Benzodiazepine prescribing in opioid agonist therapy: the risks and the benefits

TAE WOO PARK
DEPARTMENT OF PSYCHIATRY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
Acknowledgements

Mentorship team: Richard Saitz
Mari Lynn Drainoni
Alexander Walley

Research team: Jennifer Sikov
Marisa Aurora

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Benzodiazepine prescribing attitudes

![Figure: The spectrum of attitudes toward prescribing benzodiazepines]

- **Conservative**: Only for alcohol withdrawal and acute mania in supervised setting
- **Moderate**: Short-term use for insomnia, panic in those without active substance use disorder (SUD)
- **Liberal**: Long-term use for patients with psychosis or anxiety, even those with an SUD history

Geppert, 2007
A benzodiazepine epidemic?

Perspective
Our Other Prescription Drug Problem

Anna Lembke, M.D., Jennifer Papac, M.D., and Keith Humphreys, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

Lembke, 2018
Benzodiazepine-related mortality

![Graph showing the increase in deaths involving benzodiazepines from 1999 to 2015. The graph includes bars for total deaths, male deaths, and female deaths. The number of deaths increases significantly over the years.](image)

NIDA
Benzodiazepines and opioids

Benzodiazepines are commonly involved in opioid analgesic overdose cases

Benzodiazepines can increase respiratory depression caused by opioids

Jones, 2013
White, 1999
Benzodiazepines and risk of opioid overdose

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td><strong>Benzodiazepine exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.00 (ref)</td>
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<tr>
<td>Currently prescribed</td>
<td>3.72</td>
<td>3.36-4.12</td>
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<tr>
<td><strong>Benzodiazepine dose</strong></td>
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<tr>
<td>&gt;0-10</td>
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<tr>
<td>&gt;10-20</td>
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<td>1.34-1.90</td>
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<td>&gt;20-30</td>
<td>2.27</td>
<td>1.86-2.79</td>
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<td>&gt;30-40</td>
<td>2.47</td>
<td>1.96-3.11</td>
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<tr>
<td>&gt;40</td>
<td>2.93</td>
<td>2.29-3.76</td>
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</tbody>
</table>

Park, 2015
Benzodiazepines and overdose in opioid agonist therapy

Benzodiazepine use in methadone maintenance treatment is associated with increased risk of overdose death

- Cohort study in Scotland
- Case-control study in UK

McCowan, 2009
Oliver, 2007
Benzodiazepine prescribing in opioid agonist therapy

Benzodiazepine prescribing in opioid agonist therapy varies by region
- Buprenorphine: 11-39%
- Methadone: 7-24%

Variation in practice may reflect prescriber uncertainty

Park, 2014
Efficacy of benzodiazepines

Meta-analysis for GAD, panic disorder, and SAD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
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<tr>
<td>SNRIs</td>
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<tr>
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<td>CBT + drug</td>
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<td>Relaxation</td>
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<td>CBT/exposure, individual</td>
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<td>Pill placebo</td>
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<td>Waiting list</td>
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</tbody>
</table>

Bandelow et al, 2015
Anxiety and relapse

Anxiety associated with relapse and poorer treatment outcomes in substance use disorders

- Five times increased risk of re-admission for alcohol treatment
- Associated with worse addiction treatment outcomes

Tomasson, 1998
Compton, 2003
Benzodiazepines and treatment retention

Benzodiazepine prescription associated with increased methadone treatment retention in one clinic

Benzodiazepine prescription predicted one year treatment retention in buprenorphine treatment in BMC’s Department of Psychiatry

Bakker, 2017
Montalvo, in preparation
Benzodiazepine use in opioid agonist therapy

POTENTIAL RISKS:
Overdose death
Addiction to benzodiazepine

POTENTIAL BENEFITS:
Treats anxiety
Improves treatment retention
Qualitative study: Benzodiazepine use in opioid agonist therapy
Research questions

Among patients who receive opioid agonist therapy and have used benzodiazepines, what are the:

- Motivations for benzodiazepine use?
- Patient understanding of the risks and benefits of benzodiazepine use?
- Barriers and facilitators for discontinuing benzodiazepine use?
Methods

18 participants

Inclusion criteria: Adults receiving opioid agonist therapy, have regularly used benzodiazepines, and speak English

