CANNABIS IN PALLIATIVE CARE

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OBJECTIVES

- Review the evidence for medical cannabis in palliative care
- Provide clear instructions on how to authorize cannabis for palliative care patients
- Discuss the impact of legalization of recreational marijuana on palliative care

DISCLOSURE

- No financial ties or conflicts of interest
- I trained in Vancouver in the era of "MMAR"

BACKGROUND ON CANNABINOID SYSTEM

- Mediated by CB1and CB2 receptors
- CB1: Mainly located in CNS
  - Basal ganglia, hippocampus
  - Cerebral cortex, cerebellum
  - Spinal cord, primary afferent nociceptors
  - Integrated vomiting center*
- CB2: Periphery
  - Immune and hematopoetic systems
  - Spleen, tonsils, Mast cells

ENDOCANNABINOID SYSTEM

- Widespread function
  - Memory, sleep
  - Appetite, metabolism
  - Pain perception, modulation
  - Stress response
  - Intestinal motility

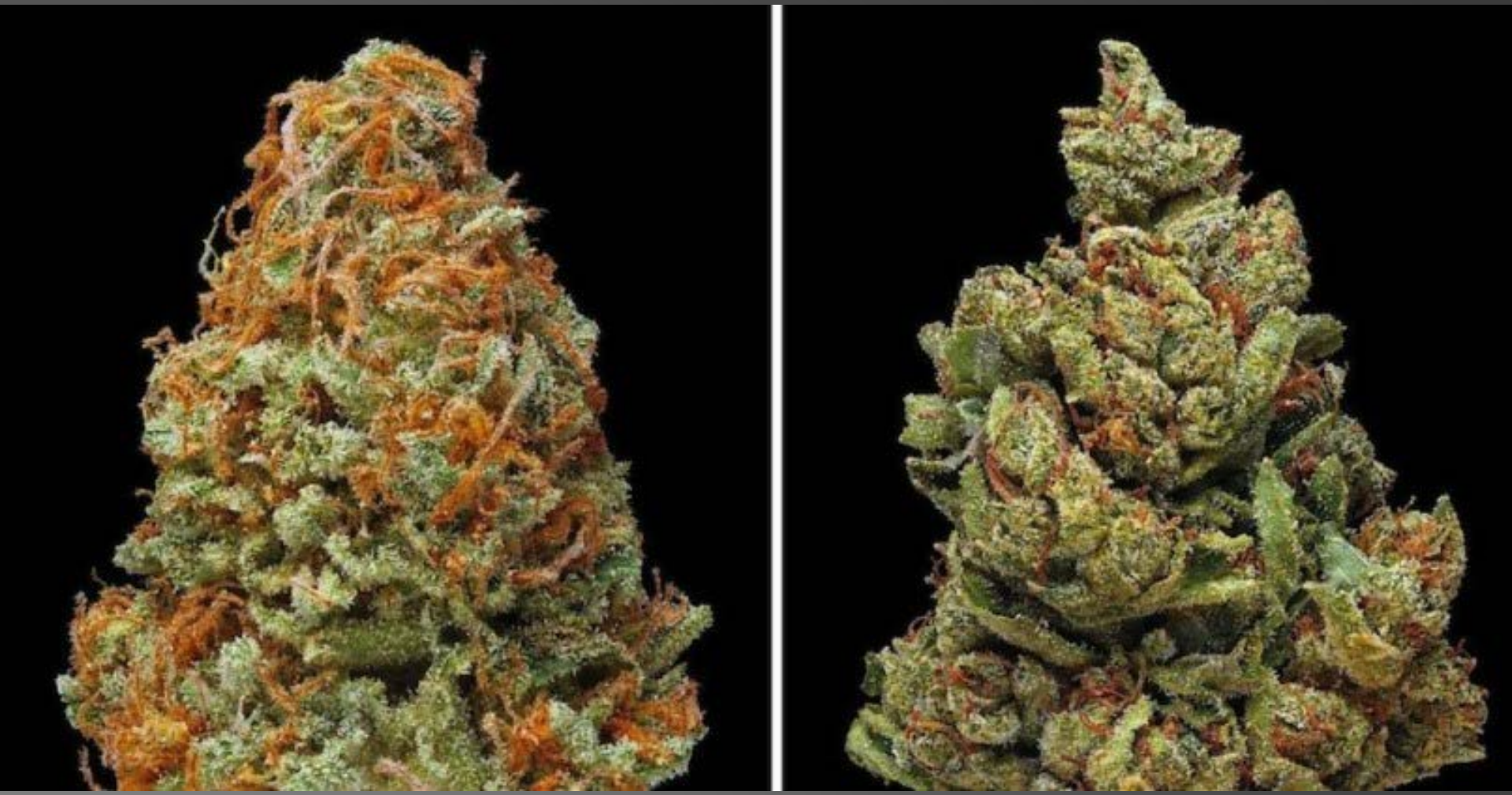
EXOGENOUS CANNABINOIDS

- Phytocannabinoids
  - Marijuana
  - Nabiximols (botanical drug/extract) (i.e. Sativex)
- Synthetic cannabinoids
  - Dronabinol (trade name Marinol)
    - Pure isomer of THC, No longer available in Canada
  - Nabilone (trade name Cesamet)
    - Synthetic THC mimic, approximately 10 x potency

CANNABIS PLANT

CANNABIS (MARIJUANA

- Cannabis Sativa
  - Traditionally higher ratio of THC to CBD
