Texas Medicaid

Benzodiazepine Anxiolytics and Controlled Sedative/Hypnotics Drug Use Evaluation (DUE)

Educational RetroDUR Mailing	❑Initial Study ☑Follow-up /Restudy

Executive Summary

Purpose:	To promote the safe and cost-effective prescribing of benzodiazepine anxiolytics and controlled sedative/hypnotics.		
Why Issue was Selected:	Benzodiazepine anxiolytic and sedative/hypnotic medications are generally well-tolerated and very effective. However, most experts and available treatment guidelines do not recommend their use on a long-term basis. Potential adverse effects of benzodiazepine anxiolytics and controlled sedative/hypnotics include psychomotor impairment and cognitive deficits.[1,2] Most sedative/hypnotics[2,3] are controlled substances and their long-term use may be associated with physical and/or psychological dependence. Alternative medications that are not controlled substances are available for most chronic health conditions and evidence indicates that psychological and behavioral treatments are preferred over controlled sedative/hypnotic medications for the management of chronic insomnia (Table 2).[2,4] Concurrent use of more than one benzodiazepine anxiolytic or controlled sedative/hypnotic has not been adequately researched. The available agents all act at the GABA/chloride receptor complex. The use of combinations of these agents results in additive effects at the receptor complex and may result in excess sedation or other adverse effects without proven clinical benefit.[5] Claims data indicates that in the Texas Medicaid Fee-For-Service Program, there were 3,672 prescriptions for benzodiazepine anxiolytics and controlled sedative hypnotics in a recent 365-day period at a total cost of $64,295.		
Program Specific Information:	**Performance Indicators**	**Exceptions**	
		(<18 Years) FFS	**(<18 Years) MCO**
	1. Chronic use of a benzodiazepine anxiolytic > 4 months with a diagnosis of	(0) 2	(8) 719

	generalized anxiety disorder (GAD) and not receiving first-line drug therapy		
	2. Chronic use of a benzodiazepine anxiolytic > 4 months with a diagnosis of GAD and receiving first-line drug therapy	(0) 1	(9) 1,768
	3. Chronic use of a benzodiazepine anxiolytic > 4 months with no diagnosis of an anxiety disorder	(2) 6	(34) 1,535
	4. Chronic use of a controlled sedative/hypnotic	(0) 3	(13) 2,854
	5. Use of a benzodiazepine anxiolytic in patients with a history of substance use disorder	(0) 9	(12) 2,935
	6. Use of a controlled sedative/hypnotic in patients with a history of substance use disorder	(0) 2	(0) 1,442
	7. Duplicate therapy with benzodiazepine anxiolytics	(0) 0	(2) 359
	8. Duplicate therapy with controlled sedative/hypnotics	(0) 0	(0) 18
	9. High dose of a controlled sedative/hypnotic	(0) 20	(0) 4,097
	10. Controlled sedative/hypnotic dose consolidation	(0) 1	(5) 81
	11. Controlled sedative/hypnotic use in youth	(1) 1	(103) 103
Setting & Population:	All patients with therapy in the most recent 45 days with a benzodiazepine anxiolytic or controlled sedative/hypnotic agent.		
Types of Intervention:	Cover letter and modified profiles.		
Main Outcome Measures:	The performance indicators will be re-measured when six months of outcome data are available.		
Anticipated Results:	Reduced unnecessary or inappropriate drug therapy with benzodiazepine anxiolytic and controlled sedative/hypnotic agents and decreased drug therapy expenditures.		

Performance Indicator #1: Chronic use of a benzodiazepine anxiolytic > 4 months with a diagnosis of generalized anxiety disorder (GAD) and not receiving first-line drug therapy

Why has this indicator been selected?	Benzodiazepine anxiolytics are recommended as short-term adjunctive therapy (2 to 4 weeks) in the management of generalized anxiety disorder (GAD) by most experts and available treatment guidelines. Other-FDA approved medications that are not controlled substances are recommended as treatments of choice for long-term use.[1]
Candidates (denominator):	All patients receiving current therapy with a benzodiazepine anxiolytic (Table 1) in the most recent 45 days.
Exception criteria (numerator):	Candidates who have received more than 120 days of therapy with a benzodiazepine anxiolytic in the past 130 days and have a diagnosis of GAD and are not receiving an SSRI or SNRI. Patients with seizure or muscle disorders in the past 730 days are allowed extended use of clonazepam,

	clorazepate or diazepam. Patients with comorbid bipolar disorder were excluded, since SSRIs and SNRIs are not first-line treatment and may worsen the condition.

Performance Indicator #2: Chronic use of a benzodiazepine anxiolytic > 4 months with a diagnosis of GAD and receiving first-line drug therapy

Why has this indicator been selected?	Benzodiazepine anxiolytics are recommended as short-term adjunctive therapy (2 to 4 weeks) in the management of generalized anxiety disorder (GAD) by most experts and available treatment guidelines. Other FDA-approved medications that are not controlled substances are recommended as treatments of choice for long-term use.[1]
Candidates (denominator):	All patients receiving current therapy with a benzodiazepine anxiolytic (Table 1) in the most recent 45 days.
Exception criteria (numerator):	Candidates who have received more than 120 days of therapy with a benzodiazepine anxiolytic in the past 130 days and have a diagnosis of GAD and are receiving an SSRI or SNRI. Patients with seizure or muscle disorders in the past 730 days are allowed extended use of clonazepam, clorazepate, or diazepam.

