BENZODIAZEPINE UTILIZATION FOR INSOMNIA

BACKGROUND

Sleep related disorders are common in the general adult population. Researchers are finding that sleep disruption is often the result of the increased presence of medical, and psychosocial comorbidities in this population.[1] Drug therapies approved by the FDA for treatment of insomnia include benzodiazepines, non-benzodiazepines, melatonin receptor agonists, antidepressants, and orexin cycle antagonists.

According to the Maine Benzodiazepine Study Group guidelines, there is evidence for the effectiveness of benzodiazepines and other sedative hypnotics in the relief of short-term (1 to 2 weeks), but not long-term, insomnia. These guidelines recommend that the treatment period should not exceed 2 weeks.[1]

A review of the risks and benefits of benzodiazepines was conducted by the Psychopharmacology Special Interest Group of the Royal College of Psychiatrists and the British Association for Psychopharmacology. This group issued a joint statement with recommendations for the use of benzodiazepines in clinical practice.[2] They concluded that adequate treatment of insomnia is often difficult, and depends on many factors such as age, presence of physical illness, pain, use of concomitant medication(s), and history of drug or alcohol misuse. The adoption of 'sleep hygiene' techniques was considered to be the initial part of management. Benzodiazepines and at that time, the newer 'Z-drugs' (zaleplon, zolpidem and zopiclone) were recognized as the most effective drugs for the short-term treatment of insomnia that is severe, disabling and causing distress. As in the treatment of patients with anxiety disorders, it was recommended that the use of benzodiazepines should generally be limited to a maximum of four weeks. It was noted that in the United Kingdom, though not in the United States, all hypnotics are licensed for short term use only. The guidelines state that prescriptions for benzodiazepines should preferably be at the lowest effective dose and given intermittently. In patients with chronic insomnia, benzodiazepines should be used only in the short term while more appropriate longer-term treatments are started.

There are four benzodiazepines that are only indicated for use as sedative hypnotics for the treatment of insomnia: estazolam (Prosom®), flurazepam (Dalmane®), temazepam (Restoril®), and triazolam (Halcion®). Temazepam and triazolam are **only** indicated for short term treatment of insomnia (generally 7-10 days).

This report focuses on the utilization of benzodiazepines in the adult population for the Mississippi Division of Medicaid (DOM). The DUR Board reviewed utilization of triazolam at the meeting in August 2015.

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[1] Maine Benzodiazepine Study Group. Guidelines for The Use of Benzodiazepines in Office Practice in The State of Maine. http://www.benzos.une.edu/documents/prescribingguidelines3-26-08.pdf accessed 9/12/2016.

[2] Baldwin DS, Aitchison K, Bateson A, et. al. Benzodiazepines: Risks and benefits. A reconsideration. *Journal of Psychopharmacology* 27(11) 967–971. 2013. DOI: 10.1177/0269881113503509.

Guidance on usage and length of therapy from triazolam prescribing information include:

Indications and Usage for Triazolam

Triazolam Tablets USP, are indicated for the short-term treatment of insomnia (generally 7 to 10 days). Use for more than 2 to 3 weeks requires complete reevaluation of the patient (see WARNINGS).

Prescriptions for Triazolam should be written for short-term use (7 to 10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

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.

Based on recommendations from the DUR Board, DOM implemented quantity limits for triazolam as indicated in the current Universal Preferred Drug List (UPDL).

SEDATIVE HYPNOTICS			
	BENZODIAZEPINES		
	estazolam flurazepam temazepam (15mg and 30mg)	DALMANE (flurazepam) DORAL (quazepam) HALCION (triazolam) 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. **Quantity Limits – 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**

Temazepam has a similar indication as triazolam for short-term use when treating insomnia.

Indications and Usage for Temazepam

Temazepam Capsules, USP are indicated for the short-term treatment of insomnia (generally 7 to 10 days).
For patients with short-term insomnia, instructions in the prescription should indicate that Temazepam Capsules, USP should be used for short periods of time (7 to 10 days).
The clinical trials performed in support of efficacy were 2 weeks in duration with the final formal assessment of sleep latency performed at the end of treatment.

This report provides an update on triazolam utilization after implementation of new quantity limits criteria and examines utilization patterns for all benzodiazepines with insomnia indications only.

METHODS

In order to accurately reflect current prescribing patterns, a retrospective analysis was conducted using MS Medicaid pharmacy claims for all programs (fee-for-service (FFS) and coordinated care organizations (CCOs)) for the period January through July, 2016. All claims for benzodiazepines listed for sedative hypnotic use in the Universal Preferred Drug List were extracted (estazolam, quazepam, temazepam, and triazolam) and utilization patterns were examined.