  - More “activating”, euphoria, “high”
- Cannabis Indica
  - Traditionally lower ratio (more CBD)
  - More “relaxing”, sedation, “body buzz”
- Extreme breeding has led to huge variety of strains, hybids etc.



CANNABIS

- Cannabinoids
  - Psychoactive (Δ9-**Tetrahydrocannabinol (THC)**, cannabinol)
  - Active (but not psychoactive) – **cannabidiol (CBD)**
  - Unclear activity (more than 113 identified compounds)
    - Cannabichromene, Cannabigerol etc.
- Terpenes
  - Pinene (Pine), Myrcene (musky-fruity), Limonene (citrus), Humulene (hoppy), Linalool (floral-spicy)

MEDICAL 'BENEFITS'

- THC
  - Psychoactive, analgesic, antiemetic, muscle relaxant, reduce depression
  - Anxiety up/down (paranoia)
  - Can precipitate psychosis in vulnerable
- CBD
  - Non-psychoactive, analgesia, antiemetic, anti-anxiety, anti-psychotic, anti-convulsant, may reduce psychoactive effects of THC
- "Ratio" THC/CBD – shifted to more THC in street/recreational cannabis, but unclear how to choose

OBJECTIVE #1

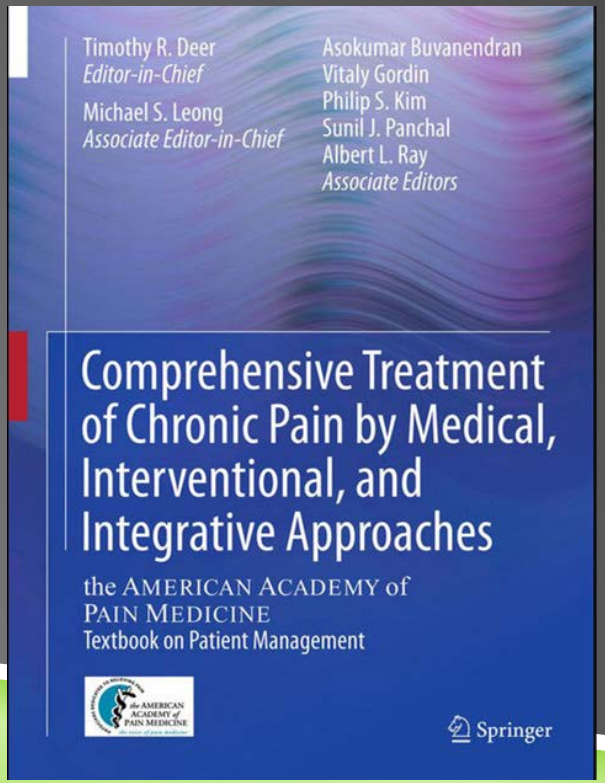
- Review the evidence for medical cannabis in palliative care

MEDICAL EVIDENCE

- Pain
  - Very limited
- Nausea
  - Moderate
- Appetite
  - Limited
- Spasticity (MS)
  - Moderate

EVIDENCE- PAIN

- Russo and Hohmann. Role of Cannabinoids in Pain Management. Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches. Pages 181-197.