Performance Indicator #3: Chronic use of a benzodiazepine anxiolytic > 4 months with no diagnosis of an anxiety disorder

Why has this indicator been selected?	Benzodiazepine anxiolytics are recommended as short-term adjunctive therapy (2 to 4 weeks) in the management of anxiety by most experts and available treatment guidelines. Other FDA approved medications that are not controlled substances are recommended as treatments of choice for long-term use.[1]
Candidates (denominator):	All patients receiving current therapy with a benzodiazepine anxiolytic (Table 1) in the most recent 45 days.
Exception criteria (numerator):	Candidates who have received more than 120 days of therapy with a benzodiazepine anxiolytic in the past 130 days and do not have an anxiety disorder diagnosis. Patients with seizure or muscle disorders in the past 730 days are allowed extended use of clonazepam, clorazepate, or diazepam.

Performance Indicator #4: Chronic use of a controlled sedative/hypnotic

Why has this indicator been selected?	Controlled sedative/hypnotic agents are generally recommended as short-term, adjunctive therapy in the management of insomnia. Most are not FDA-approved for long-term use and have been the subject of limited long-term clinical trials.[2-4]
Candidates (denominator):	All patients receiving current therapy with a controlled sedative/hypnotic (Table 1) in the most recent 45 days.
Exception criteria (numerator):	• Candidates who are receiving eszopiclone, lemborexant, or zolpidem ER chronically for > 180 days in the past 200 days. • Candidates who are receiving any other controlled sedative/hypnotic chronically for > 120 days in the past 130 days. Candidates with seizure disorders in the past 730 days are allowed extended use of phenobarbital.

Performance Indicator #5: Use of a benzodiazepine anxiolytic in patients with a history of substance use disorders

Why has this indicator been selected?	All benzodiazepine anxiolytics are controlled substances and pose a risk of physical and psychological dependence.[1] This risk is increased in patients with substance use disoders.[6]
Candidates (denominator):	All patients ≥ 12 years old receiving current therapy with a benzodiazepine anxiolytic (Table 1) in the most recent 45 days.
Exception criteria (numerator):	Candidates who have a diagnosis of substance use disorder in the past 730 days and have at least 14 days of benzodiazepine anxiolytic therapy in the past 45 days. Candidates diagnosed with seizures or muscle disorders in the past 730 days will be excluded if they are prescribed clonazepam, clorazepate or diazepam.

Performance Indicator #6: Use of a controlled sedative/hypnotic in patients with a history of substance use disorders

Why has this indicator been selected?	All sedative/hypnotic agents other than doxylamine (Unisom®), ramelteon (Rozerem®), tasimelteon (Hetlioz®) and doxepin (Silenor®) are controlled substances and pose a risk of physical and psychological dependence.[2-4] This risk is increased in patients with substance use disoders.[6]
Candidates (denominator):	All patients ≥ 12 years old receiving current therapy with a controlled sedative/hypnotic medication (Table 1) in the most recent 45 days
Exception criteria (numerator):	Candidates who have a diagnosis of substance use disorder in the past 730 days and have at least 14 days of controlled sedative/hypnotic therapy in the past 45 days. Candidates on barbiturates are excluded.

Performance Indicator #7: Duplicate Therapy: Benzodiazepine anxiolytics

Why has this indicator been selected?	Concurrent use of more than one anti-anxiety medication has not been adequately researched. The available agents all act at the GABA/Chloride receptor complex. The use of combinations of these agents results in additive effects at the receptor complex and may result in excess sedation or other adverse effects without proven clinical benefit.[5]
Candidates (denominator):	All patients receiving current therapy with a benzodiazepine anxiolytic (Table 1) in the most recent 45 days.
Exception criteria (numerator):	Candidates receiving more than one benzodiazepine anxiolytic concurrently for at least 35 days in the past 45 days. Candidates diagnosed with seizures or muscle disorders in the past 730 days will be excluded if they are prescribed clonazepam, clorazepate or diazepam.

Performance Indicator #8: Duplicate Therapy: Controlled sedative/hypnotic agents

Why has this indicator been selected?	Concurrent use of more than one sedative/hypnotic medication has not been adequately researched. The available agents all act at the GABA/Chloride receptor complex. The use of combinations of these agents results in additive effects at the receptor complex and may result in excess sedation or other adverse effects without proven clinical benefit.[5]
Candidates (denominator):	All patients receiving current therapy a controlled sedative/hypnotic medication (Table 1) in the most recent 45 days.
Exception criteria (numerator):	Candidates receiving more than one controlled sedative/hypnotic medication concurrently for at least 35 days in the past 45 days. Candidates on barbiturates are excluded.

Performance Indicator #9: High dose of a controlled sedative/hypnotic

Why has this indicator been selected?	Once an effective dose is obtained, increasing the dose rarely leads to increased efficacy, but does increase the risk of experiencing an adverse drug event.[8-10] Data regarding zolpidem indicates that blood levels in some patients may be high enough in the morning after an evening dose to impair activities that require alertness such as driving. This may be a problem with any agent taken for insomnia, but studies indicate that women eliminate zolpidem more slowly than men. Therefore, the FDA has recommended that the maximum recommended dose of zolpidem in women be lowered from the previously recommended levels.[11]
Candidates (denominator):	All patients ≥ 18 years old receiving current therapy with a controlled sedative/hypnotic (Table 1) within the past 45 days.
Exception criteria (numerator):	Candidates receiving higher than the manufacturer's recommended maximum daily dose (Table 3). Zolpimist® is excluded due to inability to calculate daily dose.