Purposive sampling from an office-based buprenorphine clinic and a methadone clinic

Interviews were conducted and transcribed by the PI and 2 research assistants

Interview guide was a semi-structured interview based on a priori topic areas
Analysis

All transcriptions were reviewed by the PI and entered into Nvivo

Data analysis was largely guided by thematic analysis

Open coding by the PI and one research assistant to develop a codebook

After coding, identified major themes and relationships between them
Study sample

N=18
Median age: 41 years old
11 females, 7 males
11 receiving methadone, 7 receiving buprenorphine
Median length of time on opioid agonist therapy: 5 years
Motivations: to feel calmer

“Without the benzos, I feel like I had a lot more panic attacks. I had a lot more going on in my head and I felt like I couldn’t get my head to stop racing, so I would say that I was a lot more pent up and fearful I guess, when I wasn’t on the benzos.”
Motivations: to get high

“When I got on methadone, yes. Definitely because I didn’t know that when you take a benzo on methadone, you get this high feeling because they say it’s like twice as much as you take. So if you take 1 Klonopin, it has the effect of two. So yeah, in the beginning definitely. I definitely took them to get that high feeling and get a head change.”
Consequences: oversedation

“When I overdo ‘em, I’m falling asleep on the train, getting woken up. There’s been periods where I get on the train at 3 o clock in the afternoon and I get woken up at 1 in the morning, trying to get off the train. So it’s no fun, you know what I mean? It’s just not the high that I like.”
Consequences: loss of memory

“Yes. Forgetting stuff. Forgetting where I put things. Losing time and not knowing what happened during that time. Which is really scary.”
Consequences: helps to feel normal

“Just simple little things like walking down the street would really bother my anxiety and now I don’t have that feeling anymore. I feel like I’m able to do normal things.”
Consequences: helps with drug cravings

“Well you want to look out a little bit more for people that are on Suboxone or methadone because they’re addicts. And if they have too many panic attacks, the first thing they’re going to think about, like I do, is using.”
Learning to use benzodiazepines appropriately

Misuse of benzodiazepines during illicit opioid use:

- Interviewer: “Did it boost the high? Of the opioids?”
- Participant: “Of the opiates? Of course, of course.”
- I: “It did. So when you used them both at the same time...”
- P: “One of the main reasons was to, when mixing the two... if you take the benzo before the opiate it puts you into an instant nod...”
Learning to use benzodiazepines appropriately

Misuse of benzodiazepines when taking methadone:

- “I was taking them all at once, whenever I was prescribed, you know? And for the day, which I don’t remember at the time when it was, but I would take them all at once. I was mixing them with the methadone. I wasn’t taking them correctly. And now, you know, I span them out throughout the day.”
Learning to use benzodiazepines appropriately

A benzodiazepine prescription is a privilege:

- “When I finally earned my prescription for Klonopin, I took it as prescribed. I’ve always taken it as prescribed because there is no point. And yet, I mean I’m not gonna lie, when I first got it, I’m sure I screwed around at the very beginning but the way I look at it now is, so many people would kill to just be able to have this (prescription).”
Preliminary conceptual framework

MOTIVATION

Inappropriate  Appropriate

RECOVERY PROCESS

Active illicit opioid use  Initial treatment phase  Later treatment phase

CONSEQUENCES

Worse  Better

Capacity to take benzodiazepines responsibly
Benzodiazepine prescribing attitudes

Figure

The spectrum of attitudes toward prescribing benzodiazepines

Conservative
Only for alcohol withdrawal and acute mania in supervised setting

Moderate
Short-term use for insomnia, panic in those without active substance use disorder (SUD)

Liberal
Long-term use for patients with psychosis or anxiety, even those with an SUD history

Geppert, 2007
Conclusions

Prescribing benzodiazepines has both risks and benefits in patients receiving opioid agonist therapy

Benzodiazepines should be considered as a potential treatment

It may be safer to treat patients with benzodiazepines when they are more stable in opioid agonist therapy
References


7. Montalvo C. Long Term Retention in Outpatient Behavioral Health Clinic with Buprenorphine. Presented at the: 7th Annual BU-CTSI Symposium; 2018; Boston, MA.


