Center for Prescription Drug Abuse Prevention
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UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

COLORADO CONSORTIUM for Prescription Drug Abuse Prevention

BENZODIAZEPINE PRESCRIBING GUIDANCE

Benzodiazepines (BZs) and Z-drugs (see table) are the most commonly prescribed medications in the benzodiazepine receptor agonist (BZRA) class. Today, there are 14 BZs and 3 Z-drugs that are FDA approved, with anxiety and insomnia being the primary approved conditions for prescribing.[1]

Restraint on BZRA prescribing is urged as they may lose efficacy and/or cause worsening adverse reactions over time including physiologic dependence with disastrous consequences. Restraint on BZRA prescribing is urged. BZRA efficacy may wane overtime, especially when use is consistent. In a subset of patients, both during titration and/ or after cessation, BZs can cause disabling discontinuation syndromes that can last years. Repeated BZ cessation can cause central nervous system sensitization, a phenomenon known as kindling. BZs are also implicated in a third of opioid-related overdose death.[2] While BZRAs do have some limited indications,[3] they are often prescribed in the absence of adequate research and for far longer[4] than the recommended time limitation of 2-4 weeks.[5,6,7] Present day prescribing guidance is limited, contradictory and based on insufficient research that has not been adequately adjudicated for quality and bias.

The recommendations in this guidance are evidence-based and/or amplified by collective clinical experience. They are not comprehensive and should not replace clinical judgement informed by individual circumstances. Other sources provide detailed background information and rationale for these recommendations,[8,9] and the reader is also referred to the Benzodiazepine Deprescribing Guidance, the companion to this document. Further sources provide rationale for these recommendations.[8,9]

CLINICAL PRACTICE BZRA PRESCRIBING RECOMMENDATIONS

1) Listen carefully and respectfully to affected individuals as they are experts on their own lived experiences and often have a sophisticated understanding of therapeutic interventions including BZRAs[9]
2) Fully assess patient concerns and medical conditions for which BZRAs might be prescribed
3) Establish the diagnosis, severity, and the need to treat
4) Screen for addiction-prone substance use risk by means of
    a) Personal and family history of substance use disorder[10] and personal history of trauma[11]
    b) Screening portion of SBIRT (Screening Brief Intervention and Referral to Treatment) to help identify and then address current addiction-prone substance use[12]
    c) Online review of prescription database to identify prescribed addiction-prone substances[13]
    d) Definitive drug testing, if indicated based on clinical judgment[14,15]

5) 1st consider non-BZRA treatments:
    a) Non-medication approaches, notably Cognitive Behavioral Therapy (CBT[16], CBT-I[17])
    b) Non-BZRA medications[18]

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6) BZRAs should be avoided when contraindicated, ineffective, or of unproven or minimal benefit:
    a) In Depression because any benefit is soon lost[19]
    b) In post-traumatic stress disorder[20,21]
    c) In obsessive compulsive disorder[18]
    d) In individuals with a history of substance use disorder (*e.g.,* alcohol) outside of treating withdrawal[1,22]
    e) Pain conditions other than burning mouth syndrome and stiff person syndrome[23]

7) Consider other contraindications to BZRA use:
    a) Prior adverse BZRA experiences[24]
    b) Non-medical use of and/or addiction to BZRAs and/or other substances[21]
    c) Drug-drug interactions with medications, notably respiratory depressants, opioids[4,25,26,27,28]
    d) Significant cognitive[29], psychomotor[30], or respiratory problems[31]
    e) Pregnancy[32,33,34] and breastfeeding[35]

8) Consider 1st line indications for BZRA therapy:
    a) Withdrawal from BZRAs and alcohol[36]
    b) Status epilepticus[37]
    c) Crisis anxiety without psychotic features[38]
    d) Procedure anesthesia (analgoanesthesia)[39]
    e) Pain conditions: burning mouth syndrome (clonazepam)[22,40]
    f) Acute movement disorders, such as stiff person syndrome, catatonia, status dystonicus[22,41,42,43]
    g) End of life palliative care[44,45]

9) Consider 2nd line use of BZRA therapy for short-term use:
    a) Insomnia[46,47]Anxiety disorder defined as ≥6 months, function limiting, anxiety level > actual threat[48]
    b) Certain treatment-resistant, intractable seizure disorders (clobazam, clonazepam)[49]

10) Provide information about BZRA use to the patient:
    a) Highlighting the boxed warnings required by the FDA in product labeling[50]
    b) Describe BZRA risks, benefits, and alternatives (*i.e.,* informed consent[51])
    c) Highlighting the risks of long-term use - BZRA physiologic dependence and withdrawal syndrome with rapid taper and/or discontinuation[8,9]
    d) Make clear that adverse effects and loss of efficacy might not be evident during use[8]

