Carolinas HealthCare System

A Case for Appropriate Prescribing of Benzodiazepines

NCPA Annual Meeting
Asheville, NC
September 9,2016

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No Financial Disclosures

Educational Objectives

- At the conclusion of this activity participants should be able to:
  - have a basic understanding of the pharmacology and pharmacodynamics of benzodiazepines.
  - have a working understanding the strengths and weaknesses of the benzodiazepines.
  - consider various clinical areas in which benzodiazepines can be used most effectively.

Treatment of Anxiety in the Vulnerable Population

- Intentional abusers of benzodiazepines usually have other substance abuse problems.
- Benzodiazepines are usually a secondary drug of abuse-used to:
  - augment the “high” from another drug
  - to offset the adverse effects of other drugs.
- Specific drug use patterns
  - To ease the "crash" from cocaine
  - 29%-33% of alcohol abusers take BZs
  - Up to 80% of opiate abusers have taken BZs

O’Brien C, J Clin Psychiatry 2005;66 (suppl 2)

Benzodiazepine Dependence, Toxicity, and Abuse:

Task force report, APA, 1990

Promote Healthy Behaviors

- Promote healthy behaviors to reduce anxiety.
  - exercise;
  - sleep hygiene;
  - decreased use of caffeine, tobacco, alcohol, and other potentially deleterious substances.

Epidemiology of Benzodiazepines

- Most patients take benzodiazepines for periods of < 1 month.
- 12% of the U.S. population used a benzodiazepine for medical purposes at least once during a 1-year period,
- 6 month use occurs in about 3% of the population
- 1% using the medication for a year or longer
- long-term users are more likely to be older, female, with more significant chronic health and/or emotional problems

Epidemiology of Benzodiazepines

- About 30% of psychiatric patients receive benzodiazepines
- Greatest use in patients with affective disorders, long duration of mental illness, and high users of psychiatric services
- Generally most patients tend to decrease anxiolytic doses over time.
- The use of antidepressants to treat anxiety has increased in recent years and the proportion of patients treated with anxiolytics has fallen slightly
- There are certain groups of high-risk patients where long-term use, misuse, and abuse is greater than in patients with anxiety disorders.

Epidemiology

- Drug Abuse Warning Network (DAWN) researchers identified an 89% increase in ED visits associated with benzodiazepines between 2004 and 2008.
- The estimated number of visits for alprazolam in 2008 (104,800) was more than twice the number for the next most common benzodiazepine, clonazepam (48,400).
- The relative magnitudes of the rates shown generally reflect prescription volumes.
  - 44 million alprazolam prescriptions in 2008.
- New York City Department of Health also showed benzodiazepines were tied to more than 30 percent of all the city's overdose deaths in 2009.

How reinforcing are Benzodiazepines?

- Humans
  - Normal (light drinkers without anxiety or insomnia)
    - BZ (diazepam, lorazepam, flurazepam) not preferred to placebo
    - Moderate social drinkers, no hx alcohol problems
      - Benzodiazepines (po) are reinforcers
      - Three studies confirm
- Animals
  - Oral BZs
    - 8/18 studies in primates and rats did not show evidence of reinforcement
  - IV
    - Reinforcement demonstrated with a variety of benzodiazepines

Griffiths & Weerts Psychopharmacology (Berl). 1997;134(1):1-37

Conventional Wisdom

- Most chronic benzodiazepine users do not escalate their original dose, even after many years.
- The reinforcing effects are considerably weaker than other sedative hypnotics, stimulants, and opiates, but stronger than drugs with little abuse potential, e.g., chlorpromazine.

