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OHSU Drug Effectiveness Review Project Summary Report – Benzodiazepines

Date of Review: September 2018   **Literature Search:** 9/1/2016-4/27/2018

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. What are the comparative benefits and harms of benzodiazepines to treat mental illnesses compared with other treatments?
2. What are the benefits and harms of co-prescribing benzodiazepines and opioid narcotics in the outpatient setting?
3. What is the evidence for the tapering of benzodiazepines?
4. How do these outcomes vary by specific drug(s) used, patient characteristics (e.g., demographics, severity of illness), co-interventions, duration of treatment, etc.?

Conclusions:
- For treatment of panic disorder, there was low quality evidence that benzodiazepines had statistically improved response rates compared to tricyclic antidepressants (TCAs; relative risk [RR] 1.13; 95% confidence interval [CI] 1.01 to 1.27).[1,2] Response rates from individual studies included in the analysis ranged from 48 to 90% for benzodiazepines and from 20 to 86% for tricyclic antidepressants.[2] Evidence is limited as there was high heterogeneity between studies (I^2>95%), there was no difference in response rates between groups upon multiple sensitivity analyses, and studies failed to adequately define how treatment response was evaluated. There was insufficient evidence comparing benzodiazepines to first-line pharmacological treatments for panic disorder including selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).[1]
- There was low quality evidence that fewer patients treated with benzodiazepines for general anxiety disorder discontinued treatment compared to TCAs (primarily imipramine and clomipramine; RR 0.40; 95% CI 0.29 to 0.57).[1] Treatment discontinuation due to adverse events and absolute difference in discontinuation rates were not reported though rates of discontinuation in individual trials ranged from 5-35% with benzodiazepines compared to 6-50% with TCAs.[2] A similar trend was observed in patients for treatment of depression (RR 0.84; mean difference [MD] -0.04 [95% CI -0.07 to 0.00]; number needed to harm [NNH] 25 [95% CI 14 to 100], I^2 = 35%).[1,3] However, most trials examined comparisons to older antidepressants and did not include comparisons to SSRIs or SNRIs.
- For treatment of general anxiety disorder, there was low quality evidence of no difference in treatment response between antidepressants (SSRIs, SNRIs, or TCAs) and benzodiazepines over 4 to 8 weeks.[1] Evidence was limited by conflicting evidence and lack of reported data. Similarly, there was insufficient evidence for other anxiety disorders including mixed anxiety disorders and social phobias.
- For treatment of depression, evidence was limited to comparisons of alprazolam to TCAs. No difference was observed in average symptom severity score, but fewer patients treated with alprazolam achieved a 50% reduction in score compared to TCAs (MD -0.11, 95% CI -0.24 to 0.01; I^2 = 58%; number needed to treat [NNT] 9, 95% CI 4 to 100; low quality evidence).[1,3]

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- There is insufficient evidence to assess efficacy of benzodiazepines for treatment of post-traumatic stress disorder (PTSD). Guidelines from the Veterans Administration and Department of Defense recommend against use of benzodiazepines in this population due to the limited evidence regarding efficacy and risks associated with therapy.[4]
- Evidence for treatment of schizophrenia only included comparison of benzodiazepines to older antipsychotics (primarily haloperidol and chlorpromazine) and was limited by methodological flaws and risk of bias. Evidence was insufficient to determine differences in response rate or patient discontinuation due to adverse events within 0.5-12 hours or within 2-4 weeks of treatment.[1] Treatment with benzodiazepines or combination treatment with a benzodiazepine and antipsychotic did result in greater short-term sedation (at 20-40 minutes after administration) compared to use of an antipsychotic alone (RR 1.13 to 2.25).[1]
- Low quality evidence from observational studies indicates that concomitant use of benzodiazepines and opioid medications may be associated with increased risk of death.[1] Due to the retrospective nature of these data, the exact risk associated with concomitant benzodiazepine and opioid use is unclear.
- Evidence supporting tapering of benzodiazepines included 4 systematic reviews including more than 16,000 patients.[1,5,6] In general, patients who utilized tapering alone, tapering combined with psychological interventions, patient education or medical substitution had greater cessation rates (combined mean of 60%, range 25 to 85%) compared to usual care (range 9 to 21%).[1] The most common tapering methods used were a 25% reduction in dose every 1-2 weeks.[1]
- Overall, there was insufficient evidence to assess long-term efficacy or safety of benzodiazepines for mental health conditions and insufficient evidence to assess safety or efficacy in specific patient populations.