EVIDENCE- PAIN

Table 18.1 Randomized controlled trials of cannabinoids in pain

Agent	*N*=	Indication	Duration/type	Outcomes/reference
Ajulemic acid	21	Neuropathic pain	7 day crossover	Visual analogue pain scales improved over placebo ($p=0.02$)/Karst et al. [92]
Cannabis, smoked	50	HIV neuropathy	5 days/DB	Decreased daily pain ($p=0.03$) and hyperalgesia ($p=0.05$), 52 % with >30 % pain reduction vs. placebo ($p=0.04$)/ Abrams et al. [94]
Cannabis, smoked	23	Chronic neuropathic pain	5 days/DB	Decreased pain vs. placebo only at 9.4 % THC level ($p=0.023$)/Ware et al. [98]
Cannabis, smoked	38	Neuropathic pain	Single dose/DBC	NSD in pain except at highest cannabis dose ($p=0.02$), with prominent psychoactive effects/Wilsey et al. [95]
Cannabis, smoked	34	HIV neuropathy	5 days /DB	DDS improved over placebo ($p=0.016$), 46 % vs. 18 % improved >30 %, 2 cases toxic psychosis/Ellis et al. [97]
Cannabis, vaporized	21	Chronic pain on opioids	5 days/DB	27 % decrement in pain/Abrams et al. [118]
Cannador	419	Pain due to spasm in MS	15 weeks	Improvement over placebo in subjective pain associated with spasm ($p=0.003$)/ Zajicek et al. [120]
Cannador	65	Postherpetic neuralgia	4 weeks	No benefit observed/Ernst et al. [122]
Cannador	30	Postoperative pain	Single doses, daily	Decreasing pain intensity with increased dose ($p=0.01$)/Holdcroft et al. [123]
Marinol	24	Neuropathic pain in MS	15–21 days/DBC	Median numerical pain ($p=0.02$), median pain relief improved ($p=0.035$) over placebo/Svendsen et al. [76]
Marinol	40	Postoperative pain	Single dose/DB	No benefit observed over placebo/Buggy et al. [77]
Marinol	30	Chronic pain	3 doses, 1 day/DBC	Total pain relief improved with 10 mg ($p<0.05$) and 20 mg ($p<0.01$) with opioids, AE prominent/Narang et al. [79]

EVIDENCE- PAIN

Nabilone	41	Postoperative pain	3 doses in 24 h/DB	NSD morphine consumption. Increased pain at rest and on movement with nabilone 1 or 2 mg/Beaulieu [85]
Nabilone	31	Fibromyalgia	2 weeks/DBC	Compared to amitriptyline, nabilone improved sleep, decrease wakefulness, had no effect on pain, and increased AE/ Ware et al. [90]
Nabilone	96	Neuropathic pain	14 weeks/DBC vs. dihydrocodeine	Dihydrocodeine more effective with fewer AE/Frank et al. [88]
Nabilone	13	Spasticity pain	9 weeks/DBC	NRS decreased 2 points for nabilone ($p<0.05$)/Wissel et al. [87]
Nabilone	40	Fibromyalgia	4 weeks/DBC	VAS decreased in pain, Fibromyalgia Impact Questionnaire, and anxiety over placebo (all, $p<0.02$)/Skrabek et al. [89]
Sativex	20	Neurogenic pain	Series of 2-week N-of-1 crossover blocks	Improvement with Tetranabinex and Sativex on VAS pain vs. placebo ($p<0.05$), symptom control best with Sativex ($p<0.0001$)/Wade et al. [132]
Sativex	24	Chronic intractable pain	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo ($p<0.001$) especially in MS ($p<0.0042$)/ Notcutt et al. [133]
Sativex	48	Brachial plexus avulsion	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with Tetranabinex ($p=0.002$) and Sativex ($p=0.005$) over placebo/Berman et al. [134]
Sativex	66	Central neuropathic pain in MS	5 weeks	Numerical Rating Scale (NRS) analgesia improved over placebo ($p=0.009$)/Rog et al. [135]

