BLINDED BY THE LIGHT

MARIJUANA

a Medication by any other Name

AKA - AUNT MARY, BUD, DOOBIE, DOPE, FATTY, GRASS, HASHISH, HERB, HOMEGROWN, LOCO WEED, LOVE WEED, MAGIC SMOKE, MARIHUANA, MARIJUANA, MARY JANE, MAUI-WOWIE, POT, REEFER, ROACH, WHACKY TABACKY, WEED

My Agenda

Discuss the best available evidence

Put the evidence into context

How to figure out if something is working for a specific patient

Answer questions as we go along

Simplified guideline for prescribing medical cannabinoids in primary care

G. Michael Allan MD CCFP Jamil Ramji Danielle Perry Joey Ton PharmD Nathan P. Beahm PharmD Nicole Crisp RN MN NP-Adult Beverly Dockrill RN Ruth E. Dubin MD PhD FCFP DCAPM Ted Findlay DO CCFP FCFP Jessica Kirkwood MD CCFP Michael Fleming MD CCFP FCFP Ken Makus MD FRCPC Xiaofu Zhu MD FRCPC Christina Korownyk MD CCFP Michael R. Kolber MD CCFP MSc James McCormack PharmD Sharon Nickel Guillermina Noël MDes PhD Adrienne J. Lindblad ACPR PharmD

Can Fam Phy 2018;64:111-120

Systematic review of systematic reviews for medical cannabinoids

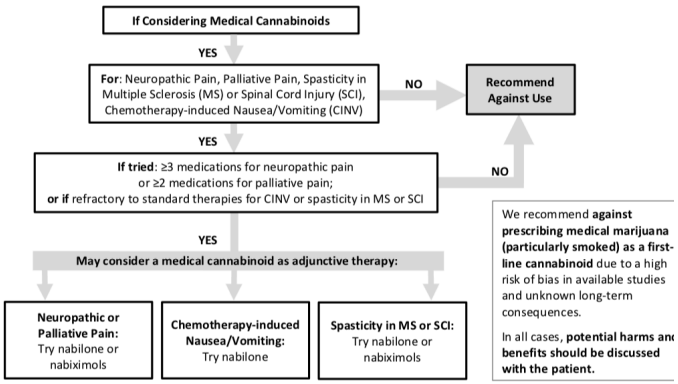
Pain, nausea and vomiting, spasticity, and harms

G. Michael Allan MD CCFP Caitlin R. Finley MSc Joey Ton PharmD Danielle Perry Jamil Ramji Karyn Crawford MLIS Adrienne J. Lindblad ACPR PharmD Christina Korownyk MD CCFP Michael R. Kolber MD CCFP MSc

Can Fam Phy 2018;64:e78-94

Medical Cannabinoids: Guideline Summary

Figure 1. Medical cannabinoid prescribing algorithm.



We recommend **against prescribing medical marijuana (particularly smoked) as a first-line cannabinoid** due to a high risk of bias in available studies and unknown long-term consequences.

In all cases, **potential harms and benefits should be discussed with the patient.**

Percentage of people experiencing harms

Type of harm	Cannabinoids	Placebo
Sedation	50%	30%
"Feeling high"	35%	3%
Dizziness	32%	11%
Speech disorders	32%	7%
Ataxia/Muscle twitching	30%	11%
Hypotension	25%	11%
Numbness	21%	4%
Psychiatric	17%	5%
Euphoria	15%	2%
Dysphoria	13%	0.3%
Impaired memory	11%	2%
Withdraw due to harms	11%	~3%
Dissociation/Acute psychosis	5%	0%

Percentage of people experiencing benefits

Benefits	Cannabinoids	Placebo
Chronic Pain (≥30% reduction after 4 weeks)		
Neuropathic pain	38%	30%
Palliative pain	30%	23%
Chemotherapy-induced nausea/vomiting (in 1 da		
Control of nausea & vomiting	47%	13%
Spasticity (≥30% improvement after 6 weeks)		
Spasticity	35%	25%

Daily doses and costs

Drug	Daily Dose[2]	Approximate cost/month
Nabilone*[1]	2 to 6 mg	$94 to $305
Nabiximols*	4 to 12 sprays	$226 to $903
Medical Marijuana *Dried*	1 to 3 g *typical use*	$250 to $750 Based on $8.37/

