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Research paper

Benzodiazepine withdrawal in pregnant women with opioid use disorders: An observational study of current clinical practices at a tertiary obstetrical hospital

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ABSTRACT

Background: As more patients are admitted for medical complications related to opioid use disorders, physicians are called upon to manage withdrawal from co-occurring substance use disorders. We present an observational study of pregnant women with comorbid opioid and sedative-hypnotic use disorders hospitalized for benzodiazepine withdrawal.

Objectives: Our primary aims were to assess current practices in withdrawal management in the perinatal period in patients admitted to an antepartum unit at a tertiary care setting with comorbid opioid and sedative-hypnotic use disorders; specifically, to identify patterns of withdrawal management, including the type of withdrawal protocol utilized, the total dosage of benzodiazepine used during that protocol, to assess patient variables associated with higher dosing, and to analyze neonatal outcomes.

Methods: A chart review of psychiatry consultations for benzodiazepine withdrawal in antepartum women was conducted for patients seen over a 3 year period with manual extraction of patient age, number of pregnancies, modality of benzodiazepine withdrawal management (symptom-triggered versus standing benzodiazepine taper), total amount of benzodiazepine used during the detoxification period, active methadone conversion versus stable methadone dose on admission, and average fetal heart tones during the withdrawal detoxification period.

Results: The majority of patients (83%) were undergoing methadone conversion or were stable on methadone maintenance. The mean cumulative benzodiazepine dose used was 8.3 ± 10.5 mg in lorazepam equivalents. Women placed on a symptom-triggered protocol received lower mean benzodiazepine doses (2.4 ± 6.9 mg) compared to those on a benzodiazepine taper in conjunction with a symptom-triggered protocol (17.9 ± 20.6 mg; $p < 0.001$). Women who started methadone during admission tended to receive lower mean lorazepam doses (7.1 ± 10.4) compared to women admitted on stable outpatient doses of methadone (11.5 ± 10.6; $p = 0.07$). Using *t*-test and chi-square analyses on a subgroup of women (N = 50), no differences were found between women placed on a taper compared to a symptom-triggered scale alone in neonatal outcomes such as APGARS, NICU admissions, and preterm delivery with low rates of complications in both groups.

Conclusions: A symptom-triggered benzodiazepine withdrawal protocol was associated with significantly lower total benzodiazepine use compared to standing taper regimens. Women started on methadone during admission tended to receive lower lorazepam doses compared to women admitted on stable doses of methadone. Preliminary maternal/neonatal outcomes were similar between symptom-triggered and taper groups.

1. Introduction

The opioid crisis has called national attention to addiction in the United States. As more patients are admitted for medical complications related to opioid use disorders, physicians are called upon to manage withdrawal from co-occurring substance use disorders. Like opioid use, sedative-hypnotic use has similarly escalated in recent years, with the misuse of benzodiazepines and narcotics together increasing 570% from 2000 to 2010 [1]. Additionally, data from SAMHSA indicates that in the non-pregnant population, benzodiazepine-related hospital admissions have increased from 1.3% of total substance use admissions in 1998 to 3.2% of total admissions in 2008. These percentages correspond to growth of benzodiazepine-related hospital admissions from 22,400 to 60,200 over ten years. Of these benzodiazepine-related hospital admissions, 95% involved another substance and in 83% of cases, benzodiazepines were the secondary drug of misuse [2]. As such, effective strategies for management of withdrawal from multiple substances become imperative for the hospital-based physician.

While management of opioid use disorders in pregnancy has been studied extensively [3], rates of benzodiazepine misuse in pregnancy are not clearly known, and clinical management strategies are largely anecdotal and found in the case literature [4]. Abrupt discontinuation of benzodiazepines poses life-threatening risk, yet there are no studies that have investigated benzodiazepine withdrawal management in the perinatal period.

Benzodiazepines are agonists at the receptor for the inhibitory

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neurotransmitter gamma-aminobutyric acid (GABA), and are known to cross the placenta based on individual drug pharmacokinetic factors, such as protein-binding [5]. Benzodiazepine withdrawal symptoms range from milder symptoms, such as anxiety, headache, sleep disturbance, increased heart rate, elevated blood pressure, and tremors to more serious adverse effects, including seizures and delirium tremens [6]. Management strategies for benzodiazepine withdrawal in non-pregnant populations typically include the use of symptom-triggered protocols or fixed-dose benzodiazepine and barbiturate tapers. Front-loading, fixed-dose protocols (using 1–2 initial doses of long-acting agents) and continuous infusion protocols may be used. Numerous adjunctive agents may also be considered including adrenergic agents (specifically, alpha-agonists) and antiepileptic drugs such as valproic acid in non-pregnant patients [6].

