

Cross-Sectional Study



Prescription Opioid Use and Laboratory Value Derangements: A Cross-Sectional Analysis of NHANES Data

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Background: The use of opioids for the treatment of pain is a risk versus benefit analysis and metabolic disease is an often overlooked variable in the equation and may lead to increased risk of comorbidities of cardiovascular and cerebrovascular disease and diabetes.

Objectives: Our objective was to identify and describe abnormalities among the comprehensive metabolic and lipid panels of individuals taking prescription opioids.

Study Design: We performed a cross-sectional study of the laboratory values with 3 cycles (2011–2016) of the National Health and Nutrition Examination Survey (NHANES) in March 2020.

Setting: NHANES sampling is conducted using a multistaged, stratified, cluster sampling technique to create a representative sample of the United States.

Methods: We excluded patients with histories of cancer and under the age of 25 years. Our final sample size was 11,061 ($n = 162,547,635$), with 797 reportedly using a prescription opioid in the past 30 days—a weighted percent representing 22.95% of the US population. Our analyses identified mean differences in biomarkers between individuals taking prescription opioids and the US population.

Results: Laboratory values from the comprehensive metabolic panel were all within reference ranges for both groups, with only bilirubin levels being statistically lower in the group currently taking prescription opioids. Values from the lipid panel of both the opioid using and comparison groups were above reference range for total cholesterol and fasting glucose. The opioid using group was also higher than the reference range for triglycerides (mean [M] = 165.4, standard deviation [SD] = 14.2) and insulin (M = 15.5, SD = 2.2), whereas the comparison group was not. The oral glucose measure was within normal ranges for both groups; however, the opioid using group was 13.7 points higher than the comparison group (M = 122.3, SD = 1.8; M = 108.6, SD = 4.0; $P < 0.01$).

Limitations: While our study uses a large sample for a robust generalizable analysis it is a correlation study and a longitudinal cohort would provide better evidence linking potential disease states to prescription opioid use.

Conclusions: Although all Americans should be alarmed at the lipid levels reported in this study, specific combinations of heightened lipid laboratory values among prescription opioid users accelerate the trajectories toward comorbidities—heart disease, cerebrovascular disease, and diabetes—leading to diminished quality of life. Therefore pain management and comprehensive drug recovery programs should include nutritional counseling and physical activity as part of their overall treatment plan.

Key words: Opioid use, NHANES, pain management, lab values, analgesics

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Chronic pain is a significant issue in the United States and affects 1 in 10 citizens (1). Opioids are frequently used for the treatment of pain even though the side effects of opioid use are extensive and include nausea, vomiting, constipation, addiction, and respiratory depression (2). Studies in rats and small cohorts of males have shown opioid use causes significant increases in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, blood urea nitrogen (BUN), and creatinine (3,4). Another small study identified an association between hyperglycemia and acute opioid use (5).

Further, the use of opioids for pain is a risk versus benefit analysis, and metabolic disease is an often overlooked variable in the equation. One study in rats showed alterations in serum concentrations of triglycerides, plus total high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol (6). Moreover, opioid-induced endocrinopathies to include decreased free and total testosterone have recently been discovered and may have an impact on hyperlipidemia (7,8). A cohort study of over 20,000 veterans with long-term opioid use and low testosterone found an increased risk of hyperlipidemia in patients receiving testosterone supplementation. Definitive evidence of lipid aberrancy in human opioid users is, however, lacking.

The use of long-acting opioids to treat opioid use disorder is also on the rise. From 2003 to 2016, opioid use disorder treatment programs increased by 39% (9). Although opioids are increasingly being prescribed for justifiable reasons, such as in the treatment of opioid use disorder, many physicians do not consider the nutritional and metabolic impact of opioid use. One study found that only 7% of residential treatment facilities included the services of dietitians (10). As a result, the need for increased awareness and understanding of metabolic derangements in opioid users is apparent. Despite the attempt to identify laboratory derangements in opioid users by multiple researchers, no study has analyzed these effects in a large, representative US sample. Thus our objective was to identify and describe abnormalities among the comprehensive metabolic and lipid panels of individuals taking prescription opioids.

METHODS

We performed a cross-sectional study of the laboratory value derangements among individuals taking prescription opioids using the (2011–2016) National Health and Nutrition Examination Survey (NHANES) dataset.

