Benzodiazepine Information Coalition
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September 1, 2017

BIC Position Statement on the Use of Benzodiazepines in Patients Receiving Buprenorphine Treatment

Background:

The danger of combining benzodiazepines and opioids is well known. In August 2016, the FDA issued a boxed warning, citing that the combination may lead to "excessive sleepiness, respiratory depression, coma, and death".[1] The addition of benzodiazepines to opioids increases the risk of psychomotor impairment, overdose, and suicide.[2-5] Nearly 30% of overdose deaths associated with opioids also involve benzodiazepines.[3] Benzodiazepine use is also associated with lower success rates with medication assisted treatment (MAT) of opioid use disorder. [5]

Deaths due to the combined use of buprenorphine and benzodiazepines is supported by preclinical laboratory research that suggests that co-administration of benzodiazepine agents can remove buprenorphine's "protective ceiling" effect on respiratory depression in the same pattern as co-administration with methadone.[6]

A series of case reports in France documented 6 overdose deaths due to the combination of buprenorphine and benzodiazepines. [7] Another 12-month study documented an increase in the frequency of ED visits related to the combination of buprenorphine and benzodiazepines.[8] This harmful association between benzodiazepines and buprenorphine is confirmed independently by emergency room data.[9]

Some prescribers have advocated for concurrent benzodiazepine maintenance during buprenorphine substitution management. One recent single-practice case study suggested improved treatment adherence and lower mortality for patients who combined benzodiazepine use with opioid maintenance therapy. That retrospective report is based on plausible but untestable assumptions that benzodiazepine treatment combined with opiate substitution treatment must have terminated when the practice closed, but during previous treatment, "supplementation with illicit benzodiazepines (based on self-report) seemed rare."[10] In contrast, the larger Harvard report found no increase in treatment retention among patients who concurrently used benzodiazepines with buprenorphine treatment, but the combined therapy was associated with significantly more emergency

room visits and accidental injuries, especially among female patients during the 12 month study.[8]

Of note, the FDA package insert recommends no use of sedatives while taking buprenorphine. There is a dearth of literature regarding the specific combination of buprenorphine and benzodiazepines, and we endorse the need for further long-term prospective studies.

Studies estimate that between 18-50% of opioid users presenting for MAT are also misusing benzodiazepines.[5] Benzodiazepines alone carry with them the risk of tolerance, suicide [11,12], seizures after abrupt cessation, and a protracted withdrawal syndrome that may last for months in some individuals. Discontinuation symptoms following cessation of benzodiazepines can be encountered even in those who take these medicines strictly according to prescription[13].

We recognize that this problem is extremely complex. Many of those with opioid use disorder and/or dependency present with benzodiazepine misuse or dependency, while fear and other symptoms of anxiety are common features of opioid withdrawal. Benzodiazepines are not recommended as first line treatment for Anxiety Disorders, Bipolar Disorder or Posttraumatic Stress disorder, all of which are more frequently associated with Substance Use Disorders.

Because benzodiazepines can cause sedation, cognitive effects, dependence, and loss of anxiolytic efficacy, guidelines for management of anxiety disorders generally support adjunct benzodiazepines only when necessary, with restriction to short-term, scheduled dosing, in those with low risk of misuse.[8, 14]

We have reviewed the 2015 ASAM National Practice Guidelines for the Use of Medications in the Treatment of Addiction Involving Opioid Use and the 2013 IRETA report entitled Management of Benzodiazepines in Medication-Assisted Treatment. Most of these guidelines are very reasonable, with the exception of the recommended rate of benzodiazepine tapering. We have listed our recommendations below for the management of buprenorphine and benzodiazepines based on our review of the literature, published guidelines and our experience with benzodiazepines.

Recommendations:

1. According to ASAM guidelines, patients using benzodiazepines should “receive more intensive monitoring during office-based treatment with buprenorphine to minimize risk of adverse events. Alternatively, patients with these co-occurring disorders may be better treated in a setting with greater supervision”.[15]
2. Outpatients who are chemically-dependent on benzodiazepines:

a. Should not have their medication stopped abruptly due to risk of seizure and death,[13] and the benzodiazepine should be tapered once reaching a stable dose of buprenorphine.[16] Concurrent intensive psychological therapy is advisable.

b. Long-term, dependent benzodiazepine users should be tapered. This process may require a year or more in a few highly sensitive individuals. We differ from the IRETA guidelines in that we recommend tapering at a rate of <5-10% every 2-4 weeks based on patient symptoms.[13,17-18]

c. Consider changing to a long-acting benzodiazepine for tapering. We recommend diazepam according to the Ashton manual due to the ability to make small dosage reductions.[13]

3. Some success in safely reducing post-acute benzodiazepine withdrawal symptoms has been reported with buspirone, melatonin, beta-adrenergic blockers, and anticonvulsant agents.[19] Inpatient detoxification may be particularly indicated for benzodiazepine dependent patients with severe comorbid mental illness that is compromised by ongoing benzodiazepine use. In the inpatient setting short-term use of phenobarbital may be effective for detoxification.[20]

4. Patients should not be continued on benzodiazepines long-term due to the risk of adverse effects as described above.

5. Physicians should undergo training regarding the safe tapering of benzodiazepines, especially in the context of opioid use.

6. Patients should be given informed consent, intensive education, and literature about the extensive risks of benzodiazepines combined with MAT[5]

7. Any patient presenting for MAT who is not already taking benzodiazepines should not be given a prescription for a benzodiazepine.[5]

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