Performance Indicator #10: Controlled sedative/hypnotic dose consolidation

Why has this indicator been selected?	Manufacturer recommendations for most controlled sedative/hypnotics include once daily dosing. Multiple daily doses may be an indication of a lower than effective dose or another issue worth reviewing.[8-10]
Candidates (denominator):	All patients with current therapy of a controlled sedative/hypnotic (Table 1) in the past 45 days.
Exception criteria (numerator):	Candidates receiving more than one unit of the identified controlled sedative/hypnotic per day when a single dose per day of the same dosage is possible. Candidates on barbiturates are excluded.

Performance Indicator #11: Controlled sedative/hypnotic use in youth

Why has this indicator been selected?	Few controlled sedative/hypnotic agents are FDA-approved for use in patients less than 18 years of age and literature describing their safety and/or studies supporting their efficacy are lacking.[12,13]
Candidates (denominator):	All patients < 18 years old receiving current therapy with a controlled sedative/hypnotic (Table 1) within the past 45 days.
Exception criteria (numerator):	Candidates who received a controlled sedative/hypnotic agent not approved for use in their age (Table 4).

References:

1. National Collaborating Center for Mental Health. Generalized Anxiety Disorder and Panic Disorder in Adults: Management. January 2011. Available at: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997 Accessed October 25, 2020.
2. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13(2):307–349. Available at: https://aasm.org/resources/pdf/pharmacologictreatmentofinsomnia.pdf. Accessed October 25, 2020.
3. Qaseem A, Kansagara D, Forciea MA, Cooke M, and Denberg TD for the Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline from the American College of Physicians. Ann Intern Med. 2016;165. Available at: https://www.acpjournals.org/doi/10.7326/M15-2175. Accessed October 25, 2020.
4. Brasure M, MacDonald R, Fuchs E, Olson CM, Carlyle M, Diem S, et al. Management of Insomnia Disorder. Comparative Effectiveness Review 159. (Prepared by the Minnesota Evidence-based Practice Center under contract 290-2012-00016-I.) AHRQ Publication no. 15(16)-EHC027-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2015. Available at: https://www.ncbi.nlm.nih.gov/books/n/cer159/pdf/. Accessed October 25, 2020.
5. Carter CR, Kozuska JL, Dunn SM. Insights into the structure and pharmacology of GABA(A) receptors. Future Med Chem. 2010; 2:859-75.
6. FDA Drug Safety Communication: FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class. Accessed December 1, 2020.
7. NIDA. Principles of Effective Treatment. National Institute on Drug Abuse website. September 18, 2020. Available at: https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/principles-effective-treatment. Accessed December 1, 2020.
8. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: https://www.clinicalkey.com/pharmacology/. Accessed October 26, 2020.
9. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed October 26, 2020.
10. Matheson, E., & Hainer, B. L. (2017). Insomnia: Pharmacologic Therapy. Am Fam Physician, 96(1), 29–35. Available at: https://www.aafp.org/afp/2017/0701/p29.html. Accessed October 25, 2020.
11. FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-new-label-changes-and-dosing-zolpidem-products-and. Accessed October 25, 2020.
12. Pelayo, R., Huseni, S. Pharmacotherapy of Insomnia in Children. Curr Sleep Medicine Rep 2, 38–43 (2016). Available at: https://link.springer.com/article/10.1007/s40675-016-0036-1. Accessed October 25, 2020.
13. Owens JA, Babcock D, Blumer J, et al. The use of pharmacotherapy in the treatment of pediatric insomnia in primary care: rational approaches. A consensus meeting summary. J Clin Sleep Med. 2005; 1:49-59. Available at https://jcsm.aasm.org/doi/pdf/10.5664/jcsm.26297. Accessed October 25, 2020.
14. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. Sleep. 2006;29(11):1415–1419. Available at https://aasm.org/resources/pdf/pharmacologictreatmentofinsomnia.pdf. Accessed October 26, 2020.
15. Phenobarbital elixir [package insert]. Chestnut Ridge, NY: Par Pharmaceutical; 2019.

Appendix

Table 1: Benzodiazepine Anxiolytic and Controlled Sedative/Hypnotic Medications

Benzodiazepine Anxiolytics	Controlled Sedative / Hypnotics
alprazolam	butabarbital
chlordiazepoxide	estazolam
clonazepam	eszopiclone
clorazepate dipotassium	flurazepam
diazepam	lemborexant
lorazepam	phenobarbital
oxazepam	quazepam
	secobarbital
	suvorexant
	temazepam
	triazolam
	zaleplon
	zolpidem tartrate

Table 2: Psychological/Behavioral Interventions for Insomnia Disorder[3,4,14]

