Opiates and Gastrointestinal System

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SUBSTANCE ABUSE

Definition of Substance Abuse



SUBSTANCE ABUSE

Substance use refers to the consumption of psychoactive substances, including drugs and alcohol, that alter the mood, behavior, or perception of an individual. Substance use can range from occasional use to dependency and addiction and can have significant physical, psychological, and social consequences. Substance use is a major public health concern worldwide and is often associated with a range of health and social problems.

9 TYPES OF DRUGS

1. **Alcohol:** A depressant affecting brain function and coordination.
2. **Opioids:** Powerful pain relievers with high addiction potential. Examples: Heroin, fentanyl, oxycodone.
3. **Benzodiazepines:** Sedative drugs prescribed for anxiety and insomnia. Examples: Xanax, Valium, Klonopin.

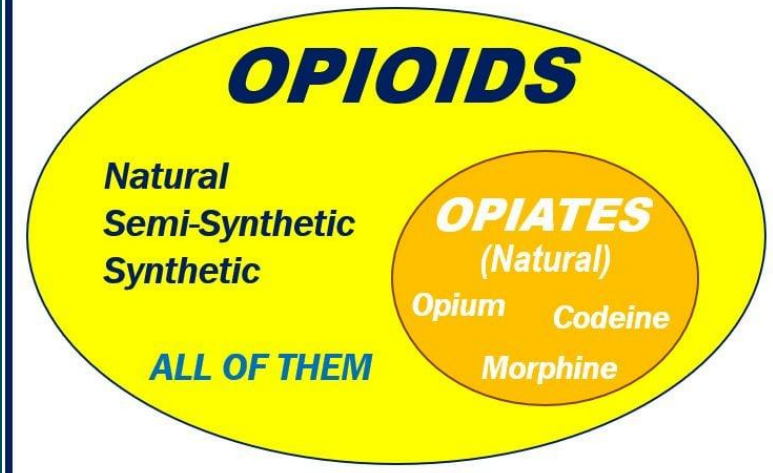




4. **Barbiturates:** Depressants once used for sleep disorders but highly addictive.
5. **Marijuana (Cannabinoids):** Affects mood, cognition, and perception. Examples: THC, CBD compounds.
6. **Inhalants:** Produce psychoactive effects when inhaled. Examples: Paint thinners, aerosol sprays, nitrous oxide.
7. **Stimulants:** Increase alertness and energy. Examples: Cocaine, methamphetamine, Adderall.
8. **Hallucinogens:** Alter perception and mood. Examples: LSD, psilocybin, MDMA.
9. **Prescription Drugs:** Medications misused for non-medical purposes. Examples: OxyContin, Ritalin, Xanax.



Opioids versus Opiates



All Opiates Are Opioids – Not All Opioids Are Opiates

Opioids refer to all natural, semisynthetic (oxycodone, hydrocodone, hydromorphone, and oxymorphone), and synthetic (methadone) opioids. Opioids used to be called narcotics.

Opiates refer to natural opioids such as heroin, crock*, morphine and codeine.

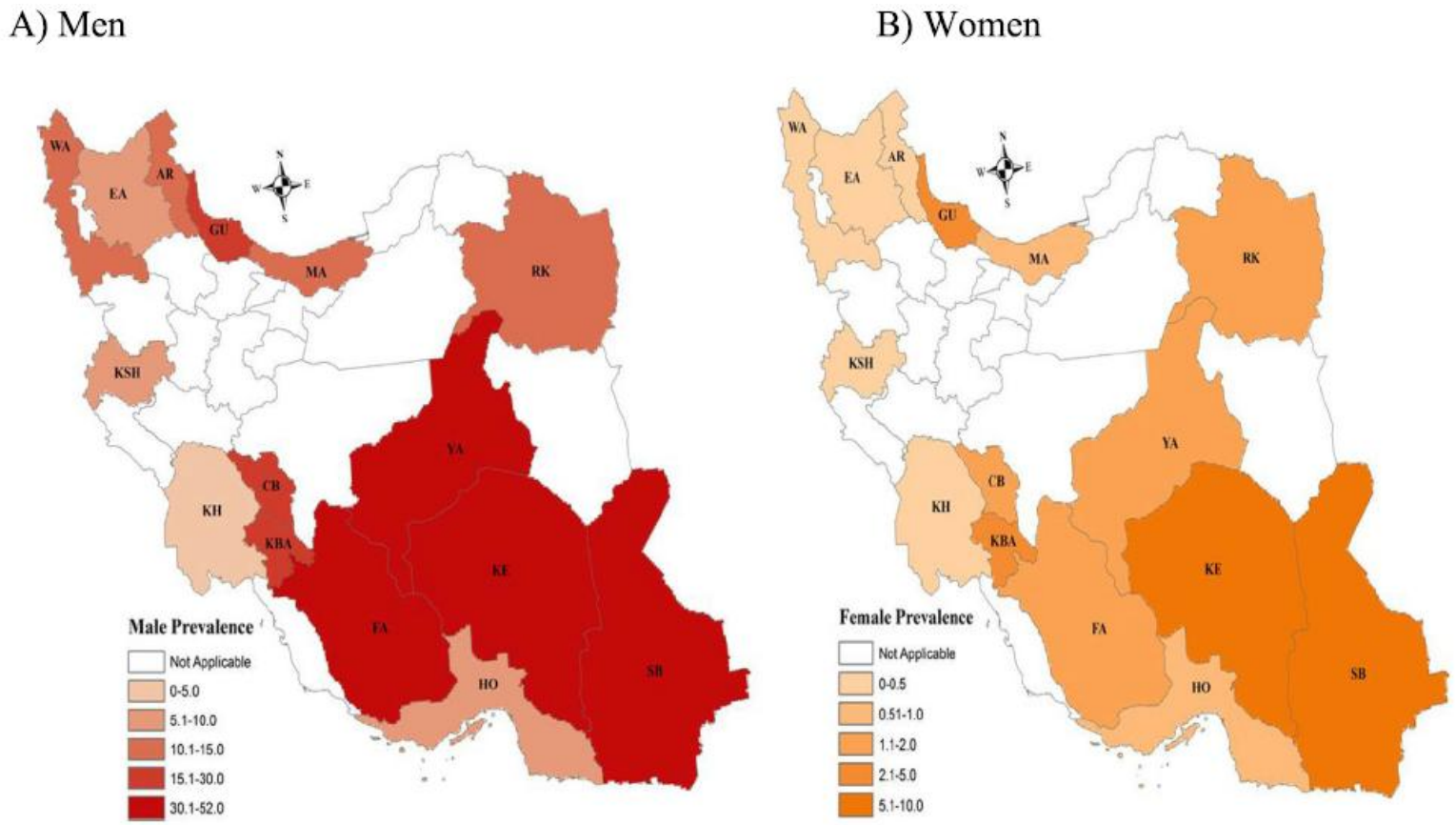
* It is different from crack that is stimulant agent and derived from cocaine .

Based on the WHO, Iran has the highest rate of opium abusers in the world, and opium use in Iran is three times the global average. The statistics show that there are about 2 million people use illicit drugs at a daily basis in Iran, which is about 2.7% of the population.

Our meta-analysis showed that

11.9% (24.1% among men versus 2.2% among women) of the adult population in Iran used the illicit drug more than one time in their lifetime.

14 and 9% of the participants were a current smoker and had history of alcohol consumption, respectively.



Prevalence of drug use in men and women across 15 provinces in Iran

Moradinazar et al. BMC 2020. 15:39.

نگاهی به وضعیت اعتیاد در ایران

ISNA

آمار مربوط به نیمه دوم سال ۹۸ و اوایل سال ۹۹ است

میانگین سن مصرف مواد مخدر در ایران ۲۴ سال است

بیشترین آمار زنان مبتلا به اعتیاد در گروه سنی ۲۳ تا ۴۴ سال است

شیوع مصرف مواد در پسران ۷/۶ درصد و در دختران ۲/۱ درصد است





یک میلیون و ۶۰۰ هزار مصرف‌کننده تفننی در کشور وجود دارد

پرمصرف‌ترین انواع مواد مخدر



تریاک



حشیش و ماری‌جوانا و گل



هروئین



مخدر شیشه

Case presentation

- A 60-year-old man → Epigastric pain
- Previously treated for *Helicobacter pylori* after confirmation of positive serology.
- Upper endoscopy → Nodularity and erythema in the stomach
- Biopsies of the stomach → multifocal intestinal metaplasia, but ***no Helicobacter pylori.***
- Habit: TERIAK(opium) daily for many years.
- FH: his brother died from gastric cancer at age 59; Her father died from MI at age 35.