EVIDENCE- PAIN

Agent	*N*=	Indication	Duration/type	Outcomes/reference
Sativex	125	Peripheral neuropathic pain	5 weeks	Improvements in NRS pain levels (p=0.004), dynamic allodynia (p=0.042), and punctuate allodynia (p=0.021) vs. placebo/Nurmikko et al. [136]
Sativex	56	Rheumatoid arthritis	Nocturnal dosing for 5 weeks	Improvements over placebo morning pain on movement (p=0.044), morning pain at rest (p=0.018), DAS-28 (p=0.002), and SF-MPQ pain at present (p=0.016)/Blake et al. [138]
Sativex	117	Pain after spinal injury	10 days	NSD in NRS pain scores, but improved Brief Pain Inventory (p=0.032), and Patients' Global Impression of Change (p=0.001) (unpublished)
Sativex	177	Intractable cancer pain	2 weeks	Improvements in NRS analgesia vs. placebo (p=0.0142), Tetranabinex NSD/ Johnson et al. [139]
Sativex	135	Intractable lower urinary tract symptoms in MS	8 weeks	Improved bladder severity symptoms including pain over placebo (p=0.001) [200]
Sativex	360	Intractable cancer pain	5 weeks/DB	CRA of lower and middle-dose cohorts improved over placebo (p=0.006)/ [201]

EVIDENCE – CANCER PAIN

- Maida et al. (2008)
  - Prospective observational study N = 112
  - Adjuvant nabilone vs no treatment for pain / symptoms experienced by advanced cancer pts
  - Pain scores and morphine equivalent daily dose (of opioid) lower in treatment group (P <0.0001)
    - Baseline pain 7.1/10 for nabilone, 5.6/10 for untreated
    - Final pain 3/10 for nabilone, 5.5/10 for untreated

EVIDENCE – CANCER PAIN

- RCT (Johnson, J.R. et al 2010):
- Multicentre, double-blind, placebo-controlled, parallel-group trial
- N=177 with "unrelieved pain despite chronic opioid dosing", randomized to THC:CBD extract (Sativex), THC extract or placebo
  - 43% of those using Sativex had >30% reduction in pain, vs. 23% for THC and 21% for placebo
- "Sativex is effective for relief of advanced cancer pain not fully relieved by strong opioids"

EVIDENCE – NEUROPATHIC PAIN

- Several small RCTs
  - 2 (Abrams 2007,Ellis 2009) for HIV-associated sensory neuropathy
    - Smoked cannabis
    - ~50% vs ~20% (placebo) had 30%+decrease in pain, NNT 3.6
  - 1(Svendsen 2004) for MS-associated central neuropathic pain
    - Dronabinol, NNT 3.5 (50% pain reduction)
  - 1(Nurmikko 2007) for peripheral neuropathic pain
    - DBRCT, placebo-controlled, Sativex
    - 26% had 30%+decrease (vs. 15% placebo), 20% had 50%+(vs 8)

EVIDENCE – NAUSEA/VOMITING

- Tramer (2001) – Systematic Review (30 RCT)
  - Cannabinoids for 'complete control': nausea NNT = 6 vomiting NNT = 8
  - Not more effective than established agents
- Machado Rocha (2008) – 2nd SR of 30 RCTs
  - Nabilone not statistically significantly better than conventional antiemetics

EVIDENCE – APPETITE / CACHEXIA

- Mixed results from trials
  - Dronabinol improves appetite and food intake in some patients
  - Weight gain only achieved in some patients (body fat)
- Strasser (2006) – RCT (Cannabis extract, THC, placebo)
  - Improved appetite in 73% CE, 58% THC, 69% placebo
  - No differences for appetite, QOL, toxicity

EVIDENCE – APPETITE / CACHEXIA

- Brisbois (2011) – DBRCT (Dronabinol, placebo)
  - Increased "chemosensory perception", food appeal, appetite.
  - No real calorie increase (1594 to 1726)
- Jatoi (2002) – RCT (Dronabinol vs Dronabinol + megestrol acetate vs megace alone)
  - 75% megace improved appetite vs 49% dronabinol
  - 11% megace reported >10% weight gain vs 3% dronabinol
  - Combination therapy not really better than megace alone.