Psychological and Behavioral Treatments for Insomnia	Description
Sleep hygiene education	Educate patients about health and environmental factors that can be changed to improve sleep, such as avoiding caffeine and nicotine, limiting consumption of alcoholic beverages, maintaining a regular sleep schedule, avoiding napping, exercising regularly, and maintaining a quiet and dark bedroom.
Stimulus control	Assist patients to change behaviors associated with bed and bedroom and establish consistency in sleep patterns. Techniques include restricting bedroom for sleep only; going to bed only when sleepy; avoiding reading, television, phone, etc., in the bedroom; leaving the bedroom when unable to sleep; regular sleep schedule; no snooze button.
Sleep restriction	Instruct patients to limit time in bed to sleep time, gradually increasing time in bed as sleep efficiency improves. Techniques include setting strict bedtime and rising schedules, and keeping a set wakeup time, with modifications based on sleep efficiency after a certain duration of time.
Relaxation training	Train patients to reduce somatic tension and control bedtime thought patterns that impair sleep. Techniques include progressive muscle relaxation, guided imagery, and paced breathing.
Cognitive behavioral therapy	Apply combined treatments that include cognitive and behavioral components, including stimulus control, sleep restriction, and sometimes relaxation training.
Multicomponent therapy or brief behavioral therapy	Apply multicomponent behavioral therapies without cognitive therapy.

Table 3: Controlled Sedative/Hypnotic Medications Maximum Daily Dose in Adults[8,9.15]

Controlled Sedative/Hypnotics	Adult maximum daily dose 18-64 years (in mg)	Adult maximum daily dose ≥ 65 years (in mg)	Female adult maximum daily dose (in mg)	Male adult maximum daily dose (in mg)
butabarbital	120	120	-	-
estazolam	2	2	-	-
eszopiclone	3	2	-	-
flurazepam	30	30	-	-
lemborexant	10	10	-	-
phenobarbital	600	600	-	-
quazepam	15	15	-	-
secobarbital	300	300	-	-
suvorexant	20	20	-	-
temazepam	30	30	-	-
triazolam	0.5	0.25	-	-
zaleplon	20	10	-	-
zolpidem tartrate • Extended-release tablets • Immediate-release tablets • Sublingual tablets (Edluar®) • Sublingual tablets (Intermezzo®)	-	-	 6.25 5 5 1.75	 12.5 10 10 3.5

Table 4: Controlled Sedative/Hypnotic FDA-approved Minimum Age in Youth[8,9,15]

Controlled Sedative/Hypnotics	Minimum Age (in years)
butabarbital	0
estazolam	Not FDA-approved for age < 18 years
eszopiclone	Not FDA-approved for age < 18 years
flurazepam	15
lemborexant	Not FDA-approved for age < 18 years
phenobarbital	0
quazepam	Not FDA-approved for age < 18 years
secobarbital	2
suvorexant	Not FDA-approved for age < 18 years
temazepam	Not FDA-approved for age < 18 years
triazolam	Not FDA-approved for age < 18 years
zaleplon	Not FDA-approved for age < 18 years
zolpidem tartrate	Not FDA-approved for age < 18 years

TEXAS
Health and Human Services

Cecile Erwin Young
Executive Commissioner

<<Date>>

«dea»
«name»
«add1»
«add2»
«add3»

RE: Caring for Your Patients on Benzodiazepine Anxiolytics and/or Controlled Sedative/Hypnotics

Dear Dr. <<Name>>:

Thank you for providing quality care for Texas Fee-For-Service (FFS) Medicaid patients. The content of this letter has been approved by the Texas Drug Utilization Review (DUR) Board, whose function is to promote safe and cost-effective drug therapy and provide opportunities for continuous improvement of care.

This retrospective claims review was designed to assist you in caring for your patients receiving benzodiazepine anxiolytics or controlled sedative/hypnotic agents.

The epidemic of opioid overdose, misuse, and addiction is a critical public health issue that affects the lives of millions of Americans, including those who are enrolled in Medicaid. Benzodiazepines are commonly involved in deaths related to overdose with opioid analgesics. The Center for Medicare and Medicaid Services (CMS) bulletin on best practices to address prescription opioid overdoses, misuse, and addiction states that the primary driver of increased drug overdose deaths is due to increased number of prescriptions for opioid pain medications, especially high doses, longer course of treatment, and in conjunction with benzodiazepines.[1] The bulletin is available at: https://www.medicaid.gov/federal-policy-guidance/downloads/cib-02-02-16.pdf. Furthermore, all benzodiazepine anxiolytics and controlled sedative/hypnotics pose a risk of physical and psychological dependence.[2-5]

Benzodiazepine anxiolytics are recommended as short-term, adjunctive therapy in the management of generalized anxiety disorder (GAD) and other anxiety disorders.[2] Non-pharmacologic interventions for chronic GAD include cognitive-behavioral therapy, cognitive restructuring, and applied relaxation. First-line medications for chronic treatment of GAD include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), which are listed in Table 1.[2] Controlled sedative/hypnotic agents are generally recommended as short-term, adjunctive therapy in the management of insomnia. Most are not FDA-approved for long-term use and have been the subject of limited long-term clinical trials.[3-5,7,8] Non-pharmacologic approaches to insomnia disorder for adults are listed in Table 2. Few controlled sedative/hypnotic agents are FDA-approved for use in patients less than 18 years of age and literature describing their safety and/or studies supporting their efficacy are lacking. The consensus in the literature is that non-pharmacologic treatment approaches (see Table 3) should be the mainstay of treatment for sleep disorders in youth, with drug therapy used as a short-term adjunctive measure.[10-12]

Claims data indicate that in the Texas Medicaid FFS Program, there were 3,672 prescriptions for benzodiazepine anxiolytics and controlled sedative hypnotics in a recent 365-day period. The total Texas Medicaid FFS performance indicators for all patients (including those < 18 years) with opportunities for benzodiazepine anxiolytic or controlled sedative/hypnotic management are shown in the table below.

