Clinical Review of Social Anxiety, Generalized, and Hoarding Disorders

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Supplemental Research Concerning Benzodiazepine Prescribing

Medication (Baldwin, 2020).

- Anxiolytics
  - Antidepressants
    - SSRI's or SNRI's – Somewhat effective for mild GAD
      - First-line Medications for Acute GAD (He et al., 2019) - China
        - Meta-analysis of 41 studies
        - Hamilton Anxiety Scale change from baseline
        - Results
          - Cymbalta (duloxetine) & Lexapro (escitalopram) most effective
          - Trintellix (vortioxetine) worst response rate that Cymbalta or Lexapro, but better acceptability & tolerability
    - Thymanax (agomelante) - Somewhat effective for acute GAD
      - Thymanax (agomelante) for Acute GAD (Stein, 2021) – South Africia
        - Meta-analysis: Thymanax comparable to Lexapro (excitalopram)
        - Not available in USA
        - NE, DA, Melatonin agonist & 5HT2C antagonist
    - Buspar (buspirone) – Somewhat effective for acute GAD
    - Lyrica (pregabalin) – Somewhat effective for acute GAD
    - Seroquel (quetiapine) – Minor effectiveness, but substantial side-effects
  - Benzodiazepines – Most effective for chronic GAD
    - Valium
    - Xanax (alprazolam)
    - Ativan
    - Klonopin

Little empirical evidence not to use benzodiazepines for anxiety

- Unsupported beliefs about benzodiazepines (Silverman, et al. 2021) - USA
  - BZO prescribed for anxiety are likely to be abused
    - No empirical evidence that pts without a history of substance abuse will abuse BZO
  - Only about 17% of pts with anxiety disorders *overuse* BZO's
    - Overuse is not abuse
    - Overuse due to:

        - Suboptimal prescribing
        - Poor prescriber-patient communication
        - Pts attempting to eradicate all anxiety with meds
    - Pts develop tolerance to BZO's & need to increase dose
        - No empirical evidence
    - Pts. develop tolerance to sedating & psychomotor effects of medication; not the anti-anxiety effects of the meds
    - BZO's are dangerous due to overdose potential
        - OD deaths on BZO's alone are rare
    - Extremely high levels of OD deaths are due to combination of BZO's, opioids, ETOH, etc.
    - Long-term use of BZO's leads to dependence
    - Physiological withdrawal is only one of eleven substance abuse symptoms
    - SNRI's, anti-psychotics, etc. demonstrate withdrawal symptoms
    - Gateway Theory of Addiction (Kandel, 1975)
        - No empirical support for the theory (Degenhart et al., 2010)

- **Comparative efficacy of benzodiazepines and antidepressants** (Beyer, C. et al., 2024) - USA
    - Efficacy of benzodiazepines vs antidepressants of 24 randomized controlled studies
        - BZO's = Five studies
        - Antidepressants = 18 studies
    - BZO's were significantly more effective than antidepressants in reducing GAD psychological & somatic symptoms ($Chi^2 = 5.81$, $p = 0.02$),
    - Conclusion
        - BZO's were more effective than antidepressants in treating GAD
        - BZO's had less side-effect than antidepressants

Benzodiazepines in the treatment of GAD (Fernandes, et al., 2025). - Portugal

- Method
    - Systematic review and network meta-analysis
    - 56 placebo control studies. N=7,556 participants
- Results
    - 861 GAD symptoms comparisons of BZO's efficacy
        - 40 = very low
        - 7 = low
        - 814 = very high
    - All BZO's were significantly better than placebo
    - No significant differences in treatment effectiveness among BZO's
    - No significant treatment tolerances of BZO's vs. placebo
- Conclusions
    - BZO's are an efficacious treatment for GAD & have favorable safety profiles

Effectiveness of long-term benzodiazepines for GAD (Chang, et al., 2024). - China

- Mechanisms of benzodiazepines (BZO's)

- Inhibition of the Corticotrophin-Releasing Hormone (CRH) by BZD
  - Reduces adrenocorticotropic hormone (ACTH) produced by the pituitary
    - Dampens the Hypothalamic-Pituitary-Adrenal (HPA) Axis
    - Reduces cortisol for only three weeks
- BZO's modulates the regulatory effect of the cannabinoid system on neuroendocrine function
  - Diazepam (Valium) plus endogenous cannabinoid reuptake inhibitor significantly reduces plasma corticosterone levels
  - Temazepam, lorazepam, & clonazepam also modulates the HPA axis.
  - Lorazepam & clonazepam suppresses stress-induced interleukin-6 (IL-6) levels leading to reduced neuroinflammatory activity
- BZO's reduces neuroinflammation via GABAergic processes

- BZO's rapid reduction of anxiety symptoms
  - BZO's demonstrated significantly greater efficacy in treating GAD vs Placebo and antidepressants
    - Citalopram, Imipramine, Maprotiline, Vilazodone and Vortioxetine
  - Tolerance to the anxiolytic effects of BZO's does not develop over time
  - Efficacy of long-term treatment of GAD remains consistent over time

- Individuals with a history of substance abuse should not be prescribed BZO's

- **CBT plus valium** (diazepam) (Power et al., 1990) - UK
  - Comparison among treatment groups: CBT; CBT + placebo; CBT + diazepam
    - CBT + diazepam was the most effective treatment
      - CBT + Buspar: Buspar did not add any treatment benefits (Lader & Bond, 1998) - UK
      - CBT + Effexor (venlafaxine): Effexor did add any additions improvements
  - Drop-out rate
  - 16% (Gersh et al., 2017)
  - Difficulty concentrating (Hallion, et al., 2018) - USA
  - Training in mental imagery may help reduce worry (Skodzik, et al., 2017) - Canada

- **Long-term use of benzodiazepines in Denmark** (Wium-Andersen et al., 2023)
  - N = 950,767 benzodiazepine receptor agonist (BZO's) Danish patients
    - 15% (142,615) became long-term users over one year
    - 7% (50,642) became long-term users over three years
    - 3% (28,523) became long-term users over seven years
    - 7% of BZO's (3,545 patients) escalated doses above recommended levels over-3years of continuous use
    - *3,545/950,767 = 0.37% of total sample escalated dose*
  - Psychiatric comorbidity, *especially substance abuse disorder* was associated with dose escalation
  - Conclusions

- This study does not support the belief that BZRA use frequently results in dose escalation

- Long-term BZO's should be used for individuals with treatment resistant anxiety, especially chronic Generalized Anxiety Disorder

Long-term benzodiazepine use in Finland (Taipale et al., 2020)

- N=129,732 new benzodiazepine (BZO) individuals in Finland
  - First use of BZO during 2006
  - Age ≤ 18 years old
  - Mean age = 52.6 (17.7)
  - 78,017 were women (60.1%)
  - 28,781 (22.0%) became long-term users at the six-month follow-up
  - More older (≥ 60 years old) became long-term users (11,805 – 33.7% of older cohort) than younger users (16,781 – 17.7%)
  - Medications:
    - Top four BZO's prescribed (most to least prescribed)
      - zopiclone
      - oxazepam
      - temazepam
      - alprazolam

  - Long-term users disorders
    - Anxiety
    - SZO
    - Bipolar disorders
    - Comorbid disorders
      - Hypertension
      - Cancer
      - COPD
      - Parkinson disease
      - Alzheimer's disease
      - Chronic heart Failure
      - Inflammatory bowel disease
      - MS
      - ADHD

  - Reasons for using BZO's
    - Lack of more effective and safer alternative to BZO's
    - SSRI's & SNRI's
      - More side-effects
      - Less effective than BZO's

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