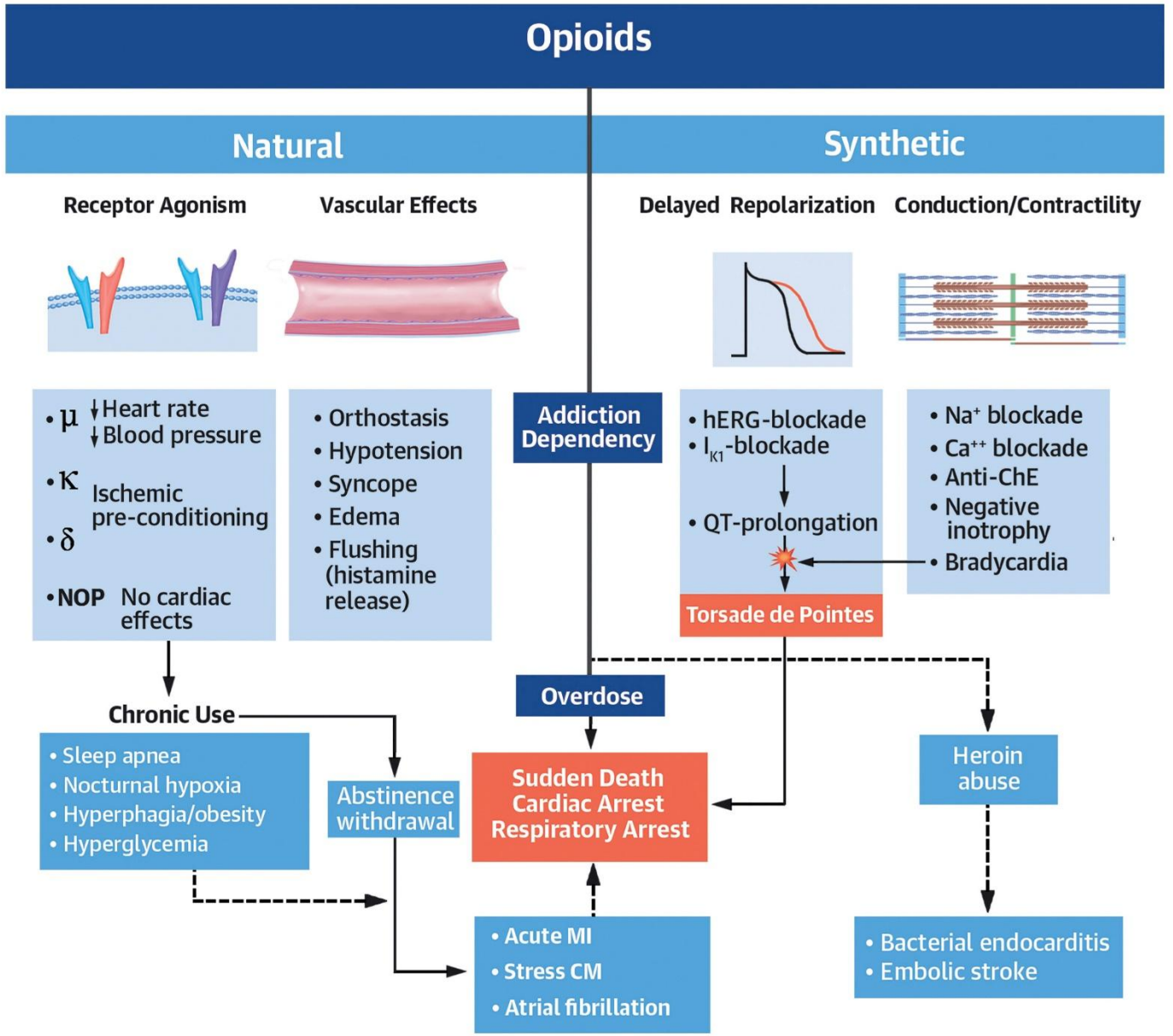
He believes the opium is a protective agent against GI cancers and cardiovascular diorders.

Opium consumption

↓ Plasma testosterone and oestrogen
↑ Plasma prolactin
↑ Insulin resistance
↑ Inflammation
↑ Oxidative stress
↑ Fibrinogen
↑ Factor VII
↓ Apolipoprotein A
↑ Apolipoprotein B
↓ Cardiac pain sensation
↓ Physical activity

↑ Coronary atherosclerosis
↑ Cardiovascular mortality

CENTRAL ILLUSTRATION: Mechanistic Framework for Cardiovascular Complications of Opioids



Krantz, M.J. et al. J Am Coll Cardiol. 2021;77(2):205-23.

Association Between Opium Consumption and Stable CAD and its Outcomes

Sadeghian et al, 2007 [22]	Cross-sectional	Use of opium ≥ 1 time in life	N = 2405 (322 opium users and 2083 nonusers)	A higher presence of CAD was observed in opium users than in nonusers (OR = 1.8, 95% CI = 1.1 to 3.1; *P* = 0.015). A significant dose-response relationship was detected between the dose of opium consumption and the severity of CAD based on the clinical vessel score (*r* = 0.2).
Masoomi et al, 2010 [28]	Cross-sectional	Addiction	N = 299 (118 opium addicts and 181 nonusers)	After adjustments for potential confounders, patients who frequently consumed opium were more expected to have severe CAD (OR = 1.82, 95% CI = 0.93 to 3.58; *P* = 0.08).
Masoomi et al, 2010 [27]	Nested case-control	Addiction	N = 91 (58 patients with CAD and 33 cases of normal coronary arteries)	Opium addiction was an independent risk factor for CAD in non-cigarette smoking cases (OR = 38; 95% CI = 2.7 to 531.7). However, in cigarette smokers, opium was not a significant risk factor (OR = 13.2; 95% CI = 0.85 to 206.5).
Sadeghian et al, 2010 [23]	Cross-sectional	Opium use	N = 940 (387 men aged < 45 y)	Opium usage was the most important risk factor for CAD in male patients younger than 45 years in Iranian sample (OR = 4.47, 95% CI: 1.49 to 13.38; *P* < 0.01).
Hosseini et al, 2011*[29]	Cross-sectional	Use of opium for ≥ 3 mon*	N = 456 (228 opium-using diabetic patients and 228 non-opium-using diabetic patients)	Higher severity and extension of coronary atherosclerosis were reported among opium-using diabetics than among age, sex, and smoking-matched non-opium-using diabetics. A significant independent dose-response relationship was observed between the dose of opium and the severity of opium consumption (β = 0.27; *P* = 0.04).
Rezvani et al, 2011 [31]	Cross-sectional	Addiction	N = 558 (161 opium addicts and 397 nonusers)	No association was found between opium consumption and ischemic heart disease.
Hosseini, 2012 [24]	Cross-sectional	Opium consumer	N = 5442 (2874 opium users and 2568 nonusers)	Opium was an independent risk factor for CAD (OR = 1.31, 95% CI = 1.01 to 1.69; *P* = 0.042).
Khademi et al, 2012 [30]	Cohort	Use of opium at least once a week for ≥ 6 mon	N = 50045 (8487 opium users and 41558 nonusers)	Increased risks of all-cause mortality were reported in opium users (adjusted HR = 1.86; 95% CI = 1.68 to 2.06). Increased risks of death from ischemic heart disease were reported in opium users (adjusted HR = 1.9, 95% CI = 1.57 to 2.29).
Darabad et al, 2014 [25]	Cross-sectional	Addiction	N = 1170 (121 opium-dependent cases and 1049 nonusers)	Opium dependence was independently associated with the presence of CAD (OR = 2.08; *P* = 0.019).
Nadimi et al, 2016 [26]	Cross-sectional	Addiction	N = 250 (125 patients with MCD and 125 individuals for comparison)	Opium addiction was an independent predictor of MCD (OR = 3.575, 95% CI = 1.42 to 9.02; *P* = 0.0069).

Arch Iran Med, 2022

Opium use and subsequent incidence of cancer: results from the Golestan Cohort Study

Mahdi Sheikh, Ramin Shakeri*, Hossein Poustchi, Akram Pourshams, Arash Etemadi, Farhad Islami, Masoud Khoshnia, Abdolsamad Gharavi, Gholamreza Roshandel, Hooman Khademi, Sadaf G Sepanlou, Maryam Hashemian, Abdolreza Fazel, Mahdi Zahedi, Behnoush Abedi-Ardekani, Paolo Boffetta, Sanford M Dawsey, Paul D Pharoah, Masoud Sotoudeh, Neal D Freedman, Christian C Abnet, Nicholas E Day, Paul Brennan†, Farin Kamangar†, Reza Malekzadeh†*

Summary

Background Evidence is emerging for a role of opiates in various cancers. In this study, we aimed to investigate the association between regular opium use and cancer incidence.

Methods This study was done in a population-based cohort of 50 045 individuals aged 40–75 years from northeast Iran. Data on participant demographics, diet, lifestyle, opium use, and different exposures were collected upon enrolment using validated questionnaires. We used proportional hazards regression models to estimate hazard ratios (HRs) and corresponding 95% CIs for the association between opium use and different cancer types.

Findings During a median 10 years of follow-up, 1833 participants were diagnosed with cancer. Use of opium was associated with an increased risk of developing all cancers combined (HR 1·40, 95% CI 1·24–1·58), gastrointestinal cancers (1·31, 1·11–1·55), and respiratory cancers (2·28, 1·58–3·30) in a dose-dependent manner (p_{trend}<0·001). For site-specific cancers, use of opium was associated with an increased risk of developing oesophageal (1·38, 1·06–1·80), gastric (1·36, 1·03–1·79), lung (2·21, 1·44–3·39), bladder (2·86, 1·47–5·55), and laryngeal (2·53, 1·21–5·29) cancers in a dose-dependent manner (p_{trend}<0·05). Only high-dose opium use was associated with pancreatic cancer

Lancet Glob Health 2020; 8: e649–60

See Comment page e613

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Digestive Oncology Research Center (M Sheikh MD, R Shakeri PhD, Prof A Pourshams MD, A Etemadi PhD, F Islami PhD, M Khoshnia MD, A Gharavi MD, G Roshandel PhD, H Khademi MD, M Hashemian PhD, Prof M Sotoudeh MD, Prof R Malekzadeh MD), Liver and Pancreatobiliary Diseases

Opium Use and Risk of Lung Cancer (IROPICAN Study)



Pathologically confirmed incident lung cancer patients

N = 627

Healthy hospital visitor controls, relatives or friends who were companions or visitors of hospitalized patients in non-oncology wards

N = 3477

OR: 3.4

(95% CI: 2.1-5.5)

Only Opium Users

OR: 3.6

(95% CI: 2.8-4.7)

Only Tobacco Users

OR: 13.4

(95% CI: 10.2-17.7)

Dual Users of Opium & Tobacoo

OR: 8.3

(95% CI 4.8-14.4)

Small cell carcinoma

OR: 2.9

(95% CI 2.0-4.1)

Adenocarcinoma

Never users of opium

Regular opium users vs Never users of opium

OR: 2.9

(95% CI 2.0-4.3)

Squamous cell carcinoma

OR: 4.5

(95% CI 2.7-7.5)

Other

Regular opium users

Important findings

- We found a more than 3-fold risk of developing lung cancer in regular opium users compared to never users.
- We found a strong dose-response relationship between opium use and risk of lung cancer.
- The risk of lung cancer decreased after opium cessation.
- The risk of developing small-cell carcinoma was near **three** folds higher than adenocarcinoma and squamous cell carcinoma.
- We found a strong additive interaction between the risk of lung cancer and using both tobacco and opium and relative excess risk due to interaction was 7.4 (95% CI: 4.1, 10.7).