NHANES is a nationally representative, publicly available, health survey of civilian and noninstitutionalized US citizens. The survey is composed of a health questionnaire, physical examination, and biospecimen collection performed by a trained health care professional. Sampling was conducted using a multistaged, stratified, cluster sampling technique with ethnic minority and elder population oversampling to create a representative sample of the United States. In return for participation, travel expenses and childcare were reimbursed. Following biospecimen collection, sera was stored at -70°C until quantitative analysis was performed using methods previously validated by the NHANES (11). The NHANES survey was approved by the National Center for Health Statistics research ethics institutional review board (IRB) and consent was obtained from all patients prior to data collection.

Data extracted included sociodemographics, prescription opioid use in the past 30 days, and the following laboratory values: ALT, AST, total bilirubin, alkaline phosphatase, BUN, creatinine, carbon dioxide, chloride, sodium, potassium, calcium, total protein, albumin, globulin, total cholesterol, LDL, HDL, triglycerides, fasting glucose, 2-hour oral glucose, and fasting insulin. Male and female patients younger than 25 years were excluded from the analysis due to low prevalence of reported opioid usage. Patients with a history of cancer were excluded. Prescription opioid use was self-reported. Generic opioid names were extracted and collated into a single category for statistical analysis.

Statistical analysis was performed using Stata 16.1 (StataCorp, College Station, TX) in March 2020. Appropriate weighting for the statistical analysis of the subsamples were modified to accommodate 3 cycles of data using the oral glucose weighting for oral glucose test; the fasting subsample weighting for glucose, triglycerides, and LDL tests; and the Mobile Examination Center weighting for insulin, total and HDL cholesterol. To analyze the association of opioid use on the laboratory values from comprehensive metabolic and lipid panels, a multiple linear regression model was constructed to obtain mean differences of laboratory values between groups and marginal means for each group — adjusted for age, gender, race, and body mass index (BMI). Effect sizes were calculated from the standardized coefficients of the binary opioid use variable in the regression model (12) and transformed to Cohen's *d*. This study complied with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. Data utilized in this study were deidentified and not eligible for IRB approval.

RESULTS

After excluding patients with a historical diagnosis of cancer and those under the age of 25 years, the remaining sample size was 11,061 ($n = 162,547,635$). Of the respondents, 797 had reported using a prescription opioid in the past 30 days with a weighted percent representing 22.95% of this portion of the US population. Laboratory values from the comprehensive metabolic panel were all within reference ranges for both groups, with only bilirubin levels being statistically lower in the group currently taking prescription opioids (mean $[M] = 0.6$, standard deviation $[SD] = 0.0$) from the comparison group ($M = 0.7$, $SD = 0.0$) (Fig. 1).

Values from the glucose and lipid panels showed that both the opioid using and comparison groups were above reference range for total cholesterol ($M = 208.8$, $SD = 3.3$;

$M = 201.1$, $SD = 1.2$; $P < 0.05$, Cohen's $d = 0.19$) and fasting glucose ($M = 108.6$, $SD = 3.4$; $M = 108.0$, $SD = 1.2$) (Fig. 2). The opioid using group was also higher than the reference range for triglycerides ($M = 165.4$, $SD = 14.2$; $M = 136.3$, $SD = 4.3$; $P < 0.05$) and insulin ($M = 15.5$, $SD = 2.2$; $M = 13.1$, $SD = 0.29$), whereas the comparison group was not. The oral glucose measure

