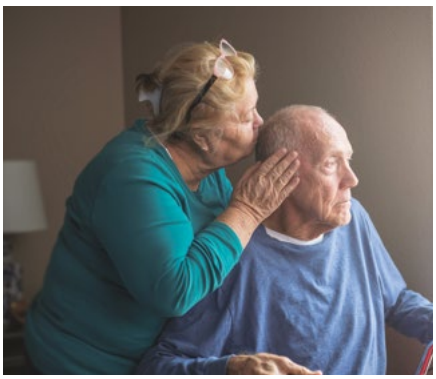
Medicinal cannabis use in palliative care



CPD

Anthony Herbert, Janet Hardy

Background
Legislative change in recent years allows the prescription of medicinal cannabis for patients receiving palliative care. There appears to be widespread community support of its use in this context.

Objective
The aim of this article is to provide an overview of current research on the use of medicinal cannabis within the palliative care context for both children and adults.

Discussion
The evidence needed to support the use of medicinal cannabis for symptom control is limited and still emerging. It is unlikely that medicinal cannabis will be used as a first-line agent for the management of pain, nausea and other specific symptoms, but it may have an adjuvant or complementary role in symptom management within palliative care. Consistent with the Therapeutic Goods Administration advice, these authors recommend that general practitioners encourage patients to participate in trials or programs that objectively monitor benefit and toxicity of medicinal cannabis.

THERE HAS BEEN INCREASING INTEREST in the use of medicinal cannabis over recent years and strong public pressure for its legalisation.[1] Recent legislative change in several Australian states has provided pathways for the use of medicinal cannabis for a range of indications including chronic pain, epilepsy, spasticity associated with multiple sclerosis, chemotherapy-induced nausea and vomiting, and the symptoms associated with terminal illness.[1,2] Despite overwhelming public belief in its value, the evidence supporting the use of cannabis in palliative care is limited.

There are currently only two cannabis products listed on the Australian Register of Therapeutic Goods. These are nabiximols, a 1:1 cannabidiol (CBD):Δ^9-tetrahydrocannabinol (THC) oromucosal spray (Sativex), licensed for treating spasticity in multiple sclerosis, and a CBD oil (Epidyolex) for rare forms of childhood epilepsy. There is a range of other unregistered medicinal cannabis products that can be prescribed through the Therapeutic Goods of Australia's (TGA's) Special Access and Authorised Prescriber Schemes. A list of approved manufacturers and suppliers can be found via the Office of Drug Control.[3] Although the number of prescriptions of medicinal cannabis supplied by medical practitioners is increasing sharply, most of the 'medicinal cannabis' used by the general population is 'community acquired' (ie provided by unregistered suppliers), with only a small proportion obtained through legal pathways.[1] The exact constitution of these products is often unknown and variable.[4]

Endocannabinoid system

The endocannabinoid system is an area of current focus in biomedical research, with interest in its widespread role within the brain and body, modulating the immune, autonomic nervous, gastrointestinal, endocrine and cardiovascular systems.[5] The cannabis plant contains almost 500 bioactive compounds, including more than 140 different cannabinoids. The two most prevalent, and best understood, cannabinoids in the plant are THC and CBD. Most currently available medicinal cannabis products in Australia contain THC, CBD or both.[1]

Clinicians remain uncertain as to which of the more than 400 compounds within the cannabis plant are most effective for individual symptoms, as well as which is the best product or combinations of the various cannabinoids, route of administration or dosing schedule.[6,7] There are also concerns about interaction with other medicines and long-term safety profiles.[8] Doses of CBD in the

range of 40–1200 mg/day have been used for a variety of different conditions, including psychiatric disorders.[9] The dose range of THC varies from 2.5 mg/day to 40 mg/day.[5,10,11] Dosing for children with advanced cancer and those receiving palliative care has yet to be adequately determined.[12] Furthermore, it is not known whether the best dose or combination of cannabinoids for one condition is the same for others.

