

HOT SPOT

The Newsletter of the Rapid Response Radiotherapy Program
of the Odette Cancer Centre

 **Sunnybrook**
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner



Volume 19, Issue 2, May 2017

Editorial

By Dr. Edward Chow

Welcome to the 2017 May edition. In this issue, Dr. Philip C. Hébert updates us on Assistance in Dying. Dr. Janet Ellis shares with us the Integrated oncology care: Preparing to implement the Psychosocial and Palliative Care Pathway into Head and Neck clinic. Her team also outlines detailed information

on opioids in the management of pain and breathlessness, and other common conditions encountered in our clinics. Continuing Medical Education information again is compiled by Ms. Toby Rodin, Odette Cancer Centre and Dr. Patrick Paladino, Oncology Education. We have two outstanding

inserts: A Review of Medical Cannabis in Cancer Pain Management by Ms. Alexia Blake, Ms. Shannon O’Hearn, and Dr. Carlo DeAngelis, and Biosimilars: The Basics by Dr. Mark Pasetka. We hope you find the information useful.

Assistance in dying

By Philip C Hébert, MD, PhD, Professor Emeritus, Family and Community Medicine, University of Toronto

We are living—as have all ages before us—in a time of great change: a sea change, one might say, in the practice of medicine. Medical assistance in death (MAiD)—heretofore known as ‘physician-assisted suicide’ or euthanasia—has become an accepted option for patients in Canada. It is a practice that was disallowed over 10 years ago when Sue Rodriguez appealed to the highest court of the land for medical assistance in dying when she found the suffering caused by her ALS to be intolerable.

What changed since then—leading the Supreme Court in the 2015 *Carter v Canada* decision to find that the absolute criminal prohibition of physician-assisted death (PAD) was unconstitutional—was the swing of Canadian public opinion in favour of this as an option and the experience from other jurisdictions (Oregon, Washington, The Netherlands,

Belgium, for example) that guidelines could prevent its abuse.

In December 2015, the Joint Centre for Bioethics at the University of Toronto, released its Task Force Report on the issue.¹ MAiD, in the purview of the Supreme Court of Canada (SCC), is the practice of consciously and openly helping grievously and irremediably ill capable adults who wish to end their lives—early, hastened—with the assistance of a physician. ‘Terminal illness’ was not a requirement; untreatability was seen from the patient’s perspective.

The report suggested that “no one should feel entirely certain and comfortable concerning this complex moral issue and evolving medical practice, especially in a pluralistic society. PAD should be considered as an option of last resort when other, less

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ethically challenging alternatives have been exhausted, failed, or are considered unsatisfactory by the individual. A request for a hastened death may be the preferred choice for a minority of people over the other options they have.”

In part on account of the heterogeneity of the Joint Centre’s Task Force, its report was extremely cautious as to the issue of MAiD. It did not recommend its extension to children and did not support the use of advance directives for this practice. It also recommended mandatory psychiatric evaluations for patients who requested MAiD on account of psychological suffering. The SCC did not explicitly rule out psychological suffering as the legitimate basis for MAiD—it said the patient’s suffering had to be “enduring and intolerable” to the patient.

The Task Force report recognized that on this issue there are markedly different professional views. The medical profession is deeply divided as to whether doctors should help their patients die. It is basic nostrum of prudent professional practice that requests for assistance in dying may be indistinguishable from suicidal requests and, as such, should be treated as calls for more help, not less. Indeed, requests for MAiD could come from feelings of abandonment and despair. It is the duty of healthcare professionals to not collude in the despair of their patients, but to evaluate each request meticulously.² For some patients, the request for death may be appropriate when their suffering is extreme and not responsive to palliation. For other patients, there may be non-lethal options that should be encouraged and explored. Moreover, what one doctor may see as untreatable, another might consider treatable.

Perhaps because we live-in questioning religious age—one in which suffering seems inexplicable and doubts about faith arise³—settled moral certainties seem not so evident at all. There are times when life is an intrinsically good thing and to be treasured for whatever little time a person may have left. At other times life cannot be endured, a person’s suffering is truly not treatable, and death is a reasonable option. It is the unenviable task of the healthcare professional to distinguish the two and know when and how to offer help and assistance and when to proffer solace and consolation. In all cases, a request for death from a patient must be treated and evaluated seriously. No healthcare professional should be required to fulfill a patient’s request for death where they object on grounds of conscience, but an ‘effective referral’ is still required. Just what such a referral should be and when it should be made are, as of now, unsettled questions and will be the subject of future articles in *Hot Spot*.

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Integrated oncology care: Preparing to implement the Psychosocial and Palliative Care Pathway into HNC clinic

By Janet Ellis, MB, BChir, MD, FRCPC, Jeff Myers, MD, MEd, CCFP, Kevin Higgins, MD, MSc, FRCSC, Danny Enepekides, MD, FRCSC, MPH, Elie Isenberg-Grzeda, MD, FRCSC, Allyson Nowell, RN, MSc, CON(C), Alva Murray, MSW, Ben Diplock, BSc, Lauren Goldberg, BAH, and Alyssa Leano, HBSc

The body of evidence that supports integrating psychosocial (PSO) and palliative care (PC) as standard elements of cancer care continues to grow. It is no longer a matter of if integration should occur, it has become about when and how. To address when integration should occur, patient, family member and system-level outcome evidence from several well-designed studies points towards integration needing to occur early in a person's illness. This article describes the commitment that one Odette Cancer Centre (OCC) site group has made to their patients and family members, by addressing how to integrate PSO and PC.

In 2013, Cancer Care Ontario (CCO) assembled an expert panel to develop a PSO and PC pathway. The evidence-based pathway describes the “standard of care and support that all cancer patients and their families should receive, regardless of their cancer type and stage”, which reinforces the approach of early PSO and PC integration. The guideline involves validated screening tools to identify patients with unmet PSO and PC needs. The Edmonton Symptom Assessment System (ESAS) screens for emotional and physical symptom severity, whereas both the Palliative Performance Scale (PPS) and the Surprise Question (SQ) are used to identify patients whose needs may be more urgent. Although guidance is provided for the assessment and management of several symptoms, the pathway was not designed to address how to meaningfully integrate PSO and PC care.