EVIDENCE- SPASTICITY

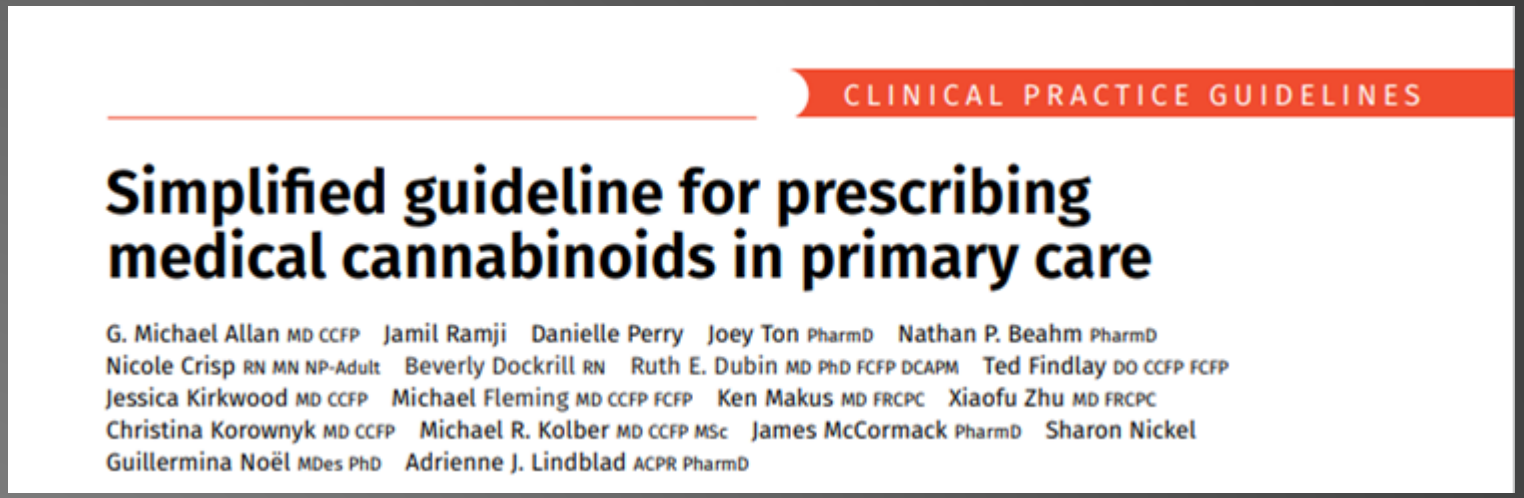
- Zajicek (2005)
  - 667 patients, cannabis extract vs THC vs placebo (15 weeks)
  - Primary outcome: spasticity scores (Ashworth scale)
    - No statistically significant improvement in Ashworth scale
  - Secondary outcomes:
    - Statistically significant effect on patient-reported spasticity and pain as well as mobility

EVIDENCE- SPASTICITY

- Wade (2007):
  - Meta-analysis of 3 RCTs (Wade 2004, Collin 2007, Collin 2010)
  - MS patients with ++spasticity +no relief with standard treatment
  - DBRCT, placebo control, Sativex spray
  - Spasticity reduced -1.30 vs -0.97 (-0.32, p=0.026)
    - Significantly more "responders" in Sativex group (OR 1.62)
    - Significantly greater improvement in Sativex group (OR 1.67)