Recommendations:
- Current evidence for these agents does not support specific changes to the current Preferred Drug List (PDL). Update prior authorization criteria to limit use for treatment of PTSD, allow patients receiving long-term therapy time to taper the dose when appropriate, and require prescribers to provide supporting medical literature and/or appropriate rationale for long-term benzodiazepine use (**Appendix 3**).

Summary of Prior Reviews and Current Policy:
Despite lack of evidence supporting long-term benzodiazepine use and guidelines recommending only short-term use, benzodiazepines are often utilized for long-term treatment. In a previous analysis of the OHP population, approximately 37% of patients were prescribed benzodiazepines longer than 90 days (mean length of long-term use was 8.5 months).[7] Current utilization is presented in the accompanying policy evaluation. Benzodiazepines are FDA indicated for treatment of alcohol withdrawal, epilepsy, anxiety and panic disorder, and are often used off-label for other mental health conditions including bipolar disorder and schizophrenia. In an effort to prevent inappropriate long-term benzodiazepine use, a policy was implemented in July 2016 to require prior approval for benzodiazepine durations exceeding 4 weeks. The policy was intended to apply only to patients newly started on a benzodiazepine (no history within the last 120 days), and all patients with a history of benzodiazepine use prior to policy implementation were grandfathered at their current dose. Approval would be granted for new starts in any of the three situations for patients newly prescribed benzodiazepines:
1. Diagnosis of malignant neoplasm or other end of life diagnosis
2. Diagnosis of epilepsy
3. OHP-funded indication and all of the following
    a. Clinical rationale to support long-term benzodiazepine use for the supplied indication(s)
    b. No history of substance abuse and no concurrent sedative/hypnotic or opioid use

Methods:
The February 2017 drug class report on benzodiazepines by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. The DERP is part of the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University. The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports. The original DERP report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

In addition, new systematic reviews and randomized controlled trials (RCTs) published since completion of the DERP report were identified. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence in this document is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

DERP Summary Findings:
Efficacy and safety of benzodiazepines for mental illness
- Anxiety and panic disorder
    - Evidence for the use of benzodiazepines for anxiety disorders included 3 systematic reviews (2871 patients) which examined efficacy of a benzodiazepine to another active medication. Comparators included TCAs (18 RCTs), SSRIs (2 RCTs), venlafaxine (2 RCTs), buspirone (3 RCTs), and pregabalin (2 RCTs).[1] On average, trials included in these reviews were 4 to 8 weeks in duration.[1] Outcomes evaluated in these trials included 50% improvement in the Hamilton Anxiety scale (HAM-A), general improvement in symptoms, remission, adverse events, and tolerability.[1] The HAM-A scale evaluates symptom severity on a scale of 0 to 55 points with larger values indicating more severe symptoms.[1]
    - Compared to TCAs, benzodiazepines had no clear differences in efficacy or safety in patients with general anxiety disorder. Change in overall symptoms was not reported, and evidence regarding specific symptoms was mixed. Differences in somatic symptoms were improved with alprazolam compared to imipramine, but imipramine reduced anxiety symptoms more than diazepam. Similar rates of adverse events were reported between groups. In patients with panic disorder, benzodiazepines had statistically improved response rates compared to TCAs (RR 1.13; 95% CI 1.01 to 1.27).[1] Evidence is limited as studies failed to report the absolute difference between groups or adequately define how response was evaluated.[1,2] Response rates from individual studies included in the analysis ranged from 48 to 90% for benzodiazepines and from 20 to 86% for antidepressants.[2] The proportion of patients who dropped out of the study (RR 0.40; 95% CI 0.29 to 0.57) and the proportion of patients with any adverse event (odds ratio [OR] 0.41; 95% CI 0.34 to 0.50) was also lower with benzodiazepines compared to TCAs.[1] The absolute difference in safety endpoints was not reported though the proportion of patients who discontinued the study ranged from 5-35% with benzodiazepines compared to 6-50% with