The next step in integration: To begin to address PSO and PC integration, the Head and Neck Site Group (HNC) stepped forward and partnered to develop a proposal that was eventually awarded an Alternative Funding Plan (AFP) innovation fund. Addressing PSO and PC integration is well suited to the HNC population, which experiences a high burden of symptom-related distress. On average, only 50% of HNC patients survive more than five years, making routine advanced care planning (ACP) essential.

A two-phased approach to integrating cancer care: Lessons learned from similar initiatives in the U.K. and from the CCO project INTEGRATE (involving routine integration of palliative care into site groups) informed that successful and sustainable implementation requires collaborative assessment of Health Care Professionals (HCPs) training needs, systemic barriers and potential solutions.

The PSO and PC pathway is being integrated in two phases at the OCC HNC clinic. Phase one (focus groups, training and skills-acquisition), involves co-designing and delivering a customized, needs-based education and training program developed through qualitative needs assessment. Phase one also involves a chart review of baseline documentation of ESAS symptoms, ER visits/unplanned admissions, PSO and PC referral, illness understanding and ACP/goals of care.

Currently, phase one is partially complete, as one-on-one phone interviews and focus groups have been conducted. Interviews assessed interprofessional HNC team members' perceptions of unmet patient and family needs, staff knowledge and skill needs, and foreseeable barriers to integrating the pathway into routine clinical care. Current practice around distress, illness understanding and ACP was also assessed.

Phase one findings: In general, interviews and focus groups revealed a HNC HCP perception of the need to increase skills in a primary palliative and psychosocial approach in HNC, improve team communication, identify at-risk patients proactively and refer for specialized help earlier. Staff described unmet patient PSO and PC needs, system and clinic challenges. HCPs felt that patients needed more preparation for end-of-life treatment. HCPs felt that many patients did not have realistic illness understanding and require increased preparation for possible progression, to prevent overwhelming distress at this stage in their treatment. The complexity of this patient population highlights the importance of interprofessional care and team communication.

Using these findings and face-to-face feedback, needs-based education and training sessions for HNC HCPs were co-developed, including a PSO and PC symptom management card (refer to Figure 1). Case-based, as well as some didactic learning on specific topics, were utilized.

Current project progress: A PC physician and psychiatrist will be starting to attend clinic to help increase knowledge, normalize and integrate point-of-care conversations and primary PSO and PC response. A chart review of unplanned admission and ER visits is also underway to examine ESAS scores and documentation of responses in the month prior to the ER visit.

Phase two—The study: Phase two of the project is a randomized control study and will commence in May 2017. It is hoped that the training, education and skill acquisition will assist the application and integration of the CCO PSO and PC pathway in HNC clinic.

The study will include a control group and an active group. For the active group, HCP will be triggered to ask themselves the Surprise Question (“Would I be surprised if this person were to die within the next six months to one year?”), review and document patients' most important concern, their PPS, emotional and physical symptoms, any discussions about their care, and illness understanding.

Through chart audits, we will determine whether integration of the PSO and PC pathway significantly changes rate of documentation of response to emotional/physical symptoms, illness understanding and ACP. Other outcomes include staff feedback (perceived utility, clinic flow), patient feedback, PSO and PC referral rates, emergency visits and unplanned hospital admission during treatment / post treatment (<3 months).

The commitment made by the HNC Site Group to integrate PSO and PC into clinic will hopefully result in improved symptom management and illness understanding of patients and family members. It is also an important contribution to the research on developing integrated care in oncology.

Opioids in the management of pain and breathlessness

By Janet Ellis, MB, BChir, MD, FRCPC, Jeff Myers, MD, MEd, CCFP, Kevin Higgins, MD, MSc, FRCSC, Danny Enepekides, MD, FRCSC, MPH, Elie Isenberg-Grzeda, MD, FRCSC, Allyson Nowell, RN, MSc, CON(C), Alva Murray, MSW, Ben Diplock, BSc, Lauren Goldberg, BAH, and Alyssa Leano, HBSc

When dosed and titrated appropriately, symptomatic patients requiring opioids should be alert and oriented.

Whether opioids are being used for pain OR for shortness of breath, prescribing principles are VERY similar:

Opioid prescribing pearls

Appropriate starting regimens for opioid naïve patient include:

- 1–2 Tylenol #3 po q4h prn OR
- morphine 2.5–5mg po q4h PLUS morphine 2.5mg q1h prn
- hydromorphone 0.5–1mg po q4h PLUS hydromorphone 0.5mg q1h prn
- IR = immediate release (duration of action = 4 hrs)
- SR = sustained release (duration of action = 8–12 hrs)
- Use an IR opioid when initiating
- If **symptom is constant**, dose at regular intervals (i.e. q4h)
- Initiate bowel regimen when dose is regular
- Consider anti-emetic when initiating

Equivalence	PO	SC/IV
Codeine	100mg	—
Morphine	10mg	5mg
Oxycodone	5mg	—
Hydromorphone	2mg	1mg

Starting dose strength and equivalencies for most common opioids:

1 Tylenol #3 = morphine po 2.5mg = hydromorphone po 0.5mg = Percocet po ¼ tab
 2 Tylenol #3 = morphine po 5mg = hydromorphone po 1mg = Percocet po ½ tab

NOTE: 1 Percocet = morphine 10mg = hydromorphone 2mg

Fentanyl should ONLY be considered when a person is already taking opioids. Fentanyl should NOT be prescribed to a person who is opioid naïve.

General titrating info

Constant pain:

- If IR is used routinely q4h and symptom not controlled, may titrate dose daily and consider SR
- If symptom is not controlled by SR plus IR breakthrough, titrate every other day
- **For unstable pain:** use IR preparations initially

Breakthrough or incident pain:

- Use IR preparations only
- Appropriate dose is 10% of total daily opioid dose
- Frequency of breakthrough is based on Cmax; oral preparations = q1h prn sub-cut = q30min prn

Side effects:

- **Constipation** – must prevent for ALL patients requiring routine opioid
 - senna 1–4 bid and/or
 - lactulose 15–45ml daily-qid
- **Nausea** – haloperidol 0.5–1.0mg q4h prn or prochlorperazine 10mg q6h prn
- **Sedation** – transient at initiation; if persists and pt remains in pain, opioid may not be the cause AND/OR consider addition of neuropathic adjuvant