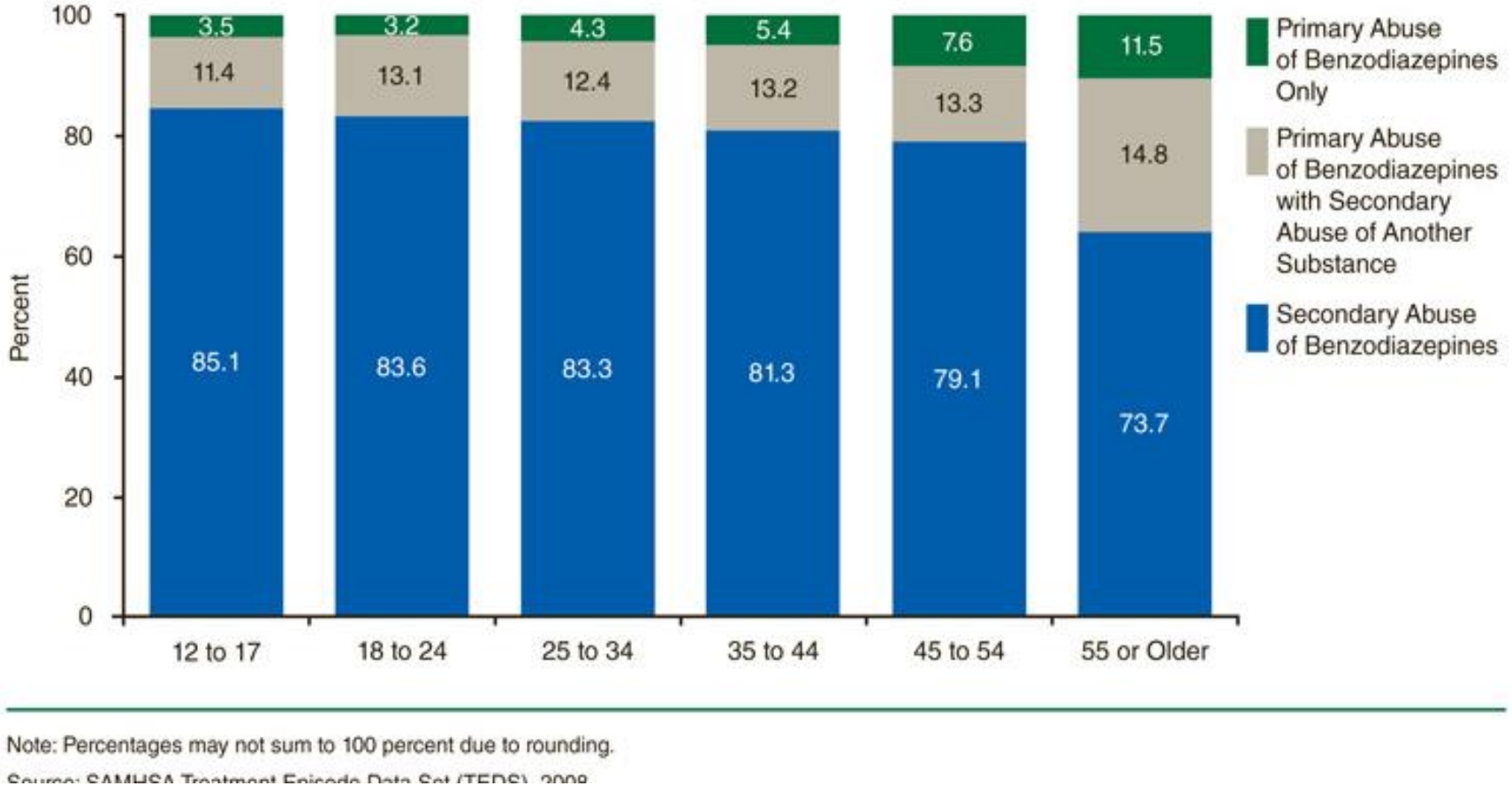
Benzodiazepine Dependence, Toxicity, and Abuse: A Task Force Report of the American Psychiatric Association. Washington, DC, APA, 1990

Benzodiazepine Use Patterns

- Recreational abuse of BZs alone is uncommon
  - Commonly taken as part of polysubstance –abuse
- Motivations
  - Euphoria
  - Augment euphoriant effect of other drugs, especially opiates
  - Up to 80% of opiate abusers take BZs
  - To ease the "crash" from cocaine
  - 29%-33% of alcohol abusers take BZs

Benzodiazepine Dependence, Toxicity, and Abuse: A Task Force Report of the American Psychiatric Association. Washington, DC, APA, 1990

Benzodiazepine Abuse



Note: Percentages may not sum to 100 percent due to rounding.