antidepressants upon analysis of individual studies.[2] Similar results were reported for the proportion of patients with any adverse event rates with 2-15% of patients treated with a benzodiazepine reporting adverse events compared to 6-40% of patients treated with TCAs.[2] All analyses were limited by high heterogeneity (I^2 >95%) between trials, and there was no difference in response rates between groups upon multiple sensitivity analyses.[1]

- o Upon direct comparison of buspirone with benzodiazepines, there was no clinically meaningful difference in the HAM-A scale between groups; the mean difference (MD) in HAM-A score compared to buspirone was 1.1 points with lorazepam (p=0.008), 1.1 points with alprazolam (p=0.009), and -0.2 points with diazepam (p=0.98).[1]
- o Evidence for other anxiety disorders including mixed anxiety disorders and social phobias was conflicting and based on a limited population of patients. No conclusive differences between benzodiazepines and other treatments could be determined.
- o Compared to placebo in 2 RCTs, patients treated with lorazepam had greater response rates at 4 to 8 weeks (OR 0.40; 95% CI 0.24 to 0.66).[1] Response was defined as more than 50% improvement in the HAM-A scale from baseline, and the average change in score was not reported.

- Depression
  - o Evidence for alprazolam was evaluated in a high-quality systematic review which included direct comparisons to TCAs in 20 RCTs (n=1765) and comparison to placebo in 7 RCTs (n=770).[1] The majority of trials were 4-6 weeks in duration with an average dose of 2.9 mg alprazolam (range 1.5 to 8 mg) and TCAs within the therapeutic range.[1] The primary outcome examined improvement in the Hamilton depression scale.[1] Compared to TCAs, alprazolam had no difference in average symptom severity (MD 0.25 points; 95% CI -0.93 to 1.43, I^2=55%) though response rate (defined as the proportion of patients with a 50% relative improvement in score) was slightly lower with alprazolam compared to TCAs (MD -0.11, 95% CI -0.24 to 0.01; I2 = 58%; NNT 9, 95% CI 4 to 100).[1,3]
  - o Compared to TCAs, there was a trend of fewer overall treatment discontinuations with alprazolam (RR 0.84; MD -0.04 [95% CI -0.07 to 0.00]; NNH 25 [95% CI 14 to 100], I^2 = 35%), and fewer patients treated with alprazolam discontinued treatment due to adverse events (RR 0.62; MD -0.04 [95% CI -0.08 to 0.01]; I2 =60%; NNH 25 [95% CI 11 to 100]).[1,3]
  - o Compared to placebo, symptoms improvement evaluated with the Hamilton depression scale (MD -5.34; 95% CI -7.48 to 3.2; I^2 = 68%) and response rate defined as 50% reduction in Hamilton depression score (MD 0.32; 95% CI 0.22 to 0.42, I^2 = 0%; NNT 3) were improved with alprazolam.[1,3] There was no difference in withdrawal due to adverse events.