Total Texas Medicaid FFS Specific Data

Benzodiazepine Anxiolytics and Controlled Sedative Hypnotics Indicator Summary	Number of Patients with Opportunities*	
	< 18 Years	**≥ 18 Years**
Chronic use of a benzodiazepine anxiolytic > 4 months with a diagnosis of generalized anxiety disorder (GAD) and not receiving first-line drug therapy	0	2
Chronic use of a benzodiazepine anxiolytic > 4 months with a diagnosis of GAD and receiving first-line drug therapy	0	1
Chronic use of a benzodiazepine anxiolytic > 4 months with no diagnosis of an anxiety disorder	2	4
Chronic use of a controlled sedative/hypnotic	0	3
Use of a benzodiazepine anxiolytic in patients with a history of substance use disorder	0	9
Use of a controlled sedative/hypnotic in patients with a history of substance use disorder	0	2
Duplicate therapy with benzodiazepine anxiolytics	0	0
Duplicate therapy with controlled sedative/hypnotics	0	0
High dose of a controlled sedative/hypnotic	0	20
Controlled sedative/hypnotic dose consolidation	0	1
Controlled sedative/hypnotic use in youth	1	0

*Based on data through 11/24/2020.

The enclosed patient profiles reflect one or more of the above issues and are provided as a medical record reminder for when your patients return for their next appointments.

We acknowledge that there may be clinical variables influencing an individual patient's management that are not apparent in claims data. However, we believe the issues identified may assist you in caring for your patient(s). It is possible that your license number may have been inadvertently assigned to the claim as an error at the pharmacy during the billing process. **Also, some prescribed medications as well as some recommended laboratory monitoring or physical examinations may not appear on the patient's profile because they may have been privately purchased or were not billable to Medicaid Services.** We thank you for reviewing this information and caring for Texas Medicaid patients, and we welcome the opportunity to discuss any comments or concerns you may have about our quality management program. Please feel free to call our office at 1-866-923-7208 with questions or concerns. If your mailing address is incorrect, it must be updated through the Texas Medical Board online at **http://www.tmb.state.tx.us/page/change-address.**

Sincerely,

Medicaid Drug Use Review Board
Vendor Drug Program H-630

Benzodiazepine Anxiolytics and Controlled Sedative/Hypnotics Indicator Summary
○ **Encourage use of benzodiazepine anxiolytic agents as short-term, adjunctive measures as recommended by most experts and treatment guidelines rather than chronic therapy:** Benzodiazepine anxiolytics are recommended as short-term, adjunctive therapy in the management of anxiety by most experts and available treatment guidelines. Other FDA-approved medications that are not controlled substances, such as second generation antidepressants or buspirone (second-line) are recommended as treatments of choice for long-term use. In addition, consideration should be given to the use of psychosocial and behavioral therapies as more definitive interventions in chronically anxious patients (see Table 1).[2]
○ **Encourage use of controlled sedative/hypnotic medications as short-term, adjunctive measures rather than chronic therapy as recommended by most experts and treatment guidelines:** Controlled sedative/hypnotic agents are generally recommended as short-term, adjunctive therapy in the management of insomnia. Most are not FDA-approved for long-term use and have been the subject of limited long-term clinical trials. Chronic insomnia is considered to be best managed with multimodal strategies, pharmacotherapy being short-term and adjunctive (see Table 2).[3-5]
○ **Promote use of non-controlled medications for the management of anxiety as recommended by most experts and treatment guidelines in individuals with a history of a substance use disorder:** All benzodiazepine anxiolytics are controlled substances and pose a risk of physical and psychological dependence. Second generation antidepressants might be better choices in such patients.[2]
○ **Promote alternatives to controlled sedative/hypnotics in individuals with a history of a substance use disorder:** Psychological and behavioral interventions for insomnia disorder are preferred (see Table 2).[3-5]
○ **Avoid duplicate therapy with benzodiazepines:** Concurrent use of more than one benzodiazepine has not been adequately researched. The available agents all act at the GABA/chloride receptor complex. The use of combinations of these agents results in additive effects at the receptor complex and may result in excess sedation or other adverse effects without proven clinical benefit.[2,6]
○ **Avoid duplicate therapy with controlled sedative/hypnotics:** Concurrent use of more than one controlled sedative/hypnotic medication has not been adequately researched. The available agents all act at the GABA/chloride receptor complex. The use of combinations of these agents results in additive effects at the receptor complex and may result in excess sedation or other adverse effects without proven clinical benefit.[3-6]
○ **Use of controlled sedative/hypnotics at a dose higher than FDA recommendations:** Once an effective dose is obtained, increasing the dose rarely leads to increased efficacy, but does increase the risk of experiencing an adverse drug event (see Table 4).[7,8] ○ **Use of zolpidem in females at a dose higher than FDA recommendations:** Data regarding zolpidem indicates that blood levels in some patients may be high enough in the morning after an evening dose to impair activities that require alertness such as driving. This may be a problem with any agent taken for insomnia, but data indicates women eliminate zolpidem more slowly than men. Therefore, the FDA has recommended that the maximum recommended dose of zolpidem in women be lowered from the previously recommended levels (see Table 4).[9]
○ **Use of more than one unit daily of a controlled sedative/hypnotic:** Manufacturer recommendations for most controlled sedative/hypnotics include once daily dosing.[7,8] Multiple daily doses may be an indication of a lower than effective dose or another issue worth reviewing.
○ **Identify use of sedative/hypnotic medication being used in youth younger than the FDA-approved age and consider alternative treatments:** Clinical studies of sedative/hypnotic medications in children and adolescents are limited and none of the newer, non-benzodiazepine agents have data to support their use in individuals less than 18 years of age. Only flurazepam and barbiturates are FDA-approved for use in children and adolescents, and flurazepam only for those greater than 15 years of age (see Table 5). Any pharmacotherapy for pediatric sleep disorders should be short-term and adjunctive to non-pharmacologic interventions (see Table 3). [7,8,10-12]

