

THE UNIVERSITY of ADELAIDE

Cannabinoids for Cancer Treatment-Related Symptoms and Side Effects: Investigating the Interplay Between Clinical Trial Design and Outcomes

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Katrina Cao, BHlthMedSc (Adv)

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Abstract

Introduction: Most cancer treatments are associated with adverse symptoms that impact quality of life, adherence, and survival. Recently, cannabinoids have gained popularity for their potential to alleviate these treatment-related symptoms. However, although many people with cancer report self-medicating with cannabinoids, few healthcare providers feel adequately equipped to prescribe due to a lack of conclusive evidence. The contradictory evidence base likely reflects the inconsistent approaches to studying cannabinoids in supportive oncology. This systematic review aims to comprehensively synthesise all existing evidence on cannabinoids as a supportive care intervention and explore the interplay between study design and outcomes, with the overarching goal of identifying key attributes to inform future cannabinoid trials.

Methods: Six databases were searched from inception of database to January 2023. Study screening, selection, and data extraction were conducted using Covidence systematic review management software by two independent reviewers. Studies were included if they were primary research comparing the effects of cannabinoids on cancer treatment-related symptoms with a control or comparison group, in all people undergoing cancer therapy, regardless of type, stage, treatment status, or age. The quality of the evidence was assessed using the Cochrane risk of bias (RoB 2) tool. The systematic review protocol was registered on PROSPERO https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42022373000.

Results: A total of 87 studies with 93 separately extracted primary outcomes involving 15,773 participants were included; 76 had a 'high risk' of bias, and the remaining 11 had 'some concerns.' Across all cancer treatment-related symptoms, there were a greater number of studies indicating the benefits of cannabinoids, although none were significant except for chemotherapy-induced nausea and vomiting (p = 0.004).

Cannabinoids were associated with a higher incidence of adverse events compared to both placebo and active comparators, as well as a higher dropout rate (36.1% vs. 26.71%), although this was not significant (p = 0.223). Regarding trial design, cannabinoids were found to be most effective in studies that administered cannabinoids prophylactically before symptom occurrence (p = 0.028).

Conclusions: The evidence base was highly variable and limited by the predominance of studies published before CONSORT and COSMIN guidelines. Moving forward, trials should adopt pragmatic design approaches that prioritise patient-centred methodological decisions. This will help expand the range of potential benefits (i.e., across multiple symptoms/side effects), as well as translational applications. Further research is needed to personalise cannabinoid treatment and determine the optimal products, self-titration/dosing schedules, formulations, and administration methods to meet individual patient goals. Additional research is required to determine the effects of individual endocannabinoid system (ECS) expression and the "entourage effect" on cannabinoid effectiveness and safety. More research is required on outcome assessment, particularly the use of patient-reported outcome measures (PROMs), the effect of response-shift, and strategies to improve PROM implementation to minimise participant burden. These findings underscore the need to establish guidelines to ensure that cannabinoid trials reflect real-world supportive oncology settings. This systematic review offers recommendations to support the translation of cannabinoid research findings into clinical practice.

Thesis Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

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Publications and presentations arising from this thesis

Publications

Wardill HR, Wooley LT, Bellas OM, **Cao K**, Cross CB, van Dyk M, Kichenadasse G, Bowen JM, Zannettino ACW, Shakib S, Crawford GB, Boublik J, Davis MM, Smid SD, Price TJ. Supporting gut health with medicinal cannabis in people with advanced cancer: potential benefits and challenges. Br J Cancer. 2024;130:19-30.

Manuscripts in progress arising from this thesis

Cao K, Bellas O, Cross C, Morcom C, Salter A, Stanhope J, Wardill HR. Cannabinoids for cancer-treatment related symptoms and side effects: A systematic review investigating the interplay between clinical trial design and outcomes.

Bellas OM*, **Cao K***, Bowen J, Smid S, Shakib S, Crawford G, Zannettino A, Kichenadasse G, Boublik J, Louise J, Marker J, Cambareri B, Price T, Wardill HR. Medicinal cannabis (CBD/THC) for symptoms and side effects of chemotherapy in people with cancer: protocol for a phase II randomised double-blind placebo-controlled trial.

*Contributed equally to this work.

Additional related manuscripts in progress

Authors	Title	Contribution
Abdalla-Aslan R, Bonomo P, Keefe D, Blijlevens N, **Cao K**, Cheung YT, Fregnani ER, Miller R, Raber-Durlacher J, Epstein J, Van Sebille Y, Fontes EK, Kandwal A, Franks EM, Chow E, McCarvell V, Zadik Y, Ottaviani G, Mendes RA, Speksnijder CM, Wardill HR, Bossi P.	Guidance on mucositis assessment from the MASCC Mucositis Study Group: an international Delphi study Submitted to eClinicalMedicine.	Conducted a literature review to identify assessment methods for mucositis, which helped inform the design of the Delphi study. Invited by the Multinational Association on Supportive Cancer care (MASCC).
Morcom C, Al-Qadami G, Bowen JM, **Cao K**, Del Fabbro E, Naito T, Yakota T, Bossi P, Wardill HR.	Mucositis and nutritional consequences in head and neck cancer patients involve biological mechanisms, not just physical limitations.	Worked with the lead author to synthesise evidence linking mucositis and cachexia. Invited by the Supportive Oncology Research Group (SORG).

Conference presentations

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Thesis Explanation

This thesis is a systematic review exploring the interplay between clinical trial design characteristics and study outcomes. It follows a traditional structure with four main chapters: Introduction, Methods, Results, and Discussion and Conclusion, in addition to a complete reference list.

The thesis also includes four appendices:

- **Appendix 1:** The registered PROSPERO protocol for the systematic review.
- **Appendix 2:** Individual risk of bias assessments for all included studies (N = 87).
- **Appendix 3:** Wardill HR, Wooley LT, Bellas OM, **Cao K**, Cross CB, van Dyk M, Kichenadasse G, Bowen JM, Zannettino ACW, Shakib S, Crawford GB, Boublik J, Davis MM, Smid SD, Price TJ. Supporting gut health with medicinal cannabis in people with advanced cancer: potential benefits and challenges. Br J Cancer. 2024;130:19-30.
- **Appendix 4:** Co-first author manuscript of a clinical trial protocol for a Phase II RCT investigating the efficacy of CBD/THC in mitigating symptom burden in people with cancer (The CANCAN Trial).

Nomenclature

This thesis contains variations in terminology, which reflects the lack of clear naming conventions for cannabinoid-based interventions and cancer treatment-related symptoms. The following list aims to provide clarity on the common terms used in this thesis.

Cannabis and cannabinoid-specific terminology:

Cannabis (or "marijuana" or "whole extract cannabis"): Any substance derived from the *Cannabis* genus, whether obtained legally through prescription or illicit means. Cannabis contains active compounds called cannabinoids, as well as other bioactive components such as flavonoids, and terpenes. In this thesis, "cannabis" refers specifically to botanical whole extracts that include these various plant-derived components, rather than cannabinoid isolates. Cannabis will be most commonly used to refer to recreational or illegally obtained cannabis.

Cannabinoids (or "exogenous cannabinoids" or "phytocannabinoids"): Group of exogenous compounds in cannabis that interact with the endocannabinoid system. In this thesis, the term "cannabinoids" is used to refer to all *exogenous* cannabinoids, including both plant-derived phytocannabinoids and synthetic derivatives. The main active cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)[(1)]. In this thesis, the term "cannabinoids" will used predominantly because the included studies reported only on THC and CBD, and did not address other bioactive components. The choice to use "cannabinoids" rather than "cannabis" reflects the limitations of the available data rather than a specific focus of this review.

Cannabinoid-based medicine/intervention: Broadly refers to any medications or interventions with cannabinoids (usually THC and/or CBD) as the primary active compound.

Chemotype ("strain" or "chemovar"): Broad classification of cannabis and cannabinoid-based medicines by their predominant cannabinoid. There are three types: THC-dominant (Type 1), mixed THC:CBD (Type 2), and CBD-dominant (Type 3). Chemotypes differ from chemovars, which consider 1-2 cannabinoids as well as terpene profiles.

'Entourage effect': A popular theory suggesting that the less-studied compounds in full-spectrum cannabis—such as terpenes, other phytocannabinoids, and flavonoids—may have synergistic interactions with THC and CBD that enhance therapeutic outcomes such as effectiveness and tolerability[2-4].

Endogenous cannabinoids ("endocannabinoids"): Endogenous lipids produced within the body, synthesised on-demand in response to physiological needs, that interact with the endocannabinoid system. The main active endocannabinoids are N-arachidonoylethanolamine (AEA or anandamide) and 2-arachidonoylglycerol (2-AG).

Medicinal cannabis (MC): Legal, regulated, medically prescribed *Cannabis*. For the purposes of this thesis, MC generally refers to whole-extract medically prescribed cannabis.

Synthetic Cannabinoids (or "Synthetic Cannabis"): A class of lab-created compounds that are chemically similar to phytocannabinoids found in cannabis plants. Synthetic analogues of THC have been the most commonly studied (e.g., nabilone and dronabinol). These substances can vary widely in their effects and may differ significantly from natural cannabinoids in their potency and safety profiles.

Terpenes: A group of compounds found in cannabis plants that contribute to their distinctive aroma and flavour. Although not well characterised, terpenes can interact

with the endocannabinoid system and may influence the effects of cannabinoids through the purported ‘entourage effect.’ Each terpene has unique properties and potential therapeutic benefits, though their impact on cannabinoid effectiveness and user experience is still under investigation[2].

Supportive oncology related terminology:

Gut injury (or “mucositis” or “mucotoxicity”): Cytotoxic and inflammatory injury to the intestinal mucosa caused by chemotherapy and/or radiotherapy.

Gut distress: Clusters of multiple symptoms/side effects related to gut injury that interact with each other.

Prophylactic (or “preventative”): used interchangeably, refers to supportive care interventions administered preventatively, prior to symptom occurrence.

Therapeutic: refers to interventions administered as treatment after the symptom has occurred.

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Chapter 1: Introduction

Supportive oncology in clinical practice

Significant advancements in clinical oncology, along with an ageing population, have resulted in more people living with or beyond a cancer diagnosis[5-9]. The most recent global cancer report estimated that there were 20 million new cancer cases worldwide in 2022, and this number is projected to rise to 35 million by 2050[10]. Additionally, the 5-year relative survival rate for all cancers now exceeds 70%[6], with individuals living almost six times longer after a cancer diagnosis compared to 40 years ago[11, 12]. While this improved prognosis is a significant achievement, it has come at a considerable cost, with many cancer survivors burdened by acute and chronic symptoms related to their life-saving treatments[13-18]. More than 30% of cancer survivors experience symptoms that interfere with their daily functioning[19], leading to increased emergency visits and hospitalisations[15, 16, 20, 21], impacting their quality of life (QoL)[5, 19, 20, 22], adherence to anti-cancer treatment[15, 20], and ability to socialise and work[5, 13, 14, 17]. Not only do these factors collectively contribute to psychological distress and financial hardship[5, 12-14, 17], there is increasing evidence that these symptoms negatively impact anti-tumour response and survival[5, 11, 23, 24].

On a global scale, the rising incidence of cancer[6, 8, 10, 25] and the associated healthcare costs[11, 21, 26, 27] continue to contribute to the international burden of cancer care. Accordingly, the focus has now shifted beyond initial treatment and survival towards improving QoL for cancer survivors so that they are not disadvantaged by their disease and its treatment. Consequently, the field of “supportive oncology,” which prioritises

the prevention and management of adverse effects associated with cancer and its treatments, has emerged as an integral part of modern cancer medicine[7, 23].

Although the field of supportive oncology is still relatively new, there have been numerous examples of its successful integration with conventional oncological advancements. For example, the protocolised use of antibiotics has significantly reduced mortality associated with neutropenia from chemotherapy and haematopoietic stem cell transplantation (HSCT), greatly improving survival in people undergoing cancer treatment[28-30]. Similarly, the development of new antiemetic medications has greatly reduced chemotherapy-induced nausea and vomiting (CINV), leading to improved treatment adherence, fewer hospital admissions, fewer chemotherapy deferrals, and better overall survival[23]. Indeed, the American Society of Clinical Oncology (ASCO) has recognised antiemetics as one of the 'five best advances in modern oncology'[23]. However, despite these accomplishments, the provision of supportive care remains inadequate due to inherent challenges in implementing evidence-based care and historical perceptions that regard it as optional, rather than an essential requirement.

Limitations of current supportive care approaches

Despite the increasing recognition of supportive oncology as an emerging priority, its implementation remains fragmented, inconsistent, and sometimes non-existent[7]. A major challenge is that many supportive care interventions, such as intravenous (i.v.) antibiotics or total parenteral nutrition, are limited to the inpatient setting. However, in the modern world, anti-cancer therapies are increasingly being administered in an outpatient setting, or even at home[31, 32]. This poses a challenge because symptoms that arise between clinic appointments are often only detected if they have become severe

enough to require a visit to the emergency department. This reactive approach to supportive care allows symptoms to escalate in severity, potentially requiring intensive intervention, hospitalisation[17], or modifications to curative treatment that can affect survival[33, 34]. Therefore, current recommendations encourage proactive and early supportive care[11, 23], with evidence suggesting that *prophylactic* intervention may reduce symptom severity, improve QoL and survival[22, 35-37].

In addition to the challenges of providing supportive care in an increasingly decentralised setting, supportive care interventions also have inherent flaws; many are undermined by their own side effects or fail to address underlying mechanisms. For example, loperamide, which is recommended for managing chemotherapy-induced diarrhoea, can cause constipation, dizziness, pain, and vomiting[20]. Similarly, while antibiotics are recognised for their benefits in immunocompromised patients, they are increasingly understood to have a range of detrimental effects, including transplant complications such as graft-versus-host disease (GvHD), slower immune reconstitution, higher rates of relapse, and the emergence of antibiotic-resistant microbes[30, 38].

Another major shortcoming is the highly compartmentalised approach to symptom control, where individual symptoms are managed separately. This siloed approach not only results in fragmented care but also fails to recognise the growing evidence suggesting that symptoms related to cancer treatment are interconnected. This concept is supported by the common observation of "symptom clusters," where multiple symptoms co-occur and self-perpetuate, presumably due to common underlying mechanisms related to direct cytotoxic injury, inflammation, and microbial dysbiosis[7, 39-41]. Despite this knowledge, the vast majority of supportive care strategies focus on addressing single symptoms in isolation[42-46]. This reductionist approach has resulted in

over 80% of cancer survivors reporting polypharmacy (taking 5 or more medications concurrently), which is associated with confusion, non-adherence, significant financial and administrative burden, and a higher risk of death and hospitalisation[47-50]. Accordingly, there is growing consensus towards prioritising supportive care strategies that acknowledge a "systems biology" approach to target common mechanisms across multiple symptoms, to ultimately provide broad and meaningful benefits to the patient.

Cannabinoids in supportive oncology

In recent years, changes in international regulations surrounding cannabis access have sparked increased public and scientific interest for its potential role in medicine. Cannabinoids, derived from plants in the *Cannabis* genus, have been used for both medical and recreational purposes for over 3000 years. The cannabis plant is pharmacologically complex, containing over 400 bioactive compounds, including more than 100 cannabinoids, terpenes, and flavonoids. Two main cannabinoids, Delta(9)-tetrahydrocannabinol (THC) and cannabidiol (CBD), have been the focus of medical research[51, 52]. As such, cannabis is classified into three main *chemotypes:* THC-dominant, CBD-dominant, and mixed THC:CBD[52]. Limited research has been conducted on other components; their effects are not well understood, and their presence is often unreported[2, 51]. Therefore, current research and manufacturing practices only enable discussion of cannabinoid-based medicines at the level of THC and CBD[52].

