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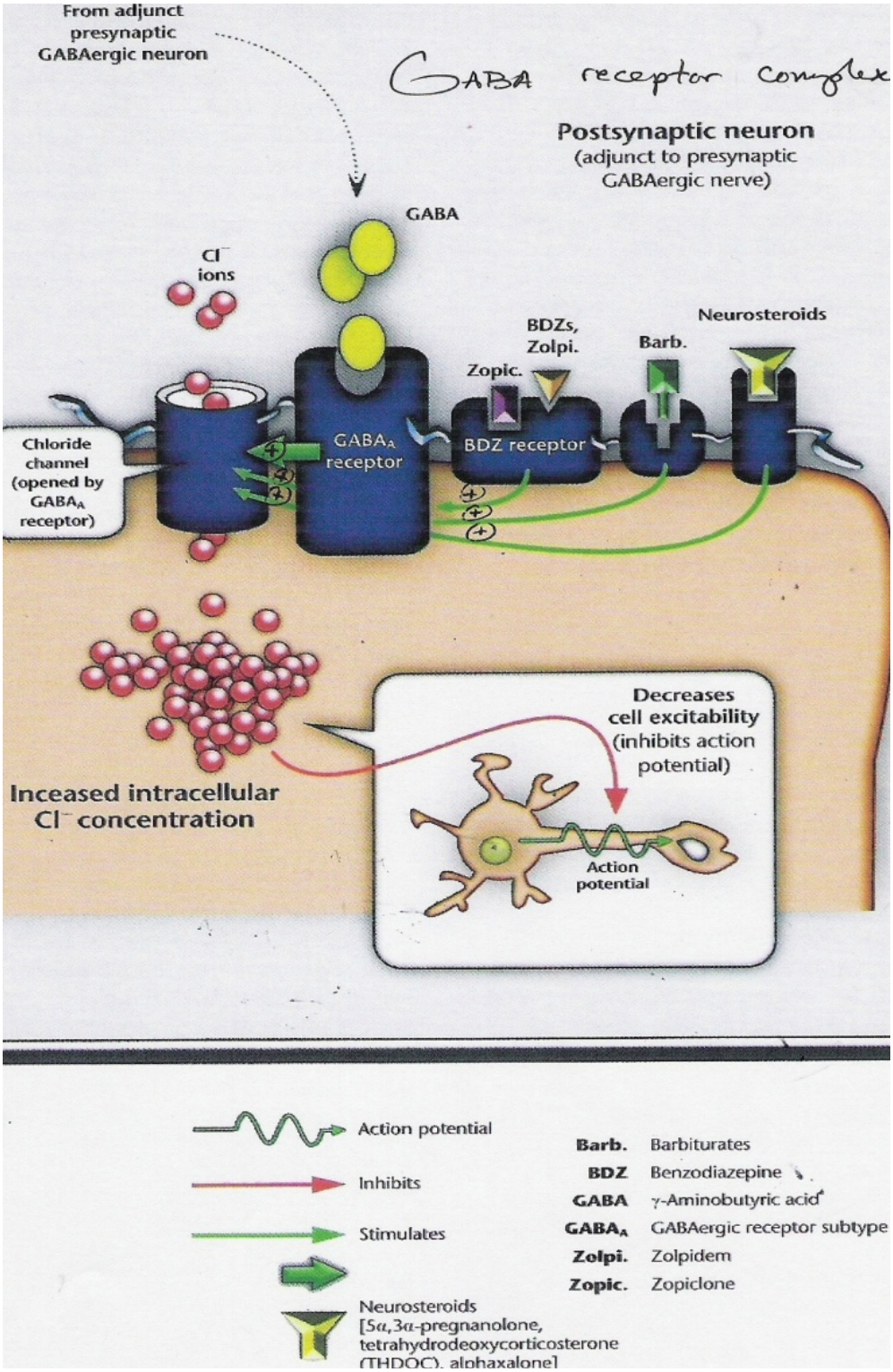
Anxiety and Depression Treatments: GABAergic Medications

Benzodiazepines (BDZ)