Table 1: Alternatives to Benzodiazepines for Chronic Anxiety Disorders[2]

Pharmacologic Interventions	Non-Pharmacologic Interventions
Selective Serotonin Reuptake Inhibitors (SSRIs)	Cognitive-Behavioral Therapy
Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)	Cognitive Restructuring
Buspirone*	Applied Relaxation

*Buspirone should be reserved as second-line therapy for individuals who are intolerant or fail to respond to SSRIs or SNRIs. It may have limited efficacy in individuals previously treated with a benzodiazepine.[14]

Table 2: Psychological/Behavioral Interventions for Insomnia Disorder in Adults[3,5,13]

Psychological and Behavioral Treatments for Insomnia	Description
Sleep hygiene education	Educate patients about health and environmental factors that can be changed to improve sleep, such as avoiding caffeine and nicotine, limiting consumption of alcoholic beverages, maintaining a regular sleep schedule, avoiding napping, exercising regularly, and maintaining a quiet and dark bedroom.
Stimulus control	Assist patients to change behaviors associated with bed and bedroom and establish consistency in sleep patterns. Techniques include restricting bedroom for sleep only; going to bed only when sleepy; avoiding reading, television, phone, etc., in the bedroom; leaving the bedroom when unable to sleep; regular sleep schedule; no snooze button.
Sleep restriction	Instruct patients to limit time in bed to sleep time, gradually increasing time in bed as sleep efficiency improves. Techniques include setting strict bedtime and rising schedules, and keeping a set wakeup time, with modifications based on sleep efficiency after certain duration of time.
Relaxation training	Train patients to reduce somatic tension and control bedtime thought patterns that impair sleep. Techniques include progressive muscle relaxation, guided imagery, and paced breathing.
Cognitive behavioral therapy	Apply combined treatments that include cognitive and behavioral components, including stimulus control, sleep restriction, and sometimes relaxation training.
Multicomponent therapy or brief behavioral therapy	Apply multicomponent behavioral therapies without cognitive therapy.

Table 3: Non-Pharmacologic Interventions for Child and Adolescent Insomnia[10-12]

Non-Pharmacologic Intervention	General Principle Summary
Good Sleep Hygiene	• Regularly scheduled bedtime and wake-up time • Consistent bedtime routine including "wind-down" • Comfortable, quiet bedroom
Early Intervention/Parent Education	• Education of parents • Establishment of appropriate sleep habits
Extinction	• Fixed bedtime • Systematically ignoring inappropriate behavior
Graduated Extinction	• Principles of Extinction • Scheduled parental checks
Extinction with Parental Presence	• Principles of Extinction • Parent feigns sleep while staying in room
Positive Bedtime Routines	• A set of calm activities the child enjoys • Associate positive behaviors with routines
Scheduled Awakenings	• Parent awakening child 15 to 30 minutes before usual spontaneous awakening or parasomnia • Console child and use positive reinforcement
Phase Advance or Delay Chronotherapy	• Systematically advancing or delaying child's sleep phase to desired sleep-wake cycle
Stimulus Control Therapy	• Conditioned response to environmental and temporal cues • Maintain a set sleep/wake schedule

Table 4: Controlled Sedative/Hypnotic Medications Maximum Daily Dose in Adults[7,8,15]

Controlled Sedative/Hypnotics	Adult maximum daily dose 18-64 years (in mg)	Adult maximum daily dose ≥ 65 years (in mg)	Female adult maximum daily dose (in mg)	Male adult maximum daily dose (in mg)
butabarbital	120	120	-	-
estazolam	2	2	-	-
eszopiclone	3	2	-	-
flurazepam	30	30	-	-
lemborexant	10	10	-	-
phenobarbital	600	600	-	-
quazepam	15	15	-	-
secobarbital	300	300	-	-
suvorexant	20	20	-	-
temazepam	30	30	-	-
triazolam	0.5	0.25	-	-
zaleplon	20	10	-	-
zolpidem tartrate • Extended-release tablets • Immediate-release tablets • Sublingual tablets (Edluar®) • Sublingual tablets (Intermezzo®)	-	-	 6.25 5 5 1.75	 12.5 10 10 3.5

Table 5: Controlled Sedative/Hypnotic FDA-approved Minimum Age in Youth[7,8,15]

