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Cannabinoid Hyperemesis Syndrome

https://www.cedars-sinai.org/health-library/diseases-and-conditions/c/cannabinoid-hyperemesis-syndrome.html

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No Disclosures

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What is cannabinoid hyperemesis syndrome?

- Cannabinoid hyperemesis syndrome (CHS) is a condition that leads to repeated and severe bouts of vomiting. It is rare and only occurs in daily long-term users of marijuana
- Marijuana is the most widely used illegal drug in the U.S. Young adults are the most frequent users. A small number of these people develop CHS. If often only happens in people who have regularly used marijuana for several years. Often CHS affects those who use the drug at least once a day.

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What causes cannabinoid hyperemesis syndrome?

Marijuana has very complex effects on the body. Experts are still trying to learn exactly how it causes CHS in some people.

In the brain, marijuana often has the opposite effect of CHS. It helps prevent nausea and vomiting. The drug is also good at stopping such symptoms in people having chemotherapy.

But in the digestive tract, marijuana seems to have the opposite effect. It actually makes you more likely to have nausea and vomiting. With the first use of marijuana, the signals from the brain may be more important. That may lead to anti-nausea effects at first. But with repeated use of marijuana, certain receptors in the brain may stop responding to the drug in the same way. That may cause the repeated bouts of vomiting found in people with CHS.

It still isn't clear why some heavy marijuana users get the syndrome, but other's don't.

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What are the symptoms of cannabinoid hyperemesis syndrome?

People with CHS suffer from repeated bouts of vomiting. In between these episodes are times without any symptoms. Healthcare providers often divide these symptoms into 3 stages: the prodromal phase, the hyperemetic phase, and the recovery phase

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Prodromal Phase

During this phase, the main symptoms are often early morning nausea and belly (abdominal) pain. Some people also develop fear of vomiting. Most people keep normal eating patterns during this time. Some people use more marijuana because they think it will help stop the nausea. This phase may last for months or years.

Hyperemetic Phase

Symptoms during this time may include:

- Ongoing nausea
- Repeated episodes of vomiting
- Belly pain
- Decreased food intake and weight loss
- Symptoms of fluid loss (dehydration)

During this phase, vomiting is often intense and overwhelming. Many people take a lot of hot showers during the day. They find that doing so eases their nausea. (That may be because of how the hot temperature affects a part of the brain called the hypothalamus. This part of the brain effects both temperature regulation and vomiting.) People often first seek medical care during this phase.

The hyperemetic phase may continue until the person completely stops using marijuana. Then the recovery phase starts.

Recovery Phase

During this time, symptoms go away. Normal eating is possible again. This phase can last days or months. Symptoms often come back if the person tries marijuana again.

How is cannabinoid hyperemesis syndrome diagnosed?

Based on symptoms, a healthcare provider may order the following:

- Blood tests for anemia and infection
- Tests for electrolytes
- Tests for pancreas and liver enzymes, to check these organs
- Pregnancy test
- Urine analysis, to test for infection or other urinary causes
- Drug screen, to test for drug-related causes of vomiting
- X-rays of the belly, to check for things such as a blockage
- Upper endoscopy, to view the stomach and esophagus for possible causes of vomiting
- Head CT scan, if a nervous system cause of vomiting seems likely
- Abdominal CT scan, to check for health problems that might need surgery

You may have CHS if you have all of these:

- Long-term weekly and daily marijuana use
- Belly pain
- Severe, repeated nausea and vomiting
- You feel better after taking a hot shower

There is no single test that confirms this diagnosis. Only improvement after quitting marijuana confirms the diagnosis.

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How is cannabinoid hyperemesis syndrome treated?

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If you have had severe vomiting, you might need to stay in the hospital for a short time. During the hyperemesis phase, you might need these treatments:

- IV (intravenous) fluid replacement for dehydration
- Medicines to help decrease vomiting
- Pain medicine
- Proton-pump inhibitors, to treat stomach inflammation
- Frequent hot showers
- Prescribed medicines that help calm you down (benzodiazepines)
- In a small sample of people with CHS, rubbing capsaicin cream on the belly helped decrease pain and nausea. The chemicals in the cream have the same effect as a hot shower

Symptoms often ease after a day or 2 unless marijuana is used before this time.