Rashidian H, International J Cancer 2023



Opium Use and Risk of Oral Cavity Cancers(OCCs)



Pathologically confirmed incident cases of OCCs

N = 133

Healthy neighbour controls (Individually matched by age and sex)

N = 266

Ever Opium Users

OR: 2.36

(%95 CI: 1.16 - 4.77)

Other Tobacco (Nass, Pipe, Hookah)

OR: 3.9

(%95 CI: 1.12 - 13.57)

Higher User of Upium

OR: 4.85

(%95 CI: 1.79 - 13.11)

Important findings

- Compared to never opium users, ever opium users had a risk of OCCs that was more than two times higher.
- We found a significant dose-response relationship between the risk of OCCs cancer and opium use.
- Early onset of opium usage was found to be strongly related with an increased risk of OCCs.
- Duration of Opium use was significantly associated with the increasing risk of OCCs.

Amount of daily opium use
(> 2 grams per day)

OR: 4.81

(%95 CI: 1.73 - 13.39)

Duration of opium use
(> 18 years)

OR: 5.04

(%95 CI: 2.00 - 12.68)

opium users vs Never users

Age at start of opium use
(< 50 years)

OR: 3.32

(%95 CI: 1.19 - 9.23)

opium users vs Never users

Route of opium use

Only Smoking

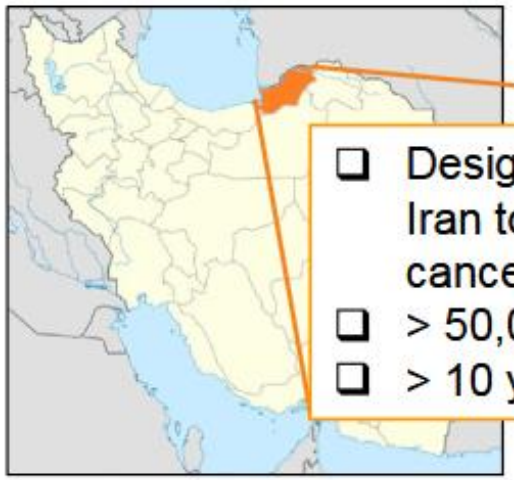
OR:2.02 (%95 CI: 1.03 - 3.94)

Smoking & Ingestion

OR:8.57 (%95 CI: 1.68 - 43.70)

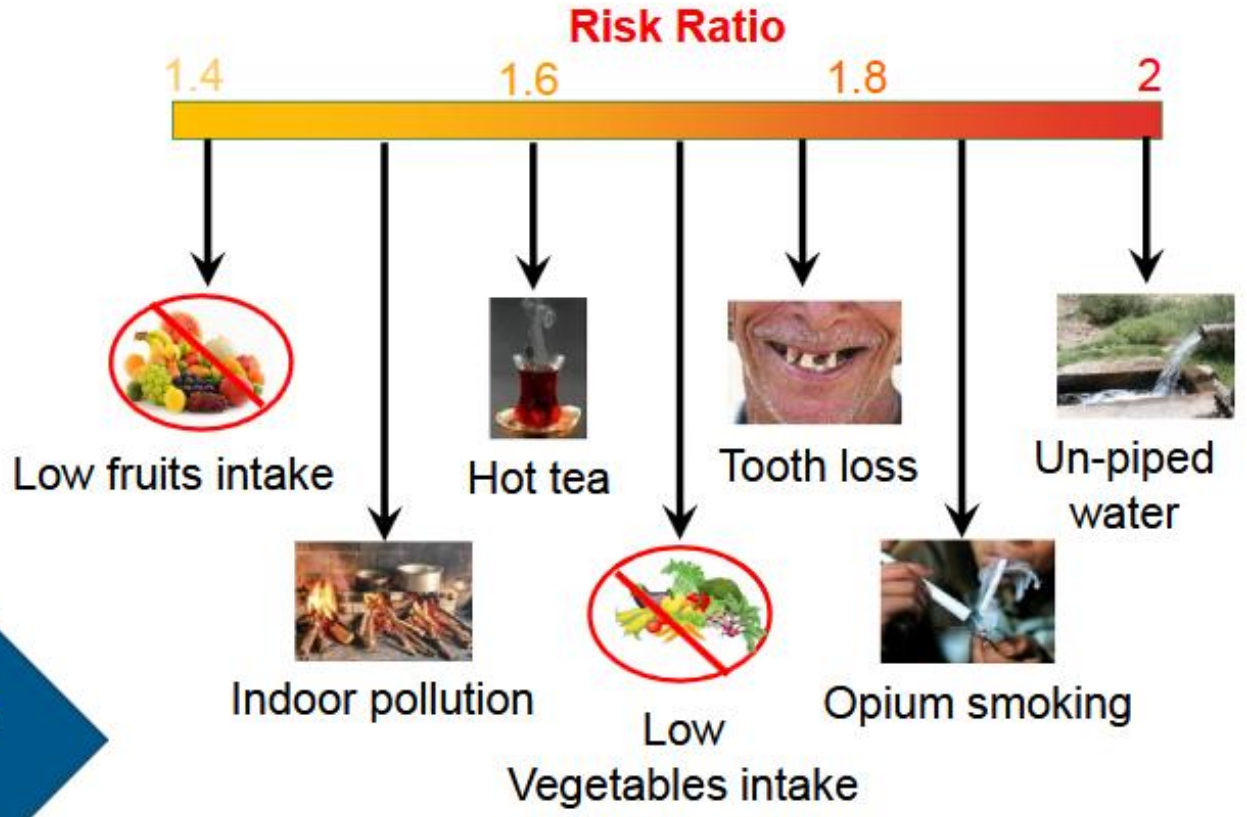
Individual and Combined Effects of Environmental Risk Factors for Esophageal Cancer Based on Results From the Golestan Cohort Study

Golestan Cohort Study



- Designed in North-East Iran to study esophageal cancer
- > 50,000 participants
- > 10 years of follow-up

76% of esophageal cancer cases are attributable to combined exposures to these risk factors



Gastroenterology

Gastroenterology 2019;156:1416–1427

Association Between Opium Consumption and Cancer and its Outcomes

Oral cancer				
Razmpa et al., 2014 [76]	Case-control	160 individuals (80 patients with oral cavity cancer)	Cancer incidence	Opium consumption was significantly related to oral cavity cancer (OR = 4.0; 95% CI = 1.2 to 13.6).
Laryngeal cancer				
Mousavi et al., 2003 [51]	Case-control	N = 410 (98 patients with laryngeal cancer and 312 cancer-free subjects)	Cancer prevalence	Opium consumption was a factor for laryngeal cancer with a crude OR of 21.55 (95% CI = 10.54 to 44; $P < 0.001$). The adjusted odds ratio showed that opium was strongly associated with laryngeal cancer (OR = 10.74; 95% CI = 5.76 to 20.02; $P < 0.0021$).
Rahmati et al., 2017 [52]	Cohort	N = 50045 (8487 opium users and 43 mortality cases due to respiratory malignancies)	Cancer mortality	Opium consumption was almost significantly associated with an increased risk of laryngeal cancer (95% CI: 0.99).
Bakhshaee et al., 2017 [53]	Case-control	N = 181 (58 cases with laryngeal cancer and 98 cases with esophageal cancer)	Cancer prevalence	The crude OR for laryngeal cancer in opium users was 9.09 (95% CI = 3.21 to 25.64; $P = 0.000$) compared to nonusers. After adjustments for opium with cigarette smoking, the OR for laryngeal cancer in opium users was 6.06 (95% CI = 1.10 to 33.23; $P = 0.05$). Laryngeal cancer was also discovered in younger patients with opium dependency (54.54 ± 10.93; $P = 0.02$).
Sheikh et al., 2020 [54]	Cohort	N = 50045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	The use of opium was associated with an increased risk of developing laryngeal cancer (HR = 2.53, 95% CI = 1.21 to 5.30; $P < 0.05$).
Lung cancer				
Rahmati et al., 2017 [52]	Cohort	N = 50045 (8487 opium users and 43 mortality cases due to respiratory malignancies)	Cancer mortality	Opium consumption was almost significantly associated with an increased risk of lung cancer (OR = 1.73; 95% CI = 0.99 to 3.03).
Sheikh et al., 2020 [54]	Cohort	N = 50045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	Opium consumption was associated with an increased risk of developing lung cancer (HR = 2.21, 95% CI = 1.44 to 3.39; $P < 0.05$).