THC is the main psychoactive and euphorigenic component of cannabis. Postulated benefits of this compound include analgesia, antinausea, muscle relaxation and improvement in quality of life.[13] The potential side effects at higher doses of THC include dizziness, psychotomimetic effects, cognitive and driving impairment, anxiety and sedation.[14] It has been suggested that these side effects may be overcome in clinical practice by gradually titrating doses of THC upwards.[15] THC is classed as a Schedule 8 medication (controlled drug).

Unlike THC, CBD is not intoxicating, even at high doses, and is said to have a range of anxiolytic, antipsychotic, anti-inflammatory, antioxidative, anticonvulsant and neuroprotective effects.[11,16,17] CBD may reduce some of the adverse psychotropic effects of THC, although these findings require further validation.[18] CBD is a Schedule 4 medication (prescription medicine). Recently it was announced that low-dose CBD (≤150 mg/day) will be made available as a Schedule 3 (pharmacist-only) medicine, but to date, no product has met all TGA registration requirements.

What do we know?

The reasons cited by adult patients with cancer wishing to use medicinal cannabis include poor control of pain, nausea, depression and sleep, and coping with stress and illness.[19,20] Alleviation of cancer pain and related symptoms is currently the third most common reason for the prescription of medicinal cannabis in Australia.[1] Patients with a high symptom burden, including children, are more likely to use cannabis and report a favourable efficacy profile.[4,20] Many still believe that it may have a beneficial effect on their cancer despite evidence to the contrary.[19] The majority would prefer to take cannabis in the form of tablets or capsules rather than mouth sprays or vaporisers.[19]

Whiting undertook a systematic review of cannabinoid use in medicine and found moderate-quality evidence for chronic non-cancer pain and spasticity, with low-quality evidence for chemotherapy-induced nausea and vomiting (CINV), sleep problems, human immunodeficiency virus–related anorexia, and Tourette syndrome.[21] In the UK, a commissioned review concluded that there was good evidence for its use in chronic non-cancer pain, spasticity, CINV and anxiety, with moderate evidence for use in chemotherapy-induced anorexia, sleep disorders, post-traumatic stress disorder, fibromyalgia and Parkinson's disease symptoms, but that much further research was needed.[22] The most recent state-of-the-art review from the US National Academies of Sciences, Engineering and Medicine found substantial evidence for the use of medicinal cannabis for treatment of chronic pain, CINV, epilepsy and spasticity in multiple sclerosis, with moderate evidence for sleep disorders.[23]

Until quite recently, there were concerns that medicinal cannabis caused cancer. While such associations have not been proven, the pendulum has swung to the point that many patients continue to access cannabis under the mistaken belief that it will help treat their cancer. Social media further emphasises this notion.[24] There are no clinical trials in humans demonstrating anticancer effects from medicinal cannabis.[25,26]

Specific symptoms

Pain relief

Early trials of cannabis for the treatment of cancer pain were consistent in showing no benefit of cannabis over placebo.[27,28] This was confirmed in two recent systematic reviews that included more than 1500 patients with cancer in five trials.[29,30] Hauser et al defined a positive benefit as patients reporting 'much' or 'very much' improvement in pain relief from baseline. This related to 710 participants from two trials. A number needed to treat (NNT) for an additional beneficial outcome of 16 was reported (95% confidence interval [CI]: 6, ∞).[29] According to the predefined criteria of an NNT being <10, there was no clinically relevant benefit from cannabis-based medicines.

The same review by Hauser et al analysed four studies with 1333 participants for a primary outcome of pain relief of 50% or greater.[29] Ninety-three of 786 (11.8%) participants in the cannabis-based medicines group and 53 of 547 (9.7%) participants in the placebo group reported pain relief of 50% or greater (95% CI: –0.03, 0.04). Similarly, there was no benefit when the data were analysed for pain relief of 30% or greater, with 786 (29.4 %) of participants in the intervention group and 145 of 547 (26.5%) of participants in the placebo group reporting benefit (95% CI: –0.02, 0.08).