The endocannabinoid system

Cannabinoids exert their effects through the endocannabinoid system (ECS), a widespread network composed of cannabinoid receptors, ligands, transporters, and

enzymes. The ECS is a sophisticated and complex signalling network that spans multiple organ systems, including the nervous, cardiovascular, endocrine, and immune systems[39, 51, 53, 54]. The extensive distribution of the ECS may explain the widespread effects of cannabinoids. Evidence suggests that the ECS plays a crucial role in central nervous system development, synaptic plasticity, and the maintenance of cognitive, behavioural, and physiological functions[39, 53, 55]. These diverse mechanisms are mediated by endogenous cannabinoids ("endocannabinoids"), which are naturally synthesised from membrane lipids in response to physiological demands[53, 55]. The main known endocannabinoids are N-arachidonoylethanolamine (AEA or anandamide) and 2-arachidonoylglycerol (2-AG). These endocannabinoids interact with a wide range of cannabinoid receptors, including G-protein coupled receptors, transient receptor potential channels (TRPs), and peroxisome proliferator-activated receptors (PPARs)[39, 53, 55]. The most well-researched cannabinoid receptors are CB1 (CNR1) and CB2 (CNR2) G-protein coupled receptors. CNR1 receptors are highly abundant in the central and peripheral nervous system[56], and are involved in motor function, cognition and memory, pain, and nausea and vomiting[39, 57-60]. CNR2 is less well-characterised, but emerging evidence suggests that it is mainly expressed within the immune system and sensory nerve terminals and microglia in the brain, and is involved in immunomodulatory and anti-inflammatory actions[61, 62].

Given the broad range of cells that express cannabinoid receptors, the ECS is involved in many crucial functions related to the symptoms and side effects of cancer treatment. The ECS is associated with mood, anxiety, cognition, appetite, sleep, and pain, all of which are well-documented to be negatively affected by chemotherapy[7, 23, 39, 56, 63, 64]. Emerging evidence suggests that the ECS has the potential to modulate gastrointestinal inflammation[65-68], mucosal defences[65], gut microbiota[66, 67], gastric motility[65-68],

nausea and vomiting[63], and nociceptive processing[64], with abundant expression of CNR1 and CNR2 receptors in biochemical pathways and organ systems associated with these functions[39]. Furthermore, the immunomodulatory capacity of the ECS has the potential to target underlying mechanisms for many of these symptoms[39, 53, 55, 61, 62, 65]. It is for these reasons that strategies to modulate the ECS have garnered significant interest for their potential benefits in people with cancer.

People with cancer are self-medicating with cannabinoids

Cannabinoids are gaining popularity in cancer care due to their potential ability to alleviate multiple symptoms through the widespread mechanisms of the ECS[69-80]. THC and CBD have demonstrated varying levels of antiemetic[63], analgesic, anti-inflammatory, psychosocial[64], and appetite-improving properties[81-83], with emerging evidence for their effectiveness in people with cancer treatment-related symptoms[64, 81, 82, 84-91]. Additionally, recent findings suggest that laws allowing recreational and medical cannabis access have been linked to a decrease in opioid dispensing among adults undergoing cancer treatment[91, 92].

Globally, many people with cancer report self-medicating with cannabinoids to control their symptoms without appropriate, evidence-based guidance[76-78, 93]. Indeed, although 9-40% of oncology patients report using medicinal cannabinoids, less than 30% discuss this with their healthcare provider[69-74, 94]. Equally concerning is that even though 74% of people with cancer would prefer to seek information about cannabinoids from their healthcare provider[72], fewer than 30% of these providers report having sufficient knowledge to provide recommendations[95-97]. This gap in clinical guidance is primarily attributed to the contradictory and insufficient evidence base for cannabinoids[98].

Lack of conclusive evidence for cannabinoids

Numerous systematic reviews have evaluated the effectiveness of cannabinoids for managing CINV[99-103], cancer-related pain[102-106], sleep difficulties[102, 103, 107, 108], cancer anorexia-cachexia[101], QoL[109], psychosocial symptoms[109, 110], as well as its safety in people with cancer[103, 111]. However, despite the enthusiasm for potential benefits, the prevailing consensus is that these systematic reviews and guidelines were unable to form conclusive recommendations due to the heterogeneity between study designs. The inconsistent evidence base likely reflects the inherent challenges involved in conducting research using cannabinoids, particularly in the complex setting of supportive oncology.

Barriers in conducting cannabinoid research

Cannabinoid pharmacology

The variability in the cultivation, composition, products, chemotypes, formulations, and pharmaceutical processing of cannabinoids can impact their pharmacology, thus the results observed in a clinical trial for one cannabinoid-based medicine may not be applicable to others[112, 113]. Moreover, despite the presence of numerous other active compounds within the *Cannabis* plant, there is limited research on their interactions with THC and CBD. While the 'entourage effect' – suggesting that these less-studied compounds may synergistically enhance therapeutic outcomes – has some supporting evidence, much of it is preclinical or anecdotal, and the concept has also faced criticism as a marketing term[2-4, 114]. As such, the impact of these compounds on the effectiveness of conventional cannabinoid-based medicines remains poorly understood[2-4, 114]. Furthermore, achieving blinding in placebo-controlled trials presents

a significant obstacle due to the distinctive psychoactive effects associated with THC[113].

Medico-legal challenges

Cannabinoids are subject to medico-legal barriers, with access pathways varying by geography and legislation. On a trial conduct level, cannabinoids require various licenses, protections for handling and storage, and sometimes collaborations with relevant regulatory bodies[115]. On a patient level, medicinal cannabis typically require expensive prescriptions for specific indications, alongside stringent regulations for driving and heavy machinery operation that can disrupt everyday activities[39, 116, 117]. These constraints hinder trial participation, and place significant administrative and financial burden outside the trial setting, contributing to patient reliance on unregulated cannabis, and impeding the clinical translation of cannabinoid research[39, 116, 117].

Complexities of supportive care trials

Unlike novel anti-cancer treatment trials, which provide tangible survival benefits, supportive care trials are often poorly prioritised by funders, healthcare professionals, and patients. These trials are often difficult to coordinate, as they involve diverse patient populations united by a common symptom rather than a diagnosis. This introduces variability in treatment regimens, requiring a larger number of participants for statistical power. However, recruitment is challenging, especially in the prophylactic setting where cancer therapy side effects have not yet been experienced by the patient, and sometimes even down-played by their clinician[118], potentially impacting their motivation to participate. Similarly, due to the diversity of treatment side effects and lack of mechanisms to enrich study populations, supportive care trials investigating

prophylactic interventions need to over-recruit to account for participants who do not develop the symptom or side effect of interest.

There are also numerous barriers to trial participation, including logistical challenges related to in-person appointments and driving restrictions, hesitancy to disrupt existing care plans, uncertainty about placebo administration, and concerns about accessing cannabinoids after study completion[39, 115, 116, 119]. Additionally, overly strict eligibility criteria, such as including only patients with advanced diseases refractory to standard care interventions, or excluding patients undergoing active cancer treatment, receiving other lines of supportive care, or participating in other trials, contribute to difficulties in recruitment[119, 120].

Improving clinical translation through consistency: a call for guidelines on conducting cannabinoid trials

The challenges associated with conducting supportive oncology trials, combined with the complexities surrounding cannabinoids, have led to a contradictory body of evidence that is undermined by methodological inconsistencies and flaws. At the trial level, there is significant variation in eligibility criteria, intervention, comparator, and outcome assessments, with study design decisions often inadequately justified. These issues are further compounded by current evidence synthesis approaches. Many systematic reviews focus on specific symptoms rather than drawing evidence from the entire field. Additionally, these reviews often have strict eligibility criteria, focusing on relatively recent mature Phase II/III trials while excluding older and observational studies. Although these older studies are of lower quality and predate CONSORT[121] guidelines, they offer a substantial body of evidence, historical context, and insights

into the evolution of cannabinoid research. While this restrictive approach is necessary for clinical practice guidelines, it overlooks 'bigger picture' evidence and the nuances of trial design, failing to capture their impact on study outcomes. As a result, the use of cannabinoids in supportive cancer care remains unclear and lacks broad applicability. These challenges have led to an extensive yet highly variable evidence base that offers limited utility beyond tightly restricted clinical indications. This highlights the need to reconsider our approaches to cannabinoid research and prioritise key methodological attributes that will generate evidence to impact the day-to-day care of people with cancer.

Before clinicians can make recommendations, it is important to establish the effectiveness and safety of cannabinoids, and importantly, the parameters under which these highly variable products achieve maximum benefit. To address these initial questions, previous research has identified that the following components of study design need to be considered (Figure 1):

a) setting (e.g., convenience for participation[122]);
b) participant characteristics (e.g., participation requirements, health conditions, and social support[117, 122]);
c) cannabinoid product (e.g., administration, dosage, safety, and cost[117, 123-126]; and
d) comparator and outcome selection (e.g. validity and synthesis[127-129] (Figure 1).

While it is recognised that these features significantly impact trial results, there is still a lack of knowledge regarding their specific effects on study outcomes in this context. Therefore, standardising or, at a minimum, acknowledging these features is crucial for improving the reliability, reproducibility, and overall quality of the evidence base for cannabinoids.

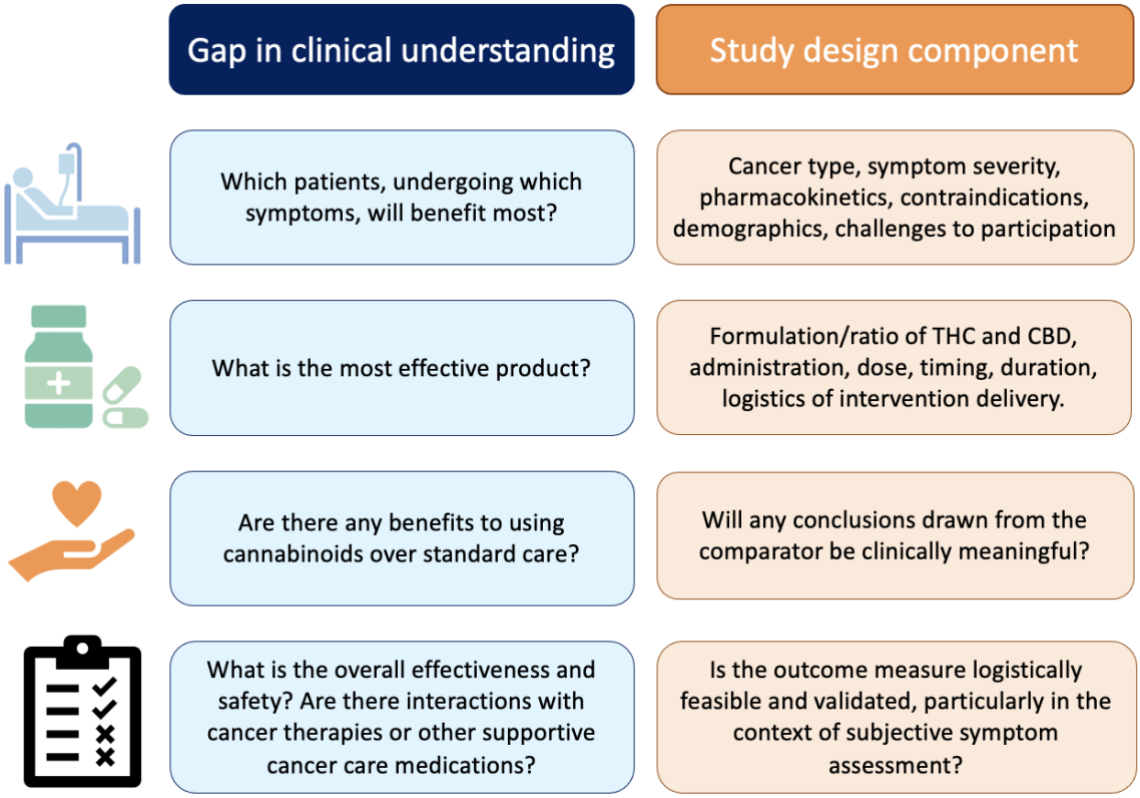


Figure 1: Gap in clinical understanding of cannabinoids, and the corresponding study design component to be considered.

Study design components have been grouped by population, intervention, comparator, and outcome measure (PICO).

Thesis overview and aims

Many people with cancer are self-medicating with cannabinoids to relieve their cancer treatment-related symptoms, yet the evidence base remains inadequate to inform this use. It has been identified that the inability to synthesise evidence is largely due to the heterogeneity in trials, yet cannabinoid research is rapidly evolving without well-established principles to guide study design.

This systematic review aimed to comprehensively synthesise evidence on cannabinoids as a supportive oncology intervention, with a focus on investigating components of trial design and their effects on study outcomes. Importantly, unlike existing reviews, we have:

i) adopted a symptom-agnostic approach, evaluating the evidence across all cancer treatment-related symptoms and side effects,
ii) extracted substantial methodological details to investigate the interplay between trial design and outcomes, and
iii) included relevant older studies, from the earliest available in databases, along with observational studies, to provide a comprehensive synthesis of the evolution of cannabinoid research.

The overarching goal of this work was to comprehensively summarise key findings from existing evidence, drawing lessons from a wide range of studies to inform future research. This broader perspective will help guide clinically meaningful design decisions, contribute to the development of clinical practice guidelines, and facilitate evidence-based cannabinoid use in cancer care.

Chapter 2: Methodology

Protocol statement

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[130] and Cochrane Collaboration recommendations[131].

This methodological chapter was based on the protocol registered on the International prospective register of systematic reviews (PROSPERO): CRD42022373000 (Appendix 1)

Eligibility criteria

Eligibility criteria is as stated in PROSPERO protocol in Appendix 1, with further elaboration in **Table 1.**

Table 1: PICOS (Population, Intervention, Comparator, Outcome, Study design) criteria for inclusion and exclusion of studies.

Criteria	Inclusion	Exclusion
Population	Children and adults with any cancer diagnosis who are undergoing or have completed active systemic anti-cancer therapy (including but not limited to chemotherapy, radiotherapy, immunotherapy, hormonal therapy and/or haematopoietic stem cell transplant).	Studies conducted in people that do not have cancer and/or do not receive anti-cancer therapy. Studies involving participants receiving only localised anti-cancer therapies that do not have systemic drug/radiation-induced toxicities (e.g., surgery only).
Intervention	Any form of cannabinoid intervention obtained in any manner, including all cannabinoids, compounds, isolates, ratios, formulations, doses, and routes of administration.	Studies where cannabinoids were not the primary intervention.
Comparator	Placebo, no cannabinoids, standard care, active pharmacological comparator, previous experiences to active comparator (where data were available for comparison), historical control or baseline before cannabinoid intervention (pre-post studies). Studies comparing different cannabinoid formulations (e.g., THC vs CBD) were also considered.	Studies without a control or comparator.
Outcome	Primary outcome must be an anti-cancer treatment-related symptom or side effect (including but not limited to, quality of life, pain, nausea and vomiting, anorexia/loss of appetite, cachexia, diarrhoea, oral mucositis, sleep disturbances, depression, anxiety, and adverse effects). Secondary outcomes assessed included tumour response, progression-free survival, and overall survival.	Studies with primary outcome focused on anti-tumour response, pharmacokinetics, or physician perceptions on cannabinoids. Studies focused on describing demographic characteristics without clinical outcomes. Studies not investigating the effect of cannabinoids on cancer treatment-related symptoms.
Study Design	Primary research in humans with a comparison group or a pre-post study design conducted in any setting. Randomised controlled trials (RCT), non-randomised clinical trials, pseudorandomised controlled trials, comparative studies with and without concurrent controls (e.g. case-control, prospective and retrospective cohort studies, historical controls, interrupted time series without a parallel control group) and case series studies were included. Studies must also have been published in full-text, in English language, and peer-reviewed.	Preclinical studies in animals and/or cells. Secondary research (reviews, editorials, errata, and commentaries), and case reports. Unpublished clinical trial protocols, duplicate studies, and/or conference or poster abstracts were excluded.