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Association Between Opium Consumption and Cancer and its Outcomes

Bladder Cancer				
Sadeghi et al., 1979 [65]	Case-control	N=189 (99 cases with bladder cancer)	Cancer prevalence	A high correlation was observed between opium addiction and bladder cancer.
Aliasgari et al., 2004 [66]	Case-control	N=160 (52 cases and 108 controls)	Cancer prevalence	Smoking cigarettes and opium usage increased the risk of BC (OR=6.2; 95% CI=2.04 to 8.70).
Ketabchi et al., 2005 [67]	Case-control	N=242 (112 cases and 130 controls)	Cancer prevalence	The amount, duration, and methods of opium consumption could be related to BC. The risk ratio associated with opium use was 8 (OR=7.99, 95% CI=5.3 to 12.5; P=0.0001).
Nourbakhsh et al., 2006 [68]	Case-control	N=510 (255 cases and 255 controls)	Cancer prevalence	Opium was a risk factor for transitional-cell carcinoma (OR=3.88, 95% CI=1.99 to 7.57; P=0.001).
Shakhssalim et al., 2010 [69]	Case-control	N=912 (418 cases and 494 controls)	Cancer prevalence	Opium could be an important factor in developing transitional cell carcinoma (P=0.0001). The risk ratio associated with opium use was 2.6 (95% CI=1.6 to 4.3).
Hosseini et al., 2010 [70]	Case-control	N=358 (179 cases with BC and 179 cancer-free subjects)	Cancer prevalence	Opium consumption was associated with a significantly increased rate of BC (OR=4.6, 95% CI=3.5 to 6.3; P<0.001). There was a synergistic association between heavy cigarette smoking and opium consumption concerning BC occurrence (OR=6.16; 95% CI=3.34 to 8.32; P=0.0001).
Ghadimi et al., 2015 [72]	Case-control	N=304 (152 cases and 152 controls)	Cancer prevalence	Opium abuse individually was associated with bladder cancer. The OR for opium was 4.96 (95% CI=1.07 to 22.92).
Alimarji et al., 2015 [71]	Case-control	N=350 (175 cases and 175 controls)	Cancer prevalence	A significant association was observed between smoking, opium consumption, and an increased risk of BC (P<0.001).
Akbari et al., 2015 [74]	Case-control	N=533 (155 cases with BC and 378 cancer-free subjects)	Cancer prevalence	A significant relationship was observed between opium usage and BC after adjustments for potential confounders including nutritional factors, alcohol, and tobacco (OR=3.9; 95% CI=1.3 to 12.0) in a dose-response manner (OR=4.9; 95% CI=1.1 to 21.9).
Lotfi et al., 2016 [75]	Case-control	N=400 (200 cases with BC and 200 cancer-free subjects)	Cancer prevalence	Opium consumption was associated with an increased risk of BC (OR=3.01, 95% CI=1.73 to 5.23; P<0.0001).
Afshari et al., 2017 [73]	Systematic review and meta-analysis	17 studies	Cancer prevalence	The OR for the association between BC and opium use (without cigarette smoking) was 3.85 (95% CI=3.05 to 4.87), while it increased to 5.7 (95% CI=1.9 to 16.3) with cigarette smoking.
Sheikh et al., 2020 [54]	Cohort	N=50045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	The use of opium was associated with an increased risk of advancing bladder cancer (HR=2.86, 95% CI=1.47 to 5.55; P<0.05).

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Association Between Opium Consumption and Cancer and its Outcomes

Esophageal cancer				
Ghadirian et al., 1985 [55]	Case-control	N=41 cases and 41 controls	Cancer prevalence	Individuals with more than 1 μg/mL of morphine metabolites in their urine had a higher rate of esophageal cancer.
Nasrollahzadeh et al., 2008 [56]	Case-control	N=871 (300 cases with ESCC and 571 cancer-free cases)	Cancer prevalence	Consuming shireh had a stronger association with ESCC than consuming usual opium (OR=3.41; 95% CI=1.35 to 8.60, and OR=1.62; 95% CI=1.09-2 to 40, respectively). Opium use and ESCC had a dose-response relationship.
Malekzadeh et al., 2013 [57]	Cohort	N=50045 (8487 opium users and 134 cases of GI mortality due to ESCC)	Cancer mortality	After adjustments for potential confounders and exclusion of those who started opium use after major chronic illnesses, the use of opium was associated with a 69% increase in the risk of ESCC-related mortality (HR=1.69, 95% CI=1.11 to 2.56; P=0.035).
Bakhshaee et al., 2017 [53]	Case-control	N=181 (58 cases with laryngeal cancer and 98 cases with esophageal cancer)	Cancer prevalence	The crude OR for esophageal cancer was 1.44 (95% CI=0.57 to 3.62; P=0.43) in opium users compared to nonusers.
Sheikh et al., 2019 [58]	Cohort	N=50045 (8487 opium users)	Cancer incidence	After adjustments for potential confounders such as age, gender, residence districts, ethnicity, and quartiles of the socioeconomic status, the results showed that smoking opium was associated with an increased risk of ESCC (HR=1.85, 95% CI=1.18 to 2.90; P=0.009).
Sheikh et al., 2020 [54]	Cohort	N=50045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	The use of opium was associated with an increased risk of developing esophageal cancer (HR=1.38, 95% CI=1.06 to 1.80; P<0.05).
Gastric Adenocarcinoma				
Malekzadeh et al., 2013 [57]	Cohort	N=50045 (8487 opium users and 125 cases with GI mortality due to gastric cancer)	Cancer mortality	After adjustments for possible confounding variables and exclusion of those who started opium use after major chronic illnesses, the use of opium was associated with a 22% increase in the risk of gastric-related mortality (HR=1.22; 95% CI=0.79 to 1.89).
Shakeri et al., 2013 [59]	Case-control	N=922 (309 cases of gastric adenocarcinoma and 613 matched controls)	Cancer prevalence	Opium increased the risk of all types of adenocarcinoma (OR=3.1; 95% CI=1.9 to 5.2). Opium consumption after a diagnosis of gastric cancer showed a significant increase in all types of gastric cancer (OR=2.9; 95% CI=1.7 to 4.8). Patients with the highest cumulative opium consumption demonstrated the potent relationship (OR=4.5; 95% CI=2.3 to 8.5).
Sadjadi et al., 2014 [60]	Cohort	N=928 Helicobacter-positive patients	Cancer incidence	Opium use increased the risk of all gastric cancers (HR=3.2; 95% CI=1.4 to 7.7).
Sheikh et al., 2020 [54]	Cohort	N=50 045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	The use of opium was associated with an increased risk of developing gastric cancer (HR=1.36, 95% CI=1.03 to 1.79; P<0.05).

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Association Between Opium Consumption and Cancer and its Outcomes

Pancreatic Cancer				
Shakeri et al., 2016 [61]	Case-control	N = 685 (357 patients with pancreatic cancer and 328 cancer-free subjects)	Cancer prevalence	After adjustments for opium consumption with potential confounders such as age and the duration and cumulative use of opium, the results demonstrated a significant relationship between opium and pancreatic cancer without a dose-response relationship (OR = 1.91; 95% CI = 1.06 to 3.43).
Moossavi et al., 2018 [62]	Cohort	N = 50045 (54 cases with pancreatic cancer)	Cancer incidence	High cumulative use of opium in comparison with the never use was strongly associated with pancreatic cancer even after adjustments for age, sex, cigarette smoking, obesity, diabetes mellitus, and alcohol (HR = 3.56, 95% CI = 1.49 to 8.50; $P = 0.090$).
Colorectal Carcinoma				
Naghibzadeh-Tahami et al., 2016 [63]	Case-control	N = 525 (175 cases with CRC and 350 cancer-free subjects)	Cancer prevalence	Opium consumption was associated with an increased risk of CRCs (adjusted OR = 4.5; 95% CI = 2.4 to 8.7). A dose-response relationship was noticed between the cumulative use of opium and the incidence of CRCs (low use OR = 3.7; 95% CI = 1.5 to 8.6, and high use OR = 8.0; 95% CI = 2.9 to 21.7).
Dianatinasab et al., 2016 [64]	Cohort	N = 220 CRCs	Cancer mortality	Opium consumption was significantly correlated with a higher risk of colorectal cancer-related death (HR = 2.49, 95% CI = 1.41 to 4.42; $P = 0.001$).

