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Prevalence and effect of cannabis use in acute pancreatitis of unknown etiology

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ABSTRACT A clinical decision report using:

Simons-Linares CR, Barkin JA, Wang Y, et al. Is There an Effect of Cannabis Consumption on Acute Pancreatitis?. *Dig Dis Sci*. 2018;63(10):2786-2791. https://doi.org/10.1007/s10620-018-5169-2

for a patient with cannabis-associated acute pancreatitis.

Keywords: *acute pancreatitis, marijuana, cannabis, prevalence, idiopathic pancreatitis*

Clinical-Social Context

Gary Adamson [pseudonym] is a 57-year-old-man with a past medical history of hypertension, HIV well-controlled with 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine (Triumeq), and subacute constipation who presented to the emergency department upon recommendation from his infectious disease physician due to elevated lipase levels. On admission, the patient presented with a 1-week onset of sharp, epigastric abdominal pain that radiated to the back, was relieved with sitting up and was exacerbated with food intake. CT abdomen and pelvis revealed peripancreatic fat stranding and blurring of pancreatic margins due to inflammation, but no necrosis. Lipase levels were elevated at over 700, consistent with over three times the upper limit of normal. Mr. Adamson was diagnosed with acute pancreatitis (AP).

In attempts to identify the etiology of Mr. Adamson's AP, detailed history and imaging was performed. On history, he denied alcohol use, and ultrasound abdomen did not reveal gallstones, making alcoholic and gallstone pancreatitis less likely. Mr. Adamson's basic metabolic panel did not show elevations in triglyceride nor calcium levels, making triglyceridemia- and hypercalcemia-induced pancreatitis less likely. Mr. Adamson's CD4 count was also within acceptable ranges per his infectious disease physician, after tolerating Triumeq well for many years, making acute drug-induced pancreatitis less likely. He also denied family history of pancreatitis and recent infections. Insignificant findings from his history, serological and radiological data made the etiology of his AP unclear.

Upon further discussion of social history, Mr. Adamson revealed that he had been smoking increased levels of marijuana in the last several months, approximately 3-4 blunts per day, several days a week and ingesting a significant amount of edible marijuana. He admitted "I know smoking all this pot is probably not good for me, but I've been really stressed out the last several months. I'm probably smoking as a way to cope." His sources of stress included recently finalizing a divorce from his ex-wife with whom he has a young daughter, moving into a new apartment by himself and experiencing a significant decrease in his income due to the COVID-19 pandemic. He also reported his marijuana usage to me hesitantly because he was afraid that reporting marijuana usage would

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interfere with his medical insurance coverage: "I know I gotta be honest with ya'll, but are you gonna report that I smoke? Will it take away my insurance?" I made sure to commend him for being upfront and honest about his health habits, and I followed up with the team about his concerns regarding his insurance coverage.

One of the most important clinical decisions is the correct diagnosis. For Mr. Adamson, the additional information he provided—at some perceived risk to himself—was formative in our attempt to find the correct diagnosis.

Clinical Question

What is the prevalence and effect of cannabis use in association with acute pancreatitis (AP) in absence of other common risk factors, such as in idiopathic pancreatitis cases?

Research Article

Simons-Linares CR, Barkin JA, Wang Y, et al. Is There an Effect of Cannabis Consumption on Acute Pancreatitis?. *Dig Dis Sci*. 2018;63(10):2786-2791. https://doi.org/10.1007/s10620-018-5169-2 [1]

Description of Related Literature

An initial PubMed literature search using keywords "acute pancreatitis" AND "cannabis" revealed 44 results. Our goal was to evaluate the prevalence of cannabis use in association with AP in absence of other risk factors, so studies of cannabis-associated pancreatitis with other associated etiologies, cannabinoids used as therapy for AP, and the effect of cannabis on multiple gastrointestinal disorders were among the results and excluded from review. To further narrow our results, filtering for publication date of 10 years and filtering for age of "Middle Aged + Aged: 45+ years" and "Middle Aged: 45-64 years," narrowed the search to 7 results.