REPORT STATUS: FINAL			
SPECIMEN: US POPULATION >24 YEARS OF AGE WITH NO HISTORY OF CANCER DX (NHANES 2011-2016)			
REQUISITION:	PATIENT INFORMATION: PATIENT CURRENTLY TAKING OPIOID RX	PATIENT COMPARISON OTHER	
LAB REF NO:	SAMPLE SIZE: 797 N = 30,346,264	SAMPLE SIZE: 10,264 N = 132,201,371	
COLLECTED: 3/10/20	AGE: 56.53 (11.80) BMI: 31.39 (8.46)	AGE: 53.88 (12.53) BMI: 29.39 (6.59)	
TEST NAME	Result *M (SE)	Flag	Reference Range
Comprehensive Metabolic Panel			
UREA NITROGEN (BUN)	13.3 (0.3)		7-25 mg/dL
CREATININE	0.9 (0.0)		0.70-1.25 mg/dL
For patients >49 years of age, the reference limit for Creatinine is approximately 13% higher for people identified as African-American.			
BUN/CREATININE RATIO	14.8		6 - 22 (calc)
SODIUM	138.7 (0.3)		135-146 mmol/L
POTASSIUM	4.0 (0.0)		3.5-5.3 mmol/L
CHLORIDE	103.1 (0.3)		98-110 mmol/L
CARBON DIOXIDE	25.1 (0.3)		19-30 mmol/L
CALCIUM	9.4 (0.0)		8.6-10.3 mg/dL
PROTEIN, TOTAL	7.0 (0.0)		6.1-8.1 g/dL
ALBUMIN	4.3 (0.0)		3.6-5.1 g/dL
GLOBULIN	2.8 (0.0)		1.9-3.7 g/dL (calc)
ALBUMIN/GLOBULIN RATIO	1.5		1.0-2.5 (calc)
BILIRUBIN, TOTAL	0.6 (0.0) **		0.2-1.2 mg/dL
ALKALINE PHOSPHATASE	69.6 (1.9)		40-115 U/L
AST	26.6 (0.9)		10-35 U/L
ALT	25.5 (1.1)		9-46 U/L

Fig. 1. Adjusted means of comprehensive metabolic panel values between individuals currently taking opioid prescriptions and those without in the US over 24 years of age, excluding those with a cancer diagnosis (NHANES 2011-2016).

^aMarginal means from regression models adjusted for age, race, gender, and BMI with statistical significance noted as (*) represents $P < 0.05$ and (**) as $P < 0.01$ compared NHANES participants over 25 years of age with no cancer diagnosis using mobile examination center (MEC) subsample and weighting modified for 3 cycles.

REPORT STATUS: FINAL			
SPECIMEN: US POPULATION >24 YEARS OF AGE WITH NO HISTORY OF CANCER DX (NHANES 2011-2016)			
REQUISITION:	PATIENT INFORMATION: PATIENT CURRENTLY TAKING OPIOID RX	PATIENT COMPARISON OTHER	
LAB REF NO:	SAMPLE SIZE: 797 N = 30,346,264	SAMPLE SIZE: 10,264 N = 132,201,371	
COLLECTED: 3/10/20	AGE: 56.53 (11.80) BMI: 31.39 (8.46)	AGE: 53.88 (12.53) BMI: 29.39 (6.59)	
Test Name	Result *M (SE)	Flag	Reference Range
LIPID PANEL			
CHOLESTEROL, TOTAL ^{b†}	208.8 (3.3)*	HIGH	125-200 ml/dL
HDL CHOLESTEROL ^b	51.7 (1.1)		≥ 46 mg/dL
TRIGLYCERIDES ^c	165.4 (14.2)*	HIGH	< 150 mg/dL
LDL-CHOLESTEROL ^c	122.0 (4.1)		< 130 mg/dL
Desirable range <100 mg/dl for patients with CHD or diabetes and <70 mg/dl for diabetic patients with known heart disease			
CHOL/HDL ^c RATIO	4.0		≤ 5.0 (calc)
NON HDL CHOLESTEROL	157.1		mg/dL (calc)
Target for non-HDL cholesterol is 30 higher than LDL cholesterol target.			
GLUCOSE PANEL			
GLUCOSE ^{d†}	108.6 (3.4)	HIGH	65-99 mg/dL
GLUCOSE ^d (2HR ORAL)	122.3 (1.8)**		< 140 mg/dL
INSULIN (FASTING) ^e	15.5 (2.2)	HIGH	<13.7 uIU/mL

Fig. 2. *Adjusted means of lipid panel values between individuals currently taking opioid prescriptions and those without in the US over 24 years of age, excluding those with a cancer diagnosis (NHANES 2011-2016).*

^aMarginal means from regression models adjusted for age, race, gender, and DMI with statistical significance noted as (*) represents $P < 0.05$ and (**) as $P < 0.01$ compared NHANES participants over 25 years of age with no cancer diagnosis.

^bUsed mobile examination center (MEC) subsample and weighting modified for 3 cycles.

^cUsed Fasting subsample and weighting modified for 3 cycles.