RESULTS

Although three benzodiazepines are listed as preferred products in the UPDL, almost all utilization was for temazepam (Table 1) within all three pharmacy programs (fee-for-service (FFS), United Healthcare (UHC), and Magnolia).

Table 1: Number of Beneficiaries Taking Benzodiazepines With Insomina Indication
(January - July, 2016 -- FFS and CCOs)

	Pharmacy Program			
Product	FFS	United HealthCare	Magnolia	Total for Product
estazolam	1	2	0	3
flurazepam	1	3	5	9
temazepam	132	361	486	979
triazolam	1	15	5	21
quazepam	0	0	0	0
Total for Program	135	381	496	1012

NOTE: generic estraolam, flurazepam, and temazepam (15mg and 30mg) are preferred products on the Universal Preferred Drug List.

Table 2: Characteristics of Beneficiaries Taking Benzodiazepines With Insominia Indications
(January - July, 2016 -- FFS and CCOs)

Characteristic		Number	Percent
Gender	Female	733	72.4%
	Male	279	27.6%
Race	Caucasian	523	51.7%
	African Amer	376	37.2%
	Hispanic	6	0.6%
	Amer Indian	2	0.2%
	Other/Unknown	105	10.4%
Age	1 - 17	10	1.0%
	18 - 44	425	42.0%
	45 - 64	560	55.3%
	65+	17	1.7%

A total of 1,012 unique beneficiaries were treated with these benzodiazepines during the first half of 2016.

These beneficiaries were predominately female (72%) and adults 18-64 years of age (97.3%) (Table 2).

Table 3 shows the maximum number of days of continuous therapy for beneficiaries being treated with these sedative hypnotics. Patients were considered to be on continuous therapy if they had refilled prescriptions for the same product, with no more than a 15-day gap in supply between prescription fills.

Table 3: Maximum Number of Days Continous Therapy With Benzodiazepines Having Insominia Indications

(January - July, 2016 -- FFS and CCOs)

	Maximum Days Continous Therapy*							
Product	1-10	11-20	21-31	32 - 62	63 - 93	94 - 186	187 +	Total
estazolam	0	0	2	0	0	0	1	3
flurazepam	0	0	5	3	1	0	0	9
temazepam	9	65	432	233	95	74	71	979
triazolam	17	1	2	1	0	0	0	21

** Continous therapy was calcuated as date of first fill to date of last fill plus days supply for last fill, allowing for a 15 day refill gap.*

NOTE: Results include all beneficiaries filling prescriptions in 2016. Beneficiaries may have started therapy before January 2016 and may have started therapy just prior to the July 2016 end data for inclusion in the analyses.

Table 4 depicts the maximum number of days of therapy for beneficiaries during this 7-month period.

Table 4: Total Days of Therapy With Benzodiazepines Having Insominia Indications

(January - July, 2016 -- FFS and CCOs)

	Total Days of Therapy							
Product	1-10	11-20	21-31	32 - 62	63 - 93	94 - 186	187 +	Total
estazolam	0	0	2	0	0	0	1	3
flurazepam	0	0	4	3	1	1	0	9
temazepam	5	18	326	188	129	215	98	979
triazolam	17	1	1	0	1	1	0	21

NOTE: Results include all beneficiaries filling prescriptions in 2016. Beneficiaries may have started therapy before January 2016 and may have started therapy just prior to the July 2016 end data for inclusion in the analyses.

Utilization patterns thus far for 2016 indicate that the monthly and annual quantity limits implemented for triazolam have definitely been of impact in limiting use to less than 10 days as indicated in the labeling. Although the labeling for temazepam is similar, utilization patterns indicate that long-term use of this product is occurring.

CONCLUSIONS AND RECOMMENDATIONS

The results indicate that the quantity limits recommended by the DUR Board last year for triazolam have been very effective. They also indicate that similar quantity limits criteria are needed for temazepam to assure appropriate use based on current labeling. Adding limits for temazepam would also make the UPDL criteria consistent for these two products that have similar labeling.

Based on these results, the following recommendation is made for DUR Board consideration:

- DOM add the following clinical edits to assure more appropriate use of temazepam and to make the criteria consistent with those for triazolam:
    a. Quantity limit of 10-day supply per month
    b. Cumulative quantity limit of 60 days within a 365-day period