Controlled Sedative/Hypnotics	Minimum Age (in years)
butabarbital	0
estazolam	Not FDA-approved for age < 18 years
eszopiclone	Not FDA-approved for age < 18 years
flurazepam	15
lemborexant	Not FDA-approved for age < 18 years
phenobarbital	0
quazepam	Not FDA-approved for age < 18 years
secobarbital	2
suvorexant	Not FDA-approved for age < 18 years
temazepam	Not FDA-approved for age < 18 years
triazolam	Not FDA-approved for age < 18 years
zaleplon	Not FDA-approved for age < 18 years
zolpidem tartrate	Not FDA-approved for age < 18 years

References:

1. Department of Health and Human Services, Center for Medicare and Medicaid Services, CMCS Informational Bulletin. Best Practices for Addressing Prescription Opioid Overdoses, Misuse and Addiction, February 28, 2016. Available at: https://www.medicaid.gov/federal-policy-guidance/downloads/cib-02-02-16.pdf. Accessed October 26, 2020.
2. National Collaborating Center for Mental Health. Generalized Anxiety Disorder and Panic Disorder in Adults: Management. January 2011. Available at: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997 Accessed October 26, 2020.
3. Qaseem A, Kansagara D, Forciea MA, Cooke M, and Denberg TD for the Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline from the American College of Physicians. Ann Intern Med. 2016;165. Available at: https://www.acpjournals.org/doi/10.7326/M15-2175. Accessed October 26, 2020.
4. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13(2):307–349. Available at: https://aasm.org/resources/pdf/pharmacologictreatmentofinsomnia.pdf. Accessed October 26, 2020.
5. Brasure M, MacDonald R, Fuchs E, Olson CM, Carlyle M, Diem S, et al. Management of Insomnia Disorder. Comparative Effectiveness Review 159. (Prepared by the Minnesota Evidence-based Practice Center under contract 290-2012-00016-I.) AHRQ Publication no. 15(16)-EHC027-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2015. Available at: https://www.ncbi.nlm.nih.gov/books/n/cer159/pdf/. Accessed October 26, 2020.
6. Carter CR, Kozuska JL, Dunn SM. Insights into the structure and pharmacology of GABA(A) receptors. Future Med Chem. 2010; 2:859-75.
7. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: https://www.clinicalkey.com/pharmacology/. Accessed October 26, 2020.
8. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed October 26, 2020.
9. FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-new-label-changes-and-dosing-zolpidem-products-and. Accessed October 26, 2020.
10. Pelayo, R., Huseni, S. Pharmacotherapy of Insomnia in Children. Curr Sleep Medicine Rep 2, 38–43 (2016). Available at: https://link.springer.com/article/10.1007/s40675-016-0036-1. Accessed October 26, 2020.

11. Owens JA, Babcock D, Blumer J, et al. The use of pharmacotherapy in the treatment of pediatric insomnia in primary care: rational approaches. A consensus meeting summary. J Clin Sleep Med. 2005; 1:49-59. Available at https://jcsm.aasm.org/doi/pdf/10.5664/jcsm.26297. Accessed October 26, 2020.
12. Vriend J, Corkum P. Clinical management of behavioral insomnia of childhood. Psychol Res Behav Manag. 2011;4:69-79. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3218792/. Accessed October 26, 2020.
13. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. Sleep. 2006;29(11):1415–1419. Available at https://aasm.org/resources/pdf/pharmacologictreatmentofinsomnia.pdf. Accessed October 26, 2020.
14. Wilson TK, Tripp J. Buspirone. [Updated 2020 Sep 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK531477/. Accessed October 26, 2020.
15. Phenobarbital elixir [package insert]. Chestnut Ridge, NY: Par Pharmaceutical; 2019.

Messid	Internal	External
3900	Duplicate Antianxiety Therapy	Concurrent Use of More Than One Benzodiazepine: Based on pharmacy claims data, it appears your patient is receiving multiple benzodiazepines concurrently. Please review the need for this combination and verify that your patient has discontinued the appropriate agent(s).
3901	Duplicate Sedative/Hypnotic Therapy	Concurrent Use of More Than One Sedative/Hypnotic Agent: Based on pharmacy claims data, it appears your patient is receiving multiple sedative/hypnotic agents. Please review the need for this combination of medications and, if you have not already done so, verify that your patient has discontinued the appropriate agent(s).
4091	Incr ADE: Sed/Hyp Dose	Sedative/hypnotic dosage that exceeds recommended adult or geriatric dosing ranges: Use of higher sedative/hypnotic doses may place patients at increased risk of experiencing adverse CNS events and developing tolerance and dependence. Please review this therapy and consider a dosage reduction. If discontinuation is considered, a gradual dosage taper may be necessary to avoid rebound insomnia and withdrawal symptoms.
9413	Non-Approved Sed/Hypn in Youth	Non-Approved Sedative/Hypnotic in Children and Adolescents: Based on pharmacy claims it appears your young patient has received a sedative/hypnotic that has not been FDA approved for use in patients less than 18 years of age. Available data indicates that medication is virtually never the first treatment strategy for insomnia in children. Most of the newer agents have not been studied in children and adolescents and their efficacy in the young remains unknown. In addition, their effectson mental acuity and academic performance have not been determined. Please re-evaluate this use and, if a sedative/hypnotic is deemed necessary, consider the use of flurazepam or chloral hydrate ,which have efficacy data in children, at as low a dose for as short a period of time as possible. Ifcontinued off-label use of the current agent is deemed necessary, please use as low a dose for as short a period of time as possible.
9418	Flurazepam in Youth	Flurazepam in Children Less Than 15 Years of Age: Based on pharmacy claims data it appears your patient, who is less than 15 years of age, has received flurazepam. Flurazepam is not FDA approved for use in children this young and few clinical studies in such populations are available. Even witha treatable diagnosis, available data indicates that medication is virtually never the first treatment strategy for insomnia in children or adolescents. Please re-evaluate this use and, if a sedative/hypnotic is deemed necessary, please use as low a dose for as short a period of time as possible.