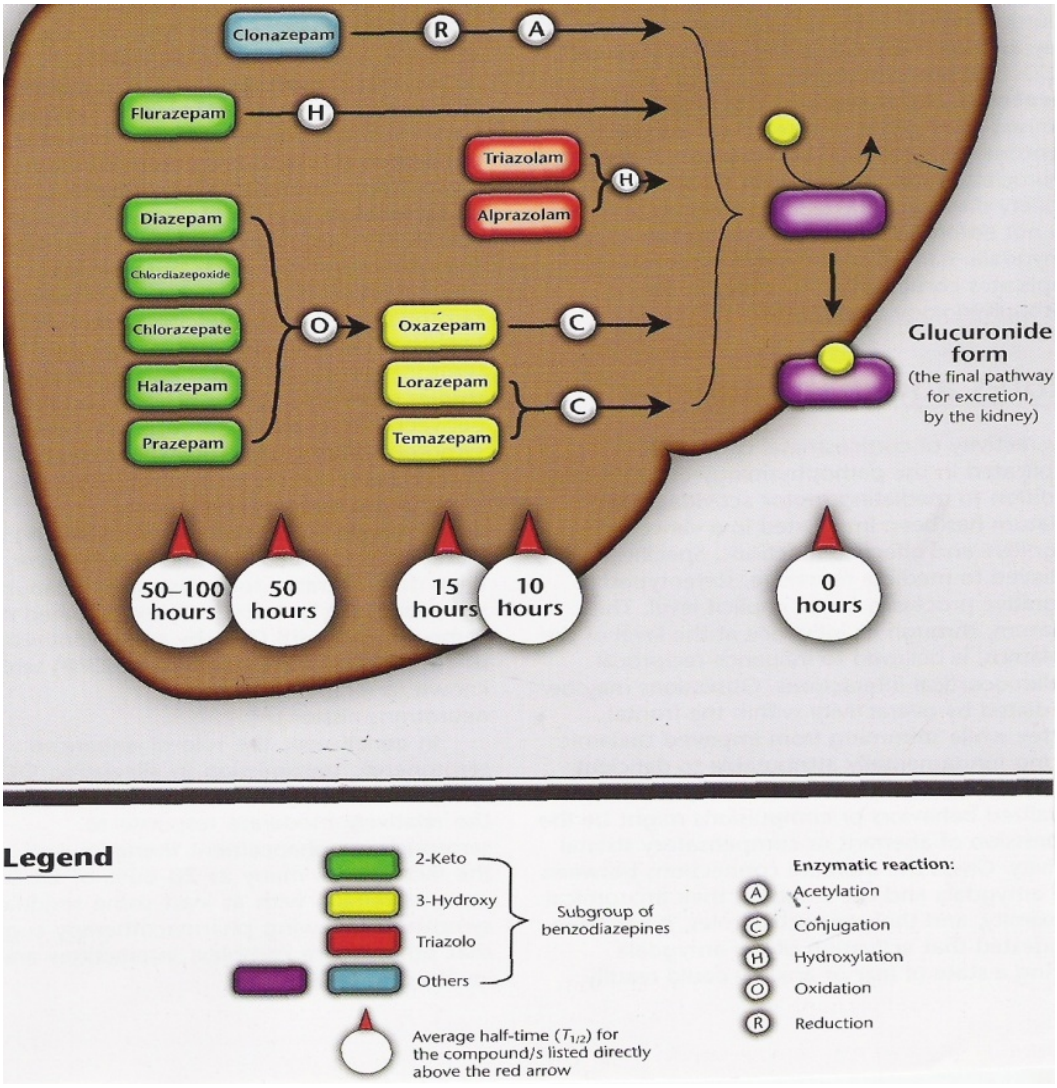
- Include
    - Klonopin (clonazepam)
    - Ativan (lorazepam)
    - Xanax (alprazolam)
    - Valium (diazepam)
    - Librium
    - Versed
    - And many others
- GABAa receptor
    - Chloride ion within the GABAa receptor admits chloride ions that hyperpolarize the neuron and decrease excitation
    - The nearby benzodiazepine binding site on the GABAa receptor increases sensitivity of GABAa receptor
    - The benzodiazepine-GABA complex controls chloride ionophore regulating the influx of negative ions
- Side effects, overall
    - Sedation, fatigue, drowsiness
    - Slurred speech
    - Decreased memory, concentration
    - Slowing of reaction time
    - Double vision
    - Incoordination
    - Tremor
    - Behavioral disinhibition in younger patients: irritability, tantrums, aggression
        - More frequent at higher doses and if brain damage is present
- Notes from 4/21/18 Psychopharmacology lecture
    - *40% of all GABAa receptors have BDZ receptor site (brain makes its own BDZ like compound)*
    - *Adenosine*
        - Calms brain down; sedative/hypnotic effects, muscle relaxant effects
        - Adenosine blockers → increased anxiety (as what happens with theophylline and caffeine)
    - Since 1960's: Librium→Valium
    - Pollack 2014 review (safe and effective)
    - Most scripts from non-psychiatrists for 3 weeks
    - In psychiatry, it's often prescribed chronically
    - Warn people about driving
    - Safe and eff for appropriate
    - Maybe safest and best understood meds of all in psychiatry
    - Controversial use as chronic hypnotic
    - Often underused, often overused
    - Data do not suggest dose escalation over time for most pts who receive therapeutic doses
    - Dose escalation more likely in
        - Substance use
        - Personality disorders
        - People who are chronically angry and feel neglected and isolated or socioeconomically stressed
    - Rational use
        - Use lowest dose for shortest amount of time
        - Do not give to known alcoholics and drug abusers