To fully get better, you need to stop using marijuana all together. Some people may get help from drug rehab programs to help them quit. Cognitive behavioral therapy or family therapy can also help. If you stop using marijuana, your symptoms should not come back.

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Key points about cannabinoid hyperemesis syndrome

CHS is a condition that leads to repeated and severe bouts of vomiting. It results from long-term use of marijuana

Most people self-treat using hot showers to help reduce their symptoms.

Some people with CHS may not be diagnosed for several years. Admitting to your healthcare provider that you use marijuana daily can speed up the diagnosis.

You might need to stay in the hospital to treat dehydration from CHS.

Symptoms start to go away within a day or 2 after stopping marijuana use.

Symptoms almost always come back if you use marijuana again.

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NASH and NAFLD

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Agenda

- Approaches to Weight Loss and Effect on the Liver
  - Diet and Exercise
- Recommended Pharmacologic Therapies for NASH
  - Vitamin E: Recent Evidence in NAFLD/NASH
  - Pioglitazone: Recent Evidence in NAFLD/NASH
- Role of Current Diabetes Therapies in NAFLD/NASH
  - GLP-1 Ras
  - SGLT2 Inhibitors

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How to Deliver Effective Lifestyle Change in the Real World

- Explain what NAFLD is and that it is reversible with lifestyle change; address misconceptions, e.g., alcohol being the cause of NAFLD
- Explain energy balance in relation to body weight changes
- Set a SMART weight loss target
- Use appropriate interventions, e.g., regular meal patterns, reduced snacking, portion control, avoid fast food and night eating
- Encourage use of self-regulation/self-monitoring tools: regular weighing, calorie and activity diary/app/website, read nutrition information labels, develop skills in meal planning, shopping, food preparation, and cooking
- Signposting to local exercise schemes, community gyms, weight management programs, walking groups

Hallsworth. JHEP Reports. 2019;1:468.

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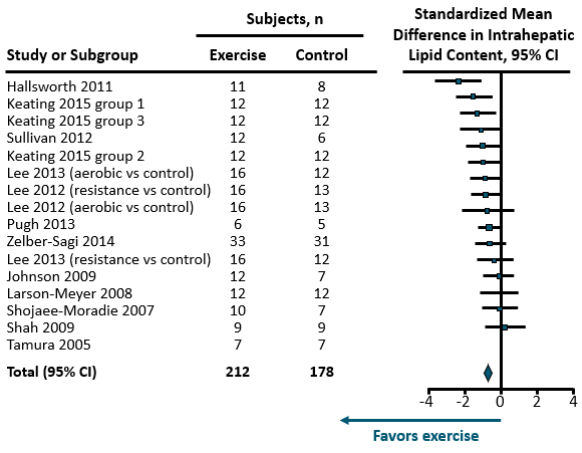
Exercise in NAFLD: Effect on Liver Fat and ALT

- 28 randomized trials of exercise-based interventions in patients with NAFLD and underlying metabolic disorders (N = 1644)
- Reduction in intrahepatic lipid content
  - Standardized mean difference:
  - -0.69 (95% CI: -0.9 to -0.48)
- Reduction in **ALT**
  - Weighted mean difference:
  - -3.30 IU/L (95% CI: 5.57 to -1.04)



Orci. Clin Gastroenterol Hepatol. 2016;14:1398.

Slide credit: clinicaloptions.com

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Lifestyle Guidelines in NASH

	AASLD 2018[1]	EASL 2016[2]	APASL 2020[3]
Program	Lifestyle modification including **dietary change**, **weight loss**, and structured **exercise** intervention		
	500-1000 kcal energy deficit to induce a weight loss of 500-1000 g/wk		
Diet	▪ Prospective trials comparing macronutrient diets in NAFLD are limited	▪ Exclusion of NAFLD-promoting components (processed food, added fructose) ▪ Mediterranean diet suggested	
Weight Loss	7% to %10% weight loss is the target of lifestyle interventions to improve NASH and fibrosis		
Exercise	▪ Exercise alone may prevent/ reduce hepatic steatosis – Effect on other aspects of liver histology unknown	▪ Both aerobic exercise and resistance training reduce liver fat – Tailor to patient preferences	
Bariatric Surgery	▪ Reduces liver fat, improves histologic lesions of NASH, including fibrosis	▪ Individualize decision in cirrhosis	

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. Eslam. Hepatol Intern. 2020;14:889.