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Gastroenterology and Hepatology From Bed to Bench.
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SYSTEMATIC REVIEW

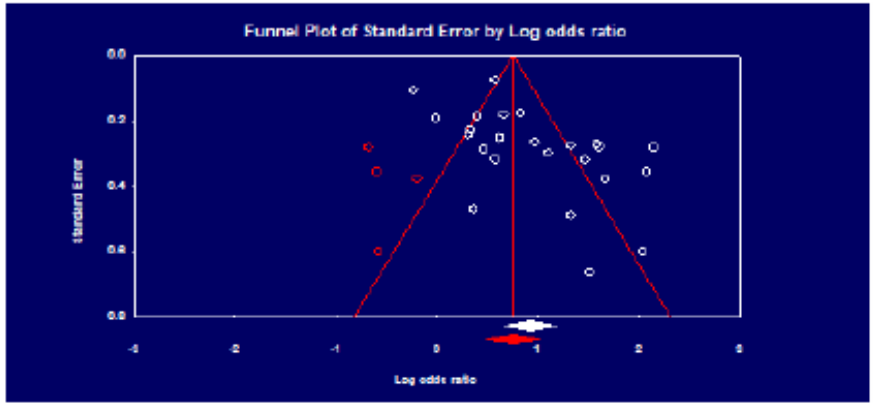
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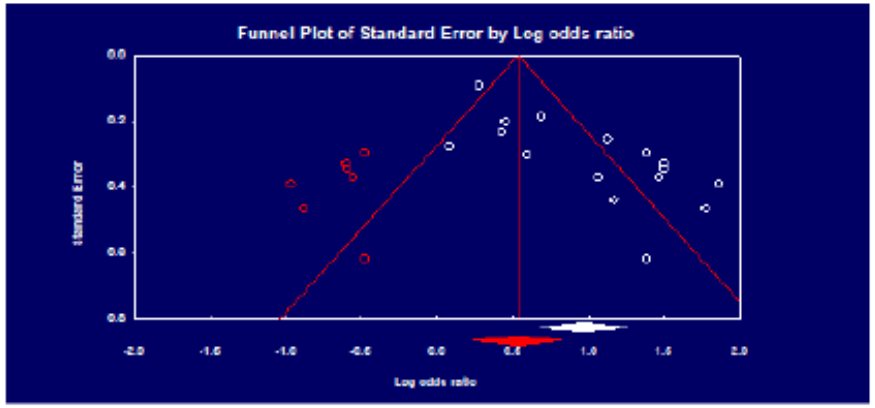
Opium use and gastrointestinal cancers: a systematic review and meta-analysis study

Mahsa Mohammadi[1], Philippe Tadger[2], Amir Sadeghi[3], Niloufar Salehi[3], Mohsen Rajabnia[4], Elham Paraandavaji[3,9], Sasan Shafiei[3,9], Ahmad Pirani[5], Mohammad Reza Hatamnejad[3], Erfan Taherifard[6], Fatemeh Kheshti[6], Arman Naderilordejani[3], Forough honarfar[3], Khaled Rahmani[3], Majid Soruri[3], Hamed Kord Varkaneh[3], Omid Dadras[7,8], Ali Jahanian[3], Sara Rasta[4], Mohammad Reza Zali[3]

Results: 22 articles that were published between 1983 and 2022 entered the analyses. There were significant relationships between opium use based on crude effect sizes (OR: 2.53, 1.95-3.29) and adjusted effect sizes (OR: 2.64, 1.99-3.51), high daily opium use (or: 3.41, 1.92-6.06), long duration of opium use (OR: 3.03, 1.90-4.84) and high cumulative opium use (OR: 3.88, 2.35-6.41), all compared to never opium use, and GI cancer. The results were not sensitive to sensitivity analyses and no influential publication biases were found in these analyses.

Conclusion: Our meta-analysis showed that opium use could be associated with increased risk of overall and some particular GI cancers including oropharyngeal, gastric, pancreatic and colorectal cancers. Opium use as a potentially modifiable factor, therefore, should be more emphasized.





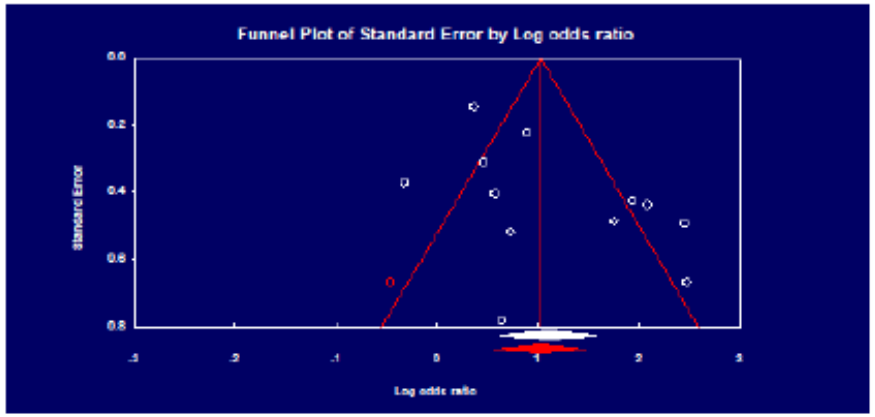


Table 2. Subgroup analyses regarding the association between opium use and GI cancer

		Number of results	Pooled OR	95% CI	P value	I-squared	Q statistics p-value
Opium use and GI cancer							
Oropharyngeal cancer	Overall	5	2.71	1.61- 4.57	<0.001	65.65	0.020
	Only adjusted studies	3	2.22	1.26- 3.90	0.006	44.02	0.168
Esophageal cancer	Overall	7	1.74	1.44- 2.10	<0.001	18.36	0.290
	Only adjusted studies	2	1.53	0.85- 2.76	0.159	69.72	0.069
Gastric cancer	Overall	6	2.21	1.80- 2.71	<0.001	9.52	0.355
	Only adjusted studies	3	3.09	2.16- 4.42	<0.001	00.00	0.990
Pancreatic cancer	Overall	4	2.05	1.42- 2.97	<0.001	47.81	0.124
	Only adjusted studies	3	2.17	1.25- 3.76	0.006	65.20	0.056
Liver cancer	Overall	2	3.35	0.98- 11.46	0.054	85.78	0.008
	Only adjusted studies	1	6.5	2.87- 13.44	<0.001	-	-
Colorectal cancer	Overall	3	2.46	0.63- 9.50	0.193	95.41	<0.001
	Only adjusted studies	2	4.49	2.81- 7.16	<0.001	00.00	0.993
Colon cancer	Overall	4	2.03	0.75- 5.50	0.165	91.98	<0.001
	Only adjusted studies	2	5.58	3.14- 9.92	<0.001	00.00	0.928
Rectal cancer	Overall (no adjusted studies)	2	0.86	0.65- 1.13	0.291	00.00	0.350
High daily use of opium compared to never use							
	Overall	10	3.41	1.92- 6.06	<0.001	71.34	<0.001
	Only adjusted studies	9	3.55	1.85- 6.79	<0.001	74.24	<0.001
	Esophagus	2	2.39	1.57- 3.64	<0.001	00.00	0.960
	Pancreas	2	2.55	0.613- 10.58	0.199	76.19	0.040
	Lower GI tract	2	7.40	3.28- 16.71	<0.001	00.00	0.812
	Colon cancer	2	8.86	3.67- 21.37	<0.001	00.00	0.840
Both smoking and ingestion of opium compared to never use							
	Overall	3	5.13	2.77- 5.21	<0.001	00.00	0.534
Teriak consumption compared to never use							
	Overall	6	2.15	1.45- 3.18	<0.001	76.56	0.001
	Case-control studies	5	2.50	1.53- 4.07	<0.001	70.71	0.008
Shireh consumption compared to never use							
	Overall	5	2.49	1.16- 5.34	0.019	63.91	0.026
	Case-control studies	4	3.52	1.96- 6.33	<0.001	00.00	0.900
Teriak and shireh consumption compared to never use							
	Overall	3	3.66	0.67- 20.10	0.135	80.91	0.005
	Case-control studies	2	8.74	2.83- 26.99	<0.001	00.00	0.985

The pathophysiology of the association between opium use and GI cancers

Individuals using opium may exhibit other lifestyle or environmental traits that elevate their susceptibility to GI cancers, such as

- consuming other illicit substances,
- engaging in risky sexual behaviors,
- suboptimal hygiene practices, and
- Malnutrition

Cancerogenic effects of opiate and its metabolites (opium pyrolysis metabolites, morphine, and nitrosamines)

- Nitrosamines are a known carcinogen in the GI tract.
- Morphine, a predominant alkaloid of opium, is a genotoxic opium metabolite through DNA methylation, inhibiting nitrosamines clearance.
- Opium pyrolysis can induce dose dependent mutations in bacteria, mammalian, and human cells

Other mechanisms

- activation of angiogenesis and neovascularization,
- increased cancer cell proliferation and migration,
- impairment of immune function ,
- increased nitric oxide ,
- decreased hydrogen peroxide , and
- prolonged exposure of some organs to the carcinogens by impairment of their normal function

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Case presentation

- A 62-year-old man presents with a history of moderate to severe knee pain. He is overweight and has experienced progressive pain in the knees for the last several months.
- In past medical history he had compensated NASH cirrhosis, cholecystectomy and under-controlled DM.
- There was no history of abdominal pain or constipation.
- He had unsatisfactory response to acetaminophen (2gr/d) and local analgesia, so for the last two months, his physician prescribed oxycodone (5mg BID) for pain relief.

Which of the following is the best analgesia for musculoscletal pain with moderate to severe intensity in cirrhotic patients?

- Acetaminophen
- NSAIDs
- COX-II inhibitors
- Opioid compounds

Opiates in cirrhosis

Opiates will remain the mainstay in the treatment of moderate- to-severe pain in the foreseeable future because the introduction of analgesic drugs with equal efficacy (eg, NSAIDs and COX-II inhibitors).

Development of **portal-systemic shunts** occurs in patients with cirrhosis, leading to decreased blood flow and subsequently halting drug metabolism by the liver. These highly hepatically metabolized agents are bypassing first-pass metabolism as a result of the shunts.

Albumin is a protein which binds to and facilitates the exertion of certain drugs. Albumin synthesis is decreased with liver disease; therefore, it leads to increased serum levels of some drugs. Thus, the risk of adverse drug reactions increases.

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Pain Management in Patients with Cirrhosis; A Mini Narrative Literature Review with Evidence-Based Recommendations

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Review Article

ABSTRACT

Cirrhosis is a significant public health concern, causing approximately 790,000 deaths annually. Despite the possibility of adverse effects from analgesics, which can be fatal and preventable, guidelines for their use in this setting do not exist, and there is a lack of research in this field. Thus, this review aims to summarize and analyze published data on different opioids in patients with liver cirrhosis to provide possible evidence-based guidelines for the safe use of opioids. Both compensated and decompensated patients should avoid NSAIDs. Because of the risk of hepatic encephalopathy, opioids must be avoided or used sparingly at low and infrequent doses. A long-term follow-up is required for toxicity, adverse effects, and complications of all pain relievers.