- Warn about dependence and withdrawal
- Warn about decreased driving skills

- Problems with benzos
  - Abuse
    - Especially huge problem with opioid addicts (they use benzos to increase high and minimize low; no evidence of benzo use → opioid addiction)
  - Common dependence and withdrawal
    - Common after 4-6 weeks of continuous use
    - Correlates with daily dose
    - Risk highest among attendees of self-help groups
    - Severity of discontinuation symptoms depends on
      - Duration of treatment and dose
      - Prior sedative/hypnotic dependence
      - Rate of discontinuation
    - Long lasting withdrawal is rare
  - Interact with alcohol
  - Driving skills and operation of complicated/heavy machinery skills impaired, especially early on; over time, it may be ok, once get right dose and get used to it and if never overlap it with etoh
  - Side effects
    - Sedation
    - Impaired motor speed and coordination
    - Impaired cognition
      - short term memory
      - does not affect long term storage/retrieval
      - dose/potency dependent
      - chronic effect
        - reversible with dose reduction/taper
        - decreased short term recall/long term decline in cognition? (or are anxiety and cognitive side effects more common with age and with cognitive decline?)
        - benefit vs risk
          - memory issues vs reduced anxiety/enhanced sleep
        - is Alz risk increased?
          - case controlled study of 1800 folks >66 yo
            - correlation of prior BDZ use with Alz develpmt
            - Risk moderate (OR 1.5); slightly higher for long acting (OR 1.6)
          - problems
            - no age breakdown
            - no dose breakdown
            - no control for alcohol/drugs (not even asked)
            - no pts seen directly
            - none directly diagnosed with dementia
            - none asked about presence of anxiety disorders
            - and are anxiety/risk for cog SE worse in elderly and in those developing cognitive decline/Alz?

- Follow-up study showed this wasn't the case (2016)