The review by Boland et al[30] included five randomised controlled trials (RCTS; all at low risk of bias) with 1442 participants and assessed changes in Numerical Rating Scale pain scores. The authors concluded that, in patients with advanced cancer, the addition of cannabinoids to opioids did not reduce cancer pain.

However, when non-malignant neuropathic, chronic and cancer pain studies were combined in a systematic review of systematic reviews,[31] meta-analysis of 15 RCTs found that a greater number of patients taking medical cannabinoids achieved a 30% pain reduction (39%) than those in the placebo group (30%), with a risk ratio of 1.37 (95% CI: 1.14, –1.64) and an NNT of 11. The majority of the RCTs included (13 of 15) examined neuropathic pain.

A more recent review pointed to the low quality of many studies and could not support nor refute claims of benefit.[32] This, along with the aforementioned reviews, illustrates the problem that different systematic reviews use different methodologies and provide disparate results. Others have reviewed the quality of systematic reviews and call for standardisation of reporting before any conclusion can be drawn as to the benefit of cannabis in non-malignant pain.[33]

Some cancer guidelines tentatively support the use of medicinal cannabis in some patients but state that cannabis should not be recommended as first-line therapy and may be considered as an adjuvant.[23] In non-malignant pain, recent evidence is pointing to a more targeted approach towards the use of cannabis in neuropathic pain.[34,35] Few studies have demonstrated any reduction in baseline analgesia in those taking cannabis.[20]

Nausea/vomiting

Medicinal cannabis has long been recognised as an antiemetic, but until recently it had never been tested against modern antiemetics. A recent pilot study in CINV compared a combination THC/CBD capsule against standard antiemetics in patients receiving emetogenic chemotherapy. Patients in the cannabis arm preferred cannabis and had less CINV.[36] The results justified progression to a phase 3 trial. The relative high frequency of side effects related to cannabis use, including nausea, suggests that this should only be used when standard antiemetics fail. As yet, there are no quality studies assessing cannabis for nausea control in the palliative care context.

There is also a small number of studies examining the use of medicinal cannabis for CINV in children, including three RCTs. These studies demonstrated that THC was more effective than prochlorperazine, domperidone and metoclopramide.[37–39] Side effects of drowsiness and dizziness were common. There has been no comparison with antiemetics such as serotonin or neurokinin 1 receptor antagonists.

Other symptoms

To date, no benefit over placebo (or standard care) has been shown for improvements in most symptoms related to advanced cancer including calorific intake, appetite, mood or sleep problems.[2] Beneficial effects on sleep, stress and anxiety hold most promise. Several trials are underway to address these issues.

Quality of life

The impact of cannabis on health-related quality of life remains unclear. A meta-analysis of 20 studies found no conclusive evidence of benefit, with great heterogeneity between studies.[40] One study of children with complex motor disorders found an improved quality of life with a combined THC:CBD product.[41] Of interest, and consistent with these authors' trial experience, many patients report subjective improvement when taking cannabis despite the lack of objective evidence of improvement.[29]

Paediatrics

Several studies, including three important phase 3 RCTs, demonstrate convincing evidence for the use of medicinal cannabis, specifically CBD, for children with treatment-refractory epilepsy.[17,42,43] Doses of up to 25 mg/kg/day of CBD titrated up over two weeks have proved effective.[12] Recent US, European and Australian therapeutic goods agency approval for 100 mg/mL CBD oil (Epidyolex) to treat childhood epilepsy underlines the safety and effectiveness of CBD, even at high doses, in vulnerable paediatric populations. Children in the community given illicit cannabis extracts tend to have more severe epilepsy and have trialed a greater number of anticonvulsants. Studies have shown high variability in the cannabinoid content and profile of extracts rated as 'effective', with no clear differences in extracts considered 'effective' and 'ineffective'.[4]

