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Association Between Prenatal Cannabis Use and Psychotropic Medication Use in Pregnant Patients with Depression and Anxiety

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Abstract

Objectives: This cross-sectional study examined associations between prenatal cannabis use and prescribed psychotropic medication use among pregnant patients with depression or anxiety in a large, integrated healthcare system.

Methods: Study patients had a confirmed pregnancy and a depressive or anxiety disorder defined by ICD codes between 2012-2018 at Kaiser Permanente Northern California. Patients were screened for prenatal substance use via a self-reported questionnaire and urine toxicology test as part of standard prenatal care. Generalized estimating equation models tested for associations between prenatal cannabis use and any dispensation of antidepressants, benzodiazepines, and hypnotics during gestation. Models were stratified by diagnosis (depression or anxiety) and depression symptom severity.

Results: This study included 35,047 pregnancies (32,278 patients; 17.6% aged <25 years, 48.1% non-Hispanic White). Adjusting for patient age, income, race/ethnicity, and depression symptom severity, the 12.6% of patients who screened positive for prenatal cannabis use demonstrated higher odds of prenatal benzodiazepine (aOR=1.40; 95%CI=1.20-1.62) and hypnotic (aOR=1.28; 95%CI=1.11-1.48), but not antidepressants (aOR=1.05, 95%CI=0.96-1.14) use. This pattern persisted when diagnostic groups were examined separately. The odds of prenatal benzodiazepine and hypnotic use associated with prenatal cannabis use were higher among pregnancies with severe depression symptom severity (31.8% of the sample).

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Conclusions: Among pregnant patients with depression or anxiety, prenatal cannabis use was associated with higher odds of prenatal benzodiazepine and hypnotic use. As patients may be using cannabis to address depression and anxiety, prescribers should remain vigilant for under- or untreated psychiatric symptoms among pregnant patients and provide evidence-based treatments.

Keywords

pregnancy; cannabis; psychotropic medications; depression; anxiety

Introduction

Rates of cannabis use during pregnancy have increased over time[1] and depression and anxiety are associated with an increased odds of prenatal cannabis use.[2] Prenatal depression and anxiety are relatively common, with an estimated prevalence of 10%[3] and 21%,[4] respectively. Studies suggest that some patients view cannabis as a safe alternative to psychotropic medications to treat prenatal anxiety and depression.[5] However, cannabis use can worsen depression and anxiety symptoms over time,[6] and U.S. professional society guidelines recommend against prenatal cannabis use given the potential health risks to the patient and the fetus.[7] Current guidelines recommend antidepressants as a first-line therapy for depression or anxiety disorders in pregnant patients where therapy alone is ineffective,[8] and evidence suggests that antidepressants may be safer compared to benzodiazepines or hypnotics to address mood and anxiety.[9] However, cannabis use is associated with increased use or misuse of benzodiazepines in U.S. adults,[10] and similar associations may be seen in pregnant patients.

Given the widespread legalization of cannabis, reported perception of safety by pregnant patients,[5] and potential substitution of cannabis for prescription psychotropic medications,[11] it is important to understand whether pregnant patients with depression and anxiety who use cannabis differ from those who do not use cannabis in utilization of commonly prescribed psychotropic medications for depression and anxiety. Using data from Kaiser Permanente Northern California's (KPNC) large, integrated healthcare system with universal screening for prenatal cannabis use and depression, this study examined whether prenatal cannabis use was associated with antidepressant, benzodiazepine, and hypnotic use among pregnant patients with depression, anxiety, or both.

Methods

Pregnant patients with live births at KPNC who were screened for self-reported prenatal substance use between 2012-2018 and had a diagnosed anxiety or depressive disorder during pregnancy were considered for inclusion. The KPNC institutional review board approved this study and waived informed consent.

Prenatal cannabis use was based on self-reported use since pregnancy and/or a positive, confirmed urine toxicology test conducted during standard prenatal care at the first prenatal visit (at ~8-weeks' gestation). Anxiety and depressive disorders were based on *ICD-9-CM* and *ICD-10-CM* codes in the electronic health record (EHR) (Supplement). Self-reported depression severity was based on universal screening, which typically occurs at the first

prenatal visit since 2012 using the Patient Health Questionnaire-9 (PHQ-9);[12,15] the highest available score was considered and total scores were dichotomized into “lower severity” (PHQ-9<10) and “severe” (PHQ-9≥10). Dispensations of ≥1 antidepressant, benzodiazepine, and hypnotic medication (Supplement) during gestation were extracted from KPNC pharmacy databases.

Using generalized estimating equation (GEE) models with SAS 9.4 (Cary, NC), we estimated adjusted odds ratios (aOR) and 95% CIs for fills of antidepressants, benzodiazepines, and hypnotics by cannabis use for patients with depression, anxiety, and depression or anxiety, accounting for patients with multiple pregnancies during the study period, and adjusting for age, neighborhood household income, race/ethnicity, and depressive severity. Analyses were also stratified by depressive symptom severity.