During pregnancy, the use of high-dose front-loading protocols and continuous infusion is not typically utilized [4], and even low doses of benzodiazepines are discouraged in pregnancy, for a number of reasons. Early studies described an association between first trimester benzodiazepine exposure and an increased risk of oral clefts [5]. Subsequent studies in larger samples and with more rigorous study methods have challenged this finding [7]; however, many practitioners refer back to earlier studies. Yonkers et al. recently reported an association between gestational exposure to benzodiazepines and higher rates of Cesarean section delivery, neonatal low birth weight, and newborn ventilatory support [8]. Neonatal withdrawal from combination regimens that include benzodiazepines was reported to be more severe than from opioids alone [9] or SSRIs alone [10]. Additionally, there are reports of in-utero benzodiazepine exposure association with long-term behavioral problems such as anxiousness, emotional reactivity, somatic complaints [11] and aggressive behaviors in childhood [12].

At our institution, benzodiazepine withdrawal management and opioid medication assisted treatment with methadone or buprenorphine is undertaken at an ambulatory detoxification or outpatient program. Pregnancy is an exclusion criterion for ambulatory withdrawal from GABAergics and for conversion to methadone due to presumed heightened risk for morbidity during withdrawal in the mother-fetal unit. Pregnant women withdrawing from opioids, or on medication-assisted opioid treatment with co-morbid alcohol or benzodiazepine withdrawal, are therefore admitted to an inpatient obstetrical unit. The Psychiatry Consultation-Liaison service is consulted to guide opioid and benzodiazepine withdrawal management during pregnancy. Because research data on perinatal benzodiazepine withdrawal management is not available to guide clinical practice, principles of GABAergic withdrawal from studies done in the general, nonpregnant population have been applied to pregnant women. The most common strategies include a symptom-triggered withdrawal protocol or a fixed-dose benzodiazepine taper with a symptom-triggered protocol.

2. Objectives

We aimed to investigate our institution's clinical practice in managing benzodiazepine withdrawal to determine the patterns of the clinical care delivered to women with perinatal benzodiazepine use disorders. Our primary goals were to assess our current practices, to identify current practices in withdrawal management in patients with comorbid opioid and sedative-hypnotic use disorder admitted to the antepartum unit, and to modify our approach if needed based on our results. Specific objectives involve identifying patterns of withdrawal management, including the type of withdrawal protocol utilized, the total dosage of benzodiazepine used during that protocol, to assess patient variables associated with higher dosing, and to analyze neonatal outcomes.

3. Methods

A retrospective chart review of psychiatry consultations for benzodiazepine withdrawal in antepartum women was conducted for patients seen over a 3 year period. All psychiatry consults seen between 2012 and 2015 were reviewed by one of the psychiatrists who conducted the consultations in addition to the 4 other psychiatrists. A formal quality check was not done. Consults requested for benzodiazepine withdrawal were identified by review of the records and patient identifiers were removed. This review was conducted under the approval of our institution's Quality and Research Board.

Inclusion criteria included the following: women who were admitted to the antepartum unit with an opioid use disorder and consult reason was for benzodiazepine withdrawal. There were no age restrictions. All consults were done on the antepartum unit of the obstetrical hospital. The following data were manually extracted from the chart for each patient: age, gestational age, number of pregnancies, modality of benzodiazepine withdrawal management (symptom-triggered versus standing benzodiazepine taper), total amount of benzodiazepine used (in lorazepam equivalents) during the detoxification period, and active methadone conversion versus stable methadone dose on admission. When available, average fetal heart tones during the withdrawal detoxification period were pulled from the electronic medical record and averaged. Discharge summaries and progress notes from the obstetrical teams were reviewed to record if withdrawal seizures in the mother or complications to the fetus occurred during the withdrawal period in the hospital. Potential confounds including history of withdrawal seizures, comorbid alcohol use, and lorazepam equivalents used prior to admission were similarly extracted. The symptom-triggered scale used at our institution is the Withdrawal Assessment Scale [13].