Source: SAMHSA Treatment Episode Data Set (TEDS), 2008

Treatment admissions

- The number of benzodiazepine admissions nearly tripled between 1998 and 2008,
  - while overall treatment admissions increased only 11 percent
- The majority of benzodiazepine admissions were:
  - male,
  - between the ages of 18 and 34,
  - non-Hispanic White
- Almost all benzodiazepine admissions (95 percent) reported abuse of another substance in addition to abuse of benzodiazepines:
  - 82.1 percent reported primary abuse of another substance with secondary abuse of benzodiazepines,
  - 12.9 percent reported primary abuse of benzodiazepines with secondary abuse of another substance

SAMHSA TEDS Data 2008

Nonmedical Use

- Most nonmedical use is occasional use of therapeutic doses for sx relief
  - Not associated with escalation or high-dose abuse

Benzodiazepine Dependence, Toxicity, and Abuse: A Task Force , Report of the American Psychiatric Association. Washington, DC, APA, 1990

That is ...

Most nonmedical use is not “recreational use”

Sedative Hypnotics

- Effective in modulating gamma aminobutyric acid (GABA)
- GABA is the major inhibitory neurotransmitter.
- Suppress central nervous system (CNS) activity
- Medical uses include
  - anxiolytic
  - hypnotic
  - anticonvulsant
  - muscle relaxant
  - anesthesia induction agent

Generic Name	Brand Name	Approximate Equivalent Dosages (mg)	Approved Dosage Range (mg/day)
Alprazolam	Xanax	1	0.75-4; 1.5-10
Chlordiazepoxide	Librium	25	25-100
Clonazepam	Klonopin	0.5	1-4
Clorazepate	Tranxene	15	7.5-60
Estazolam	ProSom	4	0.5-1
Flurazepam	Dalmane	30	15-30
Diazepam	Valium	10	2-40
Lorazepam	Ativan	2	0.5-10
Midazolam	Versed	4	N/A
Oxazepam	Serax	30	30-120
Quazepam	Doral	30	7.5-15
Temazepam	Restoril	30	15-30
Triazolam	Halcion	0.5	0.125-0.5

Pharmacokinetics Benzodiazepines

- Elimination
  - All BZ are hepatically metabolized and renally excreted
    - Oxidation (P450 3A4)
    - Glucuronide conjugation
  - Most are oxidized to desmethlydiazepam/oxazepam
  - Lorazepam, oxazepam, & temazepam are metabolized by conjugation alone
  - Clonazepam undergoes nitroreduction

Pharmacokinetics Benzodiazepines

temazepam	→	oxazepam
diazepam clorazepate prazepam halazepam	→	desmethyldiazepam oxazepam
chloridiazepoxide	→	desmethlychlordiazepoxide oxazepam
flurazepam	→	desalkylflurazepam
lorazepam	→	glucuronide
alprazolam	→	αhydroxy-alprazolam
clonazepam	→	7-amino-clonazepam

Pharmacokinetics Benzodiazepines

- Urine toxicology
  - Immunoassay screening techniques are performed most commonly .
  - Most often detect benzodiazepines (BZDs) metabolized to desmethyldiazepam or oxazepam
  - Cutoff level radioimmunoassay is 200 ng/ml
    - 48-72 hours post single dose and as long as a week post dose
  - GC/MS cutoff levels for metabolites is 100-200 ng/ml.

Qualitative screening of urine or blood may be performed but rarely influences treatment decisions and has no impact on immediate clinical care.

Cognition

Results from the 13 studies in the meta-analysis:

- Benzodiazepines use
  - the duration between 1 and 34 years (mean 9.9 years)
  - average dose equivalent was 17.2 mg/day of diazepam
- Results suggested decline in all the cognitive domains measured: visuospatial, attention/concentration, problem solving, general intelligence, psychomotor speed, sensory processing, verbal memory, non-verbal memory, speed of processing, motor control/performance, working memory, and verbal reasoning.