- Post-Traumatic Stress Disorder (PTSD)
  - o Evidence for benzodiazepine use in patients with PTSD was limited to a Cochrane review which included a single, small RCT of temazepam 30 mg versus placebo (n=22) over 1 week.[1] Patients were on average 36 years of age and initiated treatment within 2 weeks after a traumatic event.[1] The proportion of patients who met diagnostic criteria for PTSD at 6 weeks was actually higher in those treated with temazepam (55%) compared to placebo (27%), though results failed to achieve statistical significance (p=0.387).[1] No difference was reported in symptom severity or adverse events.[1]

- Schizophrenia
  - o Evidence for benzodiazepine use in schizophrenia included a single systematic review of 34 RCTs (n=2657 patients).[1] Thirteen RCTs examined benzodiazepines (most commonly diazepam, clonazepam, lorazepam and chlordiazepoxide) compared to an antipsychotic drug (most commonly haloperidol and chlorpromazine), 20 RCTs assessed benzodiazepines in combination with antipsychotics, and 7 RCTs compared benzodiazepines to placebo.[1] Overall trials were limited by small populations (12-301 patients), short duration (1-10 weeks), and important outcome reporting flaws.[1]
  - o Compared to antipsychotics, there was no difference in response rate or patient discontinuation due to adverse events within 0.5-12 hours or within 2-4 weeks of treatment.[1] Similarly, when used in combination with antipsychotics, benzodiazepines were not significantly different than antipsychotics alone upon follow-up of 1 to 10 weeks.[1] The only difference observed with benzodiazepines was increased short-term sedation with

benzodiazepines (RR 1.32 at 20 minutes and RR 1.13 at 40 minutes) or combination benzodiazepine and antipsychotic (RR 2.25 at 30 minutes and RR 1.39 at 60 minutes) compared with antipsychotics alone.[1]

- o Compared with placebo (6 RCTs, n=382 patients), there was no difference in clinically important response rate, rate of relapse, or study discontinuation with short-term treatment.[1] Patients treated with benzodiazepines more commonly reported adverse events including loss of energy and ataxia compared to placebo (ARR 21%; RR 1.44 [95% CI 1.02 to 2.04]; NNH 5 [95% CI 3 to 50]).[1,8]

Co-prescribing of benzodiazepines and opioids

Evidence assessing the benefits and harms of co-prescribing benzodiazepines and opioids included one high-quality systematic review and 2 clinical guidelines with recommendations regarding concomitant use of these medications (Centers for Disease Control and American Society of Interventional Pain Physicians).[1] The review included evidence from 71 studies related to unintended methadone overdose though only 1 systematic review, 2 retrospective cohort studies (n=5540), and 5 case series (n=1127) specifically addressed safety of concomitant benzodiazepines and methadone.[1] Co-prescribing of these medications was associated with increased risk of drug-related deaths in 2 retrospective cohort studies (adjusted hazard ratio [HR] 1.4; 95% CI 1.2 to 1.7 and HR 4.35; 95% CI 1.32 to 14.30).[1] Similarly, in 5 case series examining methadone overdose deaths, blood toxicology was positive for both benzodiazepines and methadone in 36 to 67% of deaths.[1] Due to the retrospective nature of these data, the exact risk associated with concomitant benzodiazepine and opioid is unclear.

Guidelines from the Centers for Disease Control recommend avoidance of concurrent opioids and benzodiazepines whenever possible, a recommendation based on one prospective cohort study and 1 retrospective study.[1] Guidelines from the American Society of Interventional Pain Physicians recommend evaluation of the contraindications to opioid use in chronic non-cancer pain including concomitant use of benzodiazepines based on fair to limited quality evidence.[1] Limited-evidence is described as evidence which is insufficient to assess effects on health outcomes, and fair evidence is described as evidence which is sufficient to determine effects on outcomes but strength is limited by size, number, or quality of trials, consistency of results, generalizability to practice, or use of surrogate outcomes.[1] Quality of these guidelines was assessed using the University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline criteria. Guidelines from the CDC met all quality metrics, but guidelines from the American Society of Interventional Pain Physicians were downgraded because they published in 2012, do not report conflicts of interest, and are only partially based on a systematic review of evidence.[1]