9748	Sed/Hyp w H/O Dependence	Virtually all sedative/hypnotics have been shown to cause physical and psychological dependence in some patients. Medical literature recommends that sedative/hypnotics be used with caution in patients with a potential for drug dependence. If you find that your patient has a history of drug abuse or dependence, please evaluate your patient's therapy to determine if they should continue on sedative/hypnotic therapy.
9809	Benzodiazepine Anxiolytic Use with H/O Dependence:	All benzodiazepine anxiolytics have been shown to cause physical and psychological dependence in some patients. Medical literature recommends that benzodiazepine anxiolytics be used with caution in patients with a potential for drug dependence. If you find that your patient has a history of drug abuse or dependence, please evaluate your patient's therapy to determine if they should continue onn benzodiazepine anxiolytic therapy.
10080	Chronic Benzodiazepine Anxiolytic and no Antidepressant	Based on pharmacy and medical claims data, your patient with anxiety has received benzodiazepine anxiolytics on a chronic basis for four months or longer and is not on an antidepressant indicated first-line for anxiety. Benzodiazepine anxiolytics are recommended in treatment guidelines as short-term and adjunctive in the management of anxiety disorders. Chronic therapy recommendations for anxiety generally focus on various antidepressants and/or cognitive approaches. Please review the need for continued use of the benzodiazepine anxiolytic and discuss other potential anxiety treatment options with your patient.
10081	Chronic Benzodiazepine Anxiolytic with an Antidepressant	Based on pharmacy and medical claims data, your patient with anxiety has received benzodiazepine anxiolytics on a chronic basis for four months or longer. Benzodiazepine anxiolytics are recommended in treatment guidelines as short-term and adjunctive. Chronic therapy recommendations for anxiety generally focus on antidepressants, which your patient is on, and/or behavioral therapy. Please review your patient's therapy for anxiety and determine if an adjustment in the non-benzodiazepine therapy might be appropriate to facilitate discontinuation of the chronic benzodiazepine therapy.
103294	Chronic Benzodiazepine Anxiolytic Use without Anxiety Dx	Based on pharmacy and medical claims data, your patient has received benzodiazepine anxiolytics on a chronic basis for four months or longer and does not have a diagnosis of an anxiety disorder. Even with a treatable diagnosis, available data indicate that benzodiazepine anxiolytics are best viewed as adjunctive and short-term interventions, with non-controlled substances being preferred for chronic use. While there may be clinical variables influencing this patient's management that are not apparent in the claims data, please re-evaluate this medication and if an anxiolytic is deemed necessary, please use as low a dose of benzodiazepine as possible for as short a time period as possible and consider changing to a non-controlled substance.

115581	Chronic Use of Sedative/Hypnotics	Chronic Use of Sedative/Hypnotics: According to pharmacy and medical claims data, it appears your patient has received controlled sedative/hypnotics on a chronic basis for 4 months or longer. Controlled sedative/hypnotic agents are generally recommended as short-term, adjunctive therapy in the management of insomnia. Most are not FDA-approved for long-term use and have been the subject of limited long-term clinical trials. Cognitive-Behavioral Therapy (CBT) is most effective for management of chronic insomnia. Please review the need for continued use of the controlled sedative/hypnotic and discuss other potential insomnia treatment options with your patient.
115582	Chronic Use of Select Sedative/Hypnotics	Chronic Use of Select Sedative/Hypnotics: According to pharmacy and medical claims data, it appears your patient has received select controlled sedative/hypnotics (eszopiclone, lemborexant, or zolpidem ER) on a chronic basis for 6 months or longer. Controlled sedative/hypnotic agents are generally recommended as short-term, adjunctive therapy in the management of insomnia. Most are not FDA-approved for long-term use and have been the subject of limited long-term clinical trials. Cognitive-Behavioral Therapy (CBT) is most effective for management of chronic insomnia. Please review the need for continued use of the controlled sedative/hypnotic and discuss other potential insomnia treatment options with your patient.
115613	Dose Consolidation: Controlled Sedative Hypnotics	According to submitted pharmacy claims data, your patient is currently receiving multiple dosage units per day and may be a candidate for dose consolidation. Most patients receive adequate therapeutic effect with once-daily dosing of this product. Please review your patient's profile to determine if your patient would benefit from a once-daily single dosage unit of this drug.
115620	Use of Secobarbital in Infants	Based on pharmacy claims it appears your patient, who is less than 2 years of age, has received secobarbital. Secobarbital is not FDA-approved for use in infants this young and few clinical studies in such populations are available. Available data indicates that medication is virtually never the first treatment strategy for sleep disturbances in infants. Please re-evaluate this use and, if a sedative/hypnotic is deemed necessary, please use as low a dose for as short a period of time as possible.