Search strategy and sources

Six electronic databases were searched from inception of database to January 25, 2023: MEDLINE (Ovid), PubMed, Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science Core Collection. An updated manual search in September 2023 reviewed the reference and citation lists from all included studies and pre-specified systematic reviews[101, 102, 104, 105, 132] through PubMed, Scopus, and Web of Science Core collection. There were no language or time restrictions for the search; however, articles that were not published with an English translation were manually excluded. Search strategies were designed to be broad and inclusive of all potentially relevant studies, thus search terms only included terms relating to the intervention, cannabis, and the condition being studied, cancer. We utilised a combination of subject headings (MeSH and Emtree terms) and free text. The full search strategy with search strings can be found in Appendix 1, Search Strategy. For publications that included updates, the most recent data were included.

Selection process

Search results were imported into Covidence Systematic Review management software. All stages of study screening and selection were conducted independently by two reviewers, with any uncertainty resolved through discussion, and a third reviewer consulted where consensus was not reached.

Following removal of duplicates, titles and abstracts were independently reviewed by K.C (all articles), C.C (13,303 articles) and C.M (2000 articles) against eligibility criteria. Abstracts with unclear information were included for full-text review. Full-text articles were independently reviewed by K.C (all articles), H.W (121 articles) and O.B.

(109 articles) against the same criteria. For articles containing only protocols, conference articles, or an abstract, the primary full text was sought. Authors were not contacted to retrieve full texts when they were not available, primarily due to the age of most studies. O.B manually searched all reference lists of initially included studies, and K.C manually searched all citation lists. K.C reviewed all articles to confirm inclusion or exclusion.

Data collection process

A pre-specified electronic data extraction table, following PRISMA guidelines and Cochrane Collaboration's Risk of Bias (RoB-2) tool, was developed to extract:

(1) Citation details (author, title, year, country)
(2) Study details (duration, aim, number of sites, study design, sample size)
(3) Participant information (cancer details, anti-cancer treatment details, demographics)
(4) Intervention specifications (type of cannabinoid, chemotype, supplier, timing, ratio, formulation, administration, dosing schedule, frequency, duration)
(5) Comparators (control group details, active comparator formulation, administration, dose, duration)
(6) Study outcomes (clinical context/symptom, measurement tools, statistical comparative approach, relative effect of cannabinoids, direction of effect, confidence intervals, p-values, tumour response, survival), and
(7) Cochrane RoB-2 measures.

K.C, O.B and A.S pilot tested the data extraction table with 6 articles. Data from full text articles were extracted by author K.C (all articles), with a second review by authors A.S. and H.W. Where there were discrepancies, A.S., H.W., and K.C. met to discuss the data and agree on a final decision.

Risk of bias assessment

Cochrane Risk of Bias 2 (RoB 2)

The risk of bias for each study was assessed using the RoB 2 Excel tool[133]. Domains for assessment included bias arising from:

(1) Randomisation process
(2) Deviations from intended interventions
(3) Missing outcome data
(4) Measurement of the outcome(s)
(5) Selection of the reported result, and
(6) Overall risk of bias

Criteria for *low*, *some concerns*, and *high* RoB followed the Cochrane Handbook for Systematic Reviews and algorithm suggested by the Excel Tool[133]. If at least one of the domains was rated as high, the study was considered to have a high risk of bias. If all domains were judged as low, the study was considered to have a low risk of bias. RoB 2 was used to assess all studies, regardless of study design, to ensure a uniform assessment of bias. RoB was assessed by K.C (all articles), with second review by A.S. Finally, K.C reviewed all RoB assessments to confirm accuracy.

National Health and Medical Research Council (NHMRC) Hierarchy of Evidence

Study designs were also allocated to the NHMRC Hierarchy of Evidence[134, 135]. Assessments were performed by K.C (all articles), with second review by A.S, H.W., and J.S.

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)

Although assessment of the certainty of the overall evidence using the GRADE approach[131] was specified in the protocol (Appendix 1), this was not within the scope of this thesis due to significant heterogeneity in data and time constraints of candidature, but shall be implemented prior to publication.

Extraction synthesis decisions

1. Study design allocation

Studies were categorised based on the design reported in their titles or main body. If this was unclear, studies were assigned into categories based on definitions from the NHMRC Global Health Evidence Evaluation Framework[134, 135]. These included:

(1) Randomised Controlled Trial (RCT): Prospective trials where participants were randomly assigned to either an intervention or control group, with outcomes compared between groups[134, 135]. Subcategories included parallel and cross-over RCTs.
(2) Pseudorandomised Controlled Trial (PRCT): Trials where participants were allocated to intervention or control groups using a pseudorandom method[134].
(3) Comparative study *with* concurrent controls. Studies in this category included: cohort studies and case-control studies, where observational studies compared outcomes between cannabinoid users and cannabinoid non-users.
(4) Comparative study *without* concurrent controls. Studies in this category included:
    a. Historical control studies: where control group outcomes were measured prior to the intervention group.
    b. Interrupted time series *without* a parallel control group: studies where the outcome was assessed over multiple time points before and after participants have started cannabinoid intervention.

(5) Case series: were defined as studies with single group of people treated with cannabinoid intervention. There were two subcategories of case series:
    c. Pre-test/post-test outcomes: where outcomes were compared before and after cannabinoids.
    d. Post-test only outcomes: where outcomes were measured only after cannabinoids. In this context of this thesis, we only included post-test studies comparing cannabinoids to 'previous experiences with active comparator' before study initiation that had robust data available for comparison, which was a common study design for CINV.
(6) Cross-sectional study: where participants were assessed at a particular 'cross-section' in time.

2. Sample size

Total sample sizes were defined as the number of officially enrolled participants meeting eligibility criteria and providing consent, inclusive of dropouts.

3. Population

Cancer type

Study populations were categorised based on the primary cancer diagnosis of the participant population reported in the title or methods of main body. Homogeneous cohorts included glioblastoma, lung, bone, and head and neck cancers. For synthesis purposes due to outlying single studies, studies focusing on gynaecological and/or testicular cancer were grouped as genitourinary cancer, and studies focusing on gastrointestinal (GI) or colorectal cancers were grouped as GI cancers. Studies with populations described as "various malignancies" were categorised as "multiple cancer diagnoses, heterogeneous cohort." Studies lacking specific details on cancer diagnoses, but with confirmed cancer presence, were categorised as "unreported" (studies with ambiguous cancer status were excluded).

For further analyses, these specific cancer diagnoses were aggregated into broad diagnostic tumour types. These groups were:

(1) Solid tumour
(2) Haematological cancer
(3) Mixed.

Cancer treatment

Studies with participants undergoing combined chemotherapy and/or radiotherapy within the same population were classified as chemoradiotherapy. Populations either a) undergoing three or more types of cancer therapy within the same cohort, or b) part of a registry/observational/real-life cohort, were categorised as "heterogeneous" if participants were explicitly stated to be undergoing treatment. Studies that lacked explicit reporting, were classified as "unclear."

4. Intervention

The intervention (i.e. the reported cannabinoid under investigation) was classified into the following chemotypes:

(1) THC-dominant: containing less than 5% CBD[51]
(2) CBD-dominant: containing less than 5% THC[51]
(3) Mixed THC:CBD: balanced cannabinoid composition, where dosage for both THC and CBD were clearly reported.

4a. Dosing schedule

Extracted dosing schedule details included: timing of administration (relative to symptom occurrence), single dose concentration value, dose units, frequency, and duration on cannabinoids.

Efforts were made to synthesise repeated dosing as dose per day. Several studies administered a range of doses within a group or individual. In these cases, dosing schedules were averaged for synthesis purposes. For example, if the reported dosing

was 1-2 mg, 2-3 times per day, for 1-5 days, it was synthesised as 1.5 mg, 2.5 times a day, for 2.5 days. For interventions involving mixed products (e.g., THC and CBD in different doses but *within* the same product), we reported doses of THC and CBD separately. For studies where the dosing schedule was based on weight, we reported the average dose of all classes combined, per the reported unit. For example, if the dose was specified as "levonantradol in single doses of 0.5mg (weight less than 50 kg) to 1mg (weight more than 50kg)," we reported dose as 0.75mg. For studies with heterogeneous populations with varying types of cancer treatment where the number of days was unclear and the duration could not be quantified, we extracted the information qualitatively as reported (e.g. "for as long as antiemetic coverage required for a particular regimen") and excluded these studies from quantitative analysis.

4b. Titrations

For studies with a titrated dosing schedule, the minimum and maximum dosages were extracted separately. The dose concentration was extracted as the median interquartile range (IQR) as reported, and averages were calculated for any other parameters reported as a range. For example, Grimison[84] reported an initial dose of 2.5mg, a standard dose of 5mg, and a maximum dose of 10mg. Both minimum and maximum doses were extracted, as well as the synthesised dose, that is, the reported standard dose of 5mg.

5. Primary outcome

The primary outcome was defined as the primary outcome *explicitly stated* in the primary paper. In cases where the primary outcome was unclear, or if two primary outcomes were simultaneously reported, the primary outcome from the trial protocol or registration was extracted. If trial protocol retrieval was not feasible, or if two primary outcomes were reported, the first reported data were extracted. For instances where no primary outcome was explicitly stated, the measurement and outcome most closely

aligning with the title and aim of the study were extracted. If this was still unclear, and the study had multiple measures for the same symptom/outcome, the first reported data were extracted. Studies that required inferences to decide on the primary outcome were noted and considered during risk of bias assessments.

5a. Condition-specific decisions

For studies where the primary outcome was a patient-reported outcome measure (PROM) where the specific domain of interest was not specified, we extracted the global or summary domain of the PROM. If this was not feasible, we extracted the domain most closely aligned with title and aim. If neither option was possible, the primary outcome was deemed "not extractable."

Numerous outcome measures were often reported for single symptoms/side effects, reflecting the heterogeneity in methods of assessing cancer treatment-related symptoms. This was particularly the case for studies focusing on nausea and vomiting, with multiple measures for emesis reported, even within the same study. For example, Crawford et al.[136] measured the frequency of vomiting episodes, quantity of emesis, patient-reported nausea, and preference for cannabinoid or active comparator medication as an antiemetic, which was a common approach for most CINV studies. As such, unless a primary outcome measure was explicitly stated, the observed number of vomits was extracted. This decision was made because this measure was the most uniform and consistently reported, with the least variation in assessment.

Studies on nausea and vomiting were grouped together as CINV because all included studies reported them as such, even when separate outcome measures were used. Additionally, we followed the approach of similarly broad systematic reviews[101-103], which also broadly reported on CINV without separating nausea and vomiting.

Studies focusing on cancer anorexia-cachexia and/or chemosensory perception were grouped together. This was because many studies focusing on anorexia-cachexia

initially aimed to measure biometric outcomes (such as weight gain and total caloric intake) in their trial registration but found no significant differences, and instead reported primary outcomes related to chemosensory perception and appetite as their first-reported data in the primary paper. For example, although the primary outcome for Brisbois et al.[81] in the published article was the 'total chemosensory complaints score on day 18', further investigation revealed that their initial registered primary outcome was total caloric intake.

5b. Multiple measures

For studies involving multiple measures comparing cannabinoids and the comparator (both intra-participant and between groups), we extracted the first reported data that allowed for comparison between the cannabinoid and 'no cannabinoid' groups. We adopted this approach to address the many studies that reported significant improvements over time. This enabled consistency in differentiating between participants receiving cannabinoids and those were not, rather than solely capturing changes over time within individuals.

5c. Multiple comparators

For studies with multiple comparators, such as those comparing intervention to both an active comparator arm and a placebo arm, the primary outcome was extracted separately for each comparator.

5d. Direction of cannabinoid effect

While meta-analysis was not feasible in this systematic review, attempts were made to synthesise effect outcomes based on the direction of effect and its significance. The direction of effect was determined by the absolute difference between cannabinoid and comparator, irrespective of size or statistical significance. We adopted this approach with the aim of moving beyond the binary categorisation of trials as 'significantly positive' or otherwise 'negative', and to instead acknowledge the broader continuum of

trial effectiveness[137]. For studies where the values for absolute difference were not reported, cannabinoid effect was reported as "not extractable." Studies with no absolute difference (i.e., cannabinoid and comparator had the same reported value) were categorised as "no effect." Studies that only reported "no significant difference between groups" without presenting values were categorised as "not extractable."

5e. Significance

Studies were considered significant if they reported meeting their statistical threshold and explicitly stated the p-value or z score. For studies that reported a statistical threshold as $p < 0.05$ but did not provide the exact p-value, while clearly stating in the text that results "did not reach statistical significance," we assumed $p > 0.05$. These studies were qualitatively reported as either "non-significant improvement" or "non-significant worsening" (based on the direction of the absolute difference) and were excluded during quantitative analysis as "not extractable." Studies that transparently reported 'non-significant superiority' or 'non-significant worsening' alongside absolute difference values were included in quantitative analysis. Where studies reported both adjusted and unadjusted p-values, we extracted the adjusted p-values.

Based on significance and direction of cannabinoid effect, studies were categorised into 8 groups:

(1) Significantly superior to comparator
(2) Non-significantly superior to comparator
(3) Significance not reported, superior to comparator ("not extractable" during quantitative synthesis)
(4) Significantly worse than comparator
(5) Non-significantly worse than comparator
(6) Significance not reported, worse than comparator ("not extractable" during quantitative synthesis)
(7) No effect
(8) Not extractable.

6. Dropouts

The total number of dropouts was extracted for all studies. Attempts were made to extract dropouts associated with treatment groups (i.e. cannabinoid and comparator arms) when possible, for studies that reported the differentiation. Both the absolute number of dropouts and the proportion of dropouts (dropouts/total sample size*100) were extracted, and where necessary, calculated. For trials with a parallel design, the rate of dropouts for cannabinoids and the comparator were calculated within the respective sample size for each arm, with the denominator being the specific sample size for that arm. For trials with a crossover design where it was clear which arm the dropouts could be attributed to, the total sample size (of the entire study) was divided by 2 and used as the denominator for calculating the percentage of dropouts in each arm. If it was unclear in which arm the dropouts occurred, only the total dropout rate (percentage) was reported, accompanied by "N/A - crossover, dropouts could not be assigned to a specific group." For observational pre/post studies, only the total percentage was reported, and "N/A - observational" for cannabinoid and comparator arms.

Statistical Synthesis

As anticipated by our PROSPERO protocol, meta-analysis was not feasible within the scope of this thesis due to significant heterogeneity in data, thus a narrative synthesis of findings was conducted. This was structured around the type of study design, population, cannabinoid intervention, and cancer treatment-related symptom. Summaries of intervention effects on outcomes of interest were provided for each study, with summary statistics including percentages, range, mean, median, and mode calculated for outcomes when appropriate. Chi-square statistical tests were performed to

determine significant differences between proportions across >2 groups. Fisher's exact test was used to perform single pairwise comparisons in a two-tailed analysis when appropriate. All statistically significant values presented in this thesis were performed using Fisher's exact test. Statistical significance was defined as $p < 0.05$. Data were compared using Stata Statistical Software: Release 18 (College Station, TX: StataCorp LLC) and Prism version 10.0 (GraphPad® Software, San Diego, USA).

Chapter 3: Results

Search results

On January 25, 2023, the initial database search yielded 33,300 records. Following the removal of duplicates, 15,321 studies were screened, and 267 full-text documents were reviewed. In September 2023, the reference and citation lists of the initially included studies and relevant systematic reviews were manually searched[101, 102, 104, 105, 132], identifying an additional 852 records. After de-duplication, 762 studies were screened, 30 full-text studies were assessed, and 20 further publications were included. A total of 87 studies[63, 64, 81-88, 90, 112, 115, 120, 136, 138-207], with 93 separately extracted primary outcomes and 15,773 participants, were included in this systematic review (Figure 2; Table 2).