Tylenol #1 = 8mg Codeine + 300mg Tylenol Tylenol #2 = 15mg Codeine + 300mg Tylenol Tylenol #3 = 30mg Codeine + 300mg Tylenol Tylenol #4 = 60mg Codeine + 300mg Tylenol Codeine Contin* = 50, 100, 150, 200mg	Percocet = 5mg Oxycodone + 325mg Tylenol Oxycodone IR = 5, 10, 20mg OxyNEO = 10, 15, 20, 30, 40, 60, 80mg Hydromorphone IR = 1, 2, 4, 8mg Hydromorph Contin = 3, 6, 9, 12mg
Morphine IR = 5, 10, 25, 50mg M-Eslon = 10, 15, 30, 60, 100mg MS Contin = 15, 30, 60, 100mg	Fentanyl patches = 12, 25, 50mcg/hr

**Medications in bold are sustained release preparations*

Managing Neuropathic Pain

- **Gabapentin** and **pregabalin** are commonly used to manage neuropathic pain
- Overall efficacy and side effect profile do not differ however inter-individual variability is expected
- Pregabalin has advantage of BID dosing (gabapentin is TID) and possibly a quicker onset of action

Initiating:

- Gabapentin 300mg at HS X 3 days, increase to 300mg BID X 3 days and increase to 300mg TID
- Pregabalin 50mg at HS X 3 days then increase to 50mg BID. If tolerating after 1 week then increase to 100mg BID
- Follow-up visit should be two weeks following initiation of neuropathic agent
- If creatinine clearance is normal, maximum dose of gabapentin is 1200mg TID and of pregabalin is 300mg BID (dose adjust for elevated creatinine)

Patient education:

- Patients should be warned the onset of analgesia is unlikely before two weeks
- It's important for patients to understand these differ from opioids in this way
- **Classic descriptors** of neuropathic pain (e.g., shooting, stabbing, lancinating, knife like) may not be used by patient, however it's very uncommon for a patient who has Head and Neck Cancer related pain to not have a neuropathic component.
- For patients who have **neuropathic pain AND progressive disease**, opioids remain first line
- Opioids are **NOT RECOMMENDED** for patients **with neuropathic and CURED disease** (i.e., post-treatment pain)

Cannabis in symptom management

Assess for contraindications: age < 25; personal history or strong family history of psychosis; current or past cannabis use disorder; active substance use disorder

- Must specify on every prescription the quantity of dried marijuana to be

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Opioids in the management of pain and breathlessness

- dispensed, as well as the % of THC it must contain (recommended 9% or less)
- Dose authorization of 0.5-1 gram per day is supported by limited evidence
- Vaporizing is likely the safest administration method
- Sample medical document: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/info/med-eng.pdf
- Fax prescription to authorized licensed producers: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/list-eng.php>

Assessing and managing distress Is the distress ACUTE or CHRONIC?

- **Chronic** = presence of neuro-vegetative symptoms of depression = more likely psychiatric disorder
 - Would benefit from psychiatric assessment and may require medication
- **Acute/reactive** = adjustment = able to enjoy life in between times of extreme distress
 - brief supportive interventions in clinic and psychosocial referral for therapy — validate/normalize-emphasize you will follow up in subsequent clinic visits
 - may need med for sleep/reactive anxiety/acute distress
- **First manage insomnia and ensure optimal symptom management:**
 - Trazadone 25–50 mg QHS or No more than 2–4 months of zopiclone 5–7.5 mg QHS

- Quetiapine 25–50 mg if the patient is on steroids
- **Then manage overwhelming anxiety:** i.e., extremely anxious for several days/week no safety concerns
 - Clonazepam 0.25mg BID—wean off at end of treatment by 0.125mg/week
- **If need be start treatment for depression or anxiety:**
 - Citalopram 10mg QAM—increase after 1–2 weeks to 20mg if no/little response—refer to psych/FP f/u
- **Can target symptoms: AND anxiety/depression**
 - Mirtazapine 15mg QHS —increase after 1 week to 30mg if depressed/anxious/poor sleep/appetite
 - low energy/depressed/anxious/smoking Bupropion XL 150mg QAM (if no Hx SEIZURE, bulimia)

Urgent psychiatry referral: Cognitive impaired, mania, psychosis—emergency department if ANY safety concern self/other

“Depressed”—do I treat or refer?

If someone gives a history of **weeks or more of low mood/loss of enjoyment** that is **impairing function**, plus 3 of: guilt/negative thinking/feeling bad about themselves, low energy, change in sleep, appetite, concentration, suicidal ideation and seems a dimmed/flat/low-energy version of themselves (morose/subdued), they are likely depressed (assuming they are not simply low energy/debilitated from the cancer or treatment)

- Treat and refer to psychiatry or if patient prefers, FP for follow-up
- Choice of medication: See above—consider drug interaction check, targeting other symptoms

(assuming no history of bipolar/mania—times of reduced need for sleep/high energy/fast thoughts/impulsivity/irritability/feeling powerful/confident)

If someone is depressed/down and sad, but still able to enjoy themselves and have times of being their normal selves, likely can provide support, validate, say you will discuss next clinic visit—can always ask patient if they wish to be seen for support.

Existential distress

With sadness, consider also anticipatory grief, change in role, loss of health, suffering, demoralization and underlying ANXIETY DISORDER.

Connection to others and awareness of the meaning in their life are both very helpful—find out WHO is important, supportive, and WHAT is important, a source of pride, etc.

Continuing Medical Education

By Toby Rodin, Odette Cancer Centre and Patrick Paladino, PhD, Medical Education Manager, OncologyEducation.com, elearning@oncologyeducation.com

Continuing Medical Education (CME) can update health care professionals on the latest advances for modifications to their clinical practice. At the request of the CME organizers, *Hot Spot* will list the national and international activities in palliative medicine that are of interest to our readers. Please forward details of the CME activities to: toby.rodin@sunnybrook.ca

