BENZODIAZEPINES

Side Effects and Risks

- Safety – increased risk for accidents with automobiles, machinery.
- Cognitive deficits – more than 1,000 peer-reviewed papers have been written http://baypsy.ch/QBwtLD.
  - ° Multitasking and attending, mistakes are made, accidents.
  - ° Deficits in recognition of facial expressions, leading to misunderstandings and relationship difficulties http://baypsy.ch/zZxjNG.
  - ° Impacts the encoding and consolidating of new memories by day and overnight
    - ¬ This happens when benzodiazepines bind to the translocator protein called TSPO, on the surface of cell organelles of your microglia (the primary innate immune cells of the brain). This binding signals microglia to degrade and recycle material in the synaptic gap between nerve cells—that is, the connections between the neurons. It causes long-term cognitive problems. As reported in *Nature* http://baypsy.ch/MuZRVy. All people should avoid taking drugs that bind to TSPO.
    - ¬ As a result, psychotherapy is less effective. https://www.ncbi.nlm.nih.gov/pubmed/7892364 https://www.ncbi.nlm.nih.gov/pubmed/24743802
  - ° Cognitive deficits may persist into the future, even after discontinuation. Deficits may be permanent or may take >6 months to recover http://baypsy.ch/Z3lYBG.
  - ° Puts clients at risk for Alzheimer's dementia, due to its anticholinergic effects, say many papers – though a study with >200,000 subjects states this dementia risk is not true http://baypsy.ch/XTgK8P. And indeed, benzos do not cause the anticholinergic side effects such as dry mouth, and urinary hesitancy. Stay tuned.
  - ° Cognitive risks of all kinds are worsened if the benzo is used at bedtime:

    Compresses and reduces REM and reduces slow wave sleep => less quality to sleep.
    - ¬ REM is important for learning and memory, heart rate variability and heart health, emotional rehearsal. The amygdala (a brain structure involved in processing emotions) is 30% more active in sleep than in waking life.
    - ¬ Slow wave sleep is important for rest and repair. The body opens the glymphatic system (a collaboration between the lymph/immune system and the brain) to clear out amyloid beta (involved in Alzheimer's disease) and other waste products.
- With time and daily use Klonopin specifically => depression for many clients.
- Addiction potential, particularly with Xanax. Addicts are prone, as are 1% of non-addicts who use benzodiazepines therapeutically.
- MORTALITY – In a cohort study of 5212 individuals from a large, nationally representative data set, it was found that benzodiazepine use, with or without opioid use, was associated with a doubling in all-cause mortality risk in comparison with the use of low-risk antidepressants (used to treat anxiety) http://baypsy.ch/9UB4aN . Criticisms of the study: No this is not a nationally representative sample, and all subjects have anxiety – but so do our patients considering or taking benzos. Yes, maladaptive coping including with alcohol may increase mortality, but it would then do so in those taking the antidepressants as well.
- One contributor to mortality is cancer – long-term benzodiazepine use is a significant risk.
  - ¬ Here are three studies http://baypsy.ch/WaCrtl http://baypsy.ch/sfV8Oh http://baypsy.ch/ovdVsm.
  - ¬ And a search of the literature: benzodiazepine*[ti] AND (carcinogen*[tiab] OR cancer*[ti] OR neoplasm*[tiab]) http://baypsy.ch/eIzAfg
    - ¬ NOTE this 2014 paper in particular http://baypsy.ch/tl8K5E, which comes into a finer focus on which cancers may appear, and which drug confers the most risk. Diazepam

(Valium), chlordiazepoxide (Librium), medazepam, nitrazepam, and oxazepam (Serax; note, some of these drugs are not in use in the US) were found safer among benzodiazepines, whereas clonazepam (Klonopin) was associated with a higher risk of cancers.
The paper discusses specific cancer risk observed, when compared with a population that did not use benzodiazepines, and mentions significantly increased risk of 98% for brain, 25% for colorectal and 10% for lung cancers.