Excluded studies

In accordance with PRISMA item 16b, 23 studies that initially appeared to meet the inclusion criteria were deemed ineligible for the following reasons:

- Ten studies were excluded as they did not include a comparator[208-217]. These studies were either single-arm interventional studies with complete absence of a comparator or compared nausea and vomiting to “previous experiences” occurring prior to the study. Notably, the latter category of studies did not record quantifiable outcomes, such as vomiting episodes, for meaningful comparison.
- Six studies were ineligible due to their exclusion of people undergoing cancer therapy[218-224]. All 6 studies assessed pain and justified their exclusion with concern that ongoing cancer treatment might confound outcomes.

- Four further studies were excluded because their primary outcomes did not report the impact of cannabinoids on any cancer-treatment related symptoms or side effects[225-229].
- Two studies were excluded because they were not the original paper reporting on main study findings[230, 231].
- One study was excluded due to an ineligible intervention[232]. The cannabinoid nabilone was administered both as the comparator and in combination with dexamethasone.

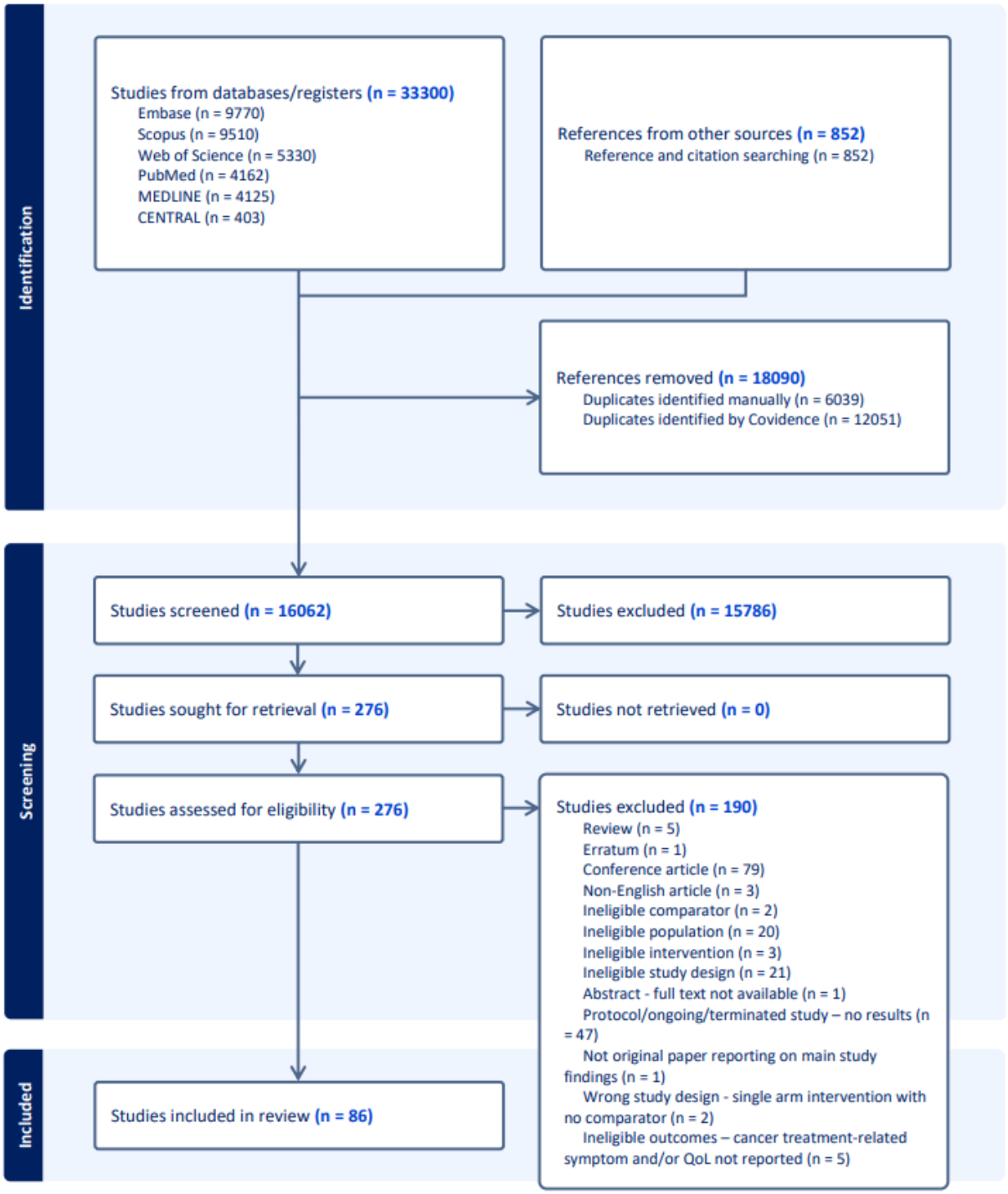


Figure 2: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) flow diagram.

N = for initial search results, manual reference searching, and citation searches have been combined for 'screening' and 'included' stages[130]. N = 86 articles were included, with N = 87 studies because one article reported on two separate studies.

Table 2: Characteristics of studies included in the systematic review (N = 87).

Reporting study type, population details, intervention details, comparators, and outcomes in order according to clinical context (by alphabetical order) and date of publication (oldest to newest). N = 86 articles were included, with N = 87 studies. Ekert 1979[164] was extracted twice as the paper reported on two separate studies. Outcomes extracted separately for multiple comparators were formatted in italics (N = 93 outcomes).

Clinical context	**Study and population characteristics**				**Intervention characteristics**		**Summary of findings**		
Cancer-treatment related symptom	**Ref; Study design; Country**	**Population; N (N_i = cannabinoid intervention N_c = comparator)**	**Cancer; Tumour type**	**Cancer therapy; Treatment status**	**Type of cannabinoid intervention - Timing - Administration route, formulation - Dose per day - Duration**	**Comparator**	**Primary outcome Measurement tool**	**Δ Relative effect of cannabinoids (absolute difference cannabinoids – comparator) Confidence interval P value**	**Significance and direction of cannabinoid effect**
Anorexia/cachexia/chemosensory perception	Jatoi et al., 2002; RCT, Parallel groups; United States	Adults (18+); N = 485 (N_i = 159 dronabinol N_c = 159 megestrol acetate N = 158 combined megestrol acetate + dronabinol)	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemoradiotherapy; Mixed (some active/complete)	Dronabinol - Therapeutic (after symptom occurrence) - Oral, capsules/pills - 5mg/day - Until symptoms resolved or AEs were deemed intolerable	Megestrol acetate	Proportion of patients reporting appetite improvement from baseline at "some point" during study period Assessed by the North Central Cancer Treatment Group questionnaires for appetite and weight Patient-reported outcome	Percentage Δ = -26.00% CI = not reported p = 0.0001	Significantly worse than comparator
Anorexia/cachexia/chemosensory perception	Strasser et al., 2006; RCT, Parallel groups; Germany	Adults (18+); N = 243 (N_i = 95 cannabis extract mixed THC:CBD N_c = 100 THC N_c = 48 placebo)	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Mixed (some active/complete)	THC:CBD - Therapeutic (after symptom occurrence) - Oral, capsules/pills - THC 5 mg/day: CBD 2 mg/day - 6 Weeks	***Natural THC***	*Mean daily appetite change (VAS score) from baseline to week 6 compared to THC* *Assessed via Visual analoque scale (VAS; 0mm worst; 100mm = best)* *Patient-reported outcome*	*Mean Δ = 3.9* *CI = not reported* *p = 0.95*	*Non-significantly superior to comparator*
						Placebo	*Mean daily appetite change compared to placebo*	*Mean Δ = -0.4mm* *CI = not reported* *p = 0.46*	*Non-significantly worse than comparator*
Anorexia/cachexia/chemos	Brisbois et al., 2011;	Adults (18+); N = 46	Multiple cancer diagnoses,	Chemoradiotherapy;	Dronabinol - Therapeutic (after symptom occurrence)	Placebo	Total chemosensory complaints score on day 18	Mean = 0.7 CI = not reported p = 0.23	Non-significantly

ensory perception	RCT, Parallel groups; Canada	(N_i = 24 THC N_c = 22 placebo)	heterogeneous cohort; Solid tumour	Mixed (some active/complete)	- Oral, capsules/pills - 5 mg/day - 18 Days		Measured on Taste and Smell Survey Patient-reported outcome		superior to comparator
Anorexia/cachexia/chemosensory perception	Turcott et al., 2018; RCT, Parallel groups; Mexico	N = 47 (N_i = 22 nabilone N_c = 25 placebo)	Lung; Solid tumour	Chemotherapy; Mixed (some active/complete)	Nabilone - Therapeutic - Oral, capsules/pills - 1 mg/day - 8 weeks The	Placebo	Mean change in appetite from baseline to 8 weeks Measured by the anorexia/cachexia subscale (A/CS) of the Functional Assessment of Anorexia-Cachexia Therapy (FAACT) questionnaire Patient-reported outcome	Mean Δ = 0.33 CI = not reported *p* = 0.93	Non-significantly superior to comparator
Anorexia/cachexia/chemosensory perception	Bar-Sela et al., 2019; Case series with pre-test/post-test outcomes; Israel	Adults (18+); N = 24	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Heterogeneous; Ongoing/active	THC:CBD - Therapeutic (after symptom occurrence) - Oral, capsules/pills - THC 19 mg/day: CBD 1 mg/day - 6 Months	Baseline before cannabinoid (pre-post)	Number of participants with weight increase of ≥10% from baseline to 6 months Weighed by scales and physical examination	3 out of 24 participants CI = not reported *p* = not reported	Not extractable
Anorexia/cachexia/chemosensory perception	Dominiak et al., 2023; Comparative study without concurrent controls, Historical control study; Denmark	Adults (18+); N = 32	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemotherapy; Ongoing/active	CBD - Prophylactic - Oral, oil - 300 - 3 Treatment cycles	Historical data	5% change in Lean Body Mass (LBM) from baseline (before first round of chemotherapy), to after 3 rounds of chemotherapy Bioelectrical impedance analysis (BIA) using the medical Body Composition Analyzer Seca 515/514 Objective quantifiable value	Δ = Not reported CI = not reported p > 0.05 (only reported no significant difference was found in LBM between the two groups)	Not extractable
Chemotherapy induced nausea and vomiting (CINV)	Sallan et al., 1975; RCT, Crossover groups; United States	Adults (18+); N = 22	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 30 mg/m^2 - 1.5 Treatment cycles	Placebo	Proportion of patients with a "positive" response (i.e. complete response of no vomiting, or partial response with at least 50% reduction in vomiting as compared to placebo after the same chemotherapy) Self-administered questionnaire and compared with nurses' notes Patient-reported outcome	Percentage Δ = 80.00% CI = not reported p < 0.001	Significantly superior to comparator
CINV	Chang et al., 1979; RCT, Crossover groups;	Adults & young adults; N = 15	Bone; Solid tumour	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 50 mg/m^2 per day - 3 Treatment cycles	Placebo	Total number of vomiting and retching episodes during first 24h of chemotherapy Observed by nursing staff and patient	Sum all episodes among all patients Δ = -437 CI = not reported < 0.02	Significantly superior to comparator

	United States								
CINV	Frytak et al., 1979; RCT, Parallel groups; United States	Adults (18+); N = 117 (N_t = 38 THC N_c = 41 prochlorperazine N_c = 37 placebo)	Gastrointestinal; Solid tumour	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 45 mg/day - 1 Treatment cycles	***Prochlorperazine***	*Proportion of patients with no nausea or vomiting on day 1 chemotherapy compared to prochlorperazine* *Observed by patients, recorded by physicians*	*Percentage Δ = 0.00%* *CI = not reported* *p > 0.05*	*No effect*
						Placebo	*Proportion of patients with no nausea or vomiting on day 1 chemotherapy compared to placebo*	*Percentage Δ = 23%* *CI = not reported* *p = 0.05*	*Non-significantly superior to comparator*
CINV	Herman et al., 1979; RCT, Crossover groups; United States	All (adults, young adults & paediatric); N = 152	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 6 mg/day - 1 Treatment cycles	Prochlorperazine	Proportion of patients with a partial response (reduction of 50% or more in duration or severity of nausea and number of vomiting episodes compared to previous courses of identical chemotherapy) Recorded in questionnaire self-rating nausea and vomiting severity and frequency Patient-reported outcome	Percentage Δ = 40.00% CI = not reported $p < 0.01$	Significantly superior to comparator
CINV	Ekert et al., 1979; RCT, Other/unclear; Australia	Paediatric (~0-14 years); N = 19	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 50 mg/m^2/day - 1 Treatment cycles	Metoclopramide	Total number of vomiting episodes Observed and recorded by patients and family on questionnaire	Total number Δ = -9 CI = not reported $p = 0.01$	Significantly superior to comparator
CINV	Ekert et al., 1979; RCT, Crossover groups; Australia	Paediatric (~0-14 years); N = 14	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 50 mg/m^2/day - 1 Treatment cycles	Prochlorperazine	Total number of vomiting episodes Observed and recorded by patients and family on questionnaire	Δ = Not extractable CI = not reported $p < 0.001$	Significantly superior to comparator
CINV	Kluin-Neleman et al., 1979; RCT, Crossover groups; Netherlands	Adults (18+); N = 11	Lymphoma; Haematologic cancer	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 30mg/m^2/day on days 1 and 8 of chemotherapy - 3 Treatment cycles	Placebo	Mean combined nausea and vomiting score on day 8 of chemotherapy Patient scored nausea and vomiting 'improvement' from 1-5, with 1 as no improvement, and 5 as complete improvement Patient-reported outcome	Mean Δ = 2.26 CI = not reported < 0.01	Significantly superior to comparator

CINV	Colls et al., 1980; RCT, Crossover groups; New Zealand	Adults (18+); N = 35	Unreported; Unreported	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 12 mg/0.33m^2 / day - 2 Treatment cycles	***Metoclopramide***	*Mean nausea/vomiting severity score compared to metoclopramide* *Assessed by staff after each chemotherapy cycle* *Clinician-reported outcome*	*Mean Δ = 0.27* *CI = not reported* *p > 0.05*	*Non-significantly worse than comparator*
						Thiethylperazine	*Mean nausea/vomiting severity score compared to thiethylperazine (TEP)*	*Mean = -0.06* *CI = not reported* *p > 0.05*	*Non-significantly superior to comparator*
CINV	Garb et al., 1980; RCT, Crossover groups; United States	Unreported; N = 22	Unreported; Unreported	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 40 mg/day - 2 Treatment cycles	Placebo	Number of participants experiencing better antiemetic effects on THC than placebo Subjective assessment by staff physician and student as “better on THC” “same on THC as on placebo” or “better on placebo” Clinician-reported outcome	Number of participants Δ = 6 CI = not reported *p* < 0.05	Significantly superior to comparator
CINV	Lucas et al., 1980; Case series with post-test only; United States	Adults (18+); N = 57	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, oil - 30mg/m^2/day - 2 Treatment cycles	Previous experience to another medication	Proportion of patients with a ‘complete response’ (no nausea and vomiting) to THC Observed during chemotherapy and patients interviewed after	Δ = Not extractable CI = not reported *p* = not reported	Not extractable
CINV	Sallan et al., 1980; RCT, Crossover groups; United States	All (adults, young adults & paediatric); N = 84	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 30 mg/m^2 - 1.5 Treatment cycles	Prochlorperazine	Proportion of patients with “complete response” to THC, i.e. no nausea and vomiting Assessed via self-graded questionnaire and compared with nurses’ notes Patient-reported outcome	Percentage Δ = 25.00% CI = not reported *p* = not reported	Significance not reported, superior to comparator
CINV	Steele et al., 1980; RCT, Crossover groups; United States	Adults (18+); N = 55	Unreported; Unreported	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 4 mg/day - 1 Treatment cycles	Prochlorperazine	Median frequency of vomiting episodes Observed, patients recorded on daily questionnaires	Median Δ = -5.5 CI = not reported *p* = not reported	Significance not reported, superior to comparator
CINV	Cronin et al., 1981;	All (adults, young adults & paediatric); N = 31	Unreported; Unreported	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 3.5 mg/day - 1 Treatment cycles	Previous experience to another medication	Achievement of “complete or partial antiemetic response” within 24-hour chemotherapy treatment course	Δ = Not extractable CI = not reported *p* = not reported	Not extractable