Methods of tapering benzodiazepines

Two systematic reviews of fair to good quality (evaluating a total of 60 studies of various types) were included in the review.[1] Trials were only included if they evaluated benzodiazepine use for greater than 3 months.[1] Mean age of participants ranged from 38 to 77 years and 45-81% of participants were female.[1] Interventions included various tapering regimens, informational or educational interventions, psychological interventions such as cognitive behavioral therapy, or medical substitution compared to normal or routine care. The primary outcome was complete discontinuation of benzodiazepines. In one systematic review, patients who utilized tapering alone, tapering combined with psychological interventions, or tapering plus medical substitution had greater cessation rates (combined mean of 60%, range 25 to 85%) compared to usual care (range 9 to 21%).[1] Stratification by dose (less than or greater than 10 mg/day diazepam equivalents) or duration of use (less than or greater than 7 years) demonstrated no differences in treatment success with cessation rates of 48-61%.[1] In the second review, addition of psychological treatment improved cessation rates compared to tapering alone (OR 1.82; 95% CI 1.25 to 2.67), but substitutive pharmacology failed to demonstrate a significant difference in rates.[1] In addition, tapering plus abrupt substitutive pharmacotherapy was less effective than tapering alone (OR 0.30; 95% CI 0.14 to 0.64).[1] Regarding adverse effects, withdrawal symptoms were frequently reported in both reviews for more than 30% of patients, though no symptoms severe enough to require medical attention were recorded.[1] The most common tapering methods used were a 25% reduction in dose every 1-2 weeks.[1]

Other Systematic Reviews
A series of Cochrane reviews was published which included evidence regarding safety and effectiveness of benzodiazepines for mental health conditions. The first examined evidence for psychological interventions compared to pharmacologic interventions (including antidepressants and benzodiazepines) for treatment of panic disorder in adults.[9] Four trials were included which examined psychological therapies compared to either diazepam or alprazolam.[9] Data was significantly limited by lack of reported methods for these trials with unclear randomization methods, unblinded groups, selective reporting, and conflicts of interest. Psychological interventions included cognitive behavioral therapy, psychodynamic therapies (focus on revealing and resolving intrapsychic or unconscious conflicts), psychoeducation, and behavior therapy.[9] Overall, there was no difference in short-term response, short-term remission, short-term improvement within 6 months of treatment initiation, or treatment discontinuation for any reason.[9] Similar results were observed upon comparison of psychological therapies compared to antidepressants alone or combination treatment with antidepressants and benzodiazepines.[9]

The second Cochrane review compared evidence regarding efficacy and safety of pharmacologic treatments for panic disorder in adults (including benzodiazepines, TCAs, SSRIs, and SNRIs).[10] For all outcomes, evidence was of low to insufficient quality. Primary outcomes included the proportions of patients that did not respond to treatment and the proportion who discontinued treatment.[10] Secondary outcomes included failure to remit, improvement in panic symptoms, anxiety or depression, frequency of panic attacks, and social functioning. Outcomes were reported on average at 12 weeks (study durations ranged from 2 to 6 months).[10] There was low quality evidence from 8 RCTs (n=2055), of no difference in the proportion of patients who responded to treatment between benzodiazepines and antidepressants.[10] Similar results were reported upon comparison of TCAs and SSRIs to benzodiazepines.[10] Evidence was limited by unclear risk of bias in included trials, though results were consistent between studies. A statistically greater proportion of participants treated with an antidepressant discontinued treatment compared to benzodiazepines (30% vs. 21%; RR 1.64; 95% CI 1.03 to 2.63).[10] However, due to wide confidence intervals, significant heterogeneity (I^2=75%), and unclear or high risk of bias, there was insufficient evidence to determine clinical differences in tolerability between groups. Similar results were observed for secondary outcomes with no difference between benzodiazepines and antidepressants, TCAs, or SSRIs.[10] There was also no difference upon direct comparison of diazepam to alprazolam and alprazolam to clonazepam in 2 RCTs (n=310).[10]

