Clues emerging to mysterious cannabinoid hyperemesis syndrome

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One morning in 2003, Mike Ackersviller was sipping a cup of coffee ahead of a computer game tournament in London, Ont., when he noticed something was off. Rushing to the bathroom, he vomited. But the nausea didn't stop. He spent the rest of the day dry-heaving on the bathroom floor. "I couldn't drink water," Ackersviller said. "I couldn't put anything into me."

By 7 p.m., intense stomach pain prompted him to visit his local emergency room.

Ackersviller said hospital staff couldn't figure out what was wrong with him and assumed he was sick from a night of drinking. So, they gave him intravenous fluids, anti-nausea pills and painkillers before discharging him.

Returning home to Stratford, Ont., Ackersviller started vomiting again when the medications wore off. He spent the next two weeks in and out of the hospital. "I had to get an IV to top me full of fluids," he said. "Anytime I tried to eat or drink anything, I just kept puking it up."

Ackersviller suffered recurring bouts of vomiting for another 17 years before he was diagnosed with cannabinoid hyperemesis syndrome (CHS). Looking back, he identifies that harrowing day in the London hotel room as his first major attack.

Cannabinoid hyperemesis syndrome is a relatively newly-defined condition. Australian physician, James Allen, first described it in 2004, one year after Ackersviller's initial episode.

Patients are often misdiagnosed with cyclical vomiting syndrome — both conditions involve abdominal cramping, nausea, and repeated severe bouts of vomiting. The main difference is CHS affects patients with a history of daily, long-term cannabis use.

Researchers are now studying why this poorly understood condition occurs, why some people are more susceptible than others, and potential treatment options.

A recent systematic review on CHS management found abstaining from cannabis use is the most successful method to alleviate symptoms of nausea and vomiting. Other treatment options include hot water hydrotherapy, topical capsaicin cream, haloperidol, droperidol, benzodiazepines, propranolol, and aprepitant. Synthetic cannabinoids, such as nabilone, are another accepted treatment option; however, there is a lack of data regarding the adverse effects of its prolonged use.

According to the 2021 Canadian Cannabis Survey, one in five Canadians who reported cannabis consumption in the last 12 months were daily users.

Christopher Andrews, a Calgary-based gastroenterologist, estimates that one in every 200 frequent cannabis users between the ages of 16 and 44 will get CHS.

His research published in the journal *Alimentary Pharmacology & Therapeutics* shows that people can develop CHS unpredictably. "We see people develop it in their 50s, 60s, even later with a lifetime of use," he said. "We don't know what flips the switch."

Some have hypothesized this may be due to cannabis having different effects on the brain and digestive tract. Early on, the drug's anti-nausea effect on the brain may suppress its irritative effects on the digestive tract but, over time, changing receptor sensitivity may trigger bouts of vomiting.

Ackersviller chalked up the vomiting to smoking a laced joint at the computer game tournament and he went back to using cannabis after his initial CHS attack.

"I had no clue who I smoked with a lot of the times," he said. "So, my original reaction was maybe somebody just had something weird in their doob that threw me off."

After his first CHS episode, Ackersviller went on to experience extended bouts of nausea, vomiting and stomach pain about once every three years, then annually. The worst attack lasted almost six weeks. Ackersviller described the stomach pain during that episode as being worse than when he broke his femur snowboarding.

"If someone gave me a choice of that pain for six weeks or breaking my other leg, I'd want them to break my leg," he said.

Hot baths provided some relief, Ackersviller said. However, he still had vomiting bouts months after quitting cannabis.

Tetrahydrocannabinol, the main psychoactive component in cannabis, is fat-soluble and can stay in the body for months. One theory posits that the body releases a build-up of fat-soluble chemicals during times of stress that interact with the hypothalamus, a region of the brain responsible for maintaining physiological cycles, disrupting temperature regulation and brain–gut connections.

"That's why there could be an increase in nausea and vomiting," said Taylor Lougheed, an emergency physician and cannabinoid medicine specialist based in North Bay, Ont. It may also explain why attacks can occur even after patients quit cannabis, and why warm baths might provide temporary relief.

Tetrahydrocannabinol is only one of the chemicals that may be involved in CHS. "There are hundreds of cannabinoids, as well as other chemicals, flavonoids and terpenes," Lougheed said. "We're really just

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now starting to scratch the surface in terms of doing a deeper dive and an appreciation for how these chemicals interact and how they might have effects on the body."

Cannabinoid hyperemesis syndrome usually follows three stages. In the early "prodromal" phase patients experience mild symptoms such as nausea, decreased appetite, or an upset stomach. Some will remain in the prodromal phase long term. Others may progress to the "hyperemetic phase," and experience persistent, painful vomiting. Severe bouts of vomiting can lead to electrolyte abnormalities, dehydration, and kidney injury. The final "recovery" phase begins when a patient abstains from cannabis and their symptoms subside.

Marco Sivilotti is an emergency physician and medical toxicologist in Kingston, Ont. He is researching treatments for CHS patients in the hyperemetic phase. "It is, in some ways, just vomiting, but it's a lot of vomiting," he said. "It's very upsetting for everyone and it's still quite mysterious."

Sivilotti worked on a 2019 study that found CHS patients had the same concentrations of cannabis in their hair as control groups of recreational cannabis users without CHS and patients with unrelated conditions who had THC in their urine. The study, published in the *Canadian Journal of Emergency Medicine,* underscored that heavy cannabis use may not be the only factor involved in the development of CHS.

"Some have really bad hyperemesis and some have none at all," he said. "So, there may be something else in there that we don't yet fully understand."

Sivilotti was also the principal investigator in a clinical trial published in the *Annals of Emergency Medicine* that found IV-administered haloperidol, a drug normally used to treat mood disorders, was more effective than the anti-nausea medication ondansetron for treating CHS symptoms. Such studies can help pinpoint how cannabis interacts with certain receptors in the brain, Sivilotti said.

"The fact that you see a difference in two drugs is often how we help shed light on what's actually going on under the hood," he said. However, "it's not immediately obvious why haloperidol would be more efficacious."

The potency of certain cannabis products may also factor in CHS.

Ackersviller used to dab, a method of consuming cannabis that involves heating up and inhaling high-strength THC concentrates called wax or shatter.

Canada's *Cannabis Act* does not regulate THC potency in the recreational sale of these solid concentrated extracts, in which potency can exceed 90%. By comparison, THC levels in commercial dried cannabis average between 15% and 20%. The Canadian Institutes for Health Research (CIHR) are funding studies to learn more about the health and safety of cannabis ahead of a mandated review of the impacts and administration of the *Cannabis Act*.

Health Canada announced the launch of the legislative review in a news release in late September.

The review, which was supposed to begin in October 2021, will be led by an independent panel in consultation with experts in relevant fields, such as public health, substance use, criminal justice, law enforcement, and health care.

The minister of health will report results to Parliament 18 months after starting the review.

Christopher Andrews presented a research summary to CIHR during a three-day virtual workshop in 2020, along with 25 other research teams.

Andrews' study was the first to report that the vast majority of patients with CHS meet criteria for cannabis use disorder. Sixty-one people with CHS reported a 10-year median duration of cannabis use and 85.2% identified as daily users. In 2019, 94% had been hospitalized for at least one CHS attack.

Based on the current evidence, "I would suspect the policy-makers probably wouldn't move to ban any kind of flower you can grow," he said. "But the concentrates? If they capped it at a certain level, it might be worthwhile."

Kevin Zannese, Ottawa

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