

# Use of cannabinoids in cancer care: palliative care

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## PALLIATIVE CARE IN ONCOLOGY

All too often neglected, maximal quality improvement in the setting of life-limiting illness and noxious symptomatology is a worthy medical, public health, and humanitarian goal. The World Health Organization estimates that, globally, about 60% of all people who die would benefit from palliative care before death; however, palliative care is not exclusively reserved for patients at the end of life<sup>1</sup>.

Given the relative newcomer status of this field of medical care, some definition would be helpful. Palliative care is a multidisciplinary medical specialty—often involving social work and spiritual care—that is concerned with impeccable symptom management and supportive care for patients and their families facing life-limiting illness. It focuses on the amelioration of physical, emotional, psychological, and spiritual suffering<sup>2</sup>. Palliative care is *not* strictly reserved for practice by palliative care specialists; non-palliative care treating specialists can and should be trained to provide what is called “primary palliative care” such as basic pain management and facilitation of clinical discussions with patients and families about disease prognosis and advance care planning<sup>3</sup>.

In the oncologic setting, the recommended timing for the integration of specialist palliative care in the management of cancer patients has steadily been moving upstream, closer to time of diagnosis, because outcomes research continues to demonstrate improved quality of life and, in some instances, improved survival with the earlier involvement of palliative care specialists<sup>4</sup>. Such effects were seen in the widely publicized study by Temel *et al.*<sup>5</sup>, in which average survival time was increased by 2.7 months (11.6 months vs. 8.9 months,  $p = 0.02$ ,  $n = 151$ ) and health-related quality of life was improved for patients newly diagnosed with metastatic non-small-cell lung cancer and randomized for referral to palliative care compared with control patients not so randomized. In a similar vein, what oncologists mean by “palliation,” such as when palliative chemotherapy lines are routinely offered, might be changing as well, as stronger evidence emerges that such chemotherapy might not actually provide palliation—such as was seen in a recent prospective cohort study of 621 patients with progressive end-stage metastatic cancer who had a life expectancy of 6 months or less and who had already completed at least 1 chemotherapy regimen. In such patients, use of “palliative chemotherapy” was found to be associated with a *reduction* in the quality of life near

death for patients who had a good baseline performance status (odds ratio: 0.35; 95% confidence interval: 0.17 to 0.75) and was *not* found to be associated with quality of life near death for patients with a moderate or poor baseline performance status<sup>6</sup>.

## Cannabinoid Integrative Medicine in Oncologic Palliative Care

The opportunities to improve and expand palliative care are many. In this supplement, *Current Oncology* is presenting a discussion on cannabinoid therapeutics. I believe that, as a therapeutic class, cannabinoids have an important role to play in oncologic palliative care—a role that I predict will only grow with time, as knowledge and acceptance of these agents becomes mainstream once more, as in the 19th and early 20th century in North America and Europe.

To acknowledge the wisdom of, and draw from the lessons learned by, medical pioneers of the 19th century who made serious efforts to integrate cannabinoid preparations into their medical practice, it is worth recounting the description given by Sir W.B. O’Shaughnessy MD of his treatment of a patient with end-stage rabies who was suffering from hydrophobia, a terrifying neurologic sequela of that viral syndrome, in which all attempts to take in liquid per os are met with violent paroxysms and convulsions. In cancer patients, refractory nausea and vomiting, especially in the setting of highly emetogenic chemotherapy, can present similarly. O’Shaughnessy’s case description is likely the first modern medical description of the use of a cannabis preparation to palliate symptoms in the final days of life. The description of his patient’s presentation in the last days and hours of life, including breathing pattern and alteration in mental status, can frequently be seen in cancer patients.

The description starts with a clinical encounter from 22 November 1838, when a patient named Hakim Abdullah, who had been bitten by a rabid dog 3 weeks earlier, came to O’Shaughnessy’s chambers in Kolkata<sup>7</sup>. On exam, Abdullah’s pulse was found to be 125 bpm, and his skin, cold and moist. The left forearm showed a small, red, painful cicatrix—likely the site of the dog bite. He found that the patient was “unable to swallow liquid or quench thirst—every attempt to swallow water or trickle drips on tongue led to severe paroxysms.”