The third Cochrane report evaluated pharmacotherapy for social anxiety disorder.[11] Overall, there was insufficient direct evidence comparing benzodiazepines to other treatments, and placebo-controlled evidence was of low to insufficient quality for outcomes of interest.[11] Two RCTs provided low quality evidence that treatment response was improved with benzodiazepines compared to placebo (81% vs. 20%; RR 4.03; 95% CI 2.45 to 6.65, n=132) with no difference in treatment relapse or dropout rate.[11] Response rate was defined as a score of either 1 or 2 (much or very much improved) on the Clinical Global Impressions Improvement (CGI-I) scale (range 1-7).[11] Evidence for other secondary outcome measures including reduction in symptoms and associated disability was limited by high heterogeneity and/or small treatment effects.[11] Of note, only SSRIs demonstrated an improvement in preventing relapse compared to placebo (moderate quality evidence).[11] Authors recommend that potential benefits of benzodiazepines be considered within the context of potential for abuse and adverse effects.[11]

An AHRQ report examined evidence for treatment of anxiety in children.[12] Overall, there was insufficient direct comparative data of drug treatments for improvement in primary anxiety symptoms.[12] Compared to placebo, there was low quality evidence that benzodiazepines did not have any significant improvement in primary anxiety symptoms for children.[12] Evidence was based on a single small RCT with severe imprecision.[12]

A Cochrane review assessing pharmacological interventions to facilitate discontinuation in chronic benzodiazepine users found only insufficient to low quality of evidence that pharmacological substitution improves outcomes of benzodiazepine discontinuation, withdrawal symptoms, anxiety symptoms, or relapse to benzodiazepine use.[5] Medications assessed included valproate, pregabalin, tricyclic antidepressants, paroxetine, carbamazepine and flumazenil.[5] Data were

limited by high risk of bias, imprecision, small sample size, and variation between the types of interventions.[5] Similarly, there was insufficient evidence to assess harms associated with benzodiazepine discontinuation.[5] Authors concluded that it was not possible to draw firm conclusions regarding effectiveness or harms of pharmacological interventions for benzodiazepine discontinuation.[5]

A systematic review published in 2017 described methods used to discontinue benzodiazepines and other sedative hypnotics in patients older than 65 years of age.[6] Seven studies were included in the review and data were limited by small sample size and significant variation in studies.[6] Interventions typically included tapering in combination with provider outreach, pharmacological substitution, patient education, and/or psychological support.[6] Due to the wide variety of interventions and outcomes studied, results were described only descriptively. Pharmacologic substitution included use of trazodone, lometazepam (not available in the US), or melatonin.[6] When used with or without psychological support, rates of benzodiazepine discontinuation ranged from 40 to 80% compared to patients randomized to placebo.[6] Patient education was assessed in 2 studies and included a 1 hour lecture on safety of benzodiazepines including fall risk or a patient education booklet to facilitate discontinuation over 6 months. More patients discontinued treatment compared to usual care (treatment difference of 39% and 22% for each intervention).[6] One study described a discontinuation rate of 80% at 6 months with tapering and psychological support.[6] Overall, authors conclude that withdrawal of benzodiazepines and sedative medications is feasible with use of multiple interventions, but evidence on clinical outcomes was limited.[6]

Guidelines
Updated guidelines from the Veterans Administration and Department of Defense for the management of PTSD and acute stress disorder were published in 2017.[4] Recommended first-line pharmacotherapy for treatment of PTSD is sertraline, paroxetine, fluoxetine, or venlafaxine (strong recommendation).[4] Alternative options are nefazodone, imipramine, or phenelzine monotherapy if either the recommended first-line pharmacotherapy, trauma-focused psychotherapy or non-trauma-focused psychotherapy are ineffective, unavailable, or not tolerated (weak recommendation).[4] Guidelines recommend against the use of benzodiazepines (as monotherapy or combination therapy) for treatment of PTSD due to the lack of evidence supporting efficacy and known risks associated with treatment (strong recommendation).[4]