- **May 8–9, 2017.** World Health Summit (WHS) Regional Meeting – North America, Montreal, Palais des congrès de Montréal, Montréal, Québec. Institut de recherches cliniques de Montréal (IRCM) / Montreal Clinical Research Institute + Université de Montréal. <https://www.ircm.qc.ca/>
- **May 18–20, 2017.** EAPC 2017, 15th World Congress of the European Association for Palliative Care, Progressing Palliative Care, Madrid, Spain. <http://www.eapc-2017.org/> http://eapc2017congress.org
- **May 26–27, 2017.** BCHPCA's Conference 2017, British Columbia Hospice and Palliative Care Association, Extending the Circle of Compassion. Radisson Vancouver Airport Hotel, Richmond, British Columbia. <https://bchpca.org/>
- **June 2–6, 2017.** ASCO Annual Meeting, American Society of Clinical Oncology, American Society of Clinical Oncology McCormick Place, Chicago, Illinois. <https://am.asco.org/>
- **June 16, 2017.** Best of ASCO Toronto 2017. Parkview Manor, Toronto, Ontario. <http://www.oncologyeducation.com/events/upcoming-events/best-of-asco-toronto-2017/conference-home/>
- **June 20, 2017.** Best of ASCO Montréal 2017. Le Centre Sheraton Hotel, Montréal, Québec. <http://www.oncologyeducation.com/events/upcoming-events/best-of-asco-montreal-2017/conference-home/>
- **June 22–24, 2017.** MASCC/ISOO Annual Meeting on Supportive Care in Cancer, Washington, DC. <http://mascc2017.com/>
- **July 7, 2017.** Best of ASCO Vancouver 2017. The Westin Bayshore, Vancouver, British Columbia. <http://www.oncologyeducation.com/events/upcoming-events/best-of-asco-vancouver-2017/conference-home/>
- **September 8–12, 2017.** ESMO Congress, Madrid, Spain. <http://www.esmo.org/Conferences/ESMO-2017-Congress>
- **September 13–16, 2017.** CARO Annual Scientific Meeting, Toronto, ON. <http://www.caro-acro.ca/>

- **September 14–15, 2017.** 26th Annual Provincial Palliative Care Conference, Victoria Inn Hotel and Convention Centre, Winnipeg, Manitoba. <http://palliativemanitoba.ca/events/conference/>
- **September 17–20, 2017.** 5th International Public Health & Palliative Care Conference, Ottawa Conference and Event Centre, 200 Coventry Road, Ottawa, ON. <http://www.iphpc2017.com/about/>
- **September 18–20, 2017.** National Hospice and Palliative Care Organization, NHPCO's 2017 Interdisciplinary Conference, San Diego Marriott Marquis and Marina, San Diego, CA. <http://nhpco.confex.com/nhpc0/fc17/cfp.cgi>
- **September 20–23, 2017.** Canadian Hospice Palliative Care Conference, Ottawa Conference and Event Centre, 200 Coventry Road, Ottawa ON <http://conference.chpca.net/about-the-conference/> <http://www.casw-acts.ca/en/2017-canadian-hospice-palliative-care-conference>
- **November 1–2, 2017.** 7th World Congress on Breast Cancer, Toronto, ON. <http://breastcancer.alliedacademies.com/>

CME Programs

New! What I-O Really Means for Your NSCLC Patients. In this video, International guest speaker, Prof. Solange Peters, shares the stage with Dr. Sunil Verma to discuss the latest trends on I-O in NSCLC. Patient advocacy group, Lung Cancer Canada, also provides invaluable patient perspectives. <http://www.oncologyeducation.com/events/oncologyeducation-events-video-archives/clco-2017-what-i-o-really-means-for-your-nsclc-patients/>

This program meets the accreditation criteria as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada and has been accredited by the Office of Continuing Professional Development, Faculty of Medicine, McGill University for up to 1 Section 1 credits. Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™. Information on the process to convert Royal College MOC credit to AMA credit can be found at www.ama-assn.org/go/internationalcme. This program is accredited until March 2017.

Course: Optimizing Outcomes in Advanced Prostate Cancer - This course will review the clinical implications of prostate cancer heterogeneity, data on sequencing drugs in mCRPC, and will also focus on recent CRPC guidelines and advanced hormone-sensitive disease. <http://www.oncologyeducation.com/events/cmecourses/currently-accredited-courses/optimizing-outcomes-in-advanced-prostate-cancer/>

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada. This activity was approved by the Canadian Society of Internal Medicine for a maximum of 1.5 hours. Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™. Information on the process to convert Royal College MOC credit to AMA credit can be found at www.ama-assn.org/go/internationalcme. This course is accredited until June 15, 2017.

Course: Targeted Therapies in the Management of Non-Small Cell Lung Cancer: A Multi-Disciplinary Approach

- The multi-disciplinary approach to this course provides discussion on an array of topics and perspectives related to NSCLC management including diagnosis, various treatment options and pertinent case studies. As a result, this course is relevant to a variety of oncology healthcare providers. <http://www.oncologyeducation.com/events/cmecourses/currently-accredited-courses/targeted-therapies-in-the-management-of-non-small-cell-lung-cancer/>

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada. This activity was approved by the Canadian Society of Internal Medicine for a maximum of 2 hours. Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™. Information on the process to convert Royal College MOC credit to AMA credit can be found at www.ama-assn.org/go/internationalcme. This course is accredited until May 11, 2017.

BIOSIMILARS: The Basics

By Mark Pasetka, PharmD

HOT SPOT

Introduction

- Monoclonal antibodies and recombinant human growth factors are commonly utilized in the treatment and supportive care of patients with cancer
- Access to these medications in many health-care systems is becoming more difficult to sustain due to increasing financial burden
- Generic medications are commonly employed once the patent period of the innovator's product has ended in order to reduce costs whilst maintaining safety and effectiveness
- In contrast to simpler molecules (e.g., acetaminophen, morphine), which can be identically produced, biologic medications cannot be replicated and therefore cannot be referred to as generics; therefore, new terminology has been created (Table 1)

Production of Biologic Molecules

- Biologic molecules are produced using living cells which also implement post-translational modifications (PTMs) such as glycosylation and methylation²
- Aspects of complexity exist when considering manufacture of the original or a biosimilar product; inherent complexity considers molecular aspects such as protein size, structure levels (primary, secondary, tertiary, and quaternary), physiochemistry, and heterogeneity; non-inherent

complexity considers the manufactory process (host cell, cell bank, protein production and purification, and analytical methods), formulations, as well as storage and handling²

- As processes and components (e.g., cell line information) of the innovator product are proprietary knowledge, manufacturers of biosimilars use reverse engineering to develop their own product²
- Biosimilars cannot be considered generic medications because the molecule produced is not identical to the original product secondary to the complex nature of the manufacturing process