Keywords: cirrhosis, pain management, opioid, analgesia, NSAIDs

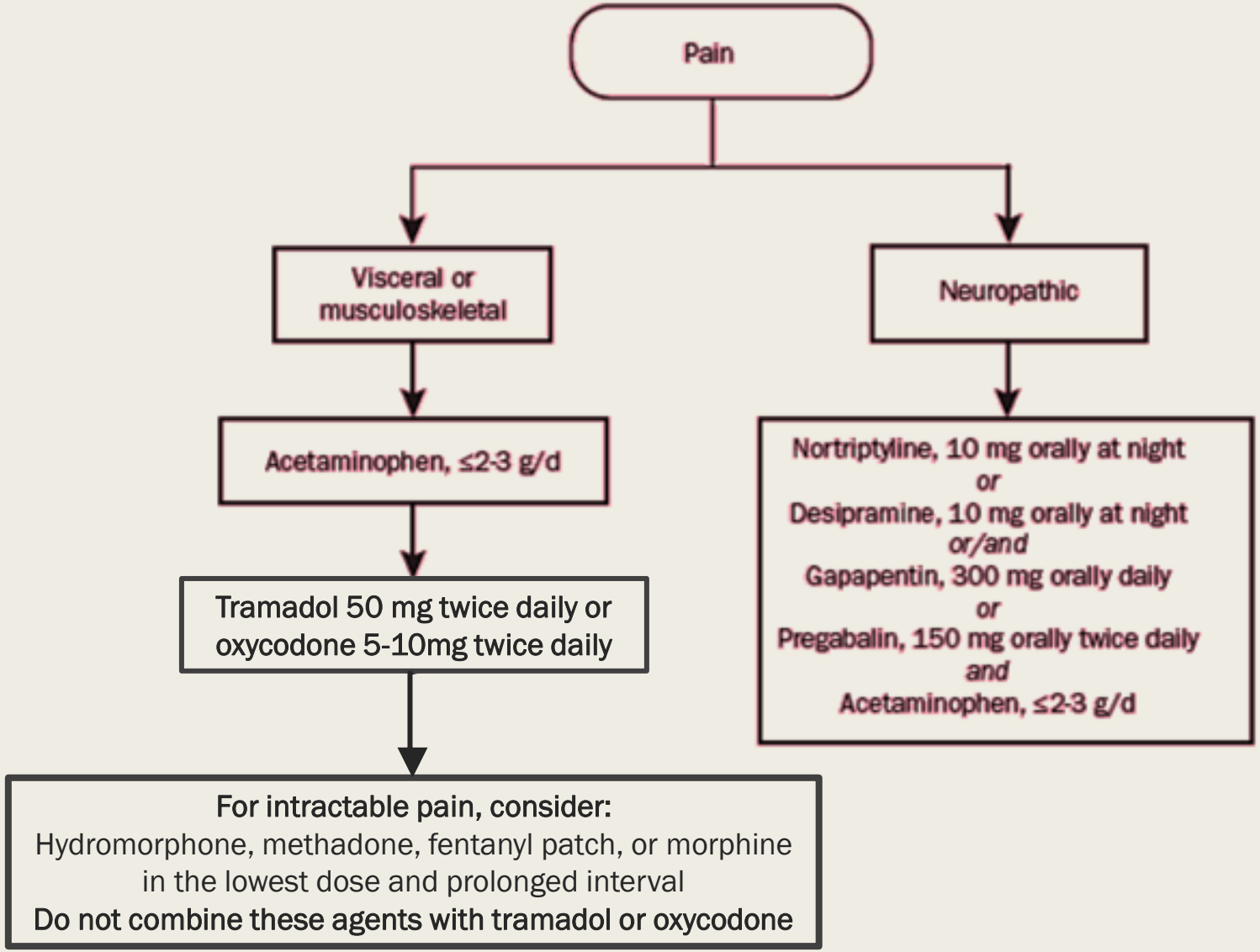
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	Recommendation	
	Child A/B cirrhosis	Child C cirrhosis
Codein	Use it with caution; use lowest available dose (15mg) and titrate up slowly; Avoid in renal insufficiency	Should be avoided
Oxycodone	Safe to use; No need to dose adjustment	Use it with caution; administered at reduced doses (30% - 50% of the standard dose) and prolonged dosing intervals; Avoid in renal insufficiency
Tramadol	Safe to use; No need to dose adjustment	Immediate-release form dose (50mg every 12h) can be used; Avoid extended-release formulation
Hydromorphone	Safe to use (preferred opiate); No need to dose adjustment	Use with caution; administered at reduced doses and prolonged dosing intervals
Morphine	Use it with caution; administered at the minimum effective dose; Avoid in renal insufficiency	Use it with caution; administered at the minimum effective dose and prolonged dosing intervals; Avoid in renal insufficiency
Buprenorphine	Use it with caution; use only the lowest dose	Should be avoided
Methadone	Safe to use; No need to dose adjustment	Use it with caution; administered at reduced doses and prolonged dosing intervals
Fentanyl (patch)	Use it with caution; Reduce dose by 50%	Use it with caution; administered at reduced doses and prolonged dosing intervals (12.5 µg Q72h)
Fentanyl (intravenous)	Safe to use	Safe to use; First opiate choice in hepatorenal syndrome
Meperidine	Use it with caution; Avoid in renal insufficiency	Should be avoided

Opiate adjustment in renal disease

GFR	Morphine	hydromorphone	oxycodone	methadone	fentanyl
>50	100%	50-100%	100%	100%	100%
10-50	50-75%	50%	50%	100%	75-100%
<10 (renal insufficiency)	Not recommended	25%	Not recommended	50-75%	50%

A pharmacological approach to analgesia in patients with advanced cirrhosis who have no renal insufficiency, active alcoholism or active substance abuse.



Case presentation

- Presented with constipation and persistent vague abdominal pain and constipation.
- Denies changes in her weight, nausea, vomiting, abdominal pain, melena, or hematochezia.
- ALT 34 UI/L , AST 45 UI/L, ALP 145 UL/L, Bili 1.2mg/dl, albumin 4 g/dL, Hb 13.8 g/dl, Ferritin 321 µg/L, MCV 88 μm^3
- Plt 134000 mcL , blood urea nitrogen 21 mg/dL, creatinine 1.16 mg/dL.
- Fasting glucose 150 mg/Dl, HbA1C 7.0%.
- HBsAg and anti-HCV negative
- Ultrasound: increased liver echogenicity with coarse texture, CBD 9mm
- Endoscopy: erythema in antrum and positive for H. pylori
- Colonoscopy: NL up to terminal ileum
- Endosonography: CBD 10mm with distal tapering but no stone or sludge

Which of the following is the most likely diagnosis?

- Sphincter of oddi dysfunction
- Opiate-induced bowel disorder
- Opium-related lead toxicity (ORLT)
- Irritable bowel syndrome

Diagnosis

Opiate-induced Bowel Disorder (OBD)

Opiate-induced Bowel Disorders (OBD)

Site	Pharmacological effect	Clinical effect
LOS	Inhibition LOS relaxation	
Gallbladder	Contraction Spasm sphincter of Oddi Decreased secretion	Biliary pain Delayed digestion
Gastroduodenum	Inhibition gastric emptying Increase duodenal motility followed by quiescence Increase pyloric tone Enhanced gastric acid secretion	Anorexia Nausea and emesis
Small bowel	Increase tone/segmentation Increase transit time Increase absorption Decrease secretion	Constipation Delayed digestion Hard, dry stool
Colon	Increase tone/segmentation Increase transit time Increase absorption Decrease secretion	Constipation Hard, dry stools Bloating and distension Spasm, cramps, pain
Anorectum	Decrease rectal sensitivity Increase internal sphincter tone	Incomplete evacuation Straining constipation

Which of the following laxatives is not effective and should be avoided ?

- Bulk-forming laxatives
- Stimulant laxatives
- Osmotic laxatives
- Lubiprostone

Opiate induced constipation

Except for bulk-forming laxatives, all other types of laxatives can be used. Stimulant laxatives such as bisacodyl, sodium picosulfate, sennosides, and macrogol have preferred by most opiate induced constipation (OIC) patients and appear to have similar efficacy.

Metabolism of **sugars (lactulose, sorbitol)** and sugar alcohols by the intestinal microbiota leads to short chain carbonic acids and gas. The ensuing abdominal distension may aggravate distension in OIC. To prevent electrolyte disturbance, one should not use osmotic laxatives for a prolonged time.

Opiate induced constipation

Polyethylene glycol (PEG) is the most effective therapy for functional constipation and appears to be similarly effective in OIC. The favorable side effect profile and low cost of PEG make it a good choice for first line treatment with or without a stimulant laxative.

Treatment of OIC with **new laxatives (prucalopride, lubiprostone)** may be promising; However, to date, there are insufficient data to warrant such treatments in OIC patients.

If the constipation is severe, one may need to use the newer **peripheral opioid antagonists like alvimopan or methylnaltrexone.**

Opiate induced constipation

Given that opioid-induced analgesia is primarily mediated by μ-opioid receptors in the CNS, the rational approach to prevent OBD would be to **combine opioid analgesics with opioid receptor antagonists that cannot penetrate the blood–brain barrier.**

This approach has been validated by the use of opioid receptor antagonists with limited systemic absorption and by the development of peripherally restricted opioid receptor antagonists (PRORAs) such as methylnaltrexone and alvimopan.