Results

Among 41,365 pregnancies, those missing urine toxicology tests (n=3,784; 9.1%), those who skipped the question about self-reported cannabis use (n=236; 0.6%), and those missing the PHQ-9 (n=2,298; 5.6%) were excluded. Among 35,047 pregnancies (32,278 patients), 48.1 % were white, 17.6% were aged <25 years (mean [SD] age, 30.1 [5.7] years), and the median (interquartile range) of median neighborhood annual household income was $67,841 ($49,913-$90,000); 67.1% had an anxiety disorder, 61.3% had a depressive disorder, 31.8% had severe depression symptoms, and 12.6% screened positive for prenatal cannabis use (Table). Antidepressant, benzodiazepine, and hypnotic medications were filled during 22.3%, 4.7%, and 5.4% pregnancies, respectively. In bivariate analyses, patients with prenatal cannabis use (compared with no use) were younger; more likely to be Black or other/unknown race; had lower estimated household income; less likely to have an anxiety disorder but more likely to have a depressive disorder, had severe depression symptom severity, and were more likely to use prescribed benzodiazepines and hypnotics (Table).

Among patients with anxiety or depressive disorders, prenatal cannabis use was associated with higher odds of using benzodiazepines (aOR=1.40; 95%CI=1.20-1.62) and hypnotics (aOR=1.28; 95%CI=1.11-1.48) but not antidepressants (aOR=1.05, 95%CI=0.96-1.14) (Figure 1a). Results were similar when anxiety and depressive disorders were examined separately. This pattern of results was similar for patients with severe depression symptoms, with even greater odds of benzodiazepine or hypnotic use among patients with severe versus lower depression symptom severity (Figure 1b and 1c). In patients with lower depression symptom severity, prenatal cannabis use was associated with higher odds of antidepressant use for patients with anxiety disorders (aOR=1.18, 95%CI=1.03-1.36), but otherwise followed similar patterns.

Discussion

Prenatal cannabis use among patients with depression and anxiety was associated with greater odds of prenatal benzodiazepine and hypnotic, but not antidepressant use. These findings are consistent with reports that adults who use cannabis are more likely to use benzodiazepines.[10] Our finding that the association between cannabis and use of

benzodiazepines and hypnotics is even stronger among patients with severe depression symptoms suggests that underrecognized and poorly controlled symptom severity (e.g., elevated worry and sleep problems) may drive some patients to seek immediate relief from benzodiazepines and hypnotics. Alternatively, patients who discontinue cannabis use during pregnancy may use benzodiazepines and hypnotics to address cannabis withdrawal symptoms. These data are inconsistent with reports that some individuals with anxiety may substitute cannabis for benzodiazepines,[11] or that prescribed benzodiazepines may encourage cannabis cessation.[13]

Interestingly, cannabis use was not associated with antidepressant use, with the exception of patients with anxiety and low depressive symptoms. This suggests that pregnant patients with anxiety or depression are generally not substituting cannabis for antidepressants. The potential harms of prenatal use of benzodiazepines, hypnotics, and cannabis may be higher than those of antidepressants;[7,9] furthermore, there may be an additive risk of these agents when used together. Future research is needed to explore concurrent use of cannabis and prescribed psychotropics over the course of pregnancy.

This study has several limitations. Data were restricted to a single healthcare system that may not be generalizable to other settings. Cannabis use screening occurred early in pregnancy and did not capture continued use or cessation. We did not have information on anxiety severity. Universal screening for prenatal depression may lead to higher identification of depressive symptoms compared with other studies.[15] Our measure of psychotropic medication use may have missed differences based on dose or duration of treatment. Patients with missing cannabis-use and depression-severity data may have exhibited different patterns of psychotropic medication use.

Conclusion

This study found that pregnant patients with depression or anxiety who used cannabis were more likely to also use rapidly acting benzodiazepines and hypnotics, but not antidepressants. Early and universal screening for substance use can help clinicians identify patients with poorly controlled depression and anxiety who would benefit from education about the health risks of prenatal cannabis use, advice to discontinue use, and tailored counseling to use alternate, evidence-based ways to manage depression and anxiety. In KPNC, patients who screen positive for prenatal substance use are offered substance use counseling integrated into prenatal care with improved maternal and neonatal outcomes.[14] Pregnant patients should also be routinely screened for depression and anxiety, and provided with education about the relative risks and benefits of different treatment options.[8] Clinicians should be vigilant for untreated symptoms especially among marginalized groups who are more likely to remain untreated or to receive non-evidence-based care.[15]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