Guidelines from the European Sleep Research Society for the diagnosis and treatment of insomnia were published in 2017.[13] Cognitive behavioral therapy for insomnia (CBT-I) was recommended as the first-line treatment for chronic insomnia in adults (strong recommendation; high quality evidence).[13] Pharmacotherapy, including benzodiazepines and benzodiazepine receptor agonists are recommended only in the short-term (≤4 weeks) if CBT-I is ineffective or unavailable, and long-term treatment with pharmacotherapy should not be recommended due to lack of evidence and risk of adverse effects (strong recommendation; low quality evidence).[13] Relevant conflicts of interest were reported for nine members (35%) of the guideline committee. Industry-related payments for speaking engagements or advisory boards and consulting fees were disclosed for behavioral therapy companies (n=4) and pharmaceutical companies (n=5). One member held patents in a behavioral medicine company and one member had research funding from pharmaceutical companies.[13]

New Formulations or Indications:
None.

New FDA Safety Alerts:
Labeling for all benzodiazepines were updated in 2016 and 2017 to include a boxed warning for concomitant use of benzodiazepines and opioids.[14] Concomitant use may result in profound sedation, respiratory depression, coma and death.[14] Recommendations in package labeling include limitation to the minimum

necessary dose and duration, concomitant use only in patients for whom alternative treatment options have failed, and monitoring for respiratory depression and sedation.[14]

Randomized Controlled Trials:
A total of 113 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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12. Wang Z WS, Sim L, et al. Anxiety in Children. Comparative Effectiveness Review No. 192. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 290-2015-00013-I.) AHRQ Publication No. 17-EHC023-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. DOI: https://doi.org/10.23970/AHRQEPCCER192.
13. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *Journal of sleep research.* 2017;26(6):675-700.
14. Food and Drug Administration. Medical Product Safety Information. http://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/ Accessed July 13, 2018.

Appendix 1: Current Preferred Drug List

FormDesc	Brand	Generic	PDL	Carve-out
TABLET	CLONAZEPAM	CLONAZEPAM	Y	N
TABLET	KLONOPIN	CLONAZEPAM	Y	N
TAB RAPDIS	CLONAZEPAM	CLONAZEPAM	N	N
TABLET	ALPRAZOLAM	ALPRAZOLAM		Y
TAB ER 24H	ALPRAZOLAM ER	ALPRAZOLAM		Y
ORAL CONC	ALPRAZOLAM INTENSOL	ALPRAZOLAM		Y
TAB RAPDIS	ALPRAZOLAM ODT	ALPRAZOLAM		Y
TAB ER 24H	ALPRAZOLAM XR	ALPRAZOLAM		Y
TABLET	XANAX	ALPRAZOLAM		Y
TAB ER 24H	XANAX XR	ALPRAZOLAM		Y
TABLET	CHLORDIAZEPOXIDE-AMITRIPTYLINE	AMITRIPTYLINE/CHLORDIAZEPOXIDE		Y
CAPSULE	CHLORDIAZEPOXIDE HCL	CHLORDIAZEPOXIDE HCL		Y
CAPSULE	CHLORDIAZEPOXIDE-CLIDINIUM	CHLORDIAZEPOXIDE/CLIDINIUM BR		N
CAPSULE	LIBRAX	CHLORDIAZEPOXIDE/CLIDINIUM BR		N
TABLET	CLORAZEPATE DIPOTASSIUM	CLORAZEPATE DIPOTASSIUM		Y
TABLET	TRANXENE T-TAB	CLORAZEPATE DIPOTASSIUM		Y
ORAL CONC	DIAZEPAM	DIAZEPAM		Y
SOLUTION	DIAZEPAM	DIAZEPAM		Y
TABLET	DIAZEPAM	DIAZEPAM		Y
TABLET	VALIUM	DIAZEPAM		Y
TABLET	ATIVAN	LORAZEPAM		Y
ORAL CONC	LORAZEPAM	LORAZEPAM		Y
TABLET	LORAZEPAM	LORAZEPAM		Y
ORAL CONC	LORAZEPAM INTENSOL	LORAZEPAM		Y
CAPSULE	OXAZEPAM	OXAZEPAM		Y