	Case series with post-test only; United States						Graded by investigator as complete response (no nausea or vomiting), partial response (1-10 episodes of vomiting), no response 9 > 10 episodes vomiting) Clinician-reported outcome		
CINV	Einhorn et al., 1981; RCT, Crossover groups; United States	All (adults, young adults & paediatric); N = 80	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 8 mg/day - 1 Treatment cycles	Prochlorperazine	Mean number of vomiting episodes during first 24h (day 1) chemotherapy Observed and recorded on a case report by patients	Mean Δ = -3.25 CI = not reported $p < 0.001$	Significantly superior to comparator
CINV	Orr et al., 1981; RCT, Crossover groups; United States	Adults (18+); N = 79	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 28 mg/m^2/day - 1 Treatment cycles	***Prochlorperazine***	*Total number of vomiting episodes compared to prochlorperazine* *Observed by patient and recorded in questionnaire. Telephone follow-up by staff*	*Total number episodes (among all participants) Δ = -32* *CI = not reported* *p = not reported*	*Significance not reported, superior to comparator*
						Placebo	*Total number of vomiting episodes compared to placebo*	*Δ = -35* *CI = not reported* *p = not reported*	*Significance not reported, superior to comparator*
CINV	Shiling et al., 1981; RCT, Crossover groups; United States	Adults (18+); N = 9	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 50 mg/m^2/day - 2 Treatment cycles	Placebo	Total number of vomiting and retching episodes during first 17h of chemotherapy Observed by nursing staff	Sum total vomits (all participants) Δ = -146 CI = not reported $p > 0.05$	Non-significantly superior to comparator
CINV	Diasio et al., 1981; Case series with post-test only; United States	Adults (18+); N = 27	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Oral, capsules/pills - 3 dosage arms: 2.25 mg/day, 4.5 mg/day, 6.75 mg/day - 1 Treatment cycles	Previous experience to another medication	Proportion of participants graded as complete, partial or no response. (Complete response = no vomiting during period on levonantradol (compared to their previous period on a standard antiemetic regimen Partial response = reduction of at least 50% in episodes of vomiting compared to previous chemotherapy course No response = no decrease or less than 50% reduction in vomiting compared with identical previous course of chemotherapy)	Δ = Not extractable CI = not reported p = not reported	Not extractable

							Observed episodes of vomiting recorded on questionnaire		
CINV	Heim et al., 1981; Case series with post-test only; Germany	Unreported; N = 12	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 3 mg/day - 1 Treatment cycles	Previous experience to another medication	Total number of vomiting episodes Observed, questionnaire completed by patient during interview with investigator	Sum of episodes among all patients Δ = -82 CI = not reported *p* = not reported	Significance not reported, superior to comparator
CINV	Laszlo et al., 1981; Case series with post-test only; United States	Adults (18+); N = 35	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Oral, capsules/pills - 4 dosage groups: 2.0 mg/day, 4.0 mg/day, 6.0 mg/day, 8.0 mg/day - Variable number of chemotherapy treatments, depending on patient.	Previous experience to another medication	Antiemetic response compared to prior courses of chemotherapy with standard antiemetics Nausea and vomiting graded via activity interference and observed number of vomiting episodes, then categorised into antiemetic response (compete response = no nausea vomiting, partial response = at least 50% reduction, no response = < 50% reduction)	Δ = Not extractable CI = not reported *p* = not reported	Not extractable
CINV	Cone et al., 1982; Case series with pre-test/post-test outcomes; United States	Adults (18+); N = 52	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 3 mg/day - 3 Days	Previous experience to another medication	Self-graded antiemetic response to nabilone (excellent, good, fair, poor) Self-reported experience Patient-reported outcome	Not extractable	Not extractable
CINV	Johansson et al., 1982; RCT, Crossover groups; Finland	Adults (18+); N = 27	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, Unreported - 4 mg/day - 1 Treatment cycles	Prochlorperazine	Mean number of vomiting episodes over 24h (1 day) chemotherapy Observed and recorded by patients on daily questionnaire	Mean Δ = -20.3 CI = not reported p < 0.001	Significantly superior to comparator
CINV	Jones et al., 1982; RCT, Crossover groups; United States	Adults (18+); N = 54	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Unreported - 4 mg/day - 1 Treatment cycles	Placebo	Mean number of vomiting episodes Observed and recorded by trial staff	Mean Δ = -11.6 CI = not reported p < 0.001	Significantly superior to comparator
CINV	Kenny et al., 1982;	Adults (18+); N = 21	Multiple cancer diagnoses,	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection	Previous experience to	Number of patients with a > 50% reduction in number of emetic episodes	Δ = 14 out of 21 patients reported > 50% reduction in emetic episodes	Not extractable

	Case series with post-test only; England		heterogeneous cohort; Mixed		- 1.5 mg/day - 1 Treatment cycles	another medication	Number of emetic episodes reported by patients, then compared to prior experience Patient-reported outcome	CI = not reported Not extractable	
CINV	Levitt et al., 1982; RCT, Crossover groups; Canada	Adults (18+); N = 58	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Unreported - 6 mg/day - 1 Treatment cycles	Placebo	Mean number of vomiting episodes Recorded by patients	Mean Δ = -4.5 CI = not reported $p < 0.001$	Significantly superior to comparator
CINV	Ungerleider et al., 1982; RCT, Crossover groups; United States	Adults (18+); N = 214	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, Unreported - 40 mg/m^2/day - 1 Treatment cycles	Prochlorperazine	Mean self-rated nausea and vomiting severity score Patient self-assessed on seven-point scale: 0 no nausea at all, 1 mild nausea, 2 moderate nausea, 3 severe nausea without vomiting or retching, 4 no episodes of vomiting but retching (dry heaves) occurred, 5 one episode vomiting, 6 multiple episodes vomiting Patient-reported outcome	Mean Δ = not reported CI = not reported $p > 0.05$	Not extractable
CINV	Wada et al., 1982; RCT, Crossover groups; United States	Adults (18+); N = 114	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 6 mg/day - 1 Treatment cycles	Placebo	Mean number of vomiting episodes per day of chemotherapy Daily observations for each chemotherapy cycle, patients interviewed.	Mean Δ = -2.89 CI = not reported $p < 0.001$	Significantly superior to comparator
CINV	Ahmedzai . et al., 1983; RCT, Crossover groups; Scotland	Adults (18+ only); N = 34	Lung; Solid tumour	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 2 mg/day - 1 Treatment cycles	Prochlorperazine	Mean emetic symptom score on day 3 of chemotherapy Measured via non-standardised self-rating symptom questionnaire, scored on 0-3 (0 no vomiting, 3 worst). Patient-reported outcome	Mean Δ = -0.6 CI = not reported $p < 0.001$	Significantly superior to comparator
CINV	Gerhartz et al., 1983; Comparative study without concurrent controls, Interrupted time series	Adults (18+); N = 20	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 1.125 mg/day - 1 Treatment cycles	Previous experience to another medication	Total number of vomiting episodes Observed by patients	Sum of vomiting episodes Δ = 35 CI = not reported $p > 0.05$	Non-significantly superior to comparator

	without a parallel control group; Germany								
CINV	Hutcheon et al., 1983; RCT, Parallel groups; Scotland	Adults & young adults; N = 108 (N_i = 27 levonantradol 0.5mg N_i = 28 levonantradol 0.75 mg N_i = 26 levonantradol 1.0 mg N_c = 27 chlorpromazine)	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 3 dosage groups: 2 mg/day, 3 mg/day, 4 mg/day - 1 Treatment cycles	Chlorpromazine	*Number of patients experiencing complete relief (no vomiting) in patients receiving **0.5mg** levonantradol* *Nausea assessed on "ordered category scales" and incidence of vomiting was recorded* *Patient-recorded outcome*	*Number of patients Δ = 9* *CI = not reported* *p < 0.05*	*Significantly superior to comparator*
							***0.75mg** levonantradol*	*Δ = 0* *CI = not reported* *p = not reported*	
							***1.0mg** levonantradol*	*Δ = -3* *CI = not reported* *p = not reported*	
CINV	Kleinman et al., 1983; RCT, Crossover groups; United States	Adults (18+); N = 16	Unreported; Unreported	Chemotherapy; Ongoing/active	THC - Prophylactic - Unreported, capsules/pills - 45 mg/day - 2 Treatment cycles	Placebo	Total number of chemotherapy cycles (among all participants) accompanied by vomiting Number of vomits recorded by patients in self-administered questionnaire 24h following chemotherapy	Total number of chemotherapy cycles with vomiting Δ = -1 CI = not reported *p* = 0.31	Non-significantly superior to comparator
CINV	Stuart Harris et al., 1983; Case series with post-test only; England	Adults (18+); N = 23	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 3 mg/day - 1 Treatment cycles	Previous experience to another medication	Patient preference for levonantradol over previous antiemetic treatment experience Self-assessment questionnaire Patient-reported outcome	Δ = N = 11 preferred levonantradol, n = 5 preferred previous anti-emetic treatment, n = 6 no preference CI = not reported *p* > 0.05	Non-significantly superior to comparator
CINV	Archer et al., 1983; RCT, Crossover groups; England	Adults (18+); N = 12	Lymphoma; Haematologic cancer	Chemotherapy; Ongoing/active	Nonabine - Prophylactic - Oral, Unreported - 1 x 15mg on days 1 and 8 of chemotherapy - 2 Treatment cycles	Chlorpromazine	Proportion of patients with no vomiting throughout 18-hour period post-chemotherapy Observed and recorded with digital counter	Percentage Δ = -1.00% CI = not reported p > 0.05	Non-significantly worse than comparator

CINV	Heim et al., 1984; RCT, Crossover groups; Germany	Adults (18+); N = 57	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 1.5 mg/day - 1 Treatment cycles	Metoclopramide	Number of vomiting episodes Observed by patient and recorded by interviewer Objective quantifiable value	Sum of vomiting episodes Δ = -161 CI = not reported $p < 0.05$	Significantly superior to comparator
CINV	Niamatali et al., 1984; Case series with post-test only; Ireland	Unreported; N = 20	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, Unreported - 3 mg/day - 1 Treatment cycles	Previous experience to another medication	Graded antiemetic response to nabilone Scale of poor to excellent. Excellent (minimal nausea, no vomiting), Good (nausea but 50% less vomiting than with previous antiemetic), Fair (no difference when compared to previous antiemetic), or Poor (less effective than previous antiemetic) Clinician-reported outcome	Descriptive statistics only: 55% Excellent, 30% Good, 5% Fair, 10% Poor CI = not reported p = not reported	Not extractable
CINV	Sheidler et al., 1984; RCT, Crossover groups; United States	Adults (18+); N = 20	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 4 mg/day - 2 Treatment cycles	Prochlorperazine	Graded antiemetic response Nausea and vomiting graded on scale of 1-4) based on activity interference and number of vomits. Further categorised into complete response (grade 1 nausea and vomiting), partial response (grades 2 and 3), and no response (grade 4) Objective quantifiable value	Δ = Not extractable CI = not reported $p = 0.61$	Not extractable
CINV	Stambaugh et al., 1984; RCT, Other/unclear; United States	Unreported; N = 20	Unreported; Unreported	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 4 dosage groups: 2.0 mg/day, 4.0 mg/day, 6.0 mg/day, 8.0 mg/day - 1 Treatment cycles	Placebo	Graded antiemetic response Assessed by physician and categorised into grades: Complete response (absence nausea vomiting), Partial response (50% reduction), No response (< 50% reduction). Expressed as numerical 'mean physician rating' score. Clinician-reported outcome	Mean (for all 4 doses of levonantradol) Δ = 3.75 CI = not reported $p < 0.01$	Significantly superior to comparator
CINV	Citron et al., 1985; RCT, Crossover groups; United States	Adults (18+); N = 46	Unreported; Unreported	Chemotherapy; Ongoing/active	Levonantradol - Prophylactic - Intramuscular, injection - 7 mg/day - 1 Treatment cycles	Natural THC	Median number of emetic episodes Observed vomiting/retching episodes	Median Δ = 1 CI = not reported $p = 0.06$	Non-significantly superior to comparator

CINV	Niiranen et al., 1985; RCT, Crossover groups; Finland	Adults (18+); N = 32	Lung; Solid tumour	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 4 mg/day - 1 Treatment cycles	Prochlorperazine	Mean number of vomiting episodes Observed and recorded by patients and investigators	Mean Δ = -4.5 CI = not reported < 0.05	Significantly superior to comparator
CINV	Crawford et al., 1986; RCT, Crossover groups; England	Adults (18+); N = 32	Genitourinary; Solid tumour	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 3 mg/day - 2 Treatment cycles	Metoclopramide	Number of vomiting episodes Observed by nursing staff	Mean Δ = 1.73 CI = not reported $p > 0.1$	Non-significantly worse than comparator
CINV	Niederle et al., 1986; RCT, Crossover groups; Germany	Adults (18+); N = 20	Genitourinary; Solid tumour	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, Unreported - 4 mg/day - 1 Treatment cycles	Alizapride	Daily median number of emetic episodes Observed by nursing staff and one of the investigators, emetic episodes recorded by patients in daily questionnaire	Median Δ = -1.8 CI = not reported p < 0.01	Significantly superior to comparator
CINV	Pomeroy et al., 1986; RCT, Parallel groups; Ireland	Adults (18+); N = 38 (N_i = 19 nabilone N_c = 19 domperidone)	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 3 mg/day - 2 Treatment cycles	Domperidone	Mean number of vomiting episodes Observed and recorded by patient diary and investigator's record form	Mean Δ = -6.28 CI = not reported p < 0.01	Significantly superior to comparator
CINV	Dalzell et al., 1986; RCT, Crossover groups; England	Paediatric (~0-14 years); N = 23	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 2.1 mg/day - 1 Treatment cycles	Domperidone	Mean number of vomiting episodes Observed	Mean Δ = -10.78 CI = not reported p < 0.01	Significantly superior to comparator
CINV	Chan et al., 1987; RCT, Crossover groups; Canada	Paediatric (~0-14 years); N = 40	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills - 2.5 mg/day - 1 Treatment cycles	Prochlorperazine	Mean number of retching/vomiting episodes throughout entirety of chemotherapy cycle Observed by nurse or parent	Mean Δ = -14 CI = not reported p < 0.05	Significantly superior to comparator
CINV	Cunningham et al., 1988;	Adults (18+); N = 80	Multiple cancer diagnoses,	Chemotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills	Metoclopramide AND dexamethasone	Median number of vomiting episodes	Median Δ = 0.47 CI = not reported	Non-significantly