In a systematic review undertaken in 2017 by the American Academy of Pediatrics (AAP), use of medicinal cannabis in children outside of the Food and Drug Administration process was not recommended.[12] This contrasts with clinical practice, where there are frequent enquiries from parents regarding the use of medicinal cannabis in children. However, the AAP also recognised that in life-limiting conditions, or severe debilitating conditions where current therapies are inadequate, medicinal cannabis can be trialled. The AAP review found 21 articles relating to the use of medicinal cannabis in children across many different conditions. This included five RCTs, five retrospective chart reviews, five case reports, four open-label trials, two parent surveys and one case series.

There have been only two studies of the use of medicinal cannabis in children receiving palliative care. Both described a cohort of patients treated between 2010 and 2017. One study from Israel included 50 children aged from seven months to 21 years with a cancer diagnosis.[44] Various formulations were used, including vaporised cannabis. Indications for use included nausea and vomiting, mood disturbance, insomnia and pain. Positive effects were reported by the children and parents in 80% of cases. Adverse effects included burning in the throat and anxiety related to use of the vaporised product. The other study of 21 children aged from 3.6 months to 19 years involved 52% of children with a neurological diagnosis and 48% with a cancer diagnosis who were administered medicinal cannabis oil drops.[45] Indications included seizures (52%) and pain (19%). Medicinal cannabis use was associated with reduced nausea and vomiting and increased appetite. Adverse effects included somnolence, insomnia and vomiting.

Other neurological conditions may also be amenable to treatment with medicinal cannabis: a German study found a positive response to synthetic THC (dronabinol) in children with dystonia and spasticity. The starting dose of this synthetic form of THC was 0.83 mg twice per day, increasing to a maximum of 1 mg/kg/day.[46] This study was a retrospective chart review that showed patients had either better symptom management or reduced use of other medicines causing side effects. In another recent trial in a paediatric population, a buccal spray containing 1:1 THC/CBD (nabiximols) was reasonably well tolerated although ineffective in the primary outcome of spasticity in a population of children with cerebral palsy or brain injury.[47] A third prospective trial compared 1:6 THC/CBD with 1:20 THC/CBD in children aged 1–17 years with complex motor disorders.[41] This study found improvements in dystonia, sleep, pain and quality of life regardless of the treatment assignment. THC-containing cannabis extracts have also been recently used, with success, in the treatment of

childhood epilepsy with a THC:CBD ratio of 1:20 and doses of CBD up to 10–12 mg/kg/day.[48]

Adverse effects

CBD when used alone seems generally well tolerated with few serious adverse effects. Documented associations with abnormal liver function tests, somnolence, sedation and pneumonia were limited to childhood epilepsy studies in one review, where CBD may have interacted with other medications such as clobazam and/or sodium valproate.[49] After excluding studies in childhood epilepsy, the only adverse outcome associated with CBD treatment was diarrhoea (which might be attributable to the carrier oil). While CBD does not affect driving ability, THC impairs driving performance,[50] and it is illegal to drive while taking THC irrespective of whether it is being taken for recreational or medical use. Patients in cannabis trials (which generally test CBD/THC combinations) commonly report more adverse events than controls and greater withdrawal due to adverse events.[31]

In their review of medicinal cannabis trials for pain in patients with cancer, Hauser et al reported on adverse events for 1332 participants in four studies.[29] They found that 148 of 785 (15.2%) participants in the intervention groups and 83 of 547 (9.7%) participants in the placebo group dropped out because of adverse events. This resulted in a number need to treat for an additional harm (NNTH) of 20 (95% CI: 11, 100).[29] According to the predefined threshold of ≤10, there was no clinically relevant harm caused by cannabis-based medicines. In further analysis, the NNTH for adverse effects related to the nervous system was 10 (95% CI: 7, 100), which was felt to be clinically significant; for gastrointestinal adverse effects the NNTH was 11 (95% CI: 7, 33), which was felt to be not clinically significant.