Data from the earliest time point of the first pregnancy for repeat admission patients and all other single-time point admissions were used in the analyses. Data were examined for outliers. We conducted analyses with removal of outliers greater than three standard deviations above the mean. *t*-Tests were used to compare total benzodiazepine dose used during withdrawal management, between women treated with a symptom-triggered protocols versus those treated with a fixed-dose taper. In this 2-group comparison, a small number of women were excluded from the analysis, whose withdrawal management was conducted differently (Table 2). *t*-Tests were used to compare women admitted on stable methadone versus those converted to methadone during hospitalization. Similarly, for this analysis, we excluded a small number of patients who were not on methadone (Table 2). Finally, we conducted a linear regression to examine patient and clinical management variables which predicted total benzodiazepine dose, with the same sample streamlining used for the *t*-tests.

A sub-analysis was conducted on the women for whom data was available for neonatal outcomes. Parameters including neonatal APGAR scores, preterm delivery versus full-term birth, neonatal intensive care unit admission, and any other obstetrical complications noted in the medical record were recorded. These outcomes were compared between women who were managed utilizing benzodiazepine taper plus symptom-triggered protocol compared to those on a symptom-triggered protocol alone utilizing *t*-test and Pearson chi-square analyses.

4. Results

During the period of study, there were 171 pregnancy-related benzodiazepine withdrawal admissions, which yielded 118 unique patients. Demographic information is in Table 1. The majority of patients were undergoing methadone conversion or were stable on methadone maintenance (83%; Table 1). There were high rates of co-occurring substance use including tobacco, cannabis, and cocaine (Table 1). Lorazepam was the most frequently used benzodiazepine for withdrawal management and withdrawal management strategy was nearly evenly divided between symptom-triggered alone and symptom triggered plus fixed dose (Table 2).

The mean cumulative benzodiazepine dose used during an admission was 9.3 ± 16.0 mg lorazepam equivalents. One patient's

Table 1
Demographic information and other data on baseline substance use.

Demographic and other factors	Fixed-dose taper plus symptom-triggered	Symptom-triggered only	Overall
White	45/48 (93.75%)	53/55 (96.36%)	112 (95.7%)
Black	3/48 (6.25%)	2/55 (3.64%)	5 (2.56%)
Average age (years)	28.5	28.6	28.7 ± 4.5 years
Single	24/48 (50%)	36/55 (64.45%)	65 (55%)
Married	6/48 (12.5%)	2/55 (3.63%)	10 (8%)
Divorced	0 (0%)	2/55 (3.63%)	3 (2%)
Unspecified	18/48 (37.5%)	15/55 (27.27%)	42 (35.5%)
Average gravida	3.3	4	
Average para	1.33	1.8	
Gestational age	14.2	14.2	

Maintenance treatments	Fixed-dose taper plus symptom-triggered	Symptom-triggered only	Overall
Methadone conversion	28/48 (58.3%)	39/55 (70.91%)	72 (61%)
On stable methadone	13/48 (27.08%)	8/55 (14.54%)	26 (22%)
No methadone	3/48 (6.25%)	7/55 (12.72%)	15 (12.7%)
Buprenorphine	4/48 (8.33%)	1/55 (1.81%)	5 (4.2%)

Other substances used

Substance used	Fixed-dose taper plus symptom-triggered	Symptom-triggered only	Overall self-report (n; %)	Overall UDS positive (n; %)
Cocaine	12/48 (25%)	18/55 (32.7%)	33; 28.2[a]	32; 27.6[b]
Marijuana	17/48 (35.4%)	12/55 (21.8%)	35; 29.9[a]	34; 29.3[b]
Other (buprenorphine, amphetamines, or barbiturates)	10/48 (20.8%)	16/55 (29.1%)	31; 26.5[a]	Buprenorphine 32; 27.6[b] Methadone 27; 23.3[b] Amphetamine 9; 7.8[b] Barbiturate 8; 6.9[b]
Alcohol	9/48	9/55	21; 18.0[a]	N/A

[a] n = 117.
[b] n = 116.

Table 2
Benzodiazepine utilization.

Benzodiazepine used for withdrawal management	Frequency (n)
None	6; 5.1%
Lorazepam	84; 71.2%
Clonazepam	55.1%
Diazepam	7; 5.9%
Chlordiazepoxide	8; 6.8%
Other (combination regimen or nonbenzodiazepine agent)	7; 5.9%
Withdrawal method used	
Symptom-triggered only	55; 46.6%
Fixed-dose taper plus symptom-triggered	48; 40.7%
Symptom-triggered switched to taper	7; 5.9%
Unspecified	8; 6.7%

benzodiazepine dose was > 3 standard deviations above the mean (135 mg) and therefore her data was excluded her data from analyses because she was an extreme outlier. In examining the frequencies of lorazepam dosing across the sample, 34% of unique patients admitted for benzodiazepine withdrawal required no lorazepam at all. Table 3 outlines differences between women on symptom-triggered protocols compared to fixed-dose taper. Most significantly, women placed on a symptom-triggered protocol received a lower mean benzodiazepine dose (2.4 ± 6.9 mg) compared to those placed on a benzodiazepine taper in conjunction with a symptom-triggered protocol (15.4 ± 11.5 mg; $p < 0.001$). The lorazepam equivalent used by mothers prior to admission in the group placed on a taper trended toward being higher than in the group who were placed on a symptom-triggered protocol (18.62 mg vs 11.67 mg; $p = 0.06$).