^dUsed Oral Glucose subsample and weighting modified for 3 cycles.

^eComparison group also higher than reference range.

was within normal ranges for both groups; however, the opioid using group was 13.7 points higher than the comparison group ($M = 122.3$, $SD = 1.8$; $M = 108.6$, $SD = 4.0$; $P < 0.01$).

DISCUSSION

Results from our analysis show that on average all US individuals over age 24 years and without cancer (controlling for age, gender, and BMI) have high cholesterol and glucose levels, whereas individuals taking

prescription opioids also have high triglycerides and insulin compared with the reference ranges. Although all Americans should be alarmed at the average lipid levels reported in this study, specific combinations of heightened lipid laboratory values in the prescription opioids users lead to multiple comorbidities.

One concerning combination of high lipid values is that of fasting glucose and high insulin. Together, glucose and insulin work together to provide energy to the body; however, prolonged (13) imbalance may lead to weight gain, insulin resistance, prediabetes, and type II diabetes mellitus. Previous research has linked opium (14) to increased serum glucose and heroin to increased insulin sensitivity (15), although there are

several small studies exploring this relationship with mixed results over the past 40 years.

Another problematic combination of lipid values among opioid users is that of high triglycerides and total cholesterol. This is a known risk factor for atherosclerosis, which can lead to ischemic heart disease and further to myocardial infarction (16) or cerebrovascular disease increasing potential risk for stroke (17). Although this is not a new conclusion, it has yet to be identified within this population.

Further, the role of cholesterol in opioid uptake may be exploited in this population. Previous research shows that total cholesterol levels and dosage of opioids, especially initial doses, were inversely related—people with higher cholesterol were more likely to respond to lower doses of opioids (18). Given the increased activity of opioids and opioid receptors within cholesterol-rich environments (19,20), and that US citizens, on average, have high cholesterol levels, this may be an unexplored linkage in the opioid addiction crisis.

Our analyses also showed that neither group was out of the reference ranges of the comprehensive metabolic panel tests, which is in line with previous small studies (21); however, the group currently taking prescription opioids had a statistically lower value for bilirubin. Although lower bilirubin levels are not generally of concern, this may be due to intake of nonsteroidal anti-inflammatory drugs (22) or caffeine (23), and is associated with other conditions such as atherosclerosis (24,25), diabetes (26-28), or ulcerative colitis (29).

Recommendations for all persons with hyperlipidemia include eating a heart-healthy diet – limiting sugar-sweetened beverages and increasing intake of fruits and vegetables, nuts, whole grains, fish and lean poultry (30), eliminating smoking, and improving cardiorespiratory fitness (31). Individuals who may be limited in movement by pain (or other condition) need to consult their physician prior to starting an exercise regimen, but should try to meet physical activity guidelines with modifications and professional guidance as needed (32).

This information highlights the need for comprehensive drug recovery programs to include nutritional counseling and physical activity as part of their overall treatment plan. Not only would improved diet and exercise reduce risk factors associated with heart disease and stroke, but significant preclinical data shows promising effects of exercise on drug self-administration

(33). In addition, gold-standard medication-assisted treatment might perpetuate nutritional risks factors thus further emphasizing the need for nutritional consultation during treatment (34). Further research is needed to show how mitigating these risks factors affects relapse rates.

To our knowledge, this study was the first to use NHANES data to explore the laboratory values of individuals currently taking opioid prescriptions, which provides for a robust generalizable analysis; however, a longitudinal cohort would provide better evidence linking potential disease states to prescription opioid use. Future research should explore associations between cholesterol and the addictive properties of opioids, which may lead to novel preventive recommendations or changes in clinical practice guidelines regarding opioid prescriptions.

CONCLUSIONS

The elevated lipid panel values illustrate a critical need for all US citizens to be aware of the implications—heart disease, cerebrovascular disease, and diabetes—all leading to diminished quality of life. Individuals currently taking opioids may have an elevated risk of and an accelerated trajectory toward these comorbidities.

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Author contributions: Dr. Micah Hartwell had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Dr. Hartwell and Dr. Greiner designed the study protocol. Dr. Greiner and Dr. Beaman managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. Drs. Dunn, Croff, and Beaman provided revision for intellectual content and final approval of the manuscript.

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