SIMPLIFIED GUIDELINE

- http://www.cfp.ca/content/cfp/64/2/111.full.pdf

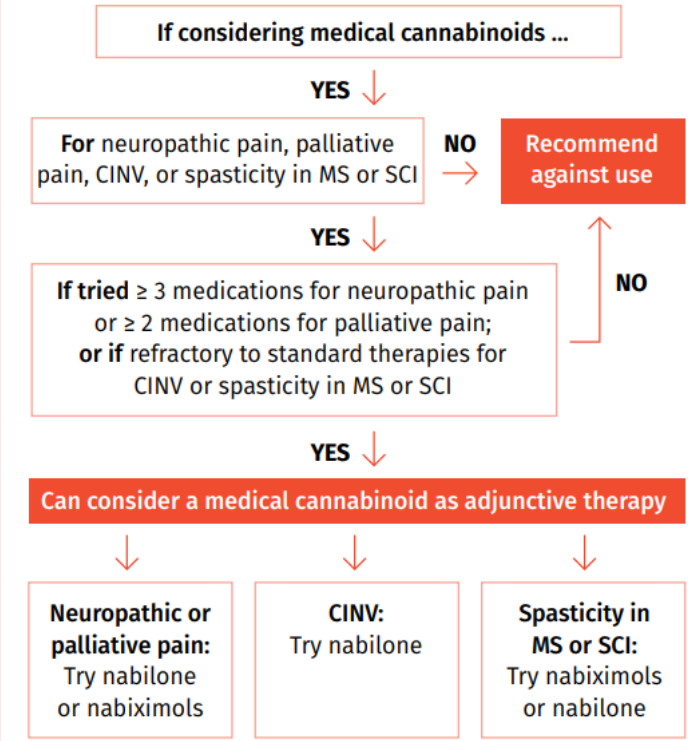


CLINICAL PRACTICE GUIDELINES

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

Figure 1. Medical cannabinoid prescribing algorithm



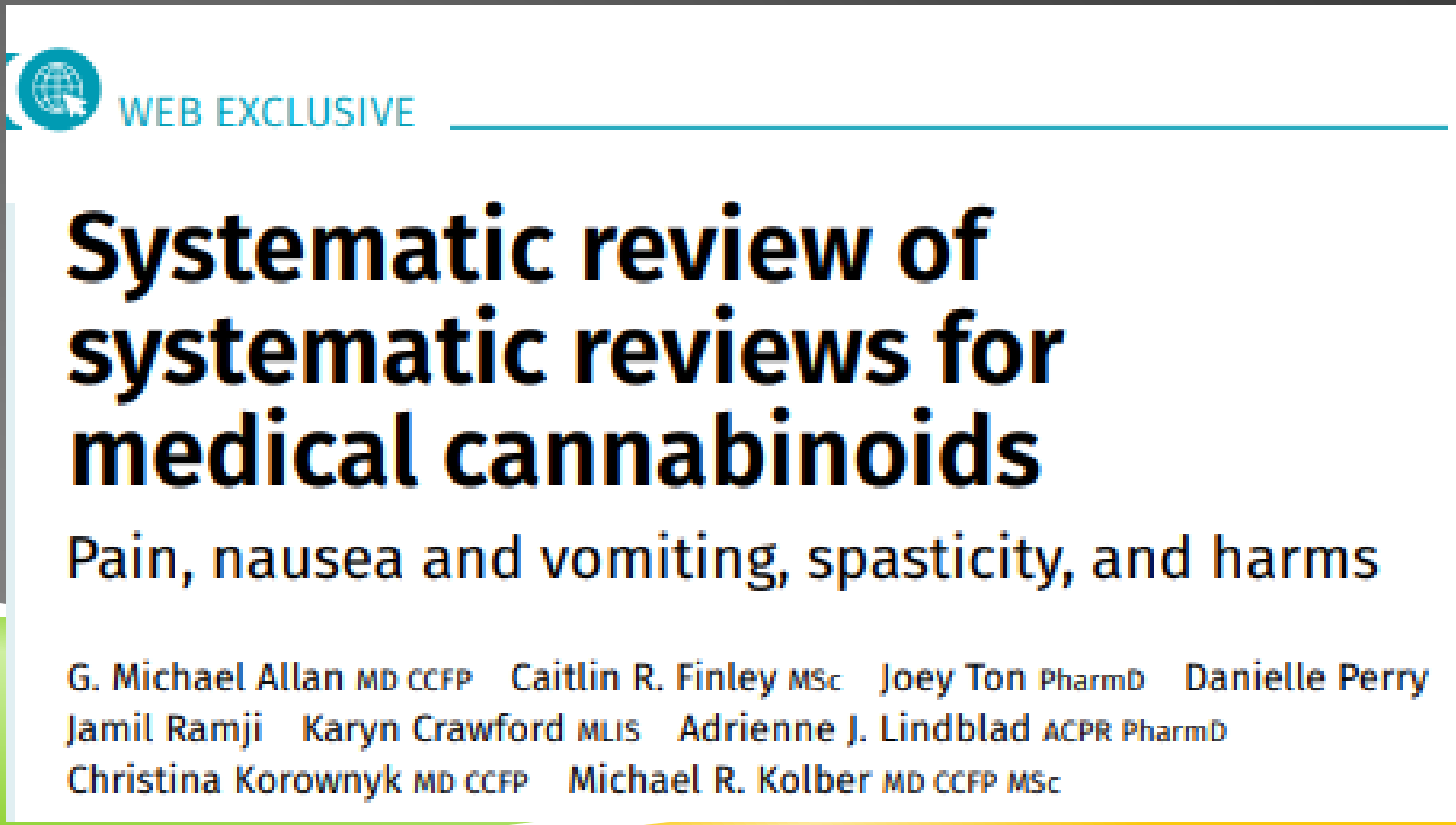
We **recommend against prescribing medical marijuana (particularly smoked) as a first-line cannabinoid** owing to a high risk of bias in available studies and unknown long-term consequences

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

CINV—chemotherapy-induced nausea and vomiting, MS—multiple sclerosis, SCI—spinal cord injury.