*Manufacturer list price, does not reflect pharmacy dispensing fees.
[1]Only generic nabilone covered by most provincial drug plans.
[2]Studied doses: Nabilone 0.5mg to 8mg/day, nabiximols 4 to 48 sprays smoked marijuana had THC concentrations ranging 1 to 8% up to three day as tolerated. Daily doses from drug monographs and Health Canac

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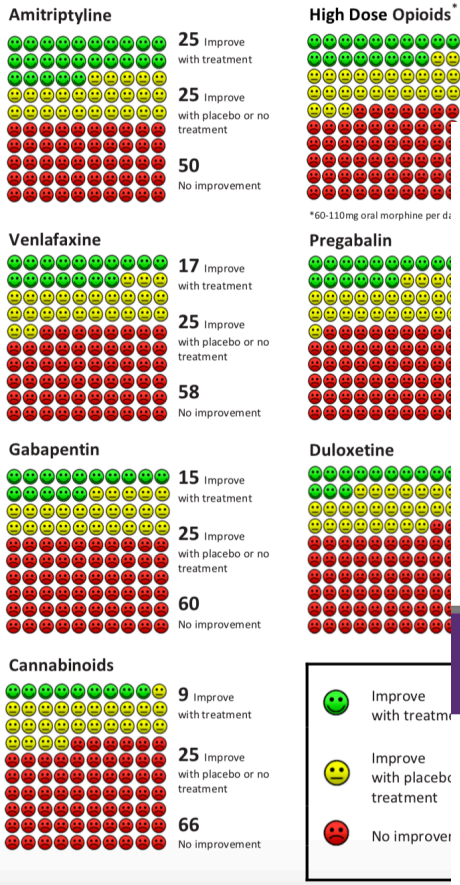
Neuropathic Pain: Pharmacotherapy Treatment

Outcome: Meaningful (~30%) Pain Improvement

Ordered by decreasing estimated efficacy



Limitations

1. Based on indirect comparisons.
2. Timeframe ~4 to 12 weeks.
3. Details on methods available in online supplement.

Common side effects

Side Effect	With Placebo	With Cannabinoids
Low blood pressure	11%	25%
Dizziness	11%	32%
Memory problems	2%	11%
Feeling sleepy	30%	50%
Feeling "high"	3%	35%
Muscle twitching	11%	30%
Feeling unhappy	Less than 1%	13%
Numbness	4%	21%
Feeling disconnected from reality	0%	5%
Trouble speaking	7%	32%

For more information please go to: www.pain-calculator.com

Start the conversation
Some people worry that their health care provider does not want to talk about cannabinoids. Talking about cannabinoids is important. Your health care provider can work with you because cannabinoids may:

- Affect your medications
- Cause side effects
- Be expensive
- Improve your symptoms, leading to a change in other medication

You should always talk to your health care provider before starting or changing treatment.

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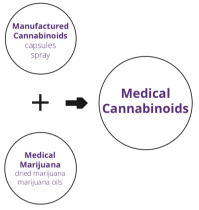
Medical Cannabinoids

There are a lot reasons people might ask their health care provider about medical cannabinoids or medical marijuana. You may have heard that it can help with some health problems.

Maybe you are interested because it is natural. Or maybe you have tried it in the past and found it helpful.

What are medical cannabinoids?

The word "cannabinoids" can mean two things: marijuana (dried plant or oils) and manufactured products (sprays or pills). Some people use cannabinoids recreationally and some people use them to treat health problems.



There are a lot options when treating health problems. It is suggested that you try some standard treatments before thinking about medical cannabinoids.

Will medical cannabinoids work for me?

There's not a lot of high quality research on medical cannabinoids. But based on the best research, cannabinoids may help people with:

- Nerve pain
- End-of-life pain
- Nausea and vomiting caused by chemotherapy
- Muscle spasticity caused by multiple sclerosis (MS) or spinal cord injury

What percentage of patients will get better?