The most common side effects reported include somnolence, dizziness, cloudy thinking and nausea.[20,27,30] In Allan's systematic review of systematic reviews, meta-analyses of overall adverse events were statistically significant, demonstrating numbers needed to harm (NNH) of 5–8.[31] A review was recently undertaken to define societal cannabis-related harms.[51] An association was found between cannabis use and psychosis, affective disorders, anxiety, sleep disorders, cognitive failures, respiratory adverse events, cancer, cardiovascular outcomes and gastrointestinal disorders. It is likely that the recreational doses assessed in this review were much higher than those used in the medical context that have generally shown to be safe. The risks of long-term use are poorly characterised in published clinical trials. High-quality trials are required to further characterise safety issues related to the use of medicinal cannabis.[15] The cost of cannabis (approximately $200–300 per 50 mL plus doctor's and dispensing fees) remains prohibitive to many patients. Financial toxicity is commonly cited as a barrier to use (unpublished data, JH).

Medication interactions

Potential medication interactions are numerous. Although the clinical relevance of these is unknown, interactions with other medications should be monitored carefully. Increased serum levels of seizure medications (eg rufinamide, topiramate and zonisamide) are seen in patients taking medicinal cannabis.[52] Abnormal liver function tests have been seen in patients taking sodium valproate.[52] There is the potential for reduction in efficacy of some anticancer agents (eg CDK 4/6 inhibitors) such that patients should be encouraged to inform their oncologists about their use of community-acquired products.[8,49]

Summary

The evidence needed to support the use of medicinal cannabis for symptom control is limited and still emerging. Medicinal cannabis should not be used as a first-line agent for the management of pain, nausea and other specific symptoms as there are standard management regimens of proven benefit. It may have a place as an adjuvant or complementary role in symptom management.[26] In adults, these authors' experience would suggest that most benefit to palliative care patients may be in neuropathic pain, sleep quality, anxiety and stress relief. Currently, there may be a role for medicinal cannabis as a 'third-line' agent (eg in CINV) if standard agents have failed. These recommendations are consistent with previous general practice guidance.[53] In children, a role in refractory epilepsy is established, with some evidence of benefit in spasticity and dystonia. When considering medicinal cannabis, there should be an open discussion with patients/parents regarding the limited benefits and more common harms.[53] Multiple trials are underway to develop the evidence base, including two Australian trials in advanced cancer studying the effects of pure CBD oil and a 1:1 THC/CBD oil product in alleviating total symptom burden in an adult palliative care population.[54,55] Other trials currently running to assess benefit in individual symptoms (eg sleep, quality of life, anorexia and pain) are listed on the Australian New Zealand Clinical Trials Registry.[56] In the interim, and consistent with the TGA advice,[2,34] these authors would urge general practitioners to encourage patients to participate in trials if available or to monitor benefit and toxicity closely and objectively in all patients prescribed medicinal cannabis.[34]

Key points

- Legislative change and community interest has meant that many patients receiving palliative care are asking about and requesting to use medicinal cannabis.
- The evidence needed to support the use of medicinal cannabis for symptom control in palliative care is limited and still emerging.
- Encouraging patients to participate in trials or programs that objectively monitor the benefit and toxicity of medicinal cannabis is important.

Authors

Anthony Herbert MBBS, BMedSci, FRACP, FAChPM, Director, Paediatric Palliative Care Service, Children's Health Queensland Hospital and Health Service,

Brisbane, Qld; Adjunct Clinical Associate Professor, Centre for Children's Health Research, Faculty of Health, Queensland University of Technology, Brisbane, Qld

Janet Hardy MbChB, BSc, FRACP, Director, Palliative and Supportive Care, Mater Health Services, Brisbane, Qld; Professor, Mater Research Institute, Faculty of Health, University of Queensland, Brisbane, Qld

Competing interests: JH is the recipient of a Medical Research Future Fund grant (administered by the National Health and Medical Research Council) to undertake clinical trials of medicinal cannabis for patients with advanced cancer.