Barker MJ, Greenwood KM, and Jackson M. et al. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. Arch Clin Neuropsychol. 2004. 19:437–454.

Pharmacokinetics Benzodiazepines

- Tolerance
  - Decreased responsiveness of the GABAa subunit to benzodiazepines
  - This is a reduction in GABA receptors and their function.
  - Tolerance is primarily a result of pharmacodynamic, and neurobiological adaptation.
  - Usually develops to the disinhibition, sedation, euphoria and drowsiness seen initially with BZ
    - Problematic when used for insomnia
  - Tolerance to the anxiolytic effect is highly variable

Pharmacokinetics Benzodiazepines

- Physical Dependence
  - Becomes apparent when withdrawal occurs upon discontinuation of the drug
    - on withdrawal of the chronic benzodiazepine administration there compensatory changes reduced GABA receptor function manifested as anxiety, insomnia, autonomic hyperactivity and possibly seizures.
  - Can occur after continued use over 2 to 4 months
  - Reported in 50% of patients on treatment for > 4-6 months

Smith DE, Wesson DR (1983). "Benzodiazepine dependency syndromes".*J Psychoactive Drugs* **15** (1–2): 85–95.

Pharmacokinetics Benzodiazepines

- Adverse Effects
  - Cardiovascular
    - Hypotension and bradycardia with rapid IV injection of Diazepam
  - Respiratory depression
    - Clinically relevant in patients with respiratory disease, in overdose situations and when combined with alcohol
- Lethal Benzodiazepine overdose as the sole drug is rare.

Dart, Richard C. Medical Toxicology (3rd ed.) 2003. USA: Lippincott Williams & Wilkins. p. 811

Considerations in use of Benzodiazepine

- The major clinical advantages:
  - high efficacy,
  - rapid onset of action
  - low toxicity
- The main actions of benzodiazepines
  - hypnotic,
  - anxiolytic,
  - anticonvulsant,
  - myorelaxant
  - amnesic.
- Rational use requires consideration of
    - large formulation differences in potency and elimination rate
    - requirements of individual patients.

Considerations in use of Benzodiazepine

- hypnotics;
  - transient or short term insomnia, limited to a few days, not exceeding 2 weeks.
  - occasional or intermittent use,
  - formulations with medium duration of action are suitable.
- anxiolytics,
  - in conjunction with other measures (psychological treatments, antidepressants, other drugs)
  - faster onset of action.
  - Indications
    - acute stress reactions,
    - episodic anxiety
    - fluctuations in generalised anxiety,
    - initial treatment for severe panic and agoraphobia.

Considerations in use of Benzodiazepine

- Adverse effects;
  - psychomotor impairment, especially in the elderly,
  - occasionally paradoxical excitement.
  - long term use,
    - tolerance
    - dependence and withdrawal effects
    - unwanted effects can largely be prevented by
      - keeping dosages minimal and courses short (ideally 4 weeks maximum),
      - careful patient selection.
    - Long term prescription is occasionally required for certain patients.

Generalized Anxiety Disorder

- Benzodiazepines (long-acting agents) are efficacious in the treatment of generalized anxiety disorder
  - concerns include misuse and dependence
  - prescribing guidelines suggest that benzodiazepines should be used only on a short-term basis (3 to 6 months), inconsistent with the chronic nature of generalized anxiety disorder.
  - many specialists believe that, with close monitoring, benzodiazepines are a reasonable option in selected patients
    - without current or past alcohol-use or other substance-use problems
    - preferred agents are ineffective or associated with a poor side-effect profile.23,43
    - concern regarding an increased risk of dementia 44
    - the use of these agents should be minimized in the elderly,

Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. J Clin Psychiatry 2010;71:839-854

Panic and Benzodiazepines

- Five classes of medication have been shown in randomized trials to be more effective than placebo:in patients with panic disorder:
  - selective serotonin-reuptake inhibitors (SSRIs),
  - serotonin-norepinephrine reuptake inhibitors (SNRIs),
  - high-potency benzodiazepines,
  - tricyclic antidepressants,
  - monoamine oxidase inhibitors
- The greater safety profile of the SSRIs make them the drug of choice.