Benefit	With Placebo	With Cannabinoids
Reduce nerve pain	30%	38%
Reduce end-of-life pain	23%	30%
Reduce nausea and vomiting caused by chemotherapy	13%	47%
Reduce spasticity caused by MS or spinal cord injury	25%	35%

Why might my health care provider say "no" to cannabinoids?

- Overall the research is poor
- For most health problems, there's not enough research to tell if they work
- Side-effects are common
- Long-term harms are unknown

Why is my health care provider suggesting manufactured cannabinoids instead of marijuana?

Manufactured products (sprays or pills) are like marijuana but have been studied more. Doses can be controlled better. Also, some of the manufactured products might be covered by your drug plan.

Things to consider

If you are thinking about using medical cannabinoids, smoked marijuana is not recommended. Smoking may cause other harms.

Comparing Treatment Options for Pain: The C-TOP Tool

Neuropathic Pain | Osteoarthritis Pain (Coming Soon) | Back Pain (Coming Soon)

Medication Options

- **Amitriptyline** (Elavil®)
- **Cannabinoids** (Nabiximols, nabilone, medical marijuana)
- **Duloxetine** (Cymbalta®)
- **Gabapentin** (Neurontin®)
- **High-Dose Opioids** (morphine, oxycodone)
- **Pregabalin** (Lyrica®)
- **All Treatments** (comparison)

Curious about capsaicin, botox, tramadol, carbamazepine, or venlafaxine for neuropathic pain? Click here to learn more.

Meaningful Pain Relief from Cannabinoids

(30% reduction in pain scores)

Cannabinoids Benefit	Placebo Benefit	No Benefit
9%	25%	66%
(ranges 3% to 16%)		

A typical placebo group response seen in pain studies is **25%** but this can be adjusted in the FAQ section.

Meaningful Pain Relief

An example of a **30% reduction** in pain scores is a decrease from **6** to **4** on a **10** point pain scale

Cannabinoids Harms

Sleepiness	50%	*30% (placebo)*
'Feeling high'	35%	*3% (placebo)*
Speech disorders	32%	*7% (placebo)*
Dizziness	32%	*11% (placebo)*
Stopped due to side effects	11%	*3% (placebo)*

Other Considerations

- Oral capsules can be taken once or twice daily, whereas oral spray can be used multiple times per day
- Side effects are likely more common (many studies included people with proven tolerance to cannabinoids)
- Approximate cost (CAD) for 30-day supply (without dispensing fee): **$94 to $305 (nabilone), $226 to $903 (nabiximols), $250 to $750 based on $8.37/g using 1-3g/day (medical marijuana)**

http://pain-calculator.com

This is an Evidence Synopsis

not a legal discussion

not a moral discussion

not an ethical discussion

simply a discussion of the evidence

Cannabinoids come in many forms

- liquid tinctures
- vaporizing/smoking dried buds
- eating
- capsules
- lozenges
- dermal patches
- oral sprays

Medical marijuana

Manufactured cannabinoids

Nabilone,
Nabiximols (Sativex®)

Medical cannabinoids

Cannabinoids/Cannabis/Cannabidiol/THcannabinol

NON-SYNTHETIC

Marijuana plants contain ~ 400 different chemicals

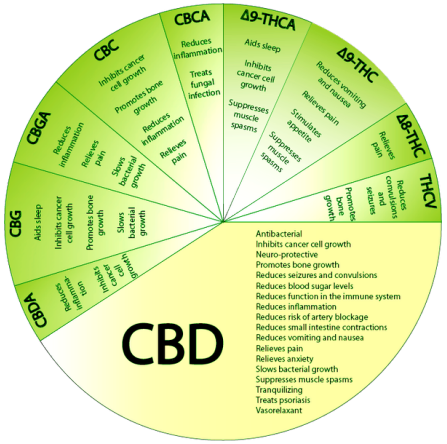
~70 cannabinoids [includes THC (psychoactive) and CBD]

Medical Marijuana (cannabis) - primarily THC but also CBD

average joint 0.5-1g of cannabis - different concentrations

HEMP - CBD - very little THC - considered a food supplement if less than 0.3%THC but not yet legal in Canada?