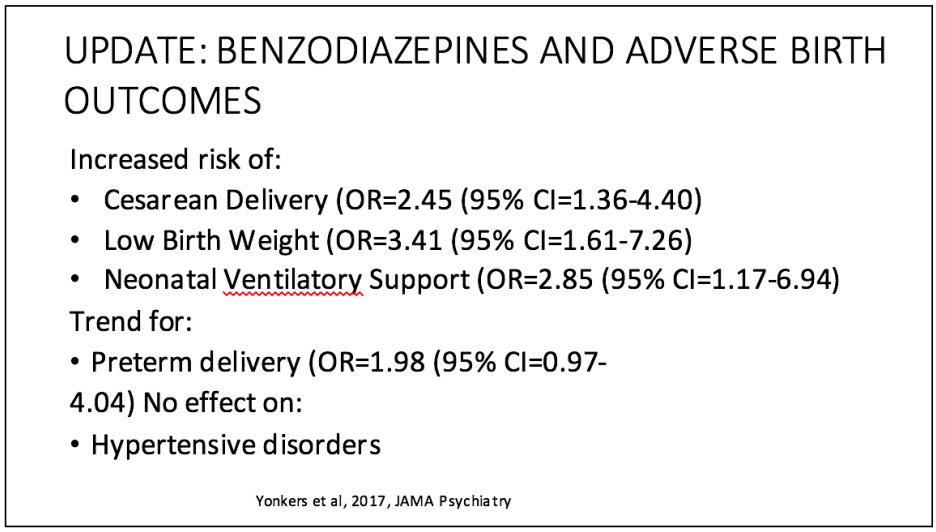
- Falls
  - Especially in
    - Elderly
    - High doses
    - Early phase of treatment
    - When mixed with etoh
  - Falls may decrease via helping with sleep (and less walking at night, less daytime drowsiness, etc). Depends on multiple factors
- Do benzos increase mortality risk (as one study suggested): likely no.



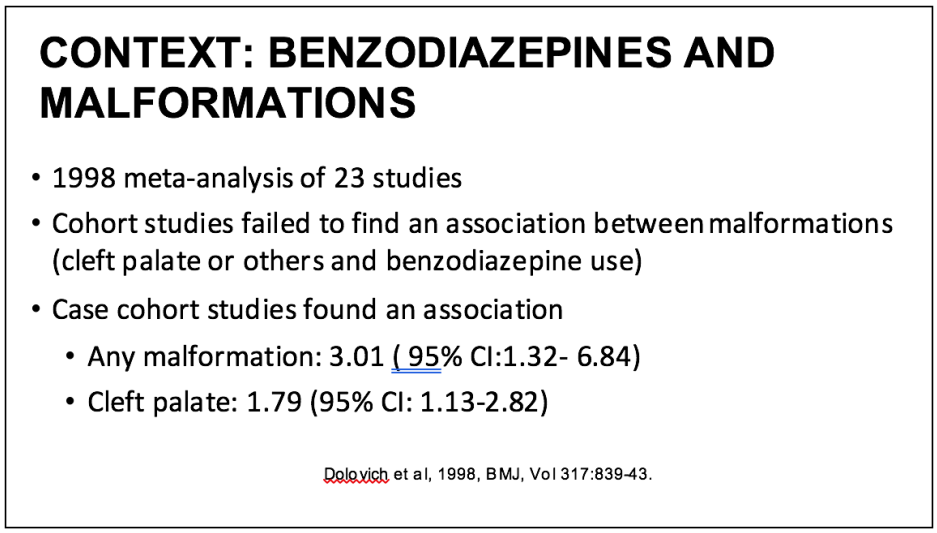
- Specific agents
  - Klonopin (clonazepam)
    - Relatively slow onset of action
    - Half-life 9-20 hours
    - Youth
      - Children:
        - 0.25 mg four times-a-day