GETTING VERY META

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5964405/



WEB EXCLUSIVE

Systematic review of systematic reviews for medical cannabinoids

Pain, nausea and vomiting, spasticity, and harms

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Jamil Ramji Karyn Crawford MLIS Adrienne J. Lindblad ACPR PharmD
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CONCLUSION

There is **reasonable evidence** that cannabinoids **improve nausea and vomiting after chemotherapy** They **might improve spasticity** (primarily in multiple sclerosis).

There is some **uncertainty** about whether cannabinoids improve pain, but **if they do, it is neuropathic pain and the benefit is likely small**.

Adverse effects are very common, meaning benefits would need to be considerable to warrant trials of therapy.

OBJECTIVES #2

Provide clear instructions on how to authorize cannabis for palliative care patients

CANNABIS RX LEGISLATION

- Current regulation for medical cannabis:
- ACMPR ("Access to Cannabis for Medical Purposes Regulation"
  - Replaced "MMPR" in 2016
    - Licensed producers, HCPs as Gatekeeper.
  - Replaced "MMAR" in 2013
    - Health Canada approval, grow/assign growing

LICENSED PRODUCERS OF CANNABIS

- Licensed Producers (253 total --> 126 Ontario)
  - 143 authorized to sell, rest to "cultivate".
- Dried or oil extracts (bottle or "gel cap")
  - Initially only dried marijuana available, but oil extracts available at many (25) due to June 2015 SCC decision to expand definition of medical marijuana from dried form only

MEDICAL CANNABIS PAPERWORK

- Application process:
  - Consult with a health care practitioner
  - Medical document completed by health care practitioner
  - Register with a licensed producer of choice (submit medical document and registration form)
  - Access online store/purchase medical marijuana
  - Shop online like Amazon – shipped directly to your door.

MEDICAL CANNABIS PAPERWORK

- Indication of a daily quantity of cannabis
  - Maximum 5g of dried cannabis per patient per day (150 g / month)
- Potential to specify percentage of THC and/or CBD

METHODS OF ADMINISTRATION

- Inhaled (Smoking or Vaporizing)
- Ingestion
  - Oil or alcohol-based tincture
  - Cannibis oil/butter
  - Edibles

ONSET / DURATION OF EFFECTS

- Inhaled: Minutes (~5) / 4-6 hours
- Ingestion: Minutes (60-90) / 8-12 hours

DOSING- CANNABIS

- Individualized, still uncertain
- Relies on (self) titration
- “Start low, go slow”, lower THC content balanced with CBD (~1:1). Can titrate the quantity (of oil/vaporized) or potency (THC or CBD)

DOSING- CANNABIS

- On average, 1-3 grams daily (smoked or vaporized)
- Average "joint" 300mg-500mg
- Average 'dose' of oil 0.5-1ml (depends on concentration, usually 1g dried = 8-10 mL oil)

Your Medical Document.

SECURE FAX COMPATIBLE: 888-977-2595

HEALTHCARE PRACTITIONER INFORMATION:

First Name: Last Name: Profession:

Office Address: City:

Province: Postal Code:

Telephone No.: Fax No.:

E-mail:

Medical Licence Number *(indicate province if different than above)*:

PATIENT INFORMATION:

First Name: Last Name: Date of Birth: DD/MONTH/YY

Location of Consultation *(if different from practitioner address above)*:

Patient Contact information *(optional)*: Email: Telephone No.:

DOSAGE INFORMATION:

Important for Practitioner: Patients may use this prescription for either dried cannabis or cannabis oils, and to select whichever strain or ingestion method they prefer. Health Canada does not require you to provide strain guidance, or to specify ingestion method. However, you may provide optional guidance or mandatory restrictions for patients, which Tweed will enforce. If authorizing Tweed 10:1 Cannabis Oils (100ml bottles), dosage is still to be entered as total grams per day. 10ml of oil is equal to 1 gram of dried cannabis.

Daily Quantity *(grams/day)*:* GRAMS / DAY Diagnosis *(Optional)*:

Period of Use *(Please indicate the period of use in months up to, but not exceeding 12 months)*:** Months

MANDATORY IF CHECKED

If neither option is checked the default is that patients can order any combination of dried cannabis or cannabis oil.

Oil Only: ◯ Dried Only: ◯

ADDITIONAL GUIDANCE *(e.g. contains CBD, THC percentage etc.)*:

MANDATORY IF CHECKED ◯

CERTIFICATION BY HEALTHCARE PRACTITIONER: *I hereby certify that the information in this document is accurate and complete.*

Signature: Name *(Printed)*: Date:

INITIAL HERE IF YOU ARE SUBMITTING THE MEDICAL DOCUMENT TO TWEED BY FAX: ☐

I have chosen to submit the original Medical Document to Tweed via Tweed's secure fax ePortal. I acknowledge that the faxed medical document is now the original Medical Document and that I have retained a copy of this document for my records only.