Simons-Linares et. al 2018 is a retrospective cohort study that identified the prevalence of cannabis use among patients with a first episode of AP, including those labeled as idiopathic etiology.[1] 21% of patients were classified as having idiopathic pancreatitis, with 10% of these patients being cannabis users, which is similar to the prevalence of marijuana use in the general population.9 Overall prevalence of cannabis-association with AP in idiopathic AP was 1.96%. This article was chosen because it not only identified the prevalence of cannabis use in AP patients, but also identified the prevalence and association of it in cases listed as idiopathic pancreatitis, which was our main clinical question.

Simons-Linares et. al 2019 is a retrospective cohort study that identified the prevalence of cannabis use among all AP cases between the years of 2003 and 2013.[2] It was the first large-scale cohort study that evaluated more than 2.8 million AP patients and found that cannabis exposure comprised of 0.3% of these patients. Cannabis exposure was associated with lower inpatient mortality, morbidity and hospitalization cost than non-cannabis exposed patients. This article was not chosen because it only compared the cannabis exposure group versus the no-exposure group. It did not distinguish the group of patients that used cannabis and had no other common risk factors or associations with AP, which was our study population of choice.

Culetto et. al 2017 is a prospective observational study that aimed to identify the percentage of AP patients over four years that was associated with cannabis exposure.[3] Cannabis use composed 2.9% of the cohort, but 17% of these patients also had co-factors, such as alcohol consumption and genetic risk that would contribute to the incidence of AP. As a result, this study was not used because it did not evaluate for prevalence of patients that only had cannabis use as their possible AP etiology. Interestingly, the authors noted that AP did not recur when patients eliminated cannabis use, and patients usually did not reveal their consumption of marijuana spontaneously, often not revealing the information until after one or more consultations.

Culetto et. al 2015 is a prospective cohort study that was not chosen because its aim was to compare the prevalence of different types of etiologies of AP between the cohort of <35 years of age and the cohort of >35 years of age.[4] The goal of our clinical question was to evaluate the prevalence of cannabis-associated AP in absence of other risk factors in the general population, not stratified by

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age. However, it was interesting to learn from this article that AP with a cannabis etiology was more prevalent in the cohort of patients aged <35 years of age than the cohort of patients aged >35 years of age (13% versus 1%, $p < 0.0001$).

Njei et. al 2014 is a retrospective cohort study that was not chosen because it studied the association of cannabis use on increased risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.[5] Our clinical question is focused specifically on cannabis-associated pancreatitis, not other etiologies of pancreatitis, such as ERCP-associated pancreatitis.

Charilaou et. al 2017 is a retrospective cohort study that aimed to evaluate the prevalence and incidence of cannabis use as seen on discharge coding between 2002 and 2011 and its associated comorbidities.[6] It was interesting how the authors identified increasing incidence of AP admissions within the cannabis use inpatient population. However, this was associated with a significant increase in incidence of gallstone disease, which is a common etiology of AP. We wanted to associate the sole effect of cannabis use on incidence of AP when no other etiologies were identified, so this data was not able to address our main clinical discussion.

de Vries et. al 2017 was not chosen because it studied the effect of THC as pain management therapy for patients with chronic abdominal pain.[7] It does not address our clinical question of etiological association between cannabis use and AP onset.

A search was repeated on PubMed in hopes of furthering our literature search by using keywords “acute pancreatitis” AND “cannabis-induced,” which gave 17 results. However, these results consisted of case reports and systematic reviews, so no articles were chosen for review. Google Scholar was explored by searching for the chosen Simons-Linares et. al 2018 article and filtering the Related Articles to include “acute pancreatitis” and “cannabis” in the title and limiting to publication range of the last 10 years. This yielded 47 results consisting of articles previously reviewed and case reports and systematic reviews. No additional articles were chosen for review. Finally, MeSH terms reviewed on PubMed for the chosen Simons-Linares et. al 2018 article included “cannabis*,” “pancreatitis/etiology*,” and “pancreatitis/mortality.” Results did not yield articles that associated cannabis use with onset of AP, so no additional articles were chosen for review.