Extrapolation

- Extrapolation is a concept that allows for the approval for use of a biosimilar in indications studied only using the iBioM¹
- Approval for extrapolation is based on the totality-of-the-evidence for the biosimilar and not solely on clinical studies¹
- The decision to employ extrapolation to other indications is dependent on the regulatory agency; therefore, the biosimilar may carry different indications reliant on the jurisdiction¹

Interchangeability & Substitution

- Although a BioS is expected to produce a comparable safety and efficacy profile as the iBioM, it is not considered automatically interchangeable upon regulatory approval¹
- Only the FDA has defined interchangeability (Table 1) and a BioS is designated as such if “the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product”⁶

In Canada, interchangeability of a BioS with the iBioM is a decision made by provincial and territorial regulatory bodies⁷

Term used	Definition	Comments
Biologic Medication	An approved product composed of proteins, nucleic acids, or combinations of these, or living entities such as cells and tissues, which is isolated from natural sources (e.g., humans, animals, and microorganisms) and produced using biotechnology.	Examples: Monoclonal antibodies – Trastuzumab Recombinant biologic molecules – Filgrastim
Generic Medication	A single molecule or low molecular weight chemically synthesized compounds	Examples: Acetaminophen, morphine
Biosimilar (formerly known as subsequent entry biologics – HC)	A new biologic medication that has been shown to have no clinically meaningful differences between itself and the original biologic in terms of safety, purity, and potency; additionally, similarity is shown with respect to quality characteristics, biologic activity, safety, and efficacy.	Example: Filgrastim iBioM (Neupogen [®]) BioS (Grastofil [®])
Extrapolation	A concept used in the approval process of biosimilars which allows for the BioS to be used for indications held by the innovator's BioM, even though it has not been studied in clinical trials (but is based on sufficient scientific justification and the totality of the evidence)	Described by Health Canada as 'Authorization of Indications'
Interchangeable Biosimilar	An agent approved as a BioS; it is expected to produce the same clinical effects as the original BioM in any given patient, and the risks (safety, diminished efficacy of alternating or switching between use of the BioS and the originator's BioM is not more than the risk of using the latter without such alteration or switch)	Only the FDA uses this term (EMA, WHO do not)
Abbreviations – BioM: Biologic Medication; BioS: Biosimilar; iBioM: Innovator Biologic Medication; FDA: Food and Drug Administration; EMA: European Medicines Agency; WHO: World Health Organization; HC: Health Canada; ORR: Overall Response Rate; pCR: Pathologic Complete Response		

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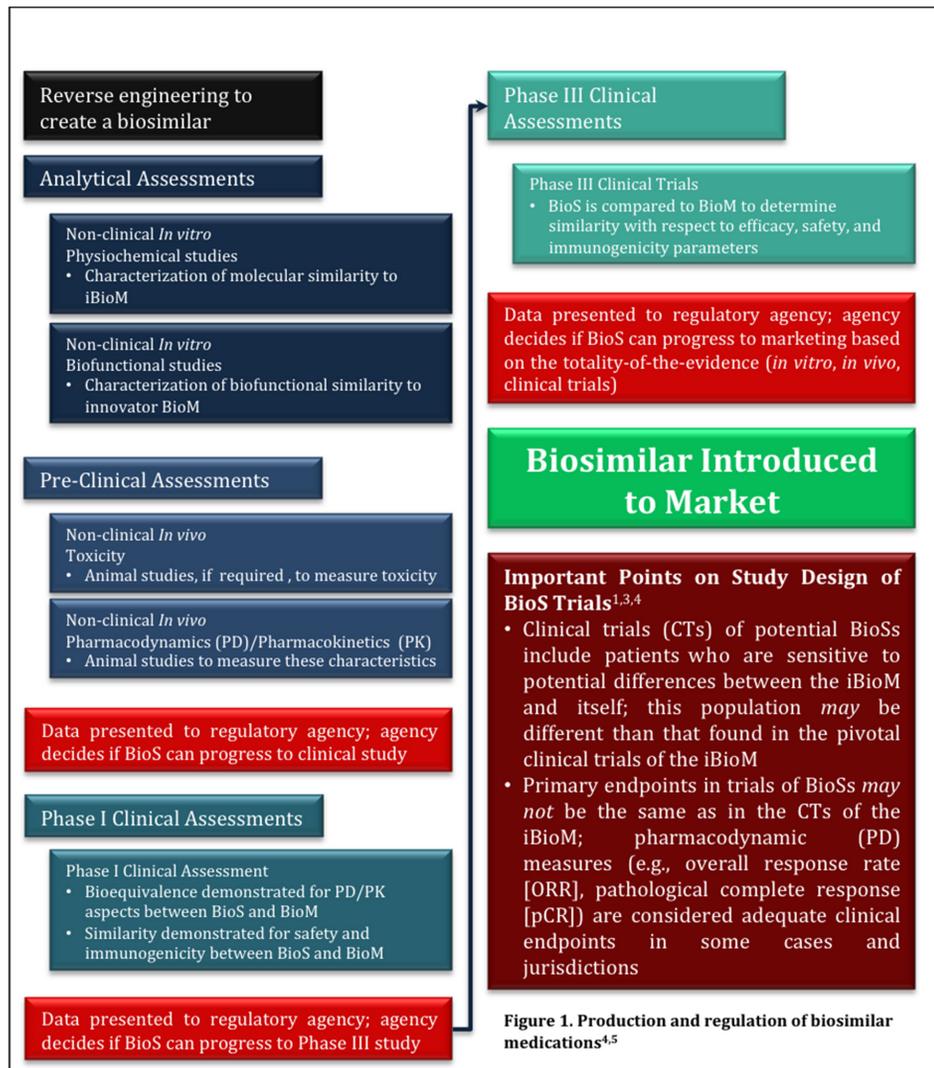


Table 2: Currently available biosimilars in Canada⁸

Molecule	Innovator	Biosimilar
Infliximab	Remicade [®] Janssen Inc.	Inflectra [®] , Remsima [®] (Celltrion Healthcare Co. Ltd.)
Filgrastim	Neupogen [®] Amgen Canada Inc.	Grastofil [®] (Apotex Inc.)
Somatropin	Genotropin [®] Pfizer Canada Inc.	Bio-Tropin [®] (Novopharm Ltd.) Omnitrope [®] (Sandoz Canada Inc.)
Insulin Glargine	Lantus [®] Sanofi-Aventis Canada Inc.	Basaglar [®] (Eli Lilly Canada Inc.)
Etanercept	Enbrel [®] Immunex Corporation	Brenzys [®] (Samsung Bioepis Co. Ltd.) Erelzi [®] (Sandoz Canada Inc.)