        - Adolescents: 0.5 mg four times-a-day; max dose 0.1-0.2 mg/kg/day
        - Riddle et al, 1999 (Kutcher and Reiter, personal communication, 1999): RCT, adolescents with panic disorder; effective
        - Grae et al, 1994: RCT, 0.5-2 mg/day, 15 youth, with anxiety disorders, no difference from placebo
        - Kutcher et al, 1988: open-label, 1 mg/day
- Ativan (lorazepam)
    - Intermediate rapidity of onset
    - Half-life 8-24 hours
    - Metabolized by **UGT 2B15**
- Valium (diazepam)
    - Rapid onset
    - Half-life 20-60 hours
- Xanax (alprazolam)
    - **FDA-approved for GAD**
    - Intermediate rapidity of onset
    - Short half-life
    - Youth
        - Children:
            - 0.125 mg twice-a-day
            - Max dose: 1-4 mg/day
        - Adolescents:
            - 0.25 mg twice-a-day or three times-a-day
            - Max dose 8-10 mg/day
        - Simeon et al, 1992: RCT, 0.5-3.5 mg/day, 30 youth, 88% response in anxiety disorders, 62% placebo;
        - Kutcher et al, 1992: open-label, 0.5-6 mg/day
        - Bernstein et al, 1989: RCT, ~1.4 mg/day, some efficacy in youth with school refusal and depression
- Temazepam
    - Half-life 8-24 hours
- Oxazepam
    - Intermediate rapidity of onset
    - Half-life 3-24 hours
    - Metabolized by **UGT 2B15**
- Librium (chlordiazepoxide)
    - Used since the early 1960's
    - Half-life 72 hours
- Triazolam
    - Rapid onset
    - Half-life 1-5 hours
- Flurazepam
    - Rapid onset
    - Metabolite is desalkyl-flurazepam
        - Half-life 48-120 hours
- Quazepam

- Benzodiazepines in pregnancy



  - **Overall**
    - **No increased risk of major malformations, including cleft palate**
    - **Clonazepam and lorazepam are preferred over diazepam and alprazolam**
    - **Limited long term studies show no adverse effects for pregnancy or lactation**
    - **Monitor baby for transient neonatal complications**



- Other GABAergic agents
  - Ambien
    - Limited human data in pregnancy and lactation
      - No increase in malformations
      - Low risk of neonatal complications
  - Lunesta/Sonata
    - Minimal data in pregnancy and lactation
  - Gaboxadol
    - Structural analog of GABA
    - Non-synaptic GABA-a agonist—called a "selective extrasynaptic GABA agonist" or SEGA.
    - 5-15 mg/day

    - Improves initiation and maintenance of sleep and increases time in restorative slow wave sleep
    - No next day sedation or lethargy, no tolerance, no cross-tolerance with benzodiazepines, no apparent abuse potential
    - However, inconsistent impact on subjective sleep-onset measures
    - Higher incidence of psychiatric side effects than in placebo
    - December, 2007: withdrawn from development as a treatment for primary insomnia
    - Half-life 1.3-1.9 hours; renal excretion
- Gabatril (tiagabine)
    - Lipophilic structural analog of GABA, but does not act directly through GABA mechanisms
    - Binds to the alpha-2 delta protein subunit of voltage-sensitive calcium channels. Specific GABA-reuptake inhibitor (SGRI)
    - Start at 2 mg/PM and slowly increase to max 4 mg twice-a-day
    - Half-life 5-7 hours.
- Neurontin (gabapentin)
    - Lipophilic structural analog of GABA, but does NOT act directly through GABA mechanisms
    - Binds to the alpha-2 delta protein subunit of voltage-sensitive calcium channels. May be GABA reuptake inhibitor.
    - Half-life 5-7 hours; 100% renal elimination
    - 100-900 mg/night for insomnia
- Depakote—evidence of safety and adequacy in children for the treatment of seizures and some evidence for the treatment of bipolar disorder in children; no evidence in treating anxiety disorders (recent small open study (Kinrys, 2003) in the treatment of social anxiety disorder.
- Vigabatrin—inhibits GABA transaminase
- Topamax—acts on GABA at ion-gated channels
- Pregabilin (Lyrica)—a derivative of Neurontin; decreases the release of norepinephrine, glutamate and substance P; some evidence of efficacy in the treatment of anxiety and chronic pain in adults; 100-300 mg twice daily. In a head to head study, Lyrica provided anxiety relief as effectively as Ativan.
- Ocinaplon , GABAa receptor modulator
    - Double blind, placebo-controlled 2-week trial doses of 180-240 mg); safe and effective (Lippa, 2005)
- Valerian
    - Extract of Valeriana officinalis
    - Several potentially active components, including valerinic acid, other sesquiterpenes, valepotriates
    - May reduce sleep latency and improve total sleep time
    - Extracts of 2-3 mg taken 1-3 times-a-day in a tincture or tea
    - Side effects
        - Sedation, drowsiness
        - Unsteadiness
        - Dizziness
        - Overdoses: cramping, tremor, unsteadiness, confusion
    - Mechanisms of action of valerenic acid (derived from valerian root):
        - inhibition of GABA catabolism
        - binds to GABA receptors
        - 5HT1a receptor activity
        - actions on adenosine receptors