- In older individuals, benzos have an enhanced risk for harm. They may
  - Increase the risk of falling with fractures by 20 to 50 percent
  - Cause excess sedation
  - Cognitive deficits may be worse, and the person themselves may not notice
  - Higher rates of motor vehicle accidents
  - Mortality rates are 1.2 to roughly 3.7 times higher in older individuals on benzodiazepines, in studies across time

Withdrawal

- Withdrawal is difficult, for some very much so (15% endure year-long tapers), and post-acute withdrawal syndrome (PAWS) can last months, causing anxiety that feels physical/neurologic, and sleep difficulties, trouble w/ focus and concentration, gastrointestinal distress.
  - Drug is tapered w/ fraction of original dose, usually 10%, then fraction of subsequent doses in the taper (not consistent drop w/ fraction of original dose each time). Dose adjustments are made weekly or biweekly.
  - Keppra, Gabapentin, Lyrica and valproate help with the taper; Valium (not in elderly) or Ativan if necessary
  - To fine-tune dose: Gram scale may help in sensitive people, or having the medicine made into a liquid
  - Resource for benzo education and taper:
    - Benzo.org.uk
    - The Ashton Manual https://www.benzo.org.uk/manual/– employs diazepam to taper; you may substitute another agent
    - Ashton manual also educates about PAWS, post-acute withdrawal http://www.benzo.org.uk/ashpws.htm, http://www.thefix.com/content/paws
    - Inner Compass guide can help with the preparation and self care and support through the withdrawal process: https://withdrawal.theinnercompass.org/
  - Online community support
    - Christian Withdrawal Support Group https://www.facebook.com/groups/455433171136238/
    - Beating Benzos https://www.facebook.com/groups/Beatingbenzos/
    - Benzodiazepine Recovery https://www.facebook.com/groups/benzorecovery/
    - Freedom from Psychiatric Meds https://www.facebook.com/groups/freedomfrompsychdrugs/
    - Anonymous Online Forum www.benzobuddies.org

I consider that these medicines put something btwn the client and the world, and think of them as attenuating healthy life.

I use them judiciously in the following scenarios:

- Overwhelming life circumstances (that overcome ability of other medicines to work) and not responsive/tolerating gabapentin or Lyrica and a good sleep protocol; this is a temporary situation
- Panic disorder while waiting for other medicine/psychotherapy to work, or as-needed infrequently for panic
- Helping a person crawl up on temporarily activating antidepressant (e.g. SERT inhibitor)
- Klonopin x6 wks for night terrors in adults
- For very occasional long-term use for speeches/airplanes/BART rides/what-have-you when propranolol doesn't help

Alternatives for anxiety with physiologic concomitants

- Lyrica and Gabapentin
  - Excellent in context of trauma history; good to glue sleep together (GBP more than Lyrica), deepen it, maintain it (but not initiate)
  - Some people get dramatic relief
  - Gabapentin is safe at very high doses (4800–5400 mg) except in renal impairment. Lyrica at 50–900 mg.
- Clonidine, guanfacine, and propranolol, for sympathetic nervous system activation
  - Clonidine and guanfacine also assist with emotional regulation
  - Propranolol is typically used for stage fright and social anxiety – speeches, taking tests – some of my clients have dropped their benzo, finding propranolol leaves them clear and sharp and calm
- Seroquel has an effect size of 1.3 in generalized anxiety trials, but may cause weight gain and carries risk for movement disorders
- Niacinamide (facilitates GABA modulation), hits NADH receptors, take up to 750 mg 3–4 times per day, approximately 2000–2500 mg per day total dose (effects in 1 week). Therapeutic effects are comparable to the benzodiazepines, though there is only a weak binding affinity for the benzodiazepine receptor. It can raise serotonin levels and modify the metabolism of blood lactate (lactic acid). Nausea and vomiting can occur when doses as high as 6,000 mg per day are used.
- Glycine antagonizes the release of norepinephrine, thus mitigating anxiety and panic and feelings of over-arousal
- Amino acids
  - GABA and L-theanine
  - GABA is calming. Blended products people like include GABA Calm (Source Naturals) and True Calm (NOW Foods)
  - L-theanine (glutamate modulator) is calming and brightening. Known for helping anxious people focus, putting them in the zone. I've helped students get through study/exams w/ this
    - ¬ Blended product is Theanine Serene (w/ or w/o Relora; Source Naturals) w/ L-theanine, GABA, taurine, magnesium, holy basil leaf extract

Alternatives for Sleep that are not anticholinergic

- Trazodone for sleep initiation
- Gabapentin for maintenance and quality
- Baclofen for initiation, maintenance, and quality
- Remeron for initiation, maintenance, and quality
- Clonidine for initiation and maintenance
- Orexin antagonists, Belsomra and Dayvigo