FURTHER INFORMATION AVAILABLE TO HEALTHCARE PRACTITIONERS.

◯ Please follow-up with my office to schedule a brief information session on medical marijuana

◯ Please deliver materials for me to review

◯ Please send me login credentials to Tweed's Practitioners Portal

**According to Health Canada the average amount of marijuana consumed by patients for medical purposes is 1-3 grams per day. There is, however, no limit to the daily allowable amount that can be authorized.*

*** Please note that within any 30-day period, Tweed will not provide a total quantity of dried marijuana that exceeds 30 times the daily authorized amount.*

Tweed

For More Information:
Tel: 855-558-9333
Email: info@tweed.com
www.tweed.com

Secure ePortal Fax Line:
888-977-2595

Your Medical Document.
Version: D01

OBJECTIVE #3

Discuss the impact of legalization of recreational marijuana on palliative care

RECREATIONAL CANNABIS

Federally legalized, under provincial jurisdiction (like alcohol and tobacco)

Allows ‘adults’ (provincially defined) to purchase cannabis (dried or oil currently - no edibles) from public (government) businesses or private businesses.

Generally can’t purchase/carry more than 30 g of dried cannabis at a time (but can possess more, just not transport it in public).

RECREATIONAL CANNABIS

They are not supposed to provide medical advice/suggestions for recreational cannabis to treat medical conditions.

Currently the plan is for **at least** 5 years to continue ACMPR with Licensed Producers being vetted by Health Canada

There is NO difference in the cannabis produced, potency, THC:CBD ratios, forms available.

WHO WILL ASK FOR MEDICAL RX?

- Those who can receive coverage for their cannabis (Veterans Affairs, Loblaw's) or get it reimbursed by a Health Spending account.
- It **can** be written off a medical expense on tax returns
- Those who want it to be clear they are using cannabis for a medical purpose rather than recreational.
- Those who hope the "medical" stream of cannabis will become refined with regards to standardized strains with medical evidence, capsules or other reliable delivery mechanism.

GREY MARKET CANNABIS

- Compassion clubs – many across Canada
- Some have veneer of "medical purposes" and will accept MMPR Rx or diagnosis from an MD (or just a scanned copy of a licensed producer prescription)
  - Others are purely interested in recreational use and profiteering
- Sell dried marijuana, oils, edibles, tinctures, etc etc.
- NOT LEGAL (but many are still operating freely)
- Potentially slightly cheaper but not subject to same rigor as licensed producer (re purity, pesticides, testing, labelling THC/CBD etc).

TAKE HOME POINTS – OBJECTIVE 1

- Cannabis has weak evidence for use in palliative care, but has potential role for pain, nausea/vomiting, anorexia.
  - The plural of "anecdote" is not "evidence"
  - Lack of evidence does not = lack of efficacy
- My personal belief is that it has an important role, but we are not able to provide good advice regarding strains, or dosing.
- I do think it is appropriate for symptom management if conventional medications are either not tolerated or effective

TAKE HOME POINTS – OBJECTIVE 2

- I will fill out the Rx for medical cannabis, specifying up to 3g per day, for patients who I believe it is a reasonable N-of-1 trial (after discussing risks and benefits).
- I do not personally mandate strains with specific THC %, but I do recommend < 10 % THC and BALANCED with CBD (~1:1).
- I recommend oral intake in general (oil now available).
  - If going to inhale, vaporizer is better than smoking

TAKE HOME POINTS – OBJECTIVE 2

- I require that they be open to discussing and trying conventional medication options
- I do not recommend a particular licensed producer. Tweed is our most "local" producer (Smith Falls). Pricing varies a little.
  - I do not direct Rx to grey-market compassion clubs.

TAKE HOME POINTS – OBJECTIVE 3

- Many will still wish for a medical authorization for cannabis
  - Financial reasons, stigma, belief it is 'different' cannabis
- Many more will be trying recreational cannabis for medical purposes
- It is difficult to provide guidance, other than pointing out safety considerations (start low, go slow, not too high THC to start) and ensuring patients are comfortable discussing their cannabis use with you.

QUESTIONS?