	RCT, Crossover groups; Scotland		heterogeneous cohort; Solid tumour		- 7 mg/day - 2 Days		Observed and "recorded by senior nursing staff or medical staff"	p = 0.051	worse than comparator
CINV	McCabe et al., 1988; RCT, Crossover groups; United States	Adults (18+); N = 36	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	THC - Prophylactic - Oral, capsules/pills - 90 mg/m^2/day - 1 Treatment cycles	Prochlorperazine	Number of participants expressing preference for THC over prochlorperazine Recorded in patient diary Patient-reported outcome	N Δ = 22 CI = not reported p = not reported	Significance not reported, superior to comparator
CINV	Lane et al., 1990; RCT, Parallel groups; United States	Adults (18+); N = 19 (N_i = 7 dronabinol N_c = 6 prochlorperazine N_c = 6 combined dronabinol + prochlorperazine)	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Dronabinol - Prophylactic - Oral, Unreported - 40 mg/day - 1 Treatment cycles	Prochlorperazine (alone)	Median number of vomiting episodes Observed by staff during chemotherapy administration, recorded by patients on diary forms for remainder of study period	Median Δ = 0 CI = not reported p > 0.05	No effect
CINV	Lane et al., 1991; RCT, Parallel groups; United States	Adults (18+); N = 62 (N_i = 21 dronabinol N_c = 21 prochlorperazine N_c = 20 combined dronabinol + prochlorperazine)	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Dronabinol - Prophylactic - Oral, capsules/pills - 40 mg/day - 1 Treatment cycles	Prochlorperazine (alone)	Proportion of patients without nausea and/or vomiting Combined Visual analog scale (VAS) 0-10 self-rated nausea (no nausea vs extreme nausea), and observed episodes vomiting Patient-reported outcome	Percentage Δ = 11.00% CI = not reported p > 0.05	Non-significantly superior to comparator
CINV	Meiri et al., 2007; RCT, Parallel groups; United States	Adults (18+); N = 64 (N_i = 17 dronabinol N_c = 16 ondansetron N_c = 17 dronabinol + ondansetron N_c = 14 placebo)	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	Dronabinol - Prophylactic - Oral, capsules/pills - 10 mg/day - 1 Treatment cycles	***Ondansetron (alone)***	*Proportion of patients with total response (no vomiting and/or retching, intensity of nausea < 5mm on a 100mm visual analog scale, and no use of rescue medication) following administration of chemotherapy, compared to Ondansetron* *Measured via observed episode vomiting and retching, and nausea Visual Analog Scale (VAS scale 0-100mm; 0mm = no nausea; 100mm = intractable nausea)* *Patient-reported outcome*	*Percentage Δ = -4.00%* *CI = not reported* *p > 0.05*	*Significance not reported, inferior to comparator*
						Placebo	*Proportion of total response, compared to placebo*	*Percentage = 34.00%* *CI = not reported* *p > 0.05*	*Non-significantly*

									superior to comparator
CINV	Grimison et al., 2020; RCT, Crossover groups; Australia	Adults (18+); N = 81	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Ongoing/active	THC:CBD - Prophylactic - Oral, capsules/pills - THC 15 mg/day: CBD 15 mg/day - 1 Treatment cycles	Placebo	Proportion of participants with complete response, defined as no vomiting and no use of rescue medications during the overall phase of treatment (0-120 h) Self-reported experience of nausea and vomiting recorded in patient diary (checked by trial staff) Patient-reported outcome	Percentage Δ = 11.00% 90% CI = 1.12 – 2.79 *p* = 0.041s	Significantly superior to comparator
CINV	Sukpiriyagul et al., 2023; RCT, Crossover groups; Thailand	Adults (18+); N = 60	Genitourinary; Solid tumour	Chemotherapy; Ongoing/active	THC:CBD - Prophylactic - Sublingual, oil - THC 0.8125 mg/day: CBD 0.8125 mg/day - 1 Treatment cycles	Placebo	Mean nausea score Self-assessed on a numerical 11-point rating scale (0 = no nausea and 10 = worst possible nausea) Patient-reported outcome	Mean Δ = -0.883 95% CI for THC:CBD = 1.940 – 2.315 95% CI for placebo = 2.795 – 3.197 *p* = 0.001	Significantly superior to comparator
Chemotherapy-induced peripheral neuropathy (CIPN)	Nielsen et al., 2022; Comparative study without concurrent controls, Historical control study; Germany	Adults (18+); N_i = 54 (N_c = 24 historical control (CINCAN-1))	Unreported; Unreported	Chemotherapy; Ongoing/active	CBD - Prophylactic - Oral, oil - 300 mg/day - 1 Treatment cycles	Historical data	Difference in vibration perception threshold (VPT) from baseline to day 4±1 after initiation of first chemotherapy cycle Measured by multi-frequency vibrometry (MF-V) with the VibroSense Meter® II medical device, extracted for first reported data: merged VPT model at Dig-32Hz	Change in baseline Δ = -0.26 95% CI = -0.72- 0.19 *p* = not reported, z score not significant	Non-significantly superior to comparator
CIPN	Waissengrin, Barliz et al., 2021; Comparative study without concurrent controls, Retrospective cohort study; Israel	Unreported; N = 513	Gastrointestinal; Solid tumour	Chemotherapy; Ongoing/active	N/A observational	Concurrent cohort of non-users	Median functionally disturbing (grade 2-3) neuropathy survival (FdNFS) defined as the time from the first cannabis treatment to the time of first appearance of Fd neuropathy among cannabis-treated patients compared to the control group CTCAE grade for neuropathy as evaluated by treating oncologist Clinician-reported outcome	Cox Hazard ratio = 0.5871 95% CI = 0.39 – 0.86 p < 0.001	Significantly superior to comparator
Graft-versus-host-disease (GVHD)	Yeshurun et al., 2015; Comparative study without	Adults (18+); N = 48	Multiple cancer diagnoses, heterogeneous cohort;	Allo-HSCT and chemotherapy; Ongoing/active	CBD - Prophylactic - Oral, oil - 300 mg/day - 37 Days	Historical data	Cumulative incidence rates (%) of patients with grades II to IV acute GVHD at day 100 post-transplant	Hazard ratio Δ = 0.3 95% CI = 0.2 to 0.6 *p* = 0.0002	Significantly superior to comparator

	concurrent controls, Historical control study; Israel	(N_c = 101 historical control)	Haematologic cancer				Assessed by Consensus grading system with histological confirmation Clinician-reported outcome		
Pain	Guy et al., 2010; RCT, Parallel groups; Spain	Unreported; N = 360 (N = parallel arms unreported)	Unreported; Unreported	Unreported; Unclear	Nabiximols - Therapeutic (after symptom occurrence) - Oral, oromucosal spray - THC 22.95 mg/day: CBD: 21.25 mg/day - 5 Weeks	Placebo	Pain Assessed using 0-10 numeric rating scale (NRS), analysed using 30% responder analysis Patient-reported outcome	Δ = Values not reported, but stated non-significantly "numerically in favour of Sativex" CI = not reported $p > 0.05$	Non-significantly superior to comparator
Pain	Lynch et al., 2014; RCT, Crossover groups; United States	Unreported; N = 18	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemotherapy; Mixed (some active/complete)	Nabiximols - Therapeutic (after symptom occurrence) - Oral, oromucosal spray - THC 21.6 mg/day: CBD 20 mg/day - 4 Weeks	Placebo	Change in neuropathic pain Measured by 11-point Numeric Rating Scale for Pain Intensity (NRS-PI) from baseline (average pain score over seven days pre-treatment) to the final week of stable dose treatment. 0 (no pain) – 10 (pain as bad as you can imagine) Patient-reported outcome	Mean Δ = -0.38 CI = not reported $p = 0.29$	Non-significantly superior to comparator
Pain	Tavhare et al., 2019; Case series with pre-test/post-test outcomes; India	Adults (18+); N = 37	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemoradiotherapy; Mixed (some active/complete)	Processed whole cannabis leaves 'Bhanga' - Therapeutic (after symptom occurrence) - Oral, capsules/pills - 750 mg/day - 4 Weeks	Baseline before cannabis (pre-post)	Difference in mean pain score from baseline (before treatment) to week 4 (after treatment) Wong-Baker Faces Pain Rating Scale (FACES) Patient-reported outcome	Mean Δ = 6.42 CI = not reported < 0.05	Significantly superior to comparator
Pain	Aviram et al., 2020; Case series with pre-test/post-test outcomes; Israel	Adults (18+); N = 293	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Heterogeneous; Ongoing/active	N/A observational	Baseline before cannabis (pre-post)	Weekly average pain intensity from baseline (T0) to 1 month follow up (T1) Measured on numerical pain scale (NPS) (0-10) Patient-reported outcome	Median Δ = -2 CI = not reported $p < 0.05$	Significantly superior to comparator
Pain	Pawasarat et al., 2020; Comparative study with concurrent	Adults (18+); N = 232	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Chemoradiotherapy; Unclear	N/A observational	Concurrent cohort of non-users	Proportion of participants with minimal clinically important difference (MCID) in ESAS pain score at most recent palliative care visit	Percentage Δ = -0.40% CI = not reported $p = 0.95$	Non-significantly worse than comparator

	controls, Retrospective cohort study; United States						Pain domain, Edmonton Symptom Assessment System (ESAS). Established MCID improvement score for an individual ESAS category is ≥1/10. Patient-reported outcome		
Pain	Zylla et al., 2021; RCT, Parallel groups; United States	Adults (18+); N = 30 (N_i = 15 early cannabis (intervention) N_c = 15 delayed cannabis (control))	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Unreported; Unclear	THC:CBD - Therapeutic (after symptom occurrence) - Administration, formulation and dosage varied (individually selected), - THC 34.4 mg/day: CBD 16.6 mg/day - 3 Months	Standard care	Mean overall pain score from baseline to 3 months Assessed by self-reported pain log (documenting average daily pain scores over a 7-day period using a 0-19 visual analog scale rating) Patient-reported outcome	Mean Δ = 0 CI = not reported *p* = not reported	No effect
Pain	Aprikian et al., 2023; Case series with pre-test/post-test outcomes; Canada	Adults (18+); N = 358	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Unreported; Unclear	Unreported/Irrelevant - N/A observational - N/A observational, N/A observational - N/A observational - N/A observational N/A observational	Baseline before cannabis (pre-post)	Change in mean pain score from baseline to 3 months Assessed by average pain domain of Brief Pain Inventory (BPI) Patient-reported outcome	Mean Δ = -1.5 CI = not reported *p* = 0.006	Significantly superior to comparator
Psychosocial, anxiety/depression	Davies et al., 1974; PRCT (Pseudorandomised controlled trial); Wales	Adults (18+); N = 12	Lung; Solid tumour	Radiotherapy; Ongoing/active	THC - Therapeutic (after symptom occurrence) - Oral, capsules/pills - 10 mg/day - 7 Days	Placebo	Self-assessed effects of THC on tension-anxiety and depression at 6 hours after administration Self-rated "Mood scales, McNair & Lorr 1964" Patient-reported outcome	Δ = Not reported CI = not reported p > 0.05 for both tension-anxiety and depression	Not extractable
Quality of life/total symptom burden	Bar-Sela et al., 2013; Case series with pre-test/post-test outcomes; Israel	Adults (18+); N = 211	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Heterogeneous; Unclear	N/A observational	Baseline before cannabis (pre-post)	Change in severity of cancer and anti-cancer treatment related symptoms from baseline interview (day of receiving cannabis license) to 6-8 weeks later Self-reported as grades: without symptom (0), minimal (1-2), or severe (3-4), aggregated as sum Patient-reported outcome	Percentage Δ = Not extractable CI = not reported *p* < 0.001	Significantly superior to comparator
Quality of life/total	Cote et al., 2016;	Adults (18+); N = 56	Head and neck cancers; Solid tumour	Chemoradiotherapy; Ongoing/active	Nabilone - Prophylactic - Oral, capsules/pills	Placebo	Proportion of participants with a 15-point improvement in the Global quality of life scale (items 29-30) of	Percentage Δ = Not extractable (ANOVA)	Not extractable

symptom burden	RCT, Parallel groups; Canada	(N_i = 28 nabilone N_c = 28 placebo)			- 1.25 mg/day - 1 Treatment cycles		the EORTC QLQ-C30 from baseline to week 7 Patient-reported outcome	CI = not reported *p* = 0.4270	
Quality of life/total symptom burden	Bar-LevSchleider et al., 2018; Case series with pre-test/post-test outcomes; Israel	All (adults, young adults & paediatric); N = 2923	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Unreported; Unclear	N/A observational	Baseline before cannabis (pre-post)	"Treatment success" change in % of patients reporting good quality of life from baseline to 6 months Self-reported quality of life assessed on Likert scales ranging from very poor, neither poor nor good, good, to very good Patient-reported outcome	Percentage Δ = 50.80% CI = not reported *p* < 0.001	Significantly superior to comparator
Quality of life/total symptom burden	Zhang et al., 2018; Comparative study with concurrent controls, Case-control study; Canada	Adults (18+); N = 148 (N_i = 74 marijuana user group N_c = 74 non-user group)	Head and neck cancers; Solid tumour	Heterogeneous; Mixed (some active/complete)	N/A observational	Concurrent cohort of non-users	Quality of life score Self-assessed by General Wellbeing domain on Edmonton Symptom Assessment System (ESAS) Patient-reported outcome	Mean Δ = 1.93 95% CI = 1.13 – 2.74 no p values reported, Wilcoxon rank sum test z score -4.43	Significantly superior to comparator
Quality of life/total symptom burden	Anderson et al., 2019; Case series with pre-test/post-test outcomes; United States	All (adults, young adults & paediatric); N = 1120	Unreported; Unreported	Heterogeneous; Unclear	N/A observational	Baseline before cannabis (pre-post)	Change in symptom severity from baseline to 4-month follow-up (for 8 symptoms) Measured via "online patient self-evaluation," tool name not provided Patient-reported outcome	Median Δ = For all 8 symptoms: Anxiety = 2.8 lack of appetite = 2.2 depression = 1.8 disturbed sleep = 3 fatigue = 1 nausea = 2.2 pain = 1.3 vomiting = 0.5 CI = not reported p < 0.001 (for all 8)	Significantly superior to comparator
Quality of life/total symptom burden	Chang et al., 2019; Cross-sectional study; United States	Adults (18+); N = 332 (N_i = 76 THC-positive group N = 256 THC-negative group)	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Unreported; Unclear	N/A observational	Concurrent cohort of non-users	Quality of life in THC-positive vs. THC-negative oncology patients Measured by Total ESAS domain on Edmonton Symptom Assessment Scale (ESAS) Patient-reported outcome	Median Δ = 8 95% CI = 1.027 (1.1012-1.041) p < 0.001	Significantly worse than comparator
Quality of life/total symptom burden	Good et al., 2019;	Adults (18+); N = 21	Multiple cancer diagnoses,	Heterogeneous; Mixed (some active/complete)	CBD - Therapeutic (after symptom occurrence) - Oral, oil	Baseline before cannabis (pre-post)	Mean change in composite ESAS TSDS from baseline to day 14	Mean Δ = -5.8 CI = not reported	Non-significantly superior to comparator