There was also a tendency for women with a history of complicated withdrawal to be given a taper plus WAS combination though this was not statistically significant (Table 3). No difference was found between women placed on a taper compared to a symptom-triggered scale alone in their baseline alcohol use (Table 3). Two of the women in the sample had withdrawal seizures; these women had a documented history of a seizure disorder.

In a regression model predicting the dependent variable lorazepam dose, method of withdrawal management ($\beta = 0.57$) was a highly significant predictor ($p < 0.001$), with symptom-triggered plus taper methods being associated with higher lorazepam dose. Whether a patient was admitted on a stable outpatient methadone dose or converted to methadone, or number of substances reported in the urine drug screen during the admission had no significant relationship with lorazepam dose. Women who started methadone during admission tended

Table 3
Differences between taper and symptom-triggered.

	Fixed-dose taper plus symptom-triggered	Symptom-triggered only	p-Value
Frequency (number, %)	48; 40.7%	55; 46.6%	
Mean lorazepam equivalents used prior to admission	18.62 mg	11.67	p = 0.06
Maternal history of withdrawal seizure/complicated withdrawal	17/36 (47.2%)	12/41 (29.2%)	0.105
Comorbid alcohol use prior to admission	9/48 (18.75%)	9/55 (16.36%)	0.750
Mean benzodiazepine dose used for withdrawal (lorazepam equivalents)	15.4 ± 11.5 mg	2.4 ± 6.9 mg	p < 0.001

Table 4
Maternal and fetal outcomes.

Outcome	Fixed-dose taper plus symptom-triggered	Symptom-triggered only	p-Value
Mean APGAR (1 min)	7.3 (n = 20; SD 1.470)	7.67 (n = 30; SD 2.155)	0.477
Mean APGAR (5 min)	8.30 (n = 30; SD 1.809)	8.57 (n = 30; SD 0.858)	0.487
NICU stay	15/20 (75%)	22/30 (73.3%)	0.895
Preterm delivery	4/20 (20%)	3/29 (10.3%)	0.342
Maternal withdrawal seizure during admission for withdrawal management	1/48 (2%)	1/55 (1.8%)	0.923
Neonatal complication during admission for withdrawal	3/48 (6.25%)	1/55 (1.8%)	0.246

to receive lower mean lorazepam doses (7.1 ± 10.4) compared to women admitted on stable outpatient doses of methadone (11.5 ± 10.6; $p = 0.07$). The regression remained significant after controlling for gestational age of the pregnancy at the time of withdrawal management and maternal age [$F(5,82) = 9.7$; $R^2 = 0.37$; $p < 0.001$]. No correlation was found between maternal benzodiazepine dose during withdrawal management and fetal heart tones during that period ($N = 101$; $\rho = 0.11$; $p = 0.26$). These results were unchanged, and there was no significant impact on lorazepam dose administered during current hospitalization when preadmission benzodiazepine use was included in the regression ($\beta = 0.12$; $p = 0.22$).

Using *t*-test and chi-square analyses on a subgroup of women ($N = 50$), no differences were found between women placed on a taper compared to a symptom-triggered scale alone in APGARS, NICU admissions, or preterm delivery. Details on maternal and fetal outcomes are outlined in Table 4. No significant differences were found between women placed on a taper compared to a symptom-triggered scale alone in terms of withdrawal seizures in the mother or in complications to the baby during the admission for withdrawal management. While not statistically significant, babies both to mothers on symptom-triggered protocols showed lower rates of NICU stay (73.3% versus 75%), lower rates of preterm delivery (10.3% versus 20%) and lower rates of neonatal complications during the admission for withdrawal (1.8% versus 6.25%). Regarding other adverse maternal outcomes, all but two of the women were explicitly noted by the obstetrical team to have no adverse events to the fetus during the withdrawal period. Of the two who were noted to have complications, one delivered during the admission at 35 weeks gestation and the other had a non-reassuring non-stress test that was followed by a normal biophysical profile.