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A review of medical cannabis in cancer pain management

By Alexia Blake, MSc, Shannon O'Hearn, MSc, and Carlo DeAngelis, DPharm

HOT SPOT

Opiates are often prescribed as a first-line analgesic treatment to reduce cancer-related pain. Cannabis and other cannabinoid-based medications, such as Sativex, may be prescribed as an alternative or adjunctive analgesic treatment. A review of clinical trials involving cannabinoid-based treatments in advanced cancer populations is presented below. The presented findings suggest that further research is needed to establish the efficacy of medical cannabis, either as an alternative to opiates or as an adjunctive therapy, and to identify how to dose and administer cannabis to achieve optimal analgesic efficacy with minimal side effects.

1. Analgesic effect of Delta-9-Tetrahydrocannabinol

Russell Noyes, JR. et al. The Journal of Clinical Pharmacology, 139–143, 1975.

Ten advanced cancer patients were randomized into different treatment groups. Dosing occurred once daily one hour after breakfast. Placebo, 5, 10, 15 and 20 mg THC were administered on successive days under a double-blind and randomized sequence.

This education grant provided by MedReleaf Corp. is gratefully acknowledged.

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Study Design

- Pain severity was scored hourly as absent (0), mild (1), moderate (2), severe (3)
- Pain relief was scored hourly as none (0), slight (1), moderate (2), a lot (3), complete (4)
- For statistical analysis, the hourly difference in pain severity or relief score was summed over six hours to determine a total relief or severity score
- A side effects inventory was administered every six hours (assessment of drowsiness, slurred speech, blurred visions, mental clouding, dizziness, headache, increased appetite, ataxia, dreaminess, disconnected thought, numbness, euphoria, visual hallucinations, and tinnitus using a 7-point scale)
- A subjective effects questionnaire was administered hourly (sleepy-awake, energetic-fatigued, sad-happy, quiet-restlessness, sociable-unsociable, dreamy-clearheaded, calm-uneasy, alert-dull, worried-peaceful, time slowed-time speeded up, trouble thinking-thinking clearly were assessed using a 7-point scale)

Results

- Pain relief increased with dose ($P < 0.001$)
- 5 subjects received substantial relief from 15 mg (relief score > 6)
- 7 subjects received substantial relief from 20 mg
- 15 and 20 mg caused severe drowsiness and decreased heart rate
- Limited statistical analysis due to small study population

Conclusion: 15mg and 20mg doses provided superior pain relief compared to placebo, but also caused significant sedation and mental clouding.

2. The analgesic properties of Delta-9-Tetrahydrocannabinol and Codeine

Russell Noyes, JR. et al. Clinical Pharmacology and Therapeutics, 19 (1): 84-89, 1975

The analgesic effect of THC was compared to codeine. Thirty-six advanced cancer patients were randomized into different treatment groups. Dosing occurred once daily one hour after breakfast. Placebo, 10 and 20 mg THC, 60 and 120 mg of codeine were administered under a double-blind and randomized sequence on successive days.

Study Design

- Pain severity was scored hourly as absent (0), mild (1), moderate (2), severe (3)
- Pain relief was scored hourly as none (0), slight (1), moderate (2), a lot (3), complete (4)
- For statistical analysis, the hourly difference in pain severity or relief score was summed over six hours to determine a total relief or severity score
- A side effects inventory was administered every six hours
- A subjective effects questionnaire was administered hourly

Results

- Significant difference in pain reduction between placebo and 20 mg THC group ($P < 0.05$) in favour of THC treatment
- Significant difference in pain reduction between placebo and 120 mg codeine group ($P < 0.05$) in favour of codeine treatment
- No significant difference in pain reduction between 10 mg THC and 60 mg codeine ($P > 0.05$)

- Number of subjects who reported substantial pain relief (total pain relief ≥ 12) after each treatment was 6 (placebo), 8 (60 mg codeine), 12 (10 mg THC), 16 (120 mg codeine), and 16 (20 mg THC)
- 20 mg THC caused serious sedation, drowsiness, and adverse reactions ($N = 4$)

Conclusion: 10 mg THC is well tolerated and may provide some analgesic effects with mild side effects.

3. Multicentre, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain

Jeremy R. Johnson, et al. Journal of Pain and Symptom Management, 39 (2): 167-179, 2010.

The focus was to determine the efficacy of a THC:CBD extract (Sativex) and THC extract in relieving pain among 177 advanced cancer patients with intractable cancer-related pain. Patients were randomized into one of three treatment groups, with dosing administered using an oromucosal spray containing:

- a. THC:CBD extract – each 100 μ L actuation provides 2.7 mg THC and 2.5 mg CBD ($N = 60$)
- b. THC extract – each 100 μ L actuation provides 2.7 mg THC ($N = 58$)
- c. Placebo ($N = 59$)

Study Design

- Subjects who recorded a pain severity score ≥ 4 using 0–10 numerical rating scale (NRS) on two-day baseline period were eligible for enrollment
- During baseline, subjects completed a daily study diary (pain scored three times/day, background medication, and breakthrough analgesic medication)
- During week one, subjects self-titrated to identify optimal dose for efficacy, safety, and tolerability, and maintained their study diary
- During week two, subjects continued on their optimal dose and maintained their study diary
- Brief Pain Inventory Short Form and European Organization for Research and Treatment of Cancer (EORTC) QOL Version 3 completed at start and end of study to assess impact of treatment on quality of life and symptom severity

Results

- Statistically significant change from baseline in mean pain NRS scores in favour of THC:CBD treatment versus placebo (improvement of -1.37 vs. -0.69)
- Non-significant change from baseline in mean pain NRS score for THC treatment versus placebo (-1.01 vs. -0.69)
- Twice as many subjects receiving THC:CBD treatment reported $> 30\%$ reduction from baseline in pain NRS score compared to placebo (23 [43%] vs. 12 [21%])
- No significant group differences in the NRS sleep quality, nausea scores, or pain control assessment
- Worsening in nausea and vomiting within THC:CBD treatment group compared with placebo ($P = 0.02$) according to EORTC QOL Questionnaire results

Conclusion: THC:CBD extract is an efficacious analgesic for patients with advanced cancer patients with opiate-refractory pain.

4. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: A randomized placebo-controlled, graded-dose trial

Russell K Portenoy, et al. The Journal of Pain, 13 (5): 438-449, 2012.

The objective was to assess the efficacy of nabiximols (Sativex) for reducing pain in advanced cancer patients with opiate-refractory pain. Three hundred and sixty subjects were randomized into three different treatment groups, with no difference across groups at baseline. Two hundred and sixty-three subjects completed the study:

- a. Low dose (1–4 sprays/day)
- b. Medium dose (6–10 sprays/day)
- c. High dose (11–16 sprays/day)

Study Design

- 5–14 day qualifying period
 - Subjects reported average pain using a 0–10 NRS through an interactive voice recording system (IVRS)
 - Subjects were eligible if they reported no change in opioid regimen and if average pain scores remained between ≥ 4 and ≤ 8 and did not change by more than two points over three days
- One week blinded-dose titration period based on their randomized treatment (i.e., high-dose treatment group instructed to titrate up to 11–16 sprays/day). Subjects unable to reach their target dose were disqualified from the study.
- Four weeks of stable, self-administered dosing. Subjects were allowed to continue opioid and/or breakthrough analgesic medication as needed.
- During dosing periods, subjects recorded the following information through the IVRS:
 - Average pain (0–10 NRS)
 - Worst pain over last 24 hours (0–10 NRS)

- Sleep disruption due to pain (0–10 NRS)
- Number of sprays administered since yesterday
- Use of fixed-dose painkillers today
- Number of doses of breakthrough painkillers taken since yesterday
- Questionnaire packet completed upon randomization and study termination visit to assess effect of treatment on quality of life and symptom severity
 - Brief Pain Inventory - Short Form (BPI-SF)
 - EORTC QLQ-C30 Version 3
 - Patient Assessment of Constipation Quality of Life (PAC-QoL)
 - Montgomery-Åsberg Depression Rating Scale (MADRS)
 - Patient Global Impression of Change (PGIC) at termination only
- Primary efficacy endpoint was pain response status (positive response defined as a 30% or greater reduction in the mean 11-point NRS pain score for average pain during the last three days of week five compared to the mean during the three-day baseline period)
- Continuous responder analysis also evaluated (differences between proportion of subjects who achieved levels of response ranging from 0% to 100% at week five versus baseline in placebo versus active drug treatment)
- Change in mean daily NRS scores for average pain and change in mean daily NRS scores for worst pain were also evaluated

Results

- Placebo groups were pooled for comparison with active drug, since there were no significant differences in pain response between different treatment groups that were randomized to placebo ($P = 0.84$)
- 30% responder rate analysis not statistically different between active drug and placebo ($P = 0.59$)
- Continuous responder rates across full range of response (0–100%) revealed that combined nabiximols groups more effective than placebo ($P = 0.035$)
- When comparing individual treatment groups to placebo, treatment effect was observed only for low dose group ($P = 0.008$) and medium dose group ($P = 0.038$), both in favour of nabiximols
- Overall treatment effect in favour of combined treatment groups vs. placebo for change in mean pain scores relative to baseline ($P = 0.072$)
 - The adjusted mean change in pain score for low dose treatment group was -1.5 points (from a mean baseline score of 5.8 points) compared to -0.8 points for placebo group (from a mean baseline score of 5.7 points). Treatment difference favouring nabiximols vs. placebo of -0.75 points ($P = 0.006$, 95% CI: -1.28, -0.22 points)
- Change in weekly mean pain on average scores relative to baseline were also compared
 - Low-dose group—treatment difference of -0.59 from placebo points favouring nabiximols ($P = 0.024$, 95% CI: -1.11, -0.08 points)
 - Medium-dose group—treatment difference of -0.36 from placebo favouring nabiximols ($P = 0.178$, 95% CI: -0.88, 0.16 points)
 - Non-significant treatment effect for high-dose group
- Overall treatment effect in favour of combined treatment groups vs. placebo for daily worst pain scores relative to baseline ($P = 0.047$)
 - Low-dose group—treatment difference of -0.73 points ($P = 0.011$, 95% CI: -1.30, -0.17 points)
 - Medium-dose group—treatment difference of -0.24 ($P = 0.40$, 95% CI: -0.8, 0.3 points)
 - Non-significant treatment effect for high-dose group

- Overall treatment effect in favour of combined treatment groups versus placebo relative to baseline for sleep disruption ($P = 0.012$). This effect was due primarily to effect of low dose group (treatment difference of -0.88 , $P = 0.003$, 95% CI: -1.45 , -0.31 points)
- No treatment differences between nabiximols groups and placebo when comparing results of BPI-SF, PGIC, PAC-QoL, and MADRS
- Larger proportion of subjects in nabiximols groups experienced nausea and vomiting compared to placebo (treatment difference of 7.57 , $P = 0.019$), primarily in high-dose group ($P = 0.009$)
- Frequency of adverse events and drop-out was dose related
- High death rate in study due to disease progression ($N = 72$), particularly in low-dose treatment group ($N = 24$)

Conclusion: Low and medium doses of nabiximols are an effective add-on analgesic therapy for advanced cancer patients with opioid-refractory pain. However, follow-up studies are needed.

5. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain

Mary E. Lynch *et al.* Journal of Pain and Symptom Management, 47 (1):166-173, 2014.

The objective of this randomized, placebo-controlled crossover pilot study ($N=16$) was to assess the efficacy of nabiximols for neuropathic pain induced by paclitaxel, vincristine, or cisplatin.

