic characteristics of sedative hypnotic users.

- Beneficiaries aged 51-64 years had the highest sedative hypnotic use across all age groups (Overall 32%).
  - 46.2 % of benzodiazepine use
  - 31.3% of non-benzodiazepine use
- 67.8% of sedative hypnotic use occurred among females.
- Across all sedative hypnotic use, Caucasians and African Americans had nearly identical proportions of use (44.6% for Caucasians and 44.5% for African Americans).
  - However among benzodiazepine use, Caucasians had a higher proportion of use at 47.7% compared to African Americans at 40.4%.

TABLE 3a. Maximum Number of Days of Continuous Therapy* with Benzodiazepines (June 2019 - May 2020)

Drug	Maximum Days of Continuous Therapy							
	1 - 10	11 - 20	21 - 31	32 - 62	63 - 93	94 - 186	187 +	Total
Temazepam	13	22	240	93	58	49	35	510
Triazolam	6	0	0	2	0	0	0	8
Estazolam	0	0	1	1	0	0	0	2
Flurazepam	0	0	1	0	0	0	0	1

*Continuous therapy was calculated as date of first fill to date of last fill, including days supply of last fill, allowing for a 15-day refill gap.

NOTE: Results include all beneficiaries filling a prescription during study period. Beneficiaries may have started therapy before June 2019 and may have started therapy just prior to May 2020 end data for inclusion in the analyses.

Table 3b. Maximum Number of Days of Continuous Therapy* with Non-benzodiazepines (June 2019 - May 2020)

Drug	Maximum Days of Continuous Therapy							
	1 - 10	11 - 20	21-31	32 - 62	63 - 93	94 - 186	187 +	Total
Trazodone	132	214	3,263	1,652	1,183	968	550	7,962
Zolpidem	71	79	546	276	163	194	136	1,465
Doxepin	8	12	177	69	36	27	13	342
Zaleplon	2	6	45	14	10	8	3	88
Eszopiclone	2	1	26	10	3	5	6	53
Suvorexant	0	0	7	3	2	3	7	22
Ramelteon	0	0	7	1	0	0	0	8
Tasimelteon	0	1	1	0	0	0	1	3

*Continuous therapy was calculated as date of first fill to date of last fill, including days supply of last fill, allowing for a 15-day refill gap.

NOTE: Results include all beneficiaries filling a prescription during study period. Beneficiaries may have started therapy before June 2019 and may have started therapy just prior to May 2020 end data for inclusion in the analyses.

Considering the maximum number of days of continuous therapy, Tables 3a/b indicate:

- The maximum days supply edit for triazolam appears to be keeping continuous days of therapy low.
- 93.1% of temazepam use is for $\geq$ 21 days of therapy, with 27.8% of beneficiaries receiving it for $\geq$ 63 days.
    - In 2016, the DUR Board considered implementing a maximum days supply edit for temazepam similar to that applied to triazolam.
- 95.7% of beneficiaries prescribed trazodone and 89.7% of beneficiaries prescribed zolpidem received them for $\geq$ 21 days.

CMS is considering updating their minimum standards to include the monitoring of concomitant use of opioids and sedatives. As part of this review of sedative hypnotics, MS-DUR also assessed concomitant use with opioids. Tables 4a/b display the number of beneficiaries and claims with concomitant use.

TABLE 4a. Concomitant Use of Benzodiazepines and Opioids - Benes and Claims by Plan (June 2019 - May 2020)

Drug	FFS		UHC		Magnolia		Molina	
	Benes	Claims	Benes	Claims	Benes	Claims	Benes	Claims
Temazepam	33	46	35	85	37	60	6	10
Triazolam	1	1	1	1	2	2	0	0
Estazolam	0	0	0	0	1	1	0	0

TABLE 4b. Concomitant Use of Non-benzodiazepines and Opioids - Benes and Claims by Plan (June 2019 - May 2020)