Slide credit: clinicaloptions.com

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Low-Carbohydrate Diet: Meta-analysis of Effect on Intrahepatic Lipid Content in NAFLD

Studies

- Meta-analysis of 10 international clinical trials of **low-carbohydrate (<50%) diets** in patients with NAFLD
  - 10 evaluated ALT (n = 238)
  - 9 evaluated AST (n = 216)
  - 5 evaluated GGT (n = 91)
  - 4 evaluated intrahepatic lipid content (n = 50)

Results

- Low-carbohydrate diets associated with **significant reduction in intrahepatic lipid content** by -11.53% (95% CI: -18.10% to -4.96%; I^2 = 83.2%)
- Nonsignificant reductions in serum ALT, AST, GGT
- An updated meta-analysis did not find a difference between **low-carbohydrate diet** and **low-fat diet**

Haghighatdoost. J Res Med Sci. 2016;21:53. Ahn. Clin Nutr. 2019;38:2023. Bueno. Clin Nutr. 2020;39:P310.

Slide credit: clinicaloptions.com

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Sustained Weight Loss Through Lifestyle Modification

Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr[1]
≥10%[1]	Fibrosis regression	<10%
≥7%[1]	NASH resolution	18%
≥5%[1-3]	Ballooning/inflammation improvement	30%
≥3%[1-4]	Steatosis improvement	Not reported

1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.
3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

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Recommended Pharmacologic Therapies for NASH

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Pharmacotherapy in NAFLD Reserved for Patients with NASH and Fibrosis

AASLD[1]	EASL-EASD-EASO[2]	APASL[3]
▪ Pharmacologic treatments should generally be limited to those with ***biopsy-proven NASH*** and fibrosis	▪ Pharmacotherapy should be reserved for *patients* ***with NASH, particularly if significant fibrosis***. ▪ Patients with less severe disease, but at high risk of progression (diabetes, MetS, persistently increased ALT, high necroinflammation) could also be candidates	▪ Patients ***without steatohepatitis or fibrosis*** should receive counseling for a healthy diet and physical activity and ***no pharmacotherapy*** for their liver disease

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. Eslam. Hepatol Intern. 2020;14:889.

Slide credit: clinicaloptions.com

Pharmacotherapy in NAFLD and NASH (Off Label)

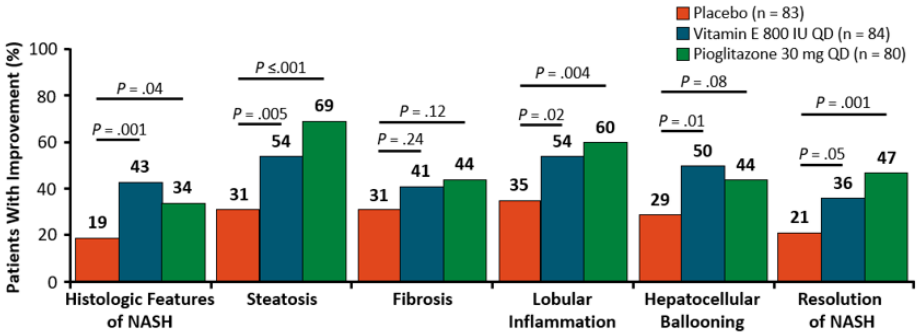
	AASLD 2018[1]	EASL-EASD-EASO 2016[2]	APASL 2020[3]
Vitamin E	**Recommended** in nondiabetic patients with biopsy-proven NASH (800 IU/day)	**Recommended** (800 IU/day)	Insufficient evidence, no firm recommendation
Pioglitazone	**Recommended** in patients with and without T2D and biopsy-proven NASH	**Recommended** in patients with T2D and biopsy-proven NASH	
Metformin	Not recommended		
Statin	▪ Can be used to treat dyslipidemia, not NASH ▪ No higher risk for serious liver injury		Reduce cardiovascular mortality, consider in all NAFLD patients with hyperlipidemia
UDCA	Not recommended		Not mentioned
Omega-3 Fatty Acids	▪ Not a specific treatment of NAFLD ▪ Consider to treat hypertriglyceridemia		Not mentioned
Obeticholic Acid	Further data needed		
GLP-1 RAs	Further data needed		Improve fibrosis, weight
SGLT2 Inhibitors	Not mentioned		Further data needed

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. Eslam. Hepatol Intern. 2020:14:889.