Benzodiazepine use and risk of mortality among patients with schizophrenia: a retrospective longitudinal study

Cynthia A Fontanella, John V Campo, Gary S Phillips, Danielle L Hiance-Steelesmith, Helen Anne Sweeney, Kwok Tam, Douglas Lehrer, Robert Klein, Mark Hurst

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OBJECTIVE: This study examined the association between benzodiazepine use alone or in combination with antipsychotics and risk of mortality in patients with schizophrenia.

METHODS: A retrospective longitudinal analysis was performed using Medicaid claims data merged with death certificate data for 18,953 patients (aged 18-58 years) with ICD-9-diagnosed schizophrenia followed from July 1, 2006, to December 31, 2013. Cox proportional hazard analyses were used to estimate the risk of all-cause mortality associated with benzodiazepine use; adjustment was made for a wide array of fixed and time-varying confounders, including demographics, psychiatric and medical comorbidities, and other psychotropic medications.

RESULTS: Of the 18,953 patients diagnosed with schizophrenia, 13,741 (72.5%) were not prescribed a benzodiazepine, 3,476 (18.3%) were prescribed benzodiazepines in the absence of antipsychotic medication, and 1,736 (9.2%) were prescribed benzodiazepines in combination with antipsychotics. Controlling for a wide array of demographic and clinical variables, the hazard of mortality was 208% higher for patients prescribed benzodiazepines without an antipsychotic (HR = 3.08; 95% CI, 2.63-3.61; P < .001) and 48% higher for patients prescribed benzodiazepines in combination with antipsychotics (HR = 1.48; 95% CI, 1.15-1.91; P = .002). Benzodiazepine-prescribed patients were at greater risk of death by suicide and accidental poisoning as well as from natural causes.

CONCLUSIONS: Benzodiazepine use is associated with increased mortality risk in patients with schizophrenia after adjusting for a wide range of potential confounders. Given unproven efficacy, physicians should exercise caution in prescribing benzodiazepines to schizophrenic patients.

Sedative Hypnotics and the Risk of Falls and Fractures in the Elderly

Chittaranjan Andrade

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Older age, poor sleep, and the use of the "Z" sedative hypnotic drugs (zopiclone, eszopiclone, zolpidem, and zaleplon) commonly go together. Each of these can increase the risk of falls and fractures through mechanisms related to cognitive and psychomotor impairment. A recent systematic review and meta-analysis examined the risk of falls and fractures associated with the use of the Z-drugs. The authors of that meta-analysis identified 14 relevant cohort and case-control studies. They found that Z-drugs increased the risk of falls in 2 out of 3 studies that provided information on this outcome; in the third, the increased risk narrowly missed statistical significance. Z-drugs increased the fracture risk in 9 of 10 studies (odds ratio [OR] = 1.63; 95% confidence interval [CI], 1.42-1.87). In secondary analyses, the fracture risk associated with the use of Z-drugs was elevated in studies that included a control group diagnosed with insomnia (OR = 1.28; 95% CI, 1.08-1.53) as well as in studies of samples restricted to subjects aged > 65 years (OR = 1.70; 95% CI, 1.36-2.12). In 2 studies, zolpidem was associated with an increased risk of injuries. Whereas confounding by indication may explain a part of the risk of falls and fractures, there is reason to consider that Z-drugs augment the risk. Either way, the use of Z-drugs emerges as a clear marker for the risk of falls and fractures. Nonpharmacologic interventions for insomnia should therefore be considered as alternatives to the use of Z-drugs. Finally, patients prescribed Z-drugs and caregivers of these patients should be warned about the risk of falls and fractures and counseled about practical measures that can reduce the risk.