Drug	FFS		UHC		Magnolia		Molina	
	Benes	Claims	Benes	Claims	Benes	Claims	Benes	Claims
Trazodone*	468	858	584	1,157	637	1,243	119	170
Zolpidem	180	366	152	421	230	556	22	35
Doxepin**	12	19	23	45	25	43	8	9
Eszopiclone	2	2	6	8	13	21	0	0
Zaleplon	13	31	9	17	9	17	2	4
Suvorexant	0	0	1	1	6	8	0	0
Ramelteon	0	0	1	1	2	5	0	0
Tasimelteon	0	0	0	0	0	0	1	2

*Trazodone - 50mg and 100mg.
**Doxepin - 3mg, 6mg, and 10 mg

- There were a total on 2,641 beneficiary specific concomitant use events during the study period. ** A beneficiary could be represented multiple times if they had concomitant events involving multiple sedative hypnotic drugs.*
    - There were 116 beneficiary specific concomitant events with benzodiazepine sedative hypnotics and opioids.
    - There were 2525 beneficiary specific concomitant events with non-benzodiazepine sedative hypnotics and opioids.

TABLE 5a. Days of Concomitant Use of Benzodiazepines and Opioids (June 2019 - May 2020)					
Drug	Number of claims				
	≤3 days	4 to 7 days	8 to 14 days	15 to 30 days	31+ days
Temazepam	34	36	29	102	0
Triazolam	4	0	0	0	0
Estazolam	0	0	0	1	0

TABLE 5b. Days of Concomitant Use of Non-benzodiazepines and Opioids (June 2019 - May 2020)					
Drug	Number of claims				
	≤3 days	4 to 7 days	8 to 14 days	15 to 30 days	31+ days
Trazodone	590	754	505	1,481	98
Zolpidem	145	298	233	702	0
Doxepin	16	21	16	63	0
Zaleplon	5	12	12	40	0
Eszopiclone	1	7	5	18	0
Ramelteon	0	0	1	5	0
Suvorexant	4	2	0	3	0
Tasimelteon	2	0	0	0	0

*Trazodone - 50mg and 100mg.
**Doxepin - 3mg, 6mg, and 10 mg

From Tables 5a/b it can be determined:

- Of the 206 concomitant opioid/benzodiazepine claims, 103 (50%) were for ≥ 15 days.
- Approximately 47.8% (2410/5039) of concomitant use of non-benzodiazepines and opioids was for ≥15 days.

TABLE 6. Demographic Characteristics of Beneficiaries who had Concomitant Use of Sedative-Hypnotics and Opioids (June 2019 - May 2020)

Variable	Benzodiazepines*									Non-benzodiazepines**									Grand Total†
	FFS		UHC		Magnolia		Molina		Total	FFS		UHC		Magnolia		Molina		Total	
Age Category (yrs)																			
0-12	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	1	0.1%	1	0.1%	0	0.0%	0	0.0%	2	2
13-20	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	16	2.4%	23	3.2%	15	1.8%	6	4.9%	60	60
21-30	3	8.8%	2	5.7%	2	5.1%	0	0.0%	7	62	9.3%	42	5.8%	72	8.8%	24	19.5%	200	207
31-40	5	14.7%	9	25.7%	13	33.3%	1	25.0%	28	130	19.5%	150	20.7%	191	23.3%	37	30.1%	508	536
41-50	8	23.5%	5	14.3%	7	17.9%	1	25.0%	21	140	21.0%	178	24.6%	194	23.6%	30	24.4%	542	563
51-64	15	44.1%	19	54.3%	17	43.6%	2	50.0%	53	280	42.0%	326	45.0%	345	42.0%	26	21.1%	977	1,030
65+	3	8.8%	0	0.0%	0	0.0%	0	0.0%	3	38	5.7%	5	0.7%	4	0.5%	0	0.0%	47	50
Total	***34***		***35***		***39***		***4***		***112***	***667***		***725***		***821***		***123***		***2,336***	***2,448***
Gender																			
Female	21	61.8%	22	62.9%	29	74.4%	2	50.0%	74	441	66.1%	509	70.2%	606	73.8%	91	74.0%	1,647	**1,721**
Male	13	38.2%	13	37.1%	10	25.6%	2	50.0%	38	226	33.9%	216	29.8%	215	26.2%	32	26.0%	689	**727**
Total	***34***		***35***		***39***		***4***		***112***	***667***		***725***		***821***		***123***		***2,336***	***2,448***
Race																			
Caucasian	15	44.1%	15	42.9%	16	41.0%	1	25.0%	47	345	51.7%	339	46.8%	353	43.0%	60	48.8%	1,097	**1,144**
African American	18	52.9%	14	40.0%	19	48.7%	1	25.0%	52	282	42.3%	282	38.9%	386	47.0%	44	35.8%	994	**1,046**
Hispanic	0	0.0%	2	5.7%	0	0.0%	0	0.0%	2	1	0.1%	8	1.1%	2	0.2%	1	0.8%	12	**14**
Other	1	2.9%	4	11.4%	4	10.3%	2	50.0%	11	39	5.8%	96	13.2%	80	9.7%	18	14.6%	233	**244**
Total	***34***		***35***		***39***		***4***		***112***	***667***		***725***		***821***		***123***		***2,336***	***2,448***