Slide credit: clinicaloptions.com

PIVENS: Pioglitazone and Vitamin E in NASH at 96 Wk

- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



Sanyal. NEJM. 2010;362:1675.

Slide credit: clinicaloptions.com

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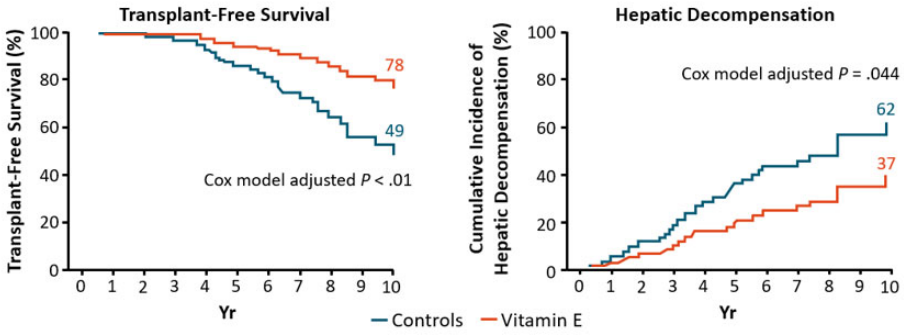
Vitamin E Improves Transplant-Free Survival and Hepatic Decompensation in NASH

- Single-center study of patients with biopsy-proven NASH and bridging fibrosis or cirrhosis (N = 236) followed for median 5.62 yr



Vilar-Gomez. Hepatology. 2020;71:495.

Slide credit: clinicaloptions.com

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Safety and Tolerability

Vitamin E (800 IU/day)

- Possible all-cause mortality risk at > 800 IU/day,[1] not confirmed by a subsequent meta-analysis[2]
- Increased hemorrhagic stroke risk[3]
  - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = .008)[4]

Pioglitazone

- Edema, weight gain (~2-3 kg over 2-4 yr)[5]
- Risk of osteoporosis in women[6]
- Equivocal bladder cancer risk
  - Increased in some studies[7]
  - No association in most studies[8]

Use of these agents should be personalized for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio

1. Miller. Ann Intern Med. 2005;142:37. 2. Abner. Curr Aging Sci. 2011;4:158. 3. Schurks. BMJ. 2010;341:c5702. 4. Klein. JAMA. 2011;306:1549.
5. Bril. Diabetes Care. 2017;40:419. 6. Yau. Curr Diab Rep. 2013;13:329. 7. Tuccori. BMJ. 2016;352:i1541. 8. Lewis. JAMA. 2015;314:265.

Slide credit: clinicaloptions.com

Statins Lower Risk of Portal Hypertension in Cirrhosis

- Systematic review and meta-analysis of statin use in patients with cirrhosis
  - 8 studies (7 RCTs, 1 cohort study; N = 3195); pooled relative risk and 95% CI calculated by random effects model
- Relative risk for primary outcome (improvement in portal hypertension) with statins vs control: 1.91 (95% CI: 1.04-3.52; I^2 = 63%)
  - Sub-analysis showed 1 mo of statin use may be sufficient vs 3 mo

Analysis	Statin		Control		Risk Ratio (95% CI)	*P* Value
	Events*	n	Events*	n		
Overall	67	148	42	153	1.91 (1.04-3.52)	.04
1 mo statin use	35	82	17	83	2.01 (1.31-3.10)	.002
3 mo statin use	32	66	25	70	3.76 (0.36-39.77)	.27

*Event: Decrease in HVPG >20% or <12 mm Hg.

Wan. BMJ Open. 2019;9:e030038.