Funding: None.

Provenance and peer review: Commissioned, externally peer reviewed.

Correspondence to:
Anthony.Herbert@health.qld.gov.au

References

1. Arnold JC, Nation T, McGregor IS. Prescribing medicinal cannabis. Aust Prescr 2020;43(5):152–59. doi: 10.18773/austprescr.2020.052.
2. Australian Government Department of Health: Therapeutic Goods Administration. Medicinal cannabis – Guidance documents. Woden, ACT: TGA, 2020. Available at www.tga.gov.au/medicinal-cannabis-guidance-documents [Accessed 13 April 2021].
3. Australian Government Department of Health: Office of Drug Control. Manufacturers and suppliers of medicinal cannabis products. Canberra, ACT: ODC, 2021. Available at www.odc.gov.au/manufacturers-and-suppliers-medicinal-cannabis-products [Accessed 13 April 2021].
4. Suraev A, Lintzeris N, Stuart J, et al. Composition and use of cannabis extracts for childhood epilepsy in the Australian community. Sci Rep 2018;8(1):10154. doi: 10.1038/s41598-018-28127-0.
5. Lu HC, Mackie K. Review of the endocannabinoid system. Biol Psychiatry Cogn Neurosci Neuroimaging 2020;S2451-9022(20)30206-8. doi: 10.1016/j.bpsc.2020.07.016.
6. Rabgay K, Waranuch N, Chaiyakunapruk N, Sawangjit R, Ingkaninan K, Dilokthornsakul P. The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: A systematic review and network meta-analysis. J Am Pharm Assoc 2020;60(1):225–34 e6. doi: 10.1016/j.japh.2019.07.015.
7. Brown D, Watson M, Schloss J. Pharmacological evidence of medicinal cannabis in oncology: A systematic review. Support Care Cancer 2019;27(9):3195–207. doi: 10.1007/s00520-019-04774-5.
8. Alsherbiny MA, Li CG. Medicinal cannabis: Potential drug interactions. Medicines (Basel) 2018;6(1):3. doi: 10.3390/medicines6010003.
9. Larsen C, Shahinas J. Dosage, efficacy and safety of cannabidiol administration in adults: A systematic review of human trials. J Clin Med Res 2020;12(3):129–41. doi: 10.14740/jocmr4090.
10. Health Canada. Cannabis (marihuana, marijuana) and the cannabinoids. Ottawa, ON: Health Canada, 2018. Available at www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html [Accessed 12 May 2021].
11. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. Am J Psychiatry 2018;175(3):225–31. doi: 10.1176/appi.ajp.2017.17030325.
12. Wong SS, Wilens TE. Medical cannabinoids in children and adolescents: A systematic review. Pediatrics 2017;140(5). doi: 10.1542/peds.2017-1818.
13. Chao Y, McCormack S. Medicinal and synthetic cannabinoids for pediatric patients: A review of clinical effectiveness and guidelines. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health, 2019.
14. Banister SD, Arnold JC, Connor M, Glass M, McGregor IS. Dark classics in chemical neuroscience: Delta(9)-tetrahydrocannabinol. ACS Chem Neurosci 2019;10(5):2160–75. doi: 10.1021/acschemneuro.8b00651.
15. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: A systematic review. CMAJ 2008;178(13):1669–78. doi: 10.1503/cmaj.071178.
16. Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. Br J Clin Pharmacol 2019;85(9):1888–900. doi: 10.1111/bcp.14038.
17. Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, et al. Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. Epilepsia 2019;60(3):419–28. doi: 10.1111/epi.14670.
18. Freeman AM, Petrilli K, Lees R, et al. How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. Neurosci Biobehav Rev 2019;107:696–712. doi: 10.1016/j.neubiorev.2019.09.036.
19. Luckett T, Phillips J, Lintzeris N, et al. Clinical trials of medicinal cannabis for appetite-related symptoms from advanced cancer: A survey of preferences, attitudes and beliefs among patients willing to consider participation. Intern Med J 2016;46(11):1269–75. doi: 10.1111/imj.13224.