* Benzodiazepines assessed included estazolam, flurazepam, triazolam, temazepam, and quazepam.

** Two of the drugs classified under non-benzodiazepines were included based on their dose as follows:
Doxepin - 3mg, 6mg, and 10 mg
Trazodone - 50mg and 100mg.

† 16 beneficiaries were prescribed both benzodiazepines and non-benzodiazepines. These beneficiaries were counted under both drug classes. The grand total is inflated to represent double counting of these beneficiaries. **There were a total of 2432 unique beneficiaries with concomitant use.**

Examining the demographics of concomitant users of sedative hypnotics and opioids:

- A total of 2,432 unique beneficiaries had concomitant events. This means approximately **24.2%** (2,432/10,054) of all beneficiaries that used sedative hypnotics had concomitant use with opioids.
    - Of the 465 beneficiaries prescribed benzodiazepine sedative hypnotics (Table 2), 112 (24.1%) had concomitant use with opioids.
- Similar to all sedative hypnotic users, beneficiaries aged 51-64 years had the highest proportion of concomitant use at 42.1%.
- Females comprised 70.3% of concomitant users.
- Although overall Caucasians made up the largest proportion of concomitant use at 46.7%, African Americans made up the highest proportion of benzodiazepine and opioid concomitant use at 46.4%.

While examining beneficiary characteristics of concomitant users of sedative hypnotics and opioids, MS-DUR reviewed their clinical history for a period of one year prior to the date of first concomitant use.

TABLE 7. Clinical History of Beneficiaries with Concomitant Use of Sedative Hypnotics and Opioids between Jun 2019 - May 2020

Diagnoses	Benzodiazepines (N = 112)		Non-benzodiazepines (N = 2,328)*	
	n	%	n	%
Spinal and Back Pain	69	61.6%	1,476	63.4%
Depression	47	42.0%	1,260	54.1%
Anxiety	64	57.1%	1,214	52.1%
Joint pain	54	48.2%	1,171	50.3%
Chronic Pain	48	42.9%	1,157	49.7%
Muscle Pain	58	51.8%	1,142	49.1%
Abdominal, Pelvic, and Renal Pain	35	31.3%	931	40.0%
Psychiatric Comorbidities**	20	17.9%	550	23.6%
Opioid Use Disorder	17	15.2%	540	23.2%
Substance Use Disorder	19	17.0%	437	18.8%
Cancer	25	22.3%	278	11.9%
Acute pain	7	6.3%	206	8.8%
Alcohol Use Disorder	12	10.7%	202	8.7%

NOTE: Clinical history was assessed in a 1-year period prior to the date of first concomitant use of sedative-hypnotic therapy and opioids.