Slide credit: clinicaloptions.com

Currently Available Agents Targeting Insulin Resistance (Off Label)

Compound	Mechanism of Action	Weight Loss	Trial in NAFLD/NASH	Outcome
Pioglitazone[1]	PPARγ agonist	-	Phase III PIVENS Multiple studies	Improvement in NAS ≥2 without fibrosis worsening
Liraglutide[2]	GLP-1 RA	+ Approved for treatment of obesity	Phase IIb LEAN	Resolution of histologic NASH without fibrosis worsening
Semaglutide[3]	GLP-1 RA	+++	Phase II	Resolution of histologic NASH without fibrosis worsening
Exenatide[4]	GLP-1 RA	+	Phase IIb	Improvement in hepatic steatosis by ultrasound
Canagliflozin[5]	SGLT2	++	Multiple studies	Improvement in liver triglycerides by ^{1}H-MRS; improvement in steatosis biomarkers
Empagliflozin[6,7]	SGLT2	+	Multiple studies	Improvement of liver fat by MRI-PDFF; improvement in CAP and liver stiffness

1. Chalasani. Hepatology. 2018;67:328. 2. Armstrong. Lancet. 2016;387:679-690. 3. Newsome. NEJM. 2021;384:1113.
4. Shao. Diabetes/Metabolism Research Reviews. 2014;30:521. 5. Cusi. Diabetes Obes Metab. 2019;21:812.
6. Kuchay. Diabetes Care. 2018;41:1801. 7. Taheri. Advanc Ther. 2020;37:4697.

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Pharmacotherapy for T2D Patients With a Need to Address Body Weight

- In adults with need to minimize weight gain or promote weight loss, guidelines recommend[1]:
  - **GLP-1 RAs** with efficacy for weight loss
  - **SGLT2** inhibitors
- Some GLP-1 Ras and SGLT2 inhibitors may have benefits in NAFLD

American Diabetes Association. Diabetes Care 2019;42(suppl 1):S90.

Slide credit: clinicaloptions.com

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SGLT2 Inhibitors in T2D and NAFLD: Umbrella Review of Systemic Reviews

Studies

- 7 systematic reviews of SGLT2 inhibitors (including between 67 and 498 patients)
  - 4 evaluated effects on **liver enzymes**
  - 4 reported changes in **liver fat**
  - 2 reported changes in **fibrosis biomarkers**

Results

- ✗ None rated as high quality, only 1 as moderate quality
- ✓ 5 systematic reviews indicated that SGLT2 inhibitors could **decrease liver fat and liver enzymes**
- ✓ 1 small, single-arm histologic study showed **improvement in steatosis**
- ✗ No evidence of **liver fibrosis** improvement

Shao. BMJ Open Diab Res Care. 2020;8:e001956.

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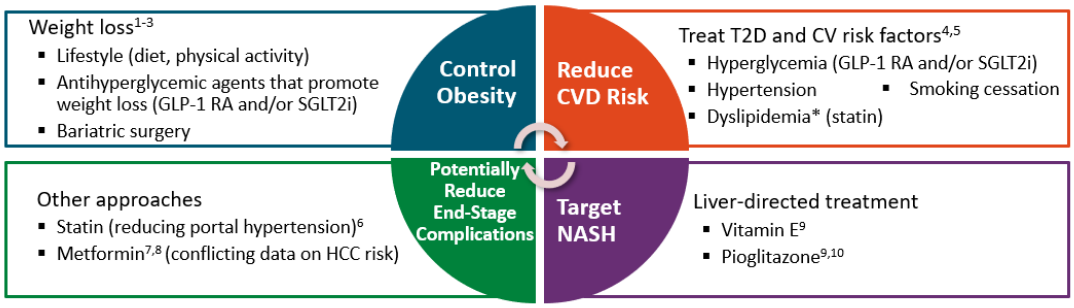
Approaches for Currently Available Treatments



*NAFLD does not increase statin risk of drug-induced liver injury.[11]
In patients with advanced liver disease, choose or dose drugs appropriately.

1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Tsochatzis. Hepatology. 2017;66:697. 7. Zhang. Scand J Gastroenterol. 2013;48:78. 8. Chen. Medicine (Baltimore). 2015;94:e1013. 9. Sanyal. NEJM. 2010;362:1675. 10. Cusi. Ann Intern Med. 2016;165:305. 11. Bril. J Clin Endocrinol Metab. 2017;102:2950.

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Summary

- Diet and exercise recommended for all
  - As little as **3%** weight loss can improve steatosis, **7% to 10%** can resolve NASH and reverse fibrosis
- No FDA-approved NASH treatments, but guidelines recommend:
  - **Vitamin E** (if no T2D)
  - **Pioglitazone**
- Diabetes therapies are being studied in NASH
  - **GLP-1 RAs** have emerging evidence for NASH resolution
  - **SGLT2 inhibitors** have emerging evidence for reducing liver fat, enzymes

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