Dried/oils/capsules/topical with many different ratios of THC/CBD



SYNTHETIC

1) THC - (tetrahydrocannabinol)

dronabinol capsules (Marinol) - **NA** in Canada - (Syndros) - FDA oral solution

nabilone capsules (Cesamet)

2) CBD - (cannabidiol)

there are FDA submissions

3) THC plus CBD

nabiximols (Sativex) 1:1 ratio - buccal spray

Some of the promoted medical uses for Cannabinoids

Tourette Syndrome
Amyotrophic Lateral Sclerosis
Huntington's Disease
Parkinson's Disease
Dystonia
Glaucoma
Traumatic Brain Injury/ Intracranial Hemorrhage
Addiction
Anxiety
Depression
Sleep Disorders
Posttraumatic Stress Disorder
Schizophrenia and Other Psychosis

Osteoarthritis
Fibromyalgia
Neuropathic Pain
HIV Pain
Dementia
Cancer
Chemotherapy-Induced Nausea and Vomiting
Anorexia and Weight Loss
Irritable Bowel Syndrome
Epilepsy
Spasticity Associated with Multiple Sclerosis or Spinal Cord Injury

Stolen from Mike Allan

Examples of Poor Research

Glaucoma: 1 RCTs with 6 people (no effect)

Anxiety: 1 RCT of 24 patients tested for simulated public speaking found more improvement on mood visual analogue scale

IBS: 1 RCT of 36 pts given dronabinol for 2.5, 5mg or placebo BID x 2 days: Focused on transit times

JAMA. 2015;313(24):2456-2473. National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. doi: 10.17226/24625.

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Two Primary Problems

- Blinding: Attempted but rarely tested
  - In 2 Inhaled cannabis cross-over RCTs
    - 1st: 57% identified all 6 phases
    - 2nd: 90% identified active vs cannabis cigs without THC/CBD
  - Dronabinol, 95% of patients identified active (as did 85% of nurses. (nabilone study similar)
- Inclusion: Previous users often focused on.
  - Of 6 inhaled RCTs: 3 required past use, 2 no limitation and 1 did not report.
  - In Nausea/vomiting, previous use led to greater response
  - Naive users (no previous report of psychosis).
- Together, these introduce profound bias

Can Fam Physician 2018

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The Evidence base

Lack of high level research

- BIAS - many studies enrolled people with a history of cannabinoid use, unblinding was common (90%), small sample size, short duration, inconsistent reporting

Reasonable evidence for

- Chronic pain - neuropathic pain and refractory pain in palliative care
- Nausea and vomiting - chemotherapy
- Spasticity - MS and special cord injury

The Evidence for Cannabinoids

BENEFIT

PAIN

15 RCTs - at least a 30% reduction

RR = 1.37 (95% CI 1.14 to 1.64) - NNT = 11 - 39% vs 30% - primarily nabiximol and some smoked - but larger (>150) and longer (9-15 weeks) trials show no effect

SPASTICITY

4 RCTs - a + global impression of change - 30% reduction

RR = 1.45 (1.08 to 1.95) - NNT = 7 - 50% vs 35%

N and V AFTER CHEMO

7 RCTs - absence of N and V after chemo

RR = 3.60 (2.55 to 5.09) - NNT = 3 - 47% vs 13% - primarily nabilone and delisted dronabinol - vs neuroleptics - NNT = 7 - patient preference higher than effectiveness

Can Fam Phy 2018;64:e78-94

Evidence in Mental Health

The evidence is at best, very poor - overwhelmingly case reports

depression - no RCTs - case reports

anxiety - 1 RCT - CBD powder - 24 patients who performed a simulated public speaking activity and then reported improvement on the mood visual analogue scale Neuropsychopharmacology 2011;36,1219–26

PTSD - 1RCT - nabilone (THC) - 10 patients - found benefit in some outcomes, but these results disagree with other research findings of marijuana use worsening post-traumatic stress disorder Psychoneuroendocrinology 2015;51,585–8