Appendix 2: Literature Search

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to April 25 2018

1	exp Benzodiazepines/	64746
2	exp Mental Disorders/	1131000
3	exp Epilepsy/	150100
4	exp "Sleep Initiation and Maintenance Disorders"/	11278
5	2 or 3 or 4	1258866
6	1 and 5	20696
7	limit 6 to (english language and humans)	15095
8	limit 7 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	5321
9	limit 8 to yr="2016 -Current"	113

Benzodiazepines

Goal(s):
- Approve only for OHP-funded diagnoses.
- Prevent inappropriate long-term benzodiazepine use beyond 4 weeks for new starts (no history within the last 120 days).
- Approve long-term use only for indications supported by the medical literature.

Length of Authorization:
- 6 months to 12 months (criteria-specific)

Requires PA:
- All benzodiazepines used beyond 4 weeks. Short-term use does not require PA.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a malignant neoplasm or other end-of-life diagnosis (ICD10 C00.xx-D49.xx or Z51.5)?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Does the patient have a seizure disorder diagnosis?	**Yes:** Approve for 12 months	**No:** Go to #5
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber evaluated the PDMP at least once in the past 3 months for this patient?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
6. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7
7. Is the request for treatment of post-traumatic stress disorder (PTSD)? Note: Risks of benzodiazepine treatment outweigh benefits for patients with PTSD. Treatment with benzodiazepines is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is the request for treatment of anxiety or panic disorder?	**Yes:** Go to #9	**No:** Go to #10
9. Is the medication prescribed by or in consultation with a psychiatrist OR does the patient have a documented trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including antidepressants AND psychotherapy (e.g. behavioral therapy, relaxation response training, mindfulness meditation training, eye movement desensitization and reprocessing)? Note: An adequate trial to determine efficacy of an SSRI or SNRI is 4-6 weeks.	**Yes:** Go to #12 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
10. Is the request for treatment of psychosis, schizophrenia or schizoaffective disorder?	**Yes:** Go to #11	**No:** Go to #12

Approval Criteria

11. Is the medication prescribed by or in consultation with a psychiatrist OR does the patient have an adequate trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including second-generation antipsychotics AND psychotherapy (e.g. counseling, cognitive behavioral therapy, social skills training, or psychoeducation)? Note: For continued symptoms, assess adherence and dose optimization. For patients on an adequate dose of antipsychotic, guidelines recommend trial of a second antipsychotic or augmentation with a mood stabilizer.	**Yes:** Go to #12 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
12. Is the patient on a concurrent sedative, hypnotic, muscle relaxant, or opioid?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. RPh only: Is there appropriate rationale to support long-term benzodiazepine use for this indication? For anxiety, panic disorder, or schizophrenia, provider rationale should include information from relevant chart notes. For other diagnoses, provider must document supporting medical literature.	**Yes:** Approve for up to 6 months.	**No:** Deny; medical appropriateness.

Renewal Criteria

1. Is the request for a decrease in daily dose OR a change in drug with the intent to taper the dose?	**Yes:** Approve for up to 6 months or length of taper, whichever is less.	**No:** Go to #2
2. Is the request for an increase in dose?	**Yes:** Go to #3	**No:** Go to #4

Renewal Criteria

3. Has the patient failed all clinically appropriate first-line adjunct treatment options OR, when applicable, is the patient adherent to recommended first-line treatment options for their condition?	**Yes:** Go to #4	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of alternative therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
4. Is there documentation based on medical records that provider and patient have discussed whether benefits of long-term therapy (e.g. symptom improvement, social function, number of hospitalizations, etc) continue to outweigh risks of therapy (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of gradual taper plan. Approval may be granted for up to 3 months to allow time to develop a taper plan. Subsequent requests must document progress toward taper.