The role of flumazenil infusion in the treatment of benzodiazepine withdrawal

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Disclosures

- I have received honoraria, fees and/or provision of professional development/funding resources from:
  - Servier
  - Otsuka/Lundbeck
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  - Camurus
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  - AHPRA
  - So What Research

- I wish to acknowledge the generosity and participation of the patients, carers, sponsors and facilities who made the research possible.
Benzodiazepine/Z-drug Dependence

- Often an iatrogenic problem in psychiatric and general practice.

- Exacerbation of most high-prevalence psychiatric conditions and accelerates some substance use disorders.

- Increase in all-cause mortality, including:
  - Falls, seizures, misadventure
  - Motor vehicle accidents
  - Overdose risks with opioids
  - Suicide (triples suicide risks in veterans)

- Pharmacoeconomic disadvantages and performance reduction

- Cognitive risks short and long term
<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lader &amp; Morton 1992</td>
<td>Pilot study n = 11</td>
<td>2 mg over 3 h, administered as 0.2 mg bolus doses</td>
<td>Flumazenil successful in alleviating long term symptoms of benzodiazepine withdrawal</td>
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<tr>
<td>Saxon et al 1997</td>
<td>Double-blind pilot n = 10</td>
<td>1 mg total in five doses over 1 h X 2</td>
<td>Flumazenil successful in alleviating long term symptoms of benzodiazepine withdrawal</td>
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<tr>
<td>Gerra et al 1993</td>
<td>Single-blind placebo controlled n = 36</td>
<td>0.5 mg 4 x per day for 4 days, then 2 x per day for 3 days</td>
<td>Flumazenil group had significantly reduced withdrawal symptoms and anxiety</td>
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<tr>
<td>Gerra et al 2002</td>
<td>RCT n = 50</td>
<td>1mg 4h⁻¹ infusion twice daily for 8 days with oxazepam taper</td>
<td>Flumazenil group had significantly reduced withdrawal symptoms, improved programme completion and reduced relapse rates</td>
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<tr>
<td>Hood et al 2009</td>
<td>Case series n = 16</td>
<td>2mg 24h⁻¹ continuous i.v. infusion with oxazepam. tapering for 4 days</td>
<td>Patients had reduced withdrawal symptoms; successfully completed withdrawal. I.V. infusion problematic</td>
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<tr>
<td>Quaglio et al 2012</td>
<td>Case series n = 29</td>
<td>1.35 mg 24h⁻¹ continuous i.v. infusion with clonazepam for 7 days</td>
<td>All patients completed the withdrawal programme with 51% abstinent at 6 months</td>
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<tr>
<td>Hulse et al 2012</td>
<td>Case series n = 23</td>
<td>4mg 24h⁻¹ continuous s.c. infusion with oxazepam taper for 4 days</td>
<td>Subjective withdrawal symptoms well managed. High patient acceptance. Improvement on measures of psychological distress over withdrawal period</td>
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</tbody>
</table>
Phase III Trial

Subcutaneous Flumazenil

- Neutral allosteric modulator, changes the GABA-A set-point
- Limits α-4 subunit containing GABA-A gene expression, yet agonises it concurrently
- Reduces inter-ictal activity
- Probably impossible to overdose on
Randomised double-blind placebo-controlled crossover trial

- 4 days x 2 (active)
- 4 days x 2 (inactive)
- CIWA-B
- Phenytoin 100mg tds
- 3 additional months of follow up

- 96hr standard infusion = 160 mcg per hour.
- Comparison to Italian balloon infusers: 7 days at 40 mcg per hour
Unverified Results

- **First Run n=9**
  - 9/9 (100%) abstinent at 3 months
  - Belies the true statistics

- **Second Run n=8**

- **Third Run n=3**
  - 3/3 (100%) abstinent at 3 months

- **Fourth Run**
  - 3/3 (100%) abstinent at 3 months

- **Fifth Run**
  - 2/2 (100%) abstinent at 3 months but 1 very unhappy after relapsing with alcohol use disorder which wasn’t fully disclosed prior to entry
Outcomes

- Initial impressions
  - No significant side effects
  - Strong signal of efficacy (difficulty with blinding)
  - Duration of active treatment is possibly too short
  - Strong support from inpatient nursing staff who were initially reluctant

- Unexpected improvement in a few other conditions, which may be the subject of discussion or future studies
Thanks!