ADHD - 1 RCT - Sativex oralmucosal spray (THC/CBD) - 30 adults - 6 weeks primary outcome (cognitive performance) no difference - some secondary outcomes showed benefit but not after adjustment for multiple testing European Neuropsychopharmacology 2017; 27,795–808

insomnia - THC may have a short-term sleep benefit - but THC is associated with habituation to the sleep-enhancing qualities Curr Psychiatry Rep 2017 19: 23

schizophrenia - 1 RCT - CBD oral solution - 88 patients - an improvement >20% in PANSS total score - no difference - rated by their clinician as “improved” on the CGI-I scale compared with those in the placebo group (79% and 55%) - treatment difference= -0.5, 95% CI= -0.8, -0.1 AJP in Advance doi: 10.1176/appi.ajp.2017.17030325

the present evidence for medical cannabinoids is insufficient to support use in mental health conditions - and it may worsen some conditions (bipolar disorder)

TABLE 1 Levels of evidence for cannabis and cannabinoids as treatment

Condition	Compound	Levels of evidence	Highest level
Social anxiety disorder	Cannabis		3
	CBD	3	
	THC		
	Synthetic cannabinoids		
Generalized anxiety disorder	Cannabis		3
	CBD		
	THC		
	Synthetic cannabinoids	3 (nabilone)	
Major depressive disorder	Cannabis	4	4
	CBD		
	THC	-3	
	Synthetic cannabinoids	4	
Bipolar disorder	Cannabis	4	4
	CBD	-4	
	THC		
	Synthetic cannabinoids		
Posttraumatic stress disorder	Cannabis	3	3
	CBD		
	THC	3	
	Synthetic cannabinoids	3 (nabilone)	
Obsessive-compulsive disorder	Cannabis		4
	CBD		
	THC		
	Synthetic cannabinoids	4 (Adj. dronabinol)	
Trichotillomania	Cannabis		3
	CBD		
	THC		
	Synthetic cannabinoids	3	
Tourette's disorder	Cannabis	4	3
	CBD		
	THC	3	
	Synthetic cannabinoids		

1, Meta-analysis with narrow confidence intervals and/or two or more RCTs with adequate sample size, preferably placebo controlled.
2, Meta-analysis with wide confidence intervals and/or one or more RCTs with adequate sample size.
3, Small-sample RCTs *or* nonrandomized, controlled prospective studies *or* case series, *or* high-quality retrospective studies.
-3, Negative, small-sample RCTs *or* nonrandomized, controlled prospective studies *or* case series, *or* high-quality retrospective studies.
4, Expert opinion/consensus.
-4, Negative, case report.

Depress Anxiety 2017;34:1006–17

“the actual science appears to have been outpaced by the development of applicable legislation and public opinion”

“the documented mental health effects associated with cannabis use also create cause for concern as existing symptomatology typically worsens with use and incidence of certain psychiatric conditions increases”

“there is little observational evidence demonstrating improvement in mental health conditions with cannabis use”

“Clinicians are consequently ill equipped to offer evidence-based advice regarding cannabis’ utility as a mental health treatment”

Depress Anxiety 2017;34:1006–17

Intractable seizures

Dravet and Lennox-Gastaut syndrome

CANNABIDIOL

open label - 214 children - 30 seizures a month down to 16 during the 12 week treatment period - severe adverse events 30% - Lancet Neurology 2015

RCT - 120 children ~20-25% greater reduction in seizure frequency - NEJM 2017

RCT - 171 children ~ 20-25% greater reduction in seizure frequency - Lancet 2018

RCT - 225 patients (avg age 15) - 14 weeks - median reduction from baseline in drop-seizure frequency - 41.9% in the 20-mg group, 37.2% in the 10-mg group, and 17.2% in the placebo group - increase of 15-25% somnolence, 10-20% decreased appetite - more in the higher dose - overall 9% in cannabidiol groups had elevated liver aminotransferases - NEJM 2018

Adverse effects - above placebo

~20%-30%
sedation, feeling high, dizziness, speech disorders

~10-20%
ataxia/muscle twitching, low blood pressure, euphoria, dysphoria

~5-10%
impaired memory, withdrawing due to side effects

~5%
dissociation/acute psychosis

Can Fam Phy 2018;64:e78-94

Cannabis-based medicines for chronic neuropathic pain in adults (Review)