O’Shaughnessy prescribed treatment: “Two grains [approximately 129 mg] of Hemp resin [*Cannabis* extract] in a

soft pillular mass were ordered every hour.” In a day-by-day report, O’Shaughnessy describes how, after the third dose, the patient was able to progressively begin to take in more liquids, starting with swallowing the juice of an orange, and after some sleep, having more juice, moistened rice, and sugarcane. He then had a “purgative enema,” and 5 days after initially presenting, he “sunk into profound stupor, the breathing slightly stertorous; in this state he continued, and without further struggle, death terminated his sufferings at 4 AM of the 27th November.”

Moving forward to the present moment, I prefer that this type of care be termed “cannabinoid integrative medicine” (CIM), which better contextualizes cannabinoid use within the overarching trends in medicine today. Where integrative medicine blends conventional with complementary and alternative therapies such as botanicals, CIM emphasizes the integrated therapeutic use of the cannabinoid-rich botanical *Cannabis*.

Guided by cannabinoid science and endocannabinoid physiology, CIM has been incorporated by law into health care in nearly half the United States and all of Canada; however, it remains underutilized. Although isolated cannabinoids have been approved by the U.S. Food and Drug Administration since 1985 and by the Therapeutic Products Directorate of Health Canada since 1991 (notably for palliative indications), many patients prefer unapproved herbal preparations cultivated by themselves, their caregivers, or local artisans. Canada has, however, begun to make whole-plant cannabis preparations more widely available, in line with the favoured natural therapeutic approaches of CIM.

Canada was one of the first countries to approve the use of a European pharmaceutically prepared whole-plant cannabis extract formulated 1:1 tetrahydrocannabinol-to-cannabidiol, which Health Canada approved for use in central pain from multiple sclerosis and in cancer pain. More recently, concerted efforts through the Canadian courts have been made to compel the national health regulatory authority to set up and regulate in-country pharmacy product stocking and mail-order dispensing systems for herbal cannabis and cannabis extracts allowed to be cultivated by a number of private producers. Although Health Canada maintains that “Dried marijuana is not an approved drug or medicine in Canada”<sup>8</sup>, it has set up a system of regulated access to cannabis medicines that does serve significant patient needs. However, whether related to cost, access, or custom, use of locally self- or caregiver-produced cannabis products by patients continues. Such uses are expected when the human–*Cannabis* relationship that has existed since before recorded history is seriously taken into account<sup>9</sup>.

Regardless of source, all cannabis-related medicinal products have yet to be well-integrated into health care, indicative of the translational gap between available scientific evidence on cannabis and cannabinoids, and current practices. The benefits of integrating CIM into palliative care have been stifled by conflicting regulations, lingering stigma, research barriers, and product scarcity—much of which stems from poor awareness and knowledge gaps for patients, clinicians, and other stakeholders.

Other contributions in this volume are covering the role of cannabinoids in the overall supportive care

of oncologic patients, and so here, I focus on the role of CIM in the palliative care of patients with advanced cancer and an anticipated survival of 6 months or less—a definition that encompasses the care of cancer patients enrolled in hospice care.

### **Symptom Palliation**

Hospice is simply a setting in which a full palliative care approach is offered for patients at or nearing the end of life, and such care can be provided in the patient’s home, a nursing home, or an inpatient hospice unit or hospital when more aggressive palliation and nursing care are required.

Symptom management using CIM will be covered in depth elsewhere, and so I will touch on that use only briefly. Well-documented and evidence-based indications for CIM include its use in severe pain, muscle spasm, intractable nausea, and cachexia. With regard to conditions relevant to oncology, cannabis medicines, both orally administered and inhaled, have been shown in randomized double-blind placebo-controlled trials to have efficacy for a number of symptoms, including opioid-refractory cancer pain, nausea and vomiting secondary to active cancer chemotherapy, appetite stimulation and weight gain in patients with AIDS wasting syndromes, painful HIV sensory neuropathy, and chronic intractable neuropathic pain from multiple causes<sup>10</sup>.