Study Design

- Subjects were included if they had neuropathic pain persisting for three months after final chemotherapy treatment, an average seven-day pain intensity ≥ 4 on 0–10 NRS, and stable concurrent analgesic treatment for 14 days prior to study initiation
- Subjects were randomized into placebo-nabiximols and nabiximols-placebo treatment order
- Pain intensity was scored daily using 0–10 NRS for one week before dosing
- Subjects started with one spray before bed and titrated by one–two sprays/day until they reached a dose that provided sufficient pain relief or caused events (maximum daily dose 12 sprays/day)
- Subjects continued optimal dose for four weeks and completed outcome measures after two and four weeks of treatment
- Subjects underwent dose reduction and two-week washout before crossover
- Primary outcome measure was change in neuropathic pain intensity (0–10 NRS) from baseline
- Secondary outcome measures included Short Form-36 Health Survey (SF-36), quantitative sensory testing (QST), and adverse events reporting

Results

- Mean nabiximols dose was eight sprays/day, and 11 sprays/day of placebo treatment
- Majority of subjects reported mild medication-related side effects
- No statistically significant difference between placebo and treatment groups
- The seven-day average NRS pain intensity score was 6.75
- The mean NRS pain intensity score during treatment with nabiximols dropped to 5.5 at mid-treatment (compared to 6.31 during placebo treatment) and to 6.00 at the end

- of four weeks of active treatment (compared to 6.38 during placebo treatment)
- Main effect for time ($P = 0.007$), but not for interaction of time and treatment ($P = 0.29$) or for between-subjects ($P = 0.52$) determined using repeated measures ANOVA
- Five subjects reported ≥ 2 -point drop in NRS pain intensity during treatment
- Two subjects reported pain reduction during placebo treatment
- Risk reduction calculated as 18.75% and number needed to treat (NNT) as five people
- Ten subjects continued into study extension
 - Pain intensity dropped from 6.9 (baseline) to 5.0 (three months) and 4.2 (six months)
 - Average dose was 4.5 sprays/day (ranged between 2–10 sprays/day)
 - Few medication-related adverse events

Conclusion: NNT is an appropriate measure for effectiveness across categories of pain drugs due to inconsistency between individual responses to other standard analgesics. A full randomized controlled clinical trial is necessary to understand how nabiximols can be used as a stand-alone or adjunctive treatment for chemotherapy-induced neuropathic pain.

6. Cannabinoids for medical use: A systematic review and meta-analysis

Penny F. Whiting *et al.* JAMA 313 (24):2456-2473, 2015.

This meta-analysis included 79 randomized clinical trials (6,462 patients) for numerous indications, including chemotherapy-induced nausea and vomiting, chronic pain, depression, anxiety, and sleep disorder.

Study Design

- Extracted data included patient and disease outcomes, activities of daily living, quality of life, global impression of chance, and adverse events
- Dichotomous data was analyzed using odds ratio and 95% CI
- Categorical data were analyzed by comparing the number of subjects with specific outcomes in each category
- Continuous data were analyzed by comparing mean and standard deviation at baseline, follow-up, and study termination, in addition to mean differences with 95% CI
- Results from inter-group statistical analyses were calculated and reported as mean difference, 95% CIs, and P values
- Adverse events were analyzed using data from all conditions
- Stratified analyses and meta-regression were conducted to determine if associations varied with cannabinoid type, study design (parallel group vs. crossover trial), comparator (active vs. placebo), and time to follow-up for the outcome of any adverse event
- Overall quality of the collected evidence, risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect was rated using GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Results

- 28 studies involved chronic pain (63 report, 2,454 participants)
 - 13 studies involved nabiximols, four involved smoked THC, five involved nabilone, three involved THC oromucosal spray, two involved dronabinol, one involved vaporized cannabis, one included ajuvenic acid capsules, one included oral THC

- Etymology of pain varied between neuropathic, cancer, diabetic peripheral neuropathy, fibromyalgia, HIV-associated sensory neuropathy, refractory pain due to multiple sclerosis, arthritis, non-cancer pain, central pain, and chemotherapy-induced pain
- Average number of subjects who reported a $\geq 30\%$ reduction in pain was greater with cannabinoids compared to placebo (OR, 1.41 [95% CI, 0.99-2.00] from 8 trials)
 - Six of these trials included neuropathic pain (OR, 1.38 [95% CI, 0.93-2.03])
 - Two of these trials included cancer pain ((OR, 1.41 [95% CI, 0.99-2.00])
- Nabiximols was associated with greater average reduction in pain when compared to placebo
 - In six trials according to 0-10 NRS (weighted mean difference -0.46, [95% CI, -0.80 to -0.11]) and brief pain inventory-short form
 - In three trials according to severity composite index (WMD, -0.17 [95% CI, -0.50 to 0.16])
- In five trials according to neuropathic pain scale (WMD, -3.89 [95%CI, -7.32 to -0.47])
- In six trials according to the proportion of subjects reporting improvement on a global impression of change score (OR, 2.08 [95% CI, 1.21 to 3.59])
- No difference in average quality of life scores was measured by the EQ-5D health status index (WMD, -0.01 [95% CI, -0.05 to 0.02] between nabiximols and placebo in three trials
- 28 studies involved nausea and vomiting due to chemotherapy (37 reports, 1772 participants)
 - 14 studies involved nabilone, three involved dronabinol, one involved nabiximols, four involved levonantradol, and six involved THC
 - Eight studies included placebo, three included placebo with active comparator, 20 included only an active comparator
 - Risk of bias was high for 23 studies and unclear for five studies
- All studies suggested cannabinoids are more effective against placebo or comparator, but no studies reached statistical significance
- In three trials, the average number of subjects demonstrating complete cessation of nausea and vomiting was greater with dronabinol or nabiximols compared to placebo (OR, 3.82 [95% CI, 1.55-9.42])
- Most studies suggested that cannabinoids were associated with improvements in symptoms, but these associations did not reach statistical significance in all studies
- GRADE approach indicates that there was
 - Moderate quality evidence supported the efficacy of cannabinoids for treating chronic neuropathic or cancer pain (smoked THC, nabiximols) and spasticity due to multiple sclerosis (nabiximols, nabilone, dronabinol and THC/CBD capsules)
- Low-quality evidence that cannabinoids lead to improvements in chemotherapy-induced nausea and vomiting (dronabinol, nabiximols), weight gain in HIV (dronabinol), sleep disorders (nabilone, nabiximols), and Tourette syndrome (THC capsules)
- Very low-quality evidence for improvements in anxiety assessed with a public speaking test (CBD)
- Increased risk of short-term adverse events with cannabinoid use (asthenia, balance problems, confusion, dizziness, disorientation, diarrhea, euphoria, drowsiness, dry mouth, fatigue, hallucination, nausea, somnolence, and vomiting)

Conclusion: There was moderate quality evidence suggesting that cannabinoids are effective treatments for chronic pain, and low quality evidence suggesting their effectiveness for improving chemotherapy induced nausea and vomiting.