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

Cochrane Library
Cochrane Database of Systematic Reviews

more with 50% or greater pain relief - 21% VS 17%; risk difference (RD) 0.05 (95% confidence interval (CI) 0.00 to 0.09); NNTB 20 (95% CI 11 to 100); 1001 participants, eight studies low quality evidence

more with 30% or greater pain relief - 39% VS 33%; RD 0.09 (95% CI 0.03 to 0.15); NNTB 11 (95% CI 7 to 33); 1586 participants, 10 studies, moderate quality evidence

more withdrew due to adverse events - 10% VS 5%; RD 0.04 (95% CI 0.02 to 0.07); NNTH 25 (95% CI 16 to 50); 1848 participants, 13 studies, moderate-quality evidence

more nervous system adverse events - 61% VS 29%; RD 0.38 (95% CI 0.18 to 0.58); NNTH 3 (95% CI 2 to 6); 1304 participants, nine studies, low-quality evidence

more psychiatric disorders - 17% VS 5%; RD 0.10 (95% CI 0.06 to 0.15); NNTH 10 (95% CI 7 to16); 1314 participants, nine studies, low-quality evidence

CD012182-2018

Smoked marijuana

The Literature

the literature around smoked medical marijuana demonstrates a considerable risk of bias

possibly exaggerated benefits and underreported harms

Long-term harms

(including smoking) and serious adverse effects would not be adequately captured in RCTs and so are largely unknown

Dosing

poses an issue, as THC and cannabidiol concentrations vary considerably with differing medical marijuana products

many dried medical marijuana products have THC concentrations of 15% or greater, while the highest concentration studied is only 9.4%

mode of delivery and volume per use can substantially change total intake

there is no evidence that the different formulations of medical marijuana, such as cannabis oil, are more effective or safer than dried medical marijuana

cases of pulmonary aspergillosis have been reported in immunocompromised patients

CBD vs THC evidence

CBD thought to have lower psychoactive properties

4 RCTs

- THC/CBD > THC - 1 RCT - cancer pain
- THC/CBD = THC - 2 RCTs - anorexia and neuropathic pain
- THC and THC/CBD > CBD - 1 RCT - chronic pain

Based on the best available data, it is unknown if using different ratios of THC:CBD or using its individual components alone would lead to improved efficacy or reduced adverse events

What to use?