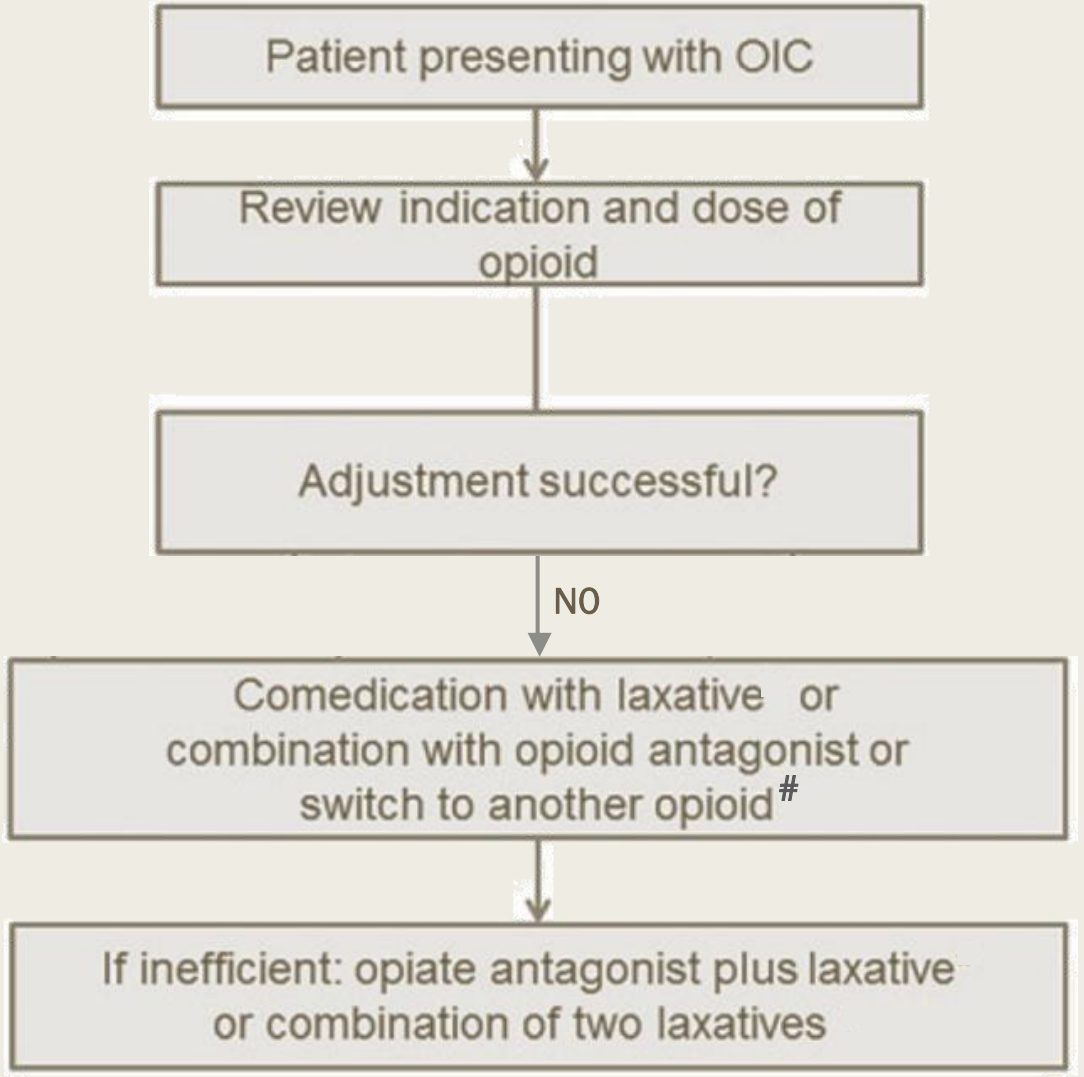
Both methylnaltrexone and alvimopan have been found to alleviate the symptoms of OBD without antagonising analgesia or precipitating signs of opioid withdrawal.

Opiate induced constipation

Naloxone is a pan-opioid receptor antagonist whose systemic bioavailability following oral administration is as low as 2% because of extensive first-pass metabolism. For this reason, oral naloxone has been found to **improve OBD without inhibiting opiate-induced analgesia.**

However, it needs to be realised that naloxone can easily cross the blood–brain barrier; therefore, naloxone can reverse analgesia if given in sufficient dosage despite its low bioavailability.

In patients with chronic cancer or noncancer pain, prolonged-release **naloxone/oxycodone combination** effectively reduces OIC while maintaining equal analgesia to prolonged-release oxycodone alone.



eg, in abdominal pain syndromes, **tramadol** has been associated with lesser gastrointestinal side effects without influencing pain control.

Case …

- Prescribe quadaple therapy for H-pylori eradication, powder pidrolax 17mg/BID and tablet sennaline every other day if needed.
- He was recommended to life style modification, exercise and lactose free and high fiber diet.
- During a follow-up telephone call 3 weeks later, she reported that she was having a bowel movement each day and that her bloating and discomfort were better.

Case (after 9mo) …

- He changed his opiate to inhaled opium (1gr/BID) six month ago because of severe pain in the knee joint.
- He presented our hospital with severe and intractable mid-abdominal pain, constipation, headache and tremor.
- Lab data: ALT 86 UI/L , AST 101 UI/L, ALP 125 UL/L, Bili 1.9mg/dl, albumin 4 g/dL, Hb 10.8 g/dl, Ferritin 258 µg/L, MCV 78 μm^3

Case ...

What's your suggestion?

A. Repeat UGIE, colonoscopy and SBE
B. Abdominal CT scan
C. Check blood lead level
D. MR enterography

Case …

- Blood lead level was 95μg/dL
- Final Diagnosis: Opium related lead toxicity with both intestinal and neurological involvement (severe toxicity)

Opium-related lead toxicity (ORLT)

Lead is absorbed by the body through the main paths of entry, ingestion, and inhalation. **Absorption of lead through ingestion is likely higher than inhalation.**

Acute or chronic abdominal symptoms in an opioid-user patient should always raise the suspicion for ORLT.

A combination of abdominal pain, anemia, and constipation in addicted patients is an important clue for ORLT.

Neurologic manifestations of ORLT include :

- movement restriction of lower and upper limbs,
- low back pain,
- myalgia,
- tremor,
- weakness,
- irritability,
- sleeplessness,
- headache, and
- coma and generalized seizure

Opium-related lead toxicity (ORLT)

The evidence shows that, lead by increasing the fragility of cell membranes declines the life of erythrocytes and through limiting the synthesis of hemoglobin by inhibiting various key enzymes directly effects on the hematopoietic system. The combination of these two processes results in **anemia.**

This toxic metal can **damage the liver, increase liver enzymes, and cause inflammation.**

Blood lead level (BLL) is the most reliable index of recent lead exposure. Since 2012, the Centers for Disease Control and Prevention (USA) have identified standard high blood lead levels for adults 10 µg/dL.

Opium-related lead toxicity (ORLT)

Treatment

- **Mild intoxication**
  - *BLL of 10–44 mg/dL with no related signs and symptoms*
    - Usually does not require chelation.
- **Moderate poisoning**
  - *BLL of 45–69 mg/dL with no related signs and symptoms*
    - Might be considered for chelation with both oral and/or parenteral agents.
- **Severe poisoning**
  - *BLL > 70 mg/dL or the presence of symptomatic encephalopathy*
    - A medical emergency that needs parenteral chelation

The Journal of Emergency Medicine, 2020.

Case …

- He was then admitted and received intramuscular injections of British anti-Lewisite (BAL) (450 mg/m2/ day in divided doses every 4 hours).
- He then received D-penicillamine, starting from 500 mg a day and increased as tolerated to 1,000 mg/day in 1 week . He stopped opium and received fluids and low-dose maintenance methadone.
- Twenty days after discharge, a short course of detoxification was completed, and consequently, his blood lead level was reported to be 22 µg/dL.
- In a 2-month follow-up, his abdominal pain had dramatically declined, but not disappeared. Lab data: ALT 32 UI/L , AST 43 UI/L, ALP 115 UL/L, Bili 1.1mg/dl, albumin 4 g/dL, Hb 13.8 g/dl, Ferritin 218 µg/L, MCV 82 μm^3 .

Case (after 5 mo) …

- He presented our institution with a 2 month history of intractable diffuse abdominal pain and refractory constipation to full-dose of pidrolax and stimulant laxatives. He described her pain as crampy, and with no relation to food intake.
- Abdominal examination revealed a soft, diffusely tender to palpation, distended abdomen with normal bowel sounds.
- ALT 92 UI/L , AST 43 UI/L, ALP 119 UL/L, Bili 1.1mg/dl, Blood lead level was 5µg/dL, Hb 13.8 g/dl, Ferritin 181 µg/L, MCV 82 μm^3
- CT abdomen revealed distention of the entire colon with no transition zone.
- At this point her daily analgesic requirements were 40mg methadone and 200 mg tramadol.

Case ...

What's the most probable diagnosis?