20. Macari DM, Gbadamosi B, Jaiyesimi I, Gaikazian S. Medical cannabis in cancer patients: A survey of a community hematology oncology population. Am J Clin Oncol 2020;43(9):636–39. doi: 10.1097/COC.0000000000000718.
21. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015;313(24):2456–73. doi: 10.1001/jama.2015.6358.
22. Barnes M, Barnes J. Cannabis: The evidence for medical use. London, UK: All-Party Parliamentary Group for Drug Policy Reform, 2016.
23. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017.
24. Shi S, Brant AR, Sabolch A, Pollom E. False news of a cannabis cancer cure. Cureus 2019;11(1):e3918. doi: 10.7759/cureus.3918.
25. PDQ® Integrative, Alternative, and Complementary Therapies Editorial Board. Cannabis and cannabinoids (PDQ®): Health professional version. In: PDQ Cancer information summaries. Bethesda, MD: National Cancer Institute (US), 2021. Available at www.ncbi.nlm.nih.gov/books/NBK65755/ [Accessed 14 April 2021].
26. Evans W, Durocher-Allen L, Daeninck P, et al. Cancer and the health effects of cannabis and cannabinoids: An update of the systematic review by the National Academies of Sciences, Engineering, and Medicine (2016). Toronto, ON: Ontario Health (Cancer Care Ontario), 2020.
27. Fallon MT, Lux EA, McQuade R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: Two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain 2017;11(3):119–33. doi: 10.1177/2049463717710042.
28. Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. J Pain Symptom Manage 2018;55(2):179–88.e1. doi: 10.1016/j.jpainsymman.2017.09.001.
29. Hauser W, Welsch P, Klose P, Radbruch L, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for cancer pain: A systematic review with meta-analysis of randomised controlled trials. Schmerz 2019;33(5):424–36. doi: 10.1007/s00482-019-0373-3.
30. Boland EG, Bennett MI, Allgar V, Boland JW. Cannabinoids for adult cancer-related pain: Systematic review and meta-analysis. BMJ Support Palliat Care 2020;10(1):14–24. doi: 10.1136/bmjspcare-2019-002032.
31. Allan GM, Finley CR, Ton J, et al. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. Can Fam Physician 2018;64(2):e78–e94.
32. Fisher E, Moore RA, Fogarty AE, et al. Cannabinoids, cannabis, and cannabis-based medicine for pain management: A systematic review of randomised controlled trials. Pain 2020. doi: 10.1097/j.pain.0000000000001929.
33. Moore RA, Fisher E, Finn DP, et al. Cannabinoids, cannabis, and cannabis-based medicines for pain management: An overview of systematic reviews. Pain 2020. doi: 10.1097/j.pain.0000000000001941.
34. Australian Government Department of Health: Therapeutic Goods Administration. Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia. Woden, ACT: TGA, 2017. Available at www.tga.gov.au/publication/guidance-use-medicinal-cannabis-treatment-chronic-non-cancer-pain-australia [Accessed 14 April 2021].
35. Uberall MA. A review of scientific evidence for THC:CBD oromucosal spray (nabiximols) in the management of chronic pain. J Pain Res 2020;13:399–410. doi: 10.2147/JPR.S240011.
36. Grimison P, Mersiades A, Kirby A, et al. Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: A randomised, placebo-controlled, phase II crossover trial. Ann Oncol 2020(11):1553–60. doi: 10.1016/j.annonc.2020.07.020.
37. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: A double-blind, crossover trial. Pediatrics 1987;79(6):946–52.
38. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: An alternative antiemetic for cancer chemotherapy. Arch Dis Child 1986;61(5):502–05. doi: 10.1136/adc.61.5.502.
39. Ekert H, Waters KD, Jurk IH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. Med J Aust 1979;2(12):657–59.
40. Goldenberg M, Reid MW, IsHak WW, Danovitch I. The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. Drug Alcohol Depend 2017;174:80–90. doi: 10.1016/j.drugalcdep.2016.12.030.