*Of 2,336 beneficiaries who had concomitant use of non-benzodiapines and opioids, 8 beneficiaries did not have medical claims to assess baseline clinical history.

**Psychiatric comorbidities included schizophrenia, schizotypal, and schizoaffective disorders, delusional disorders, psychotic disorders, manic episode, and bipolar disorder.

- A large proportion of beneficiaries had a history of the following clinical conditions:
  - Spinal/Back Pain
  - Depression
  - Anxiety
  - Joint Pain
  - Chronic Pain
  - Muscle Pain

Provider type associated with the concomitant use of sedative hypnotics and opioids was also assessed.

TABLE 8. Type of Prescriber for Second Prescription Resulting in Concomitant Episodes of Sedative-Hypnotic and Opioid Use (June 2019 - May 2020)

Benzodiazepines				Non-benzodiazepines			
Provider Type	**# of Providers**	**# of Events**	**# of Benes**	**Provider Type**	**# of Providers**	**# of Events**	**# of Benes**
MD-FP	38	20	17	MD-FP	210	1,073	497
NP-FM	39	20	20	NP-FM	202	754	425
Dentist	13	13	12	MD-IM	104	449	223
MD-IM	22	11	6	NP-Other	86	378	177
NP-Other	16	7	7	Dentist	140	266	229
MD-Hem/Onc	8	6	6	MD-EM	77	195	131
MD-Ortho	4	4	3	MD-Pain	22	143	98
MD-Pain	5	4	4	MD-Other PCP	62	109	81
MD-EM	3	3	3	MD-Ortho	44	79	70
MD-Surg	2	2	2	MD-Hem/Onc	29	63	37
MD-Other PCP	2	1	1	MD-Surg	41	63	52
Other	54	35	35	NP-Other PCP	4	6	4
				Other	534	1,462	846

- MD-FP and NP-FM made up the highest proportion of providers associated with the concomitant prescribing of sedative hypnotics and opioids.

CONCLUSIONS

Although guidelines for prescribing sedative hypnotics exist, the quality of evidence for specific clinical recommendations for pharmacotherapy is limited. However, the guidelines do stress utilizing the lowest dose for the shortest duration possible when prescribing pharmacotherapy. Among Medicaid beneficiaries, trazodone and zolpidem are the most commonly prescribed sedative hypnotics. Among benzodiazepine sedative hypnotics specifically, temazepam is the most commonly prescribed. Approximately 90% or greater of the use of trazodone, zolpidem, and temazepam was for > 21 days of continuous therapy. This may indicate that beneficiaries are remaining on these therapies for extended periods of time. The PDL days supply edits implemented in 2016 for triazolam appear to be effective in limiting the days of continuous therapy for that agent. When examining concomitant use of sedative hypnotics and opioids, 24.3% of all beneficiaries prescribed sedative hypnotics had concomitant use with opioids.

RECOMMENDATIONS

1. DOM should implement provider education around the concomitant use of sedative hypnotics and opioids.

Options for Consideration:

- MS-DUR distribute a one-time letter to all providers that prescribed concomitant sedative hypnotics and opioids to beneficiaries during the previous six months alerting them to the increased risks associated with concomitant use and CMS monitoring recommendations.
- Develop an educational piece to be included in the next DOM Provider Bulletin.

2. DOM should implement DUR review(s) around the concomitant use of sedative hypnotics and opioids.

Options for Consideration:

- Pro-DUR edit – create a pro-DUR edit alerting pharmacists to the risks associated with concomitant use but allowing the pharmacist to bypass.
- Retro-DUR notice – MS-DUR send letters monthly to providers that prescribed concomitant sedative hypnotic/opioid therapy alerting them of the potential dangers.

3. MS-DUR to further evaluate trends and risk factors (racial disparities, comorbidities, prescriber types) associated with long-term use of sedative hypnotics and their concomitant use with opioids.

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