The Grade of Recommendation for Cannabis use as a cause of acute pancreatitis is B, based on lower quality studies.[8]

Critical Appraisal

Simons-Linares et. al 2018 is a retrospective cohort study that evaluated all patients above 18 years of age admitted with a first episode of AP to a tertiary referral hospital in Chicago between January 2013 and December 2014. Mr. Adamson fell into this inclusion criteria. Patients excluded from the study included those who were pregnant, had previous history of AP or were transferred from another hospital. Mr. Adamson did not meet these exclusion criteria. This study falls under Level of Evidence 2 according to SORT criteria[8] and was not sponsored.

Data was collected from the hospital’s electronic medical record, including demographic information, clinical history including evaluation of possible AP etiologies, past medical history, social history, medications, vital signs, physical exam findings, serological data and radiographic data. AP was defined per ICD-9 code of lipase level greater than three times the upper limit of normal and abdominal pain consistent with AP. Thorough collection of data is appropriate in determining diagnoses of AP since AP can be diagnosed based on clinical presentation (epigastric pain radiating to the back), serological data (lipase level of three times the upper limit of normal) and imaging (AP findings on CT or MRI).[9] Two out of the three criteria need to be met, hence why it is necessary to evaluate for all these findings. There is no evidence of selection bias and using hospital medical records reduces the chance of recall bias. However, as demonstrated in our clinical-social context, a trusting doctor-patient relationship was required to include cannabis use in the differential diagnosis, which we cannot confirm was consistent across the study participants.

Cannabis use was identified from social history documentation or positive urine toxicology report. In Mr. Adamson’s case, his cannabis use was confirmed through both these methods. In this study, cases of idiopathic pancreatitis were evaluated further to ensure ruling out of common AP etiologies. Severity of AP was also determined by calculating the Bedside Index for Severity of Acute Pancreatitis (BISAP) and evaluating data of hospital length of stay, ICU transfer and comorbidities, including respiratory distress or failure, acute kidney injury (AKI), SIRS and pancreatic necrosis on CT scan. It is important to evaluate for etiologies of AP to address the primary problem and prevent progression of AP into chronic pancreatitis. Severity of AP is also often determined on admission

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using severity or mortality scores such as BISAP, Ranson's Criteria, and the APACHE II score to determine the current state of the pancreatitis and possibly guide management.

Authors of this study used a multivariable logistic regression model constructed from STATA software and constructed locally weighted scatterplot smoothing (LOWESS) plot models to evaluate trends and relationships between key variables. Upon evaluation, 460 patients met cohort inclusion criteria and 10% of these patients were identified as cannabis users. 21% of the 460 patients were classified as idiopathic AP and prevalence of cannabis among this idiopathic AP population was 10%. Seeing as the prevalence of cannabis use in the adult US population is around 9.5%, it is unclear whether cannabis has a statistically significant association with AP or the 10% prevalence in the general cohort and 10% prevalence in the idiopathic AP cohort is merely consistent with the prevalence of the general population.[9] Furthermore, the study lists overall prevalence of cannabis-association with AP in previously classified idiopathic AP was 2%. It is unclear how the authors of this study came to this calculation and why the other cannabis users in this idiopathic AP cohort were not considered to have cannabis-associated AP.

Univariate and multivariate analysis was used to evaluate the effect of cannabis use on AP. On univariate analysis, Acute kidney injury (AKI) was less common among non-cannabis users compared to cannabis users (OR 0.4; p = 0.02; 95% CI 0.2–0.9). After adjusting for admission age, gender, and SIRS, multivariate analysis showed that cannabis use was not found to be a significant risk for persistent SIRS, AKI, ARDS, pancreatic necrosis, mortality, ICU admission, length of stay, or in-hospital infections. Multivariate analysis also did not support a significant impact of cannabis use on AP recurrence rate within one year of initial AP diagnosis, with overall AP recurrence rate for the 460-patient cohort being 19.8% and the cannabis-using cohort being 18.8%. Evaluating the effect of cannabis on comorbidities, mortality, length of stay, in-hospital infections and AP recurrence rate make this a more patient-centered study.