41. Libzon S, Schleider LB, Saban N, et al. Medical cannabis for pediatric moderate to severe complex motor disorders. J Child Neurol 2018;33(9):565–71. doi: 10.1177/0883073818773028.
42. Devinsky O, Cross JH, Wright S. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;377(7):699–700. doi: 10.1056/NEJMc1708349.
43. Miller I, Scheffer IE, Gunning B, et al. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome: A randomized clinical trial. JAMA Neurol 2020;77(5):613–21. doi: 10.1001/jamaneurol.2020.0073.
44. Skrypek MM, Bostrom BC, Bendel AE. Medical cannabis certification in a large pediatric oncology center. Children (Basel) 2019;6(6):79. doi: 10.3390/children6060079.
45. Doherty M, Power L, Attala M, Vadeboncoeur C. Use of oral cannabis extracts in the pediatric palliative care setting: A retrospective chart review. Palliat Med 2020;34(3):435–37. doi: 10.1177/0269216320904315.
46. Kuhlen M, Hoell JI, Gagnon G, et al. Effective treatment of spasticity using dronabinol in pediatric palliative care. Eur J Paediatr Neurol 2016;20(6):898–903. doi: 10.1016/j.ejpn.2016.07.021.
47. Fairhurst C, Kumar R, Checketts D, Tayo B, Turner S. Efficacy and safety of nabiximols cannabinoid medicine for paediatric spasticity in cerebral palsy or traumatic brain injury: A randomized controlled trial. Dev Med Child Neurol 2020;62(9):1031–39. doi: 10.1111/dmcn.14548.
48. Huntsman RJ, Tang-Wai R, Alcorn J, et al. Dosage related efficacy and tolerability of cannabidiol in children with treatment-resistant epileptic encephalopathy: Preliminary results of the CARE-E study. Front Neurol 2019;10:716. doi: 10.3389/fneur.2019.00716.
49. Chesney E, Oliver D, Green A, et al. Adverse effects of cannabidiol: A systematic review and meta-analysis of randomized clinical trials. Neuropsychopharmacology 2020;45(11):1799–806. doi: 10.1038/s41386-020-0667-2.
50. Rubin R. Driving under the influence of CBD or THC: Is there a difference? JAMA 2020;324(21):2144–45. doi: 10.1001/jama.2020.22181.
51. Campeny E, Lopez-Pelayo H, Nutt D, et al. The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms. Eur Neuropsychopharmacol 2020;33:1–35. doi: 10.1016/j.euroneuro.2020.02.003.
52. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP, UAB CBD Program. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia 2017;58(9):1586–92. doi: 10.1111/epi.13852.
53. Allan GM, Ramji J, Perry D, et al. Simplified guideline for prescribing medical cannabinoids in primary care. Can Fam Physician 2018;64(2):111–20.
54. Good P, Haywood A, Gogna G, et al. Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: A double-blind, placebo controlled, randomised clinical trial of efficacy and safety of cannabidiol (CBD). BMC Palliat Care 2019;18(1):110. doi: 10.1186/s12904-019-0494-6.
55. Hardy J, Haywood A, Gogna G, et al. Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: A double-blind, placebo-controlled, randomised clinical trial of efficacy and safety of 1:1 delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Trials 2020;21(1):611. doi: 10.1186/s13063-020-04541-6.
56. Australian New Zealand Clinical Trials Registry. Available at www.anzctr.org.au [Accessed 14 April 2021].

correspondence **ajgp@racgp.org.au**