Mitte K. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. J Affect Disord 2005;88:27-45

Gould RA, et.al.. A meta-analysis of treatment outcome for panic disorder. Clin Psychol Rev 1995;15:819-844

Panic and Benzodiazepines

- Benzodiazepines can play an important role in Panic d/o treatment.
  - a more rapid response when used in combination with antidepressants
  - a reduction in the early adverse effects of SSRIs; jitteriness and agitation.
  - suggest longer half-live formulation.
  - may be effective PRN

Bradwejn J, et.al.. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry 2005;187:352-359

Goddard AW, Brouette T, Almai A, Jetty P, Woods SW, Charney D. Early coadministration of clonazepam with sertraline for panic disorder. Arch Gen Psychiatry 2001;58:681-686

Generalized Social Anxiety and Benzodiazepines

- SSRI and SNRI medication are the first line medications high frequency and unpredictable social anxiety.
- Benzodiazepines used in the treatment of patients who cannot tolerate or do not have an adequate response to SSRIs or SNRIs.
  - used in divided doses,
  - highly effective in generalized social anxiety disorder
  - high response rate in several open trials
  - mono therapy is not recommended in patients with a combination of depression and social anxiety.

Davidson JR, et. al., Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol. 1993 Dec; 13(6): 423-8

Non-Generalized Social Anxiety and Benzodiazepines

- Benzodiazepines may also be useful.
  - typically taken at least 30 minutes before an event
  - effect of a single dose may last up to several hours.
  - tolerance and physical dependence are unlikely to develop when used less than daily,
  - psychological dependence may occur,
  - immediate side effects of sedation and cognitive dulling sometimes outweigh the anxiolytic benefits.
  - patients may benefit from being given a trial dose outside their feared situation to confirm tolerability.

Liebowitz MR, et.al. Social phobia: review of a beglected anxiety disorder. Arch Gen Psychiatry 1985; 42:729-736

Schneier FR, Social Anxiety Disorder. N Engl J Med 2006; 355: 1029-1036

Summary

- Using these medications can be very helpful if they are used appropriately.
  - Screen for potential for abuse or high risk population.
    - SUD patients
    - Pain patients on opioids
    - Elderly
  - Know the pharmacology of the specific benzodiazepine you are prescribing
  - Understand the limitations of your UDS
  - Typically use these medication for shorter periods or intermittent use.
  - For certain populations they can be used very useful.

Pharmacologic Management
Acute Anxiety/PTSD

- Cochrane meta-analysis 2006,
  - 35 short-term randomized controlled trials
  - 17 of the trials, symptom severity was significantly reduced in the medication groups relative to placebo.
    - Evidence of efficacy for the SSRIs, across all symptom clusters and for co-occurring depression.

Stein DJ, Cochrane Database Syst Rev 2006

Epidemiology of Benzodiazepines

- Benzodiazepines complicate the work of substance abuse treatment providers.
- Illicit users of benzodiazepines have been found to take higher methadone doses, have more HIV/HCV risk-taking behaviour, greater poly-drug use, higher levels of psychopathology and social dysfunction.
  - This research is limited, further research is needed to demonstrate whether this is the result of cause or effect.
- Benzodiazepine use is higher among Medicaid beneficiaries with severe mental illness and co-occurring SUD than among persons with severe mental illness alone.

Chris Ford (2009) UK: Exchange Supplies, 2009 National Drug Treatment Conference.

Clark RE, et. Al., J Clin Psychiatry, 2004 Feb;65(2):151-5

Treatment Admissions

- Number of benzodiazepine and opiate combination admissions: 2000 to 2010 Increased from 5,032 to 33,701
  - 61.2 percent of benzodiazepine and opiate combination admissions reported daily use of any substance compared with 34.6 percent of other admissions

SAMHSA Treatment Episode Data Set (TEDS), 2000 to 2010.