Dosages and frequency of use vary depending on patient, condition, formulation, and route of administration; however, given the extremely impressive safety margins with cannabis use in nearly all patients (which has no known LD<sub>50</sub> in humans), a wide berth for instructions in the form of patient-controlled auto-titration and “as needed” use can be given to patients, with the common-sense pharmacotherapy initiation parameters of “start low, go slow,” coupled with ongoing medical follow-up. I expect that more evidence-based treatment guidelines will be forthcoming as research and information-sharing is expanded and as more information becomes available about the provenance, quality, and potency for marketed preparations.

Ongoing research investment in cannabis preparations for oncologic palliative care is happening in a few places. A multiphase study beginning in New South Wales, Australia, will focus on appetite stimulation and quality of life in terminally ill cancer patients (<http://www.health.nsw.gov.au/cannabis/Pages/terminal-illness.aspx>). In Israel, studies are documenting the use of CIM in oncologic practice. One was a prospective observational study conducted in the Integrated Oncology and Palliative Care Unit at Rambam Health Care Campus in Haifa. That 8-week study involved 131 patients using cannabis under medical license who participated in two structured interviews, the first in person at study beginning and the second by telephone at study end. The authors noted that all cancer-related or anticancer treatment-related symptoms were significantly improved, including nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorders, itching, and pain. Other notable findings after 8 weeks included a reduction in the dose of opioid pain medications in 31 of the 70 patients who used such medications at study start and a reduction in the dose of antidepressant or anxiety drugs in one third of the

patients taking those agents. Aside from memory loss, no other significant side effects were reported<sup>11</sup>.

A second Israeli study, this one retrospective in design, was conducted at Sheba Medical Center in Tel Aviv. Researchers used chart review and treating oncologist authorization applications to examine the characteristics of cancer patients who had received medical cannabis authorizations, seeking to understand perceived and documented benefits, as well as usage duration. Excluding patients with hematologic malignancies and children, researchers reported that of the approximately 17,000 cancer patients being treated or observed at their institution over the course of 1 year, 279 (<1.7%) received a permit for cannabis from an authorized institutional oncologist (the institution had only one). Median age of the cannabis users was 60 years (range: 19–93 years); 160 (57%) were women; and 234 (84%) had metastatic disease. Of 151 (54%) patients alive at 6 months, 70 (46%) renewed their cannabis permit (renewals were required at 6 months). Renewal was found to be more common among younger patients and those with metastatic disease. Of 113 patients alive and using cannabis at 1 month, 69 (61%) responded to a detailed questionnaire, and improvements in pain, general well-being, appetite, and nausea were reported by 70%, 70%, 60%, and 50% respectively. Side effects were mild and consisted mostly of fatigue and dizziness<sup>12</sup>.

### ***Palliation of Spiritual and Existential Suffering***

Moving now into more spiritual and existential suffering, concerns that are certainly ascendant in end-of-life care, CIM approaches afford some unique potential benefits known more through traditional medicinal and cultural uses and borne out in anecdotal reports from patients and caregivers. Consider euphoria, aversive memory extinction, sensorium enhancement, and spiritual insight catalysis. A mild euphoria or sense of well-being, if brought about through use of cannabinoid botanical products, could very well play an important therapeutic role for patients faced with the despair of a terminal malady and the loss of function that normally accompanies it.

A second potential benefit of CIM in advanced cancer is a reduction in the psychological trauma that a terminal cancer diagnosis and increasingly invasive treatments frequently cause for patients. That reduction would presumably be attributable to the stimulation of cannabinergic activity in parts of the brain that are known to have a key role in aiding extinction of aversive memories and the accompanying anxious thoughts and behaviors.

A third area of potential benefit is enhancement of the senses. *Cannabis* has long been used as an enhancer, heightening sensory perceptions and awareness. That effect can have a role in optimizing primal sensorial delights, or as Dr. B.J. Miller puts it, “tending to dignity by way of the senses”<sup>13</sup>, which could include increased appreciation of music, tastes, scents, or other aesthetic pleasures. It could also help to heighten awareness of moment-to-moment presence by allowing an individual to “stop and smell the roses,” a state of being that is all the more critical when one’s days are numbered. Such a state could also be facilitated by growing one’s own medicine through *Cannabis* gardening, which could serve as a form of horticultural therapy.