	Case series with pre-test/post-test outcomes; Australia		heterogeneous cohort; Mixed		- 300 mg/day - 28 Days		Measured on Edmonton Symptom Assessment Scale (ESAS), Total Symptom Distress Score (TSDS) Patient-reported outcome	*p* = 0.11	
Quality of life/total symptom burden	Bar-Sela et al., 2019; Comparative study with concurrent controls, Case-control study; Israel	Adults (18+); N = 85	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemoradiotherapy; Ongoing/active	N/A observational	Concurrent cohort of non-users	Change in Global Quality of Life score from baseline (T0) to 3 months (T3) Self-assessed via Global Quality of Life domain on European Organization of Research and Treatment of Cancer Quality of Life Questionnaire version 2 (EORTC-QLQ-30) Patient-reported outcome	Δ = Not extractable Not extractable p > 0.05	Not extractable
Quality of life/total symptom burden	Calcaterra et al., 2020; Cross-sectional study; United States	Adults (18+); N = 1784	Gastrointestinal; Solid tumour	Unreported; Unclear	N/A observational	Concurrent cohort of non-users	Difference in mean quality of life summary score Assessed by QLQ-C30 summary score domain in the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire version 2 (EORTC-QLQ-30), Patient-reported outcome	Mean Δ = -6.8 95% = -6.14 (-8.07 -0.420) *p* = reported statistically significant but value not provided	Significantly worse than comparator
Quality of life/total symptom burden	Macari et al., 2020; Cross-sectional study; United States	Adults (18+); N = 188	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Heterogeneous; Mixed (some active/complete)	N/A observational	Concurrent cohort of non-users	Baseline Composite Symptom Score Score calculated by adding numerical scores for severity of anxiety, nausea, insomnia, pain, poor appetite, difficulty tolerating cancer treatment, difficulty performing work or daily duties, and experiencing cloudy thinking at baseline (each item in a 4-item Likert scale, with 1 indicating no symptoms, and 4 indicating severe) Patient-reported outcome	Mean Δ = 3.1 95% CI for cannabis users = 16.0 – 19.1 95% CI for non-users = 13.6 – 15.1 p < 0.001	Significantly worse than comparator
Quality of life/total symptom burden	Schloss et al., 2021; RCT, Parallel groups; Australia	Adults (18+); N = 88 (N_i = 45 1:1 ratio N_c = 43 4:1 ratio)	Glioblastoma; Solid tumour	Heterogeneous; Ongoing/active	1:1 THC:CBD - Prophylactic - Oral, oil - THC 10.35 mg/day: CBD 10.8 mg/day - 12 Weeks	4:1 THC:CBD	Tolerability assessed by the FACT-Br from baseline (week 0) to 12 weeks compared to 4:1 THC:CBD group Functional Assessment of Cancer Therapy- Brain (FACT-Br) questionnaire, Total Fact Br domain score Patient-reported outcome	Mean Δ = 92.29 95% CI = 90.18 – 94.4 *p* = 0.904	Non-significantly superior to comparator

Quality of life/total symptom burden	Aviram et al., 2022; Case series with pre-test/post-test outcomes; Israel	Adults (18+); N = 324	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Heterogeneous; Unclear	N/A observational	Baseline before cannabis (pre-post)	Cancer symptom burden from baseline (T0) to 6 months (T6) Measured as total score on Memorial Symptom Assessment Scale (MSAS) Patient-reported outcome	Median Δ = -33 95% CI = -26.95 to -11.00 p < 0.001	Significantly superior to comparator
Quality of life/total symptom burden	Clarke et al., 2022; Case series with pre-test/post-test outcomes; Australia	Adults (18+); N = 25	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Unreported; Unclear	THC:CBD - Therapeutic (after symptom occurrence) - Buccal, oromucosal spray - THC 5 mg/day: CBD 5 mg/day - 6 Days	Baseline before cannabis (pre-post)	Quality of life, safety and tolerability from baseline (day 0) to follow-up (day 30) Measured by The European Organisation for Research and Treatment of Cancer Quality of Life for Cancer Patients Questionnaire (EORTC QLQ-C30-v3), Global Health domain Patient-reported outcome	Median Δ = Not extractable (ANOVA) CI = not reported *p* = 0.13	Non-significantly superior to comparator
Quality of life/total symptom burden	Nielsen W. et al., 2022; Cross-sectional study; Denmark	Adults (18+); N = 2839	Multiple cancer diagnoses, heterogeneous cohort; Mixed	Heterogeneous; Mixed (some active/complete)	N/A observational	Concurrent cohort of non-users	Difference in EORTC-QLQ30 Summary score Assessed via Summary Score domain on EORTC QLQ-C30 Quality of life questionnaire Patient-reported outcome	Mean Δ = -7.61 95% = -9.69; -5.53 *p* = 0.46	Non-significantly worse than comparator
Quality of life/total symptom burden	Azizoddin et al., 2023; Case series with pre-test/post-test outcomes; United States	Adults (18+); N = 270	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Heterogeneous; Ongoing/active	N/A observational	Concurrent cohort of non-users	Mean Overall Valuation of life score Assessed by Overall Valuation of Life domain on Rotterdam Symptom Checklist (RSCL) Patient-reported outcome	Mean Δ = -0.26 CI = not reported *p* = 0.076	Non-significantly worse than comparator
Radiotherapy induced nausea and vomiting	Lucraft et al., 1982; RCT, Parallel groups; England	Adults (18+); N = 43 (N_i = 14 levonantradol 0.5mg N_i = 15 levonantradol 0.75 mg N_c = 14 chlorpromazine)	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Radiotherapy; Ongoing/active	Levonantradol - Prophylactic - Unreported - Not reported - 1 Treatment cycles	Chlorpromazine	*Total number of patients who vomited within 0–4-hour period following radiotherapy receiving **0.5mg** levonantradol* *Patient interviewed within a few days of treatment*	*N Δ = 2* *CI = not reported* *p = not reported*	*Significance not reported, worse than comparator*
							***0.75mg** levonantradol*	*N Δ = 1* *CI = not reported* *p = not reported*	*Significance not reported, worse than comparator*

Radiotherapy induced nausea and vomiting	Priestman et al., 1987; RCT, Other/unclear; England	Unreported; N = 40	Multiple cancer diagnoses, heterogeneous cohort; Unreported	Radiotherapy; Ongoing/active	Nabilone - Therapeutic (after symptom occurrence) - Unreported route administration, capsules/pills - 2 mg/day - 7 Days	Metoclopramide	Mean daily scores for nausea, vomiting episodes, and appetite Self-assessed and recorded in patient diary Not extractable	Δ = Not extractable CI = not reported *p* = stated no difference	Not extractable
Safety	Duran et al., 2010; RCT, Parallel groups; Spain	Adults (18+); N = 16	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemotherapy; Ongoing/active	THC:CBD - Prophylactic - Buccal, oromucosal spray - THC 13.0 mg/day: CBD 12.0 mg/day - 1 Treatment cycles	Placebo	Tolerability defined as the % of patients that developed an adverse event Recorded in patient diary and daily telephone interviews	Percentage Δ = 19.00% 95% CI = -23.7%, 52.4% Not reported	Non-significantly worse than comparator
Safety	Twelves et al., 2021; RCT, Parallel groups; England	Adults (18+); N = 21 (N_i = 12 nabiximols N_c = 9 placebo)	Glioblastoma; Solid tumour	Chemoradiotherapy; Ongoing/active	Nabiximols - Unclear/unreported - Oral, oromucosal spray - THC 20.25 mg/day: CBD 18.75 mg/day - 12 Months	Placebo	Proportion of patients with incidence of treatment-emergent adverse events (TEAEs) leading to discontinuation Assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Clinician-reported outcome	Percentage Δ = -5.50% CI = not reported *p* = not reported	Non-significantly superior to comparator
Sleep	Giordano et al., 2023; Case series with pre-test/post-test outcomes; United States	Adults (18+); N = 28	Multiple cancer diagnoses, heterogeneous cohort; Solid tumour	Chemotherapy and immunotherapy; Mixed (some active/complete)	N/A observational	Baseline before cannabis (pre-post)	Change in sleep quality score from baseline to 2 weeks Measured by Pittsburgh Sleep Quality Index (PSQI), modified single item to ask about last 2 weeks (sleep quality rated on scale from 0 “very good” to 3 “very bad” Patient-reported outcome	Mean Δ = -0.33 CI = not reported 0.02	Significantly superior to comparator

Study characteristics

Study design

The majority of eligible studies included in our systematic review were randomised controlled trials (RCT) (53/87; 60.9%). Among these RCTs, most (33/53; 62.3%) used a crossover design (Figure 3a). Many studies were categorised as low-quality evidence, including 21 (24.1%) case series with pre/post or post-test only outcomes. Additionally, there were four (4.6%) comparative studies with concurrent controls, four (4.6%) comparative studies without concurrent controls, four (4.6%) cross-sectional studies, and one (1.2%) pseudorandomised controlled trial (PRCT) (Figure 4a). Overall, there were 71 (81.6%) interventional studies, and 16 (18.4%) observational studies.

A biphasic pattern was observed in cannabinoid research over time. The majority of studies published between 1974 and 1990, with 71.7% of RCTs were published during this period. There was a subsequent decline until a resurgence in 2015 characterised by a shift in study designs, with a surge in opportunistic observational studies leveraging medicinal cannabis registries (Figure 3b).

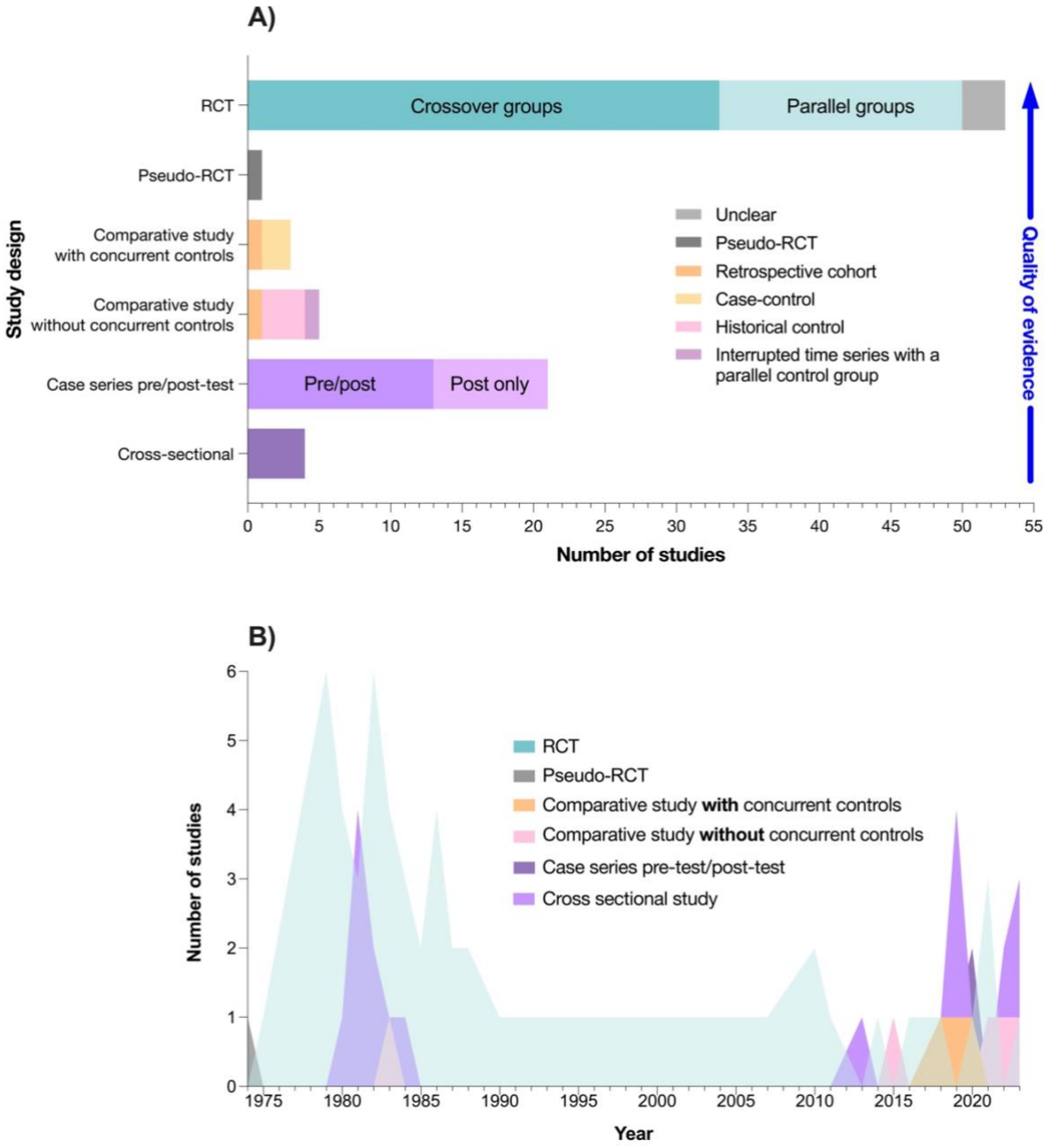


Figure 3: Temporal evolution of cannabinoid study designs.

A) Frequency of study designs as classified under the NHMRC levels of evidence, including subcategory details (N = 87). **B)** Frequency of study designs published from 1974 to 2023 (N = 87).

Study setting

Among the 87 studies, 23 (26.4%) were multi-centre, 38 (43.7%) were single-centre, and 26 (29.9%) did not report setting. The majority of studies were conducted in the United States, (n = 36; 41.4%), followed by Israel (n = 8; 9.2%), England (n = 8; 9.2%), Germany (n = 8; 9.2%), Canada (n = 6; 6.9%), and Australia (n = 6; 6.9%) (Figure 4b).

Sample size

Study sample sizes varied from 9 to 293 participants. The overall average sample size was 181, with a median of 46 and a mode of 20 participants. Interventional studies had an average size of 57 participants, while observational studies averaged 728 participants. Cannabinoid arms averaged 42 participants (median [range]: 27 [7-159]), while comparator arm(s) had an average of 51 participants (median [range]: 25 [6-256]).

Study funding and cannabinoid suppliers

Eli Lilly and Company funded the greatest number of cannabinoid trials (n = 16; 18.4%), followed by the National Institute on Drug Abuse (NIDA) with 12 (13.8%), and Pfizer with 10 (11.5%) (Figure 4c).

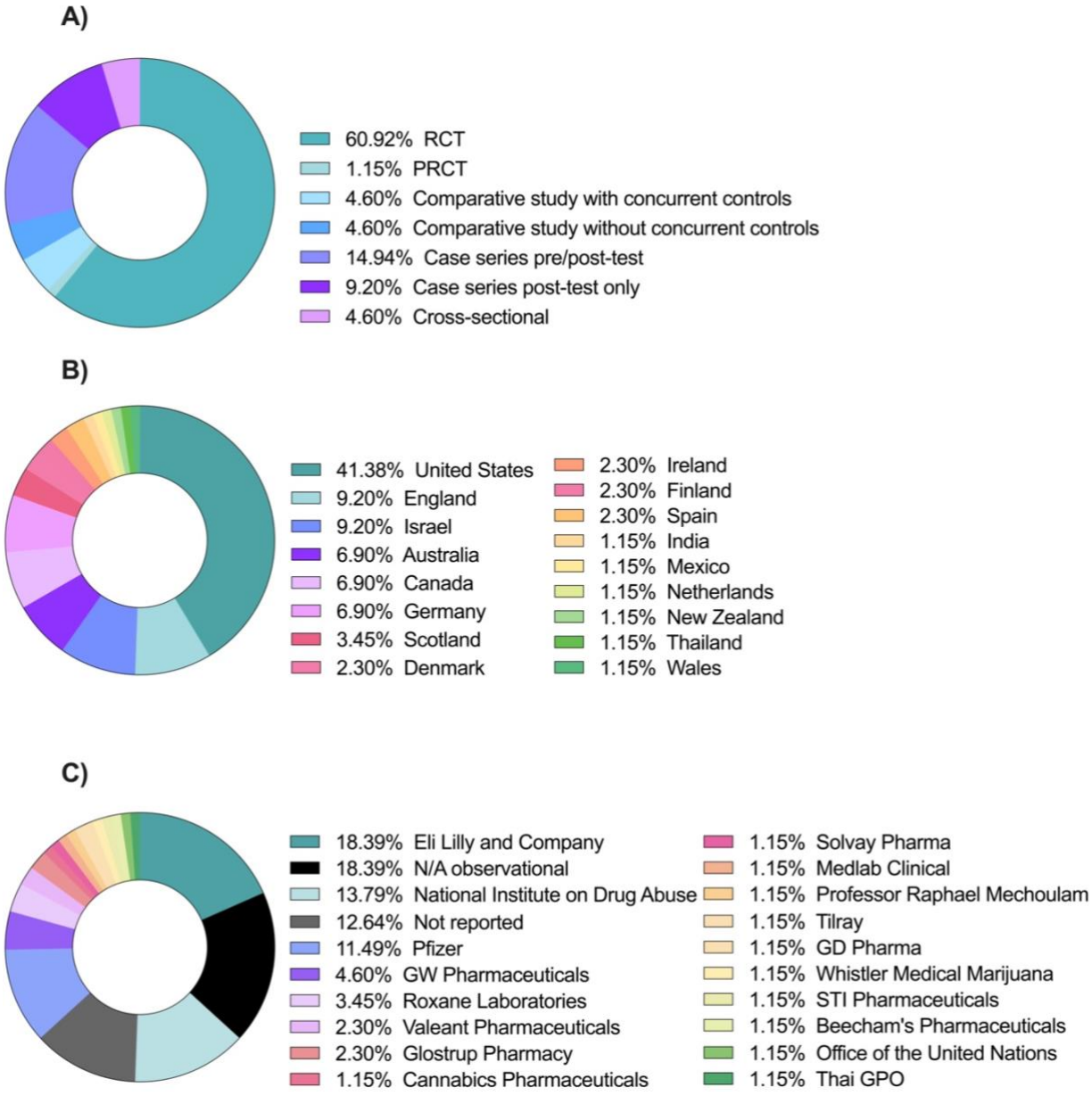


Figure 4: Study characteristics (N = 87).