5. Discussion

As national attention is called to the opioid epidemic, the comorbid use of other substances requires clinical consideration. Our study is among the first to investigate sedative-hypnotic withdrawal management in the perinatal population. We found that a symptom-triggered benzodiazepine withdrawal protocol was associated with significantly lower total benzodiazepine use compared to standing taper regimens. This suggests that, similar to non-perinatal populations, symptom-triggered protocols result in lower benzodiazepine dose administration in perinatal women and may be considered for initial management to minimize potential negative effects of benzodiazepine exposure on pregnancy outcomes.

We also found that women who started methadone during admission tended to receive lower mean lorazepam doses compared to women admitted on stable outpatient doses of methadone. A mixed withdrawal clinical picture likely drove this result, and the use of lower doses of benzodiazepines should be considered in patients who are undergoing methadone conversion. Conversely, if a woman was admitted on stable methadone dosing, she was more likely to be placed on a benzodiazepine taper on admission, suggesting that perhaps a single withdrawal syndrome prompted recommendations from the consulting psychiatrist utilizing more medications. This response may be due to physician confidence that the clinical withdrawal syndrome encountered is due to benzodiazepine withdrawal and not confounded by withdrawal from other substances, and may prevent significant withdrawal risks from the sedative-hypnotic withdrawal. Women with higher preadmission benzodiazepine utilization and a history of withdrawal seizure tended to be managed with the taper plus symptom-triggered protocol, compared to women with lower preadmission benzodiazepine utilization and without a history of withdrawal seizures.

The majority (71%) of women were treated with lorazepam, though route of administration was not recorded from the chart. Long-acting benzodiazepine agents such as diazepam could be considered initially as these are likely to result in fewer rebound symptoms, complications, and theoretically provide a more stable withdrawal course; however, this strategy could also result in longer duration of fetal concentrations. Individual dosing considerations must also drive medical decision-making, such as the presence of hepatic impairment (e.g. leading to the use of lorazepam or oxazepam), reliability of the patient's history which may determine how which management strategy to use, co-morbid substance use which may artificially inflate scores on symptom-triggered scales, and the likelihood that the patient will remain in the hospital for the entirety of the withdrawal period.

While maternal and neonatal outcomes were only available in a subset of the current sample, it is reassuring that no differences were found between women placed on a taper compared to a symptom-triggered scale alone across numerous neonatal outcomes including APGAR scores, NICU admissions, and preterm delivery. Additionally, there were no significant differences between women placed on a taper compared to a symptom-triggered scale alone in terms of maternal withdrawal seizures or in neonatal complications during the index admission for withdrawal management.

Strengths of this study include the relatively large data set on benzodiazepine withdrawal management in a perinatal population, which is a neglected area of study. Numerous parameters were extracted pertinent to benzodiazepine withdrawal. The observational design allows for real-world extrapolations. Weaknesses include the retrospective nature of the study design, the manual nature of the chart review, as well as the homogeneity in its sample in terms of race. Missing data limited the analysis of neonatal outcomes, however the available data was reassuring. Additionally, data regarding other psychiatric diagnoses and insurance status was not collected.

Areas of future study based on this analysis include further investigation of the implications of fetal benzodiazepine exposure on neonatal outcomes. As women with more than one hospital admission are likely at higher risk, targeted brief interventions such as SBIRT (screening brief intervention referral to treatment) or brief cognitive-behavioral therapy-based interventions during the withdrawal period may be considered. Finally, a prospective design would enable us to test the effect of symptom-triggered scales in the categories of women for whom this wasn't typically used.

6. Conclusions

Data from our observational study of pregnant patients admitted for benzodiazepine withdrawal management is consistent with studies in the general population. Symptom-triggered benzodiazepine withdrawal protocols compared to standing taper regimens were associated with significantly lower total benzodiazepine use. Both methods were not

associated with maternal or neonatal complications during the admission for withdrawal nor at delivery for the women for whom this information was available, suggesting that either method is safe in this population and use of symptom-triggered scales may minimize medication exposure. Whether a patient was admitted on a stable outpatient methadone dose or converted to methadone and number of substances reported in the urine drug screen had no significant relationship with lorazepam dose; stability on methadone and history of complicated withdrawal was associated with higher lorazepam utilization. Additional prospective study of the relationship between benzodiazepine dosing for GABAergic withdrawal management and maternal and infant outcomes is needed to guide clinical practice in pregnant patients with combined opioid-benzodiazepine use disorders.

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