Finally, increased awareness of the moment, coupled with the increased introspection and meditation that cannabis can catalyze and for which it has been used in various spiritual traditions, might lead to spiritual growth and development, which can play a vital role in helping to create “a good death.”

### ***Right to Access Experimental Treatment***

Having looked at symptom and existential distress palliation, the discussion now turns to a final area of advanced cancer palliative care that bears mentioning: facilitation of a patient’s right to access experimental treatments in line with their wishes and beliefs, in service of hope, which, as Alexander Pope so eloquently and proverbially wrote, “springs eternal in the human breast”<sup>14</sup>. A growing evidence base suggests that cannabinoid therapies might have disease-modifying effects in cancer and neurologic disorders. Abrams and Guzman<sup>15</sup> recently nicely reviewed the science base for cannabinoids as anticancer agents and also the ethical issues and quandaries surrounding the experimental use of cannabis extracts by cancer patients. Detailed chronological case reports, with serial imaging and laboratory markers, correlating cannabis use with antitumour effects in 3 Canadian pediatric patients, 1 with acute lymphoblastic leukemia<sup>16</sup> and 2 with pilocytic astrocytoma<sup>17</sup> now appear in the medical literature. Additionally, a pilot clinical trial carried out in Spain showed that, in at least 2 of 9 study patients with recurrent glioblastoma multiforme, local administration of tetrahydrocannabinol intracranially through an infusion catheter was safe and was associated, by magnetic resonance imaging and biomarker expression criteria, with decreased tumour cell progression.

With such evidence (albeit mostly preclinical) being published in widely accessible journals, it is not surprising that, given both the mystique of cancer and the cultural profile of cannabis, interest in using cannabis preparations to retard cancer has surged among patients. Unfortunately, because of the many barriers mentioned earlier, few scientific studies in humans to investigate CIM oncologic applications are underway. A perusal of ClinicalTrials.gov reveals a controlled human study investigating oral cannabidiol as a single-agent treatment for solid tumours (<https://clinicaltrials.gov/ct2/show/NCT02255292>), a study of a cannabis-based medicinal extract oromucosal spray (1:1 tetrahydrocannabinol-to-cannabidiol) compared with placebo in conjunction with temozolomide in recurrent glioblastoma multiforme (<http://clinicaltrials.gov/show/NCT01812616>), and a study of cannabidiol as a treatment for acute graft-versus-host disease in patients who have undergone allogeneic hematopoietic stem-cell transplantation (<http://clinicaltrials.gov/show/NCT02392780>).

What to do in the face of incomplete evidence? Abrams and Guzman<sup>15</sup> have expressed warranted concern that potentially curative standard therapies might be foregone for experimentally unproven ones. Nevertheless, they also note that because “the preclinical evidence suggests that cannabinoids might enhance the antitumour activity of conventional chemotherapeutic agents as well as ameliorate associated side effects, the addition of cannabinoid-based preparations to standard cancer therapy should not be discouraged by the treating oncologist.” Concerns to

raise with patients who might wish to experiment this way would include basic safety issues such as the fact that high-potency cannabis extracts (or “oils”) might have been produced with industrial petroleum-based solvents that could leave residues in the final product or that might chemically concentrate any mycotoxins, pesticides, or other chemicals that were present on the raw plant matter. In addition to the need for a robust clinical research program for CIM in oncology, there is a definite need for better quality control for extracts that are experimentally used.

## SUMMARY

Integrating CIM into oncologic palliative care promises to improve overall health-related quality of life, to provide further relief from distressing symptoms and spiritual suffering, and to bring hope to patients and families facing terminal illness.

O’Shaughnessy offers the following somber reflection<sup>7</sup>:

It seems evident that at least one advantage was gained from the use of the remedy—the awful malady was stripped of its horrors; if not less fatal than before, it was reduced to less than the scale of suffering which precedes death from most ordinary diseases.... Next to cure, the physician will perhaps esteem the means which enable him “to strew the path to the tomb with flowers,” and to divest of its specific terrors the most dreadful malady to which mankind is exposed.

## CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology’s* policy on disclosing conflicts of interest, and I declare that I have none.

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