11) Provide reliable, useful resources to the patient:
    a) The Ashton Manual https://www.benzo.org.uk/manual/
    b) The Benzodiazepine Information Coalition (patient-focused) https://www.benzoinfo.com/
    c) The Alliance for Benzodiazepine Best Practices (prescriber-focused) https://benzoreform.org

12) Other qualifiers to prescribing BZRAs[8]
    a) Use *only* if the medical condition causes major functional limitations
    b) Use *only* if delay in onset of action of alternative therapies place the patient in jeopardy
    c) Ensure the balance of risks and benefits favors BZRA use before prescribing
    d) Ensure decision-making is shared with fully informed patients who provide consent

13) If BZRA is prescribed
    a) Prescribe BZRA initially for no more than 7 days at the anticipated lowest effective dosage[52]
    b) Simultaneously prescribe non-BZRA therapy. BZRAs should be thought of as a bridge awaiting the onset of benefit of another medication or non-medication therapy like CBT[8]
    c) Establish 1st follow-up within 7 days, ensuring availability for problems during the interval[51]

14) On follow-up, assess progress addressing the target medical condition:
    a) BZRA efficacy – re-prescribe only as necessary at the lowest effective dosage[51]
    b) Status of non-BZRA therapy ordered at the time BZRAs are 1st prescribed
    c) Need for additional referrals

15) On follow-up, provide ongoing informed consent and identify and address any BZRA side effects:
    a) Depression[21,53], anxiety[54], suicidality, cognitive[55], psychomotor[56], respiratory[57] problems
    b) Drug-drug interactions [4,24-27]
    c) Interdose withdrawal symptoms which evolve towards the end of the dosing interval or when BZs are frequently used as needed and can be easily misdiagnosed as underlying or new organic symptoms[8, 58]
    d) Do not discount symptom reports as psychosomatic if they seem unusual or bizarre[8,59]
    e) Do not assume BZRA-related problems means BZRA addiction - this is very infrequent[3,8]

16) Continue weekly follow-ups to address efficacy and adverse outcomes[51] and provide informed consent
17) Limit duration of BZRA therapy to 4 weeks or less in the majority of circumstances[6,7,8,9,22,50, 51,60]
18) Do not abruptly discontinue BZRAs if used > 2 weeks: rather, taper off the medication[61,62]
19) Thoughtful deprescribing is essential to best practice prescribing[63] - see companion guidance

Benzodiazepine Receptor Agonist Prescribing Information Link	FDA-Approved Indications	FDA-Approved Duration Limitations
Alprazolam Xanax	Anxiety disorder Short-term relief of anxiety symptoms	4-10w duration for panic disorder
Chlordiazepoxide Chlordiazepoxide	Anxiety disorder Short-term relief of anxiety symptoms Acute alcohol withdrawal Preoperative apprehension and anxiety	Long-term use, ie >4m, has not been assessed by systematic clinical studies
Clobazam Onfi	Adjunctive for seizures associated with Lennox-Gastaut syndrome	[No listed timeframe]
Clonazepam Klonopin	Panic disorder ± agoraphobia Specified treatment-resistant seizure disorders	Effectiveness in long-term use, ie >9w, has not been systematically studied in controlled clinical trials
Clorazepate Clorazepate	Anxiety disorder Short-term relief of anxiety symptoms Acute alcohol withdrawal Preoperative apprehension and anxiety	Long-term management of anxiety, ie >4m, has not been assessed by systematic clinical studies
Diazepam Valium	Anxiety disorder Short-term relief of anxiety symptoms Acute alcohol withdrawal Adjunctively in convulsive disorders Relief of specified skeletal muscle spasm, spasticity	Effectiveness in long-term use, ie >4m, has not been assessed by systematic clinical studies
Estazolam Estazolam	Short-term management of insomnia	There is evidence to support ability of estazolam to enhance duration, quality of sleep for intervals up to 12w
Flurazepam Dalmane	Treatment of insomnia	Effective for at least 28 consecutive nights of drug administration
Lorazepam Ativan	Anxiety disorders Short-term relief of anxiety symptoms Anxiety associated with depressive Sxs	Effectiveness in long-term use, ie >4m, has not been assessed by systematic clinical studies
Midazolam Midazolam	Procedural sedation, anxiolysis, amnesia	NA
Oxazepam Oxazepam	Anxiety disorders Short-term relief of anxiety symptoms Anxiety associated with depression Acute alcohol withdrawal	Effectiveness in long-term use, ie >4m, has not been assessed by systematic clinical studies
Quazepam Doral	Treatment of insomnia	Sustained effectiveness has been established in a sleep lab study of 28 nights duration
Temazepam Restoril	Short-term treatment of insomnia (generally 7-10d)	Clinical trials performed in support of efficacy were 2w in duration
Triazolam Halcion	Short-term treatment of insomnia (generally 7-10d)	Short-term - generally 7-10 days

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