A. Irritable bowel syndrome
B. Opiate induced constipation
C. Narcotic bowel syndrome
D. Functional constipation

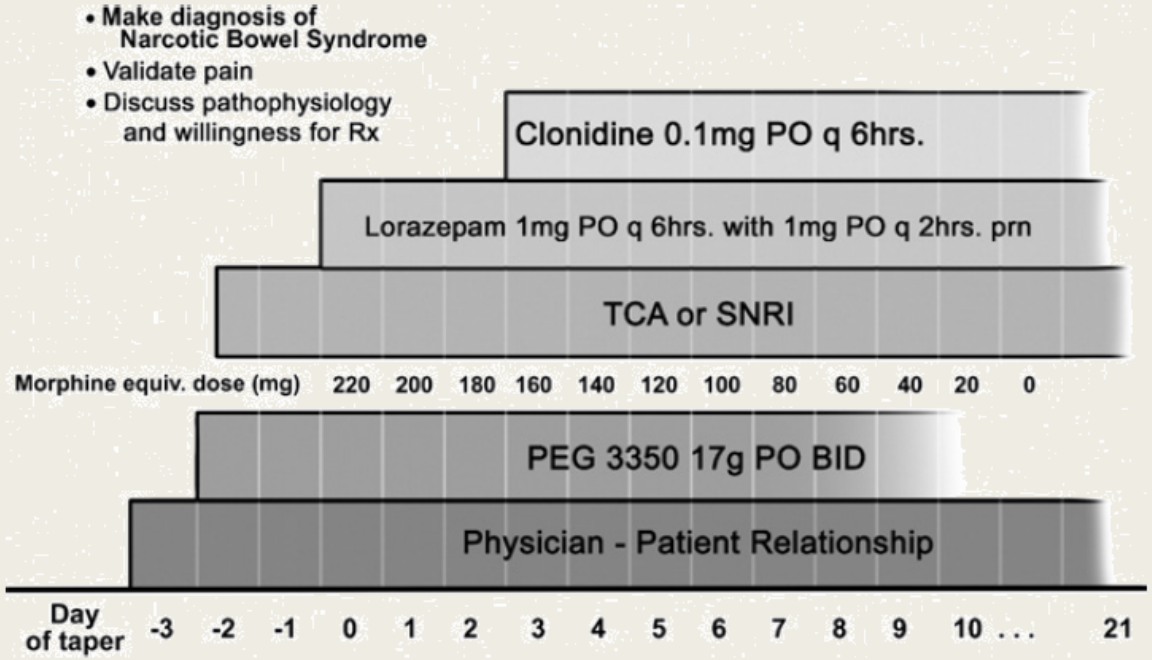
Diagnostic Criteria for NBS

"**Chronic or frequently recurring abdominal pain (occurs most days)** for 3mo, with initial onset of symptoms 6 mo before diagnosis; **treated with short-term, high-dose narcotics or long-term narcotics**; pain that is not explained by a current or previous gastrointestinal diagnosis; two or more of the following are present:

Pain worsens or incompletely resolves with continued or escalating dosages of narcotics

There is a marked worsening of pain when the narcotic dose wanes and improvement when narcotics are reinstituted

There is a progression of the frequency, duration, and intensity of the pain episodes



Treatments for NBS

Antidepressants
- Tricyclic antidepressants: desipramine or nortriptyline: 50 mg at bedtime titrated to 150 mg at bedtime
- Serotonin–noradrenergic reuptake inhibitors: duloxetine 30 mg/day titrated to 60 mg/day, venlafaxine 37.5 mg/day titrated to 225 mg/day

Sympatholytics
- Clonidine: start 0.1–0.2 mg every 6–8 h as titrated by orthostatic blood pressure

Anxiolytic
- Lorazepam: start 1 mg every 6–8 h
- or
- Clonazapam: start 0.25–0.50 mg every 8 h

Spasmolytic
- Hyoscyamine: 0.25 mg sublingual every 4 h as necessary

Cathartic
- Polyethylene glycol solution
- Consider lubiprostone

Psychologic treatment
- Cognitive-behavioral therapy
- Relaxation methods

Future therapies
- Alvimopan
- N-methylnaltrexone
- Atypical antipsychotic?

Cannabinoid Hyperemesis Syndrome (CHS)

- Cannabinoid hyperemesis syndrome (CHS) is a condition in which patients who have been using cannabis or synthetic cannabinoids for a prolonged period of time develop a pattern of episodic, severe vomiting (usually accompanied by abdominal pain) interspersed with prolonged asymptomatic periods. There are 3 key components to assess for when making a presumed diagnosis:

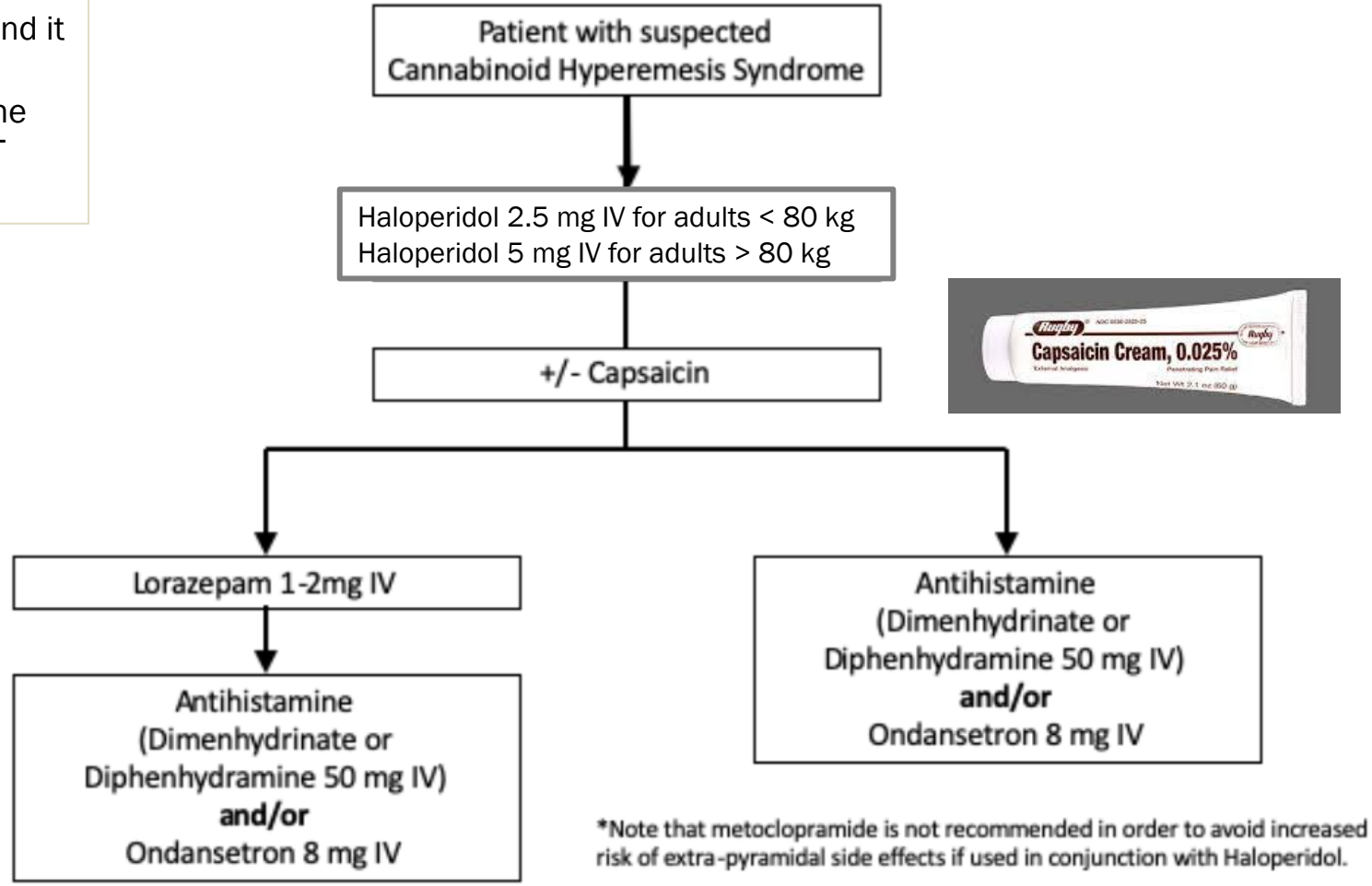
1. An episodic pattern of vomiting
    1. *Episodes of vomiting should last < 7 consecutive days*
    2. *Asymptomatic periods often last > 1 month between episodes*
2. Prolonged cannabis use
    1. *Criteria vary: normally >1 time per week (often daily) for at least 1 year*
    2. *Importantly, this is not an intoxication effect from a single large ingestion*
3. Exclusion of alternative diagnoses
    1. *Look for atypical features on history & exam including abnormal vital signs, diarrhea, focal abdominal pain, peritonitis, and jaundice*
    2. *It is important to exclude pregnancy in all female patients*
    3. *If a patient has never had an esophagogastroduodenoscopy (EGD), it is reasonable to refer newly diagnosed patients to gastroenterology for a non-emergent EGD to assess for a structural cause of the patient's symptoms*

ED Management of Cannabinoid Hyperemesis Syndrome

Unlike haloperidol, olanzapine does not prolong the QT interval and it has much lower rates of extrapyramidal side effects. Therefore, olanzapine may be a reasonable substitution for haloperidol in the following cases: documented allergy to haloperidol, prolonged QT interval, or previous extrapyramidal effects with haloperidol.

Antihistamines such as dimenhydrinate, diphenhydramine, and meclizine have no studies supporting their use, and the limited case reports available suggest they are ineffective [3]. While cases of treatment failure are more likely to be published which contributes to a reporting bias, clinical experience supports that CHS often does not respond well to these antiemetics. These medications may still have a role as an adjunct for patients who are refractory to other treatments, but given the evidence available supporting other agents, they can no longer be recommended as first-line therapy. Drawbacks to using a "traditional antiemetics first" strategies include a delay to effective treatment, prolonged ED length of stay, and prolongation of the QT interval.

Amitriptyline is recommended as a first-line prophylactic treatment for adults with cyclic vomiting syndrome as it reduces subjective symptoms scores, episode frequency, and ED utilization





با سپاس از توجه شما