Clinical Application

Mr. Adamson fits into the general picture of cannabis-associated AP, including being of the male sex and being of African American descent.[6] However, since he is 57 years old, he does not fall into the most common age range associated with cannabis use, age less than 35. Regardless, Mr. Adamson is proactive in taking care of his health, endorsing a balanced diet, daily exercise, abstinence from alcohol and compliance with his HIV antiretroviral therapy.

He acknowledged that significant cannabis use was probably not good for his health, and he was partaking in this activity almost absentmindedly as a coping mechanism for stress management. Seeing as Simons-Linares et. al 2018 did not identify a difference in AP recurrence between cannabis and non-cannabis use, we told Mr. Adamson that his acute increase in cannabis use was most likely not the cause for his AP. Since there were no other causes identified at the time, he was diagnosed with idiopathic acute pancreatitis.

Despite the diagnosis, we counselled Mr. Adamson on decreasing and ideally quitting marijuana use, seeing as some literature show that withdrawal of cannabis use leads to lower likelihood of recurrence of AP.[3,4] Mr. Adamson did not consider that his condition could come back, so he voiced that the risk of recurrence would motivate him to decrease his marijuana usage.

Abstaining from marijuana use would also allow him to save money and relieve him of a portion of financial burden, seeing as he was paying for marijuana weekly and part of his stress was due to a decrease in his income. We discussed with him healthier coping strategies to deal with stress, such as continuing with his exercise routine and interacting with peers that would support him in a healthier lifestyle.

Mr. Adamson listened and reflected on his experience the last few months. He understood that decreasing and eventually eliminating his marijuana usage would only be an additive benefit to his current healthy habits, stating, "pot is probably the only thing holding me back from being completely healthy – would probably decrease my stress level, too, if I cut back, so that I won't feel so dependent on it." As a result, he was amenable to our recommendations. The care team also made sure to commend and encourage the continuation of his current healthy behaviors.

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New Knowledge Related to Clinical Decision Science

Acute pancreatitis is the most common gastroenterology-related cause of hospitalization in the US and, cannabis is the most used illicit drug in the world.[10,11] Cannabis use frequency is also going to increase with time, seeing as many communities are legalizing and decriminalizing the use of the drug. Because of these facts, it is valuable to ask a patient about cannabis use during history taking, regardless of age of the patient. It is especially appropriate as a point of follow up in the outpatient setting. Conversations of socioeconomic determinants of health are needed to determine best practice of care for each individual and resources can be made available to help patients understand how social determinants perpetuate cannabis usage. Other socioeconomic factors that may accompany cannabis usage, such as alcohol intake, have also been found to be associated with pancreatitis and must be considered when diagnosing etiology of AP.

In addition to Mr. Adamson's demographic information and lack of risk factors, it is important to consider that he was very well informed about his medical history and was determined to understand the cause of his abdominal pain and elevated lipase level. He had researched different causes of these symptoms and had discussed them with the team on admission. After discussion, he was told by his providers that his lab values and history did not clearly point to an etiology, and this prompted him to reveal the extent of his cannabis use. Prior to this, he had been concerned that reporting this information would affect his insurance coverage. However, seeing that the most common etiologies of AP had fallen lower on the differential diagnosis, his desire to understand his condition motivated him to reveal his cannabis use to the team in hopes that the information would give further insight into the cause of his current presentation. This case illustrates that the most important clinical decision was a correct diagnosis. Additionally, it highlights the multiple social factors that were critical to obtaining correct data to make a correct diagnosis.

However, it is important to be sensitive when inquiring about marijuana usage, seeing how it still has a reputation for being an illicit drug, preventing patients from being comfortable revealing this information. As a result, healthcare providers should make sure to provide a safe and comfortable environment for the patient, and to reassure and be supportive when patients gather the courage to reveal sensitive information. It is also worth understanding how documenting usage of illicit substances can affect a patient's medical coverage and be transparent about these consequences with the patient. Although it is still unknown if and how cannabis can cause pancreatitis, the prevalence of cannabis use and association with pancreatitis cannot be ignored and requires further study.

Conflict Of Interest Statement

The author reports no conflicts of interest.

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