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The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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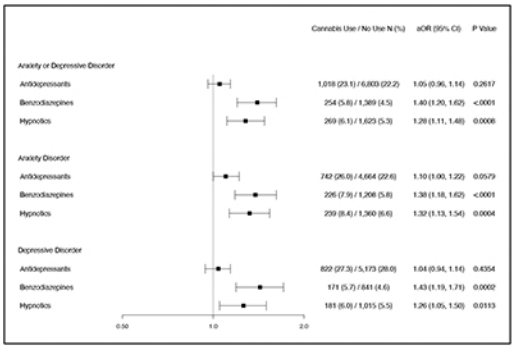
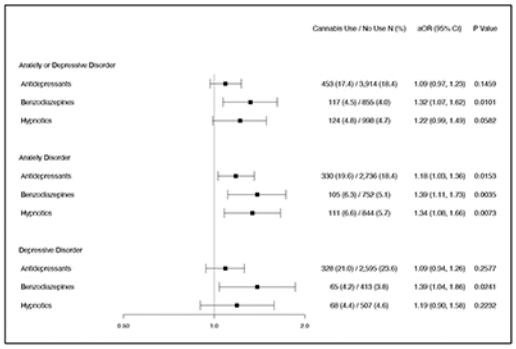
(a) Whole data



(b) Lower depression severity



(c) Higher depression severity

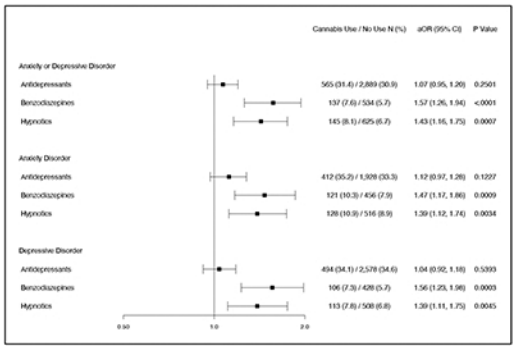


Figure.

Adjusted odds ratios of prenatal use of antidepressants, benzodiazepines, and hypnotics among patients with anxiety or depressive disorders for (A) entire study sample, (B) patients with low depressive severity, and (C) patients with high depressive severity[a].

[a] Adjusted odds ratios (aORs) represent the odds of ≥1 fill of a medication from the respective medication class by prenatal cannabis use between the last menstrual period and birth; generalized estimating equation models were applied to account for multiple pregnancies within each patient and covaried for patient age (continuous); race/ethnicity (white, non-Hispanic; Asian, non-Hispanic; Black, non-Hispanic; Hispanic, any race; other or unknown); median neighborhood household income (continuous); and depression severity (Patient Health Questionnaire-9 score [PHQ-9], continuous). PHQ-9 score was omitted in models that were stratified by depression severity (panels B and C).

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Table.

Characteristics of 35,047 pregnancies among 32,278 Kaiser Permanente Northern California pregnant patients, overall and by prenatal cannabis use.

Characteristic	**Total** **N (%)[a] = 35,047 (100.0)**	**Cannabis use during pregnancy**		
		Yes **N (column %)[a] = 4,402 (12.6)**	**No** **N (column %)[a] = 30,645 (87.4)**	**P-value[b]**
Age (y), Mean (SD)	30.1 (5.7)	26.9 (5.9)	30.6 (5.5)	<.0001
Race/ethnicity, N (%)				<.0001
Asian	4,308 (12.3)	195 (4.4)	4,113 (13.4)	
Black	2,980 (8.5)	989 (22.5)	1,991 (6.5)	
Hispanic	9,445 (27.0)	1,056 (24.0)	8,389 (27.4)	
Other/unknown	1,470 (4.2)	251 (5.7)	1,219 (4.0)	
White	16,844 (48.1)	1,911 (43.4)	14,933 (48.7)	
Median neighborhood household income ($), Mean (SD) [c]	71,813.5 (29,779.0)	62,524.0 (27,309.4)	73,147.9 (29,881.2)	<.0001
Anxiety disorder, N (%)	23,526 (67.1)	2,850 (64.7)	20,676 (67.5)	0.0003
Depressive disorder, N (%)	21,485 (61.3)	3,007 (68.3)	18,478 (60.3)	<.0001
Depression severity, Mean (SD)	7.7 (6.1)	9.1 (6.4)	7.5 (6.0)	<.0001
Depression severity, N (%)				<.0001
PHQ-9 < 9 (low)	23,885 (68.2)	2,604 (59.2)	21,281 (69.4)	
PHQ-9 ≥ 10 (high)	11,162 (31.9)	1,798 (40.9)	9,364 (30.6)	
Prenatal medication use, N (%)				
Antidepressants	7,821 (22.3)	1,018 (23.1)	6,803 (22.2)	0.1674
Benzodiazepines	1,643 (4.7)	254 (5.8)	1,389 (4.5)	0.0003
Hypnotics	1,892 (5.4)	269 (6.1)	1,623 (5.3)	0.0253

[a] Percentages may not add to 100% due to rounding to 0.1%.

[b] P-value based on Chi-square test for categorical variables and based on T-test for continuous variables.

[c] Median neighborhood household income information is missing for 37 pregnancies, we imputed missing values using the median of median neighborhood household income ($67, 841).