ORAL nabilone (THC) for nausea and vomiting

OROMUCOSAL SPRAY nabiximols (THC/CBD) for spasticity and neuropathic pain

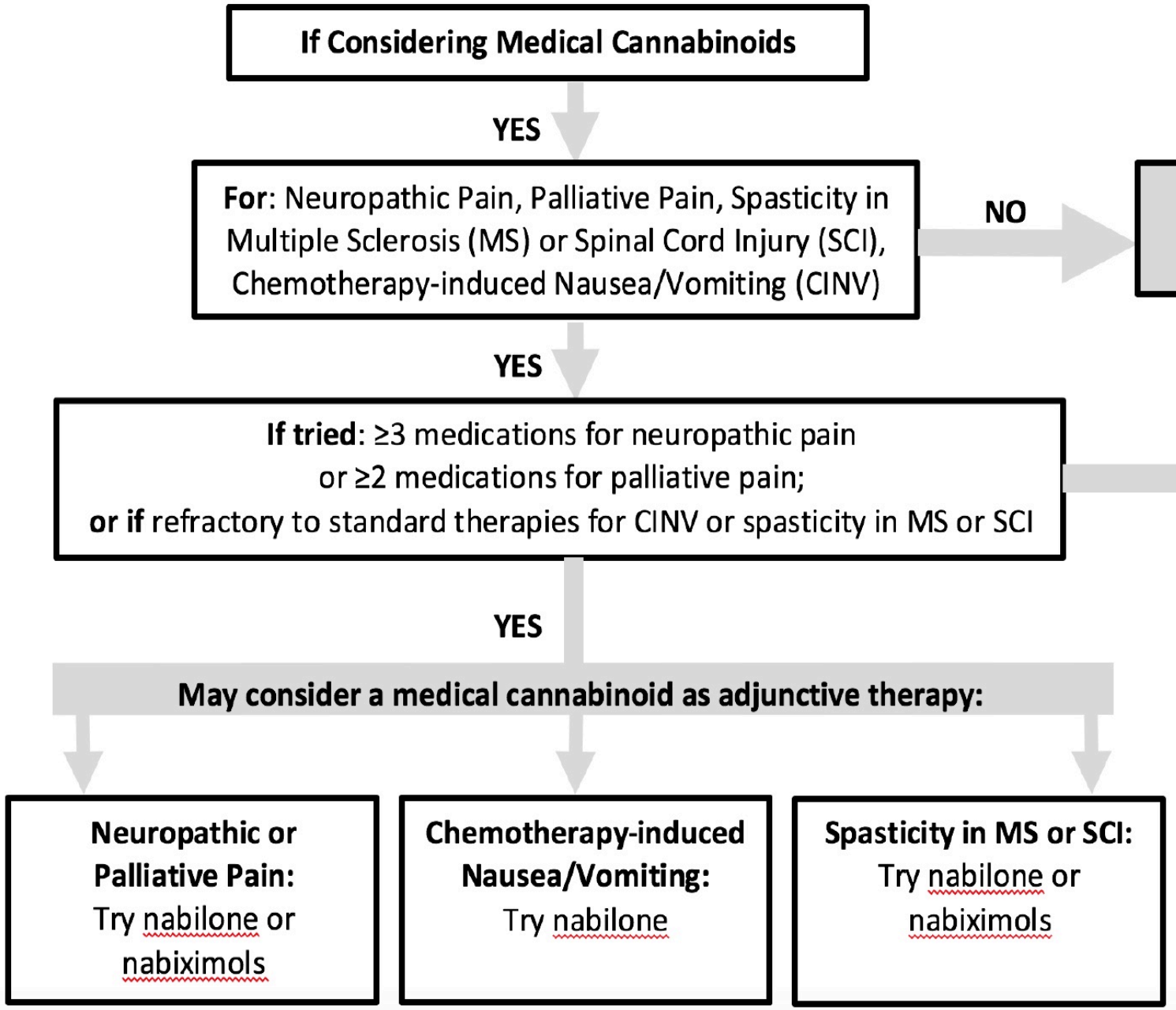
SMOKED - there is no evidence that any one formulation is more effective or safer than dried marijuana

Neuropathic Pain

Benefit Comparison

Can Fam Physician 2018 Feb.

Figure 1. Medical cannabinoid prescribing algorithm.



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Can Fam Physician 2018 Feb.

Symptoms

You primarily need to know IF it works

Safety, cost and convenience

Older medications first - safety

Head-to-head studies are uncommon

Doses in the CPS are “wrong”

N-of-1 studies

Let the patient tell you

Symptom NNTs

General anesthesia/local anesthesia - NNT ~1

PPIS, sildenafil - heartburn/“successful” intercourse NNT ~2

NSAIDs, opioids - pain NNT ~3-5

Steroids - sore throat - NNT ~3, Bell’s palsy - NNT ~10

Antibiotics - acute COPD exacerbation - NNT ~5

Topical antibiotics - bacterial conjunctivitis - NNT ~7

Antidepressants - severe depression - NNT ~10

Ipratropium - asthma attack - NNT ~11

Cholinesterase inhibitors - ADAS-Cog >4 - NNT ~10

Sleeping pills - improvement in sleep quality - NNT ~13

NNTs taken from Cochrane reviews - if a Cochrane review as N/A then from a published MA

But you need to know what goes on in the placebo group

	If person “responds”, what is the % chance it was the medication	
Response in the placebo group	If Benefit 10% - NNT 10	If Benefit 20% - NNT 5
0%	~100%	~100%
20%	~33%	~50%
40%	~20%	~33%

NNTs taken from Cochrane reviews - if a Cochrane review was N/A then from a published MA

The Placebo Group Effect

not the placebo effect and these are ballpark numbers

~0% - general anesthesia

~5% - psychosis

~10% - sildenafil, OCD

~20% - Alzheimer's meds, acetaminophen for headaches, side effects

~25% - menopausal symptoms, migraine (frequency/severity)

~30% - blood pressure goal, depression, anxiety, PTSD, PPIs/H2RA, sore throat, NSAIDs of OA, inhalers for COPD

~40% - panic disorders

Placebo effect taken from Cochrane reviews - if a Cochrane review was N/A then from a published MA

When a medication has “worked”, if you were a betting person you would bet that it probably wasn't because the medication worked.