A) Study design; **B)** Country; **C)** Study funding/cannabinoid supplier.

Participants

Tumour type

Most studies included participants with solid tumours (n = 33; 37.9%), closely followed by mixed populations with both solid and haematologic cancers (n = 31; 35.6%). Only three studies (3.45%) specifically focused on patients with haematologic cancers (Figure 5a).

Cancer diagnoses

Most studies (n = 60; 69.0%), adopted a disease-agnostic approach, including heterogeneous populations with multiple cancer diagnoses. The reporting of cancer types within heterogeneous populations was inconsistent, with most studies providing cancer names and the number of participants, some only reporting proportions, and others only reporting 'various cancers.' Among studies with homogeneous cancer populations, lung cancer was studied most frequently (n = 4; 4.6%), followed by gastrointestinal (n = 3; 3.5%), genitourinary (n = 3; 3.5%), head and neck (n = 2; 2.3%), glioblastoma (n = 2; 2.3%), lymphoma (n = 2; 2.3%) and bone cancers (n = 1; 1.2%) (Figure 5b).

Cancer treatment

Chemotherapy was the most common cancer therapy, with 57 (65.5%) studies investigating cannabinoids in this clinical context. Eleven (12.6%) studies included a heterogeneous cohort undergoing various cancer therapies, and seven (8.1%) studies included participants undergoing combined chemotherapy and/or radiotherapy. Three studies (3.4%) focused on radiotherapy only populations, one study (1.1%) included

people undergoing combined chemotherapy and immunotherapy, and another study (1.1%) focused on immunotherapy (Figure 5c).

Cancer treatment status

Most (n = 65; 74.7%) studies included participants undergoing active treatment, and 11 (12.6%) studies included mixed populations with both active and/or completed treatments. Reporting was unclear in 11 (12.6%) studies (Figure 5d).

Demographics

The majority of studies (n = 67; 77.0%) included only adults (18+ years). Six (6.9%) studies included all age groups (0-80+ years), four (4.6%) studies focused on paediatric patients (0-14 years), and two (2.3%) studies included both adults and young adults (14+ years). Age was not reported in eight studies.

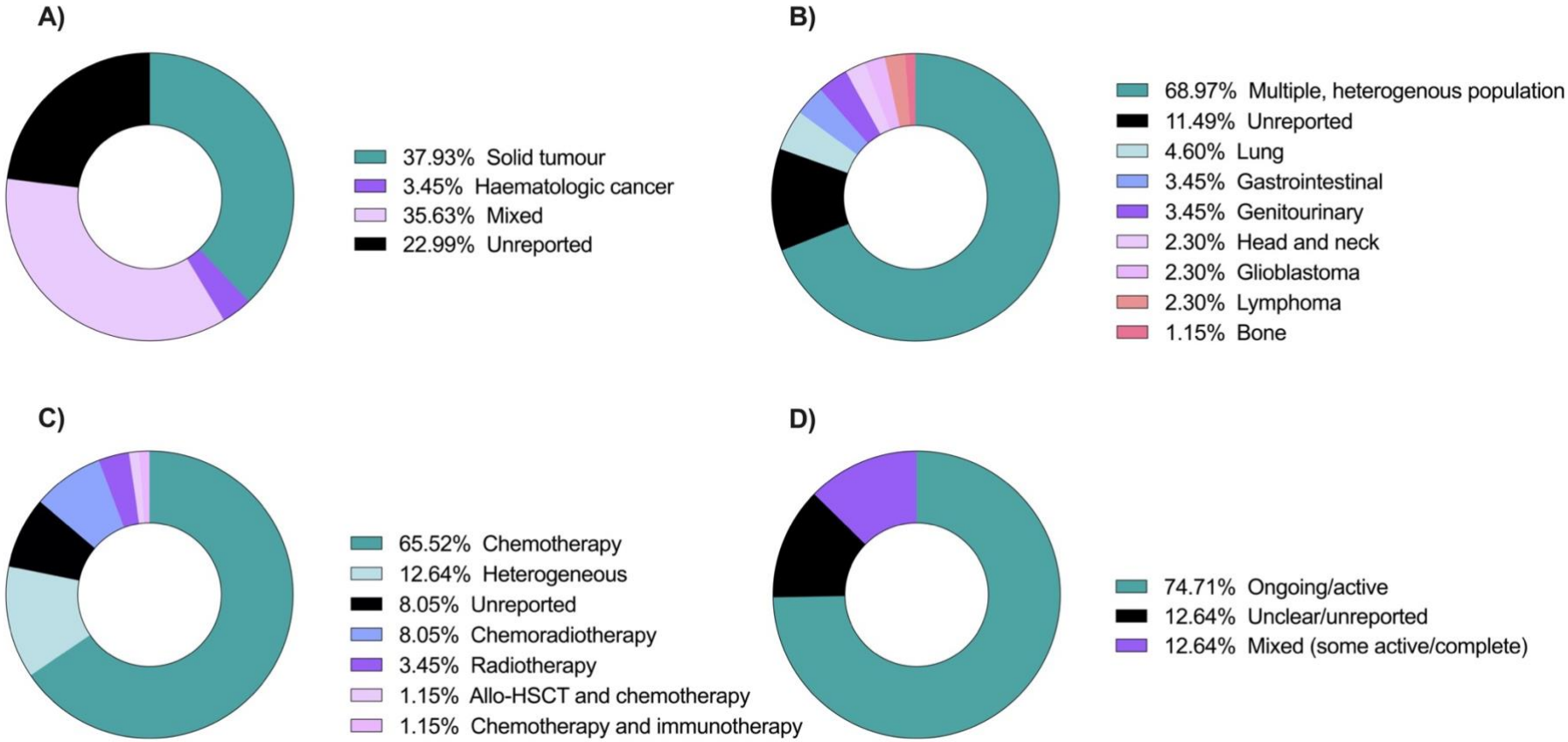


Figure 5: Participant characteristics (N = 87).

A) Broad tumour type; **B)** Cancer diagnosis; **C)** Cancer treatment; **d)** Cancer treatment status.

Previous or existing cannabinoid use or misuse

Exclusion of participants with cannabinoid misuse or high recreational use was variably implemented and poorly reported. Only 36 (41.4%) of the included studies specified whether parameters related to cannabinoid use were considered in assessing participant eligibility. Among the studies that did include cannabinoid use in their eligibility, few reported the methods to assess the parameter, with numerous heterogeneous methods summarised in Table 3.

Among the 16 observational studies, four (25%) studies involved participants self-medicating with recreational cannabis, and one (6.3%) included a mixed cohort of participants with a medical cannabis license alongside self-medicators. The remaining nine (56.3%) studies were conducted using registry data, specifically focusing on participants using licensed medicinal cannabinoids. Two (12.5%) studies did not provide details on the sourcing of their cannabinoids.

Table 3: Cannabinoid use as part of eligibility criteria - parameters and measurement methods (n = 36).

Eligibility parameters related cannabinoid use	Methods to assess parameter
Any contraindications, such as history of: Substance abuse or dependence, Hypersensitivity or allergy to cannabinoids, Previous treatment with cannabinoids, Significant psychological disturbance, Likelihood of adverse reactions toward psychoactive component.	Review of medical records Psychiatric evaluation Serum, blood count Cannabis Use Disorders Identification Test-Revised (CUDIT-R)[233]
No cannabis usage within 30 days (most common timeframe) before study, and for duration of study.	Urine drug test (UDT) to detect THC and urinalysis obtained within 30 days before entry into trial.
No use of cannabis within 3 months before study (n = 1 study focusing on Allo-HCT recipients).	Insta-check rapid urine screen immediately before trial.
Participants had to agree not to drive or operate heavy machinery.	Interview at intake Questionnaire

Intervention

Cannabinoid-based medicines

In the 71 interventional studies, 10 types of cannabinoid-based medicines were identified and categorised into three chemotype groups: CBD dominant, mixed THC/CBD, and THC dominant (Table 4). Most studies investigated THC-dominant interventions (n = 55; 77.5%), with nabilone (n = 20; 28.2%) being the most common, followed by THC (n = 16; 22.5%), levonantradol (n = 13; 18.3%), dronabinol (n = 5; 7.0%), nonabine (n = 1; 1.4%), and traditional processed whole cannabis leaves 'Bhanga' (n = 1; 1.4%). Varying ratios of mixed THC:CBD products were studied in 8 (11.3%) trials, and three trials used nabiximols. CBD-dominant interventions, were investigated in four studies (n = 4; 5.6%) (Table 4; Figure 6a; Figure 7a).

During the period from 1974 to 1990, the majority of studies focused on THC-dominant products. However, in recent years, there has been a notable increase in the popularity of mixed THC:CBD products (Figure 6b).

Mixed THC:CBD product ratios

Among the 11 studies using mixed THC:CBD products, the majority[63, 84, 152, 162, 169, 185, 198, 205] used an approximately 1:1 THC:CBD ratio (n = 8; 72.7%). The remaining studies used higher ratios of THC (19:1 and 2.5:1 THC:CBD), and the final study permitted participants to individually titrate and select their ratio based on personal therapeutic efficacy (Table 4).

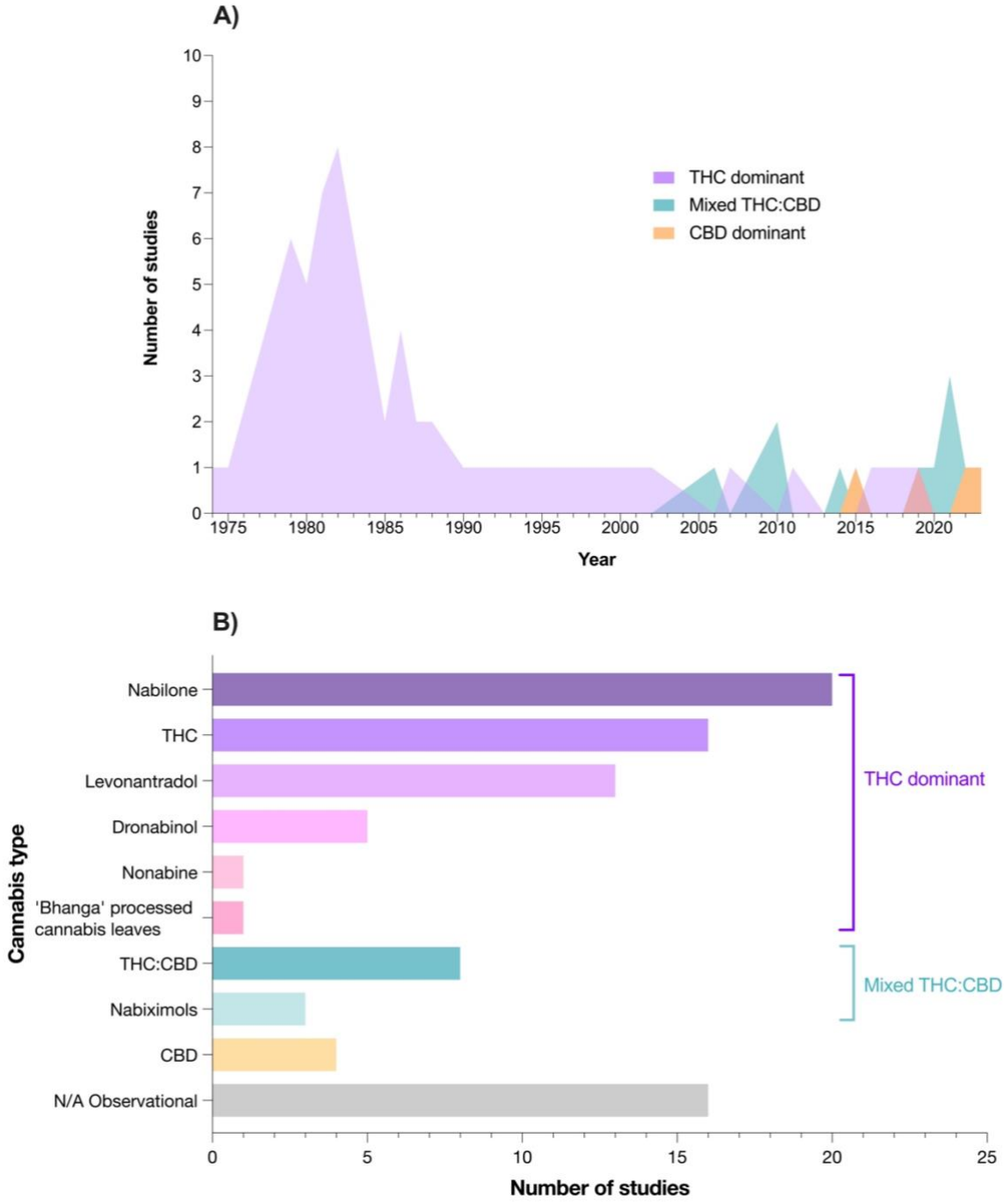


Figure 6: Temporal evolution of research on cannabinoid-based medicines.

A) Frequency of cannabinoid-based medicines researched, grouped by chemotype (n = 71); **B)** Distribution of cannabinoid-based medicines studied over time, grouped by chemotype (1974-2023) (n = 71).

Timing (relative to symptom occurrence)

Most studies (n = 57; 80.3%), administered cannabinoids prophylactically prior to symptom occurrence. Thirteen (18.3%) studies chose a therapeutic approach, administering cannabinoids after the occurrence of the target symptom (Figure 7b; Table 4).

Formulation and route of administration

Capsules/pills were the most common cannabinoid formulation (n = 39; 54.9%), followed by intramuscular injection (n = 10; 14.1%), oil (n = 6; 8.5%), and oromucosal spray (n = 5; 7.0%) (Figure 7c). The most common route of administration was oral (n = 52; 73.2%), followed by intramuscular injection (n = 10; 14.1%), buccal (n = 2; 2.8%), and sublingual (n = 1; 1.4%) (Figure 7d). One study included varied formulations and administration routes, allowing participants to select their cannabinoid-based medicine individually. Nine (12.68%) studies did not report the formulation, and five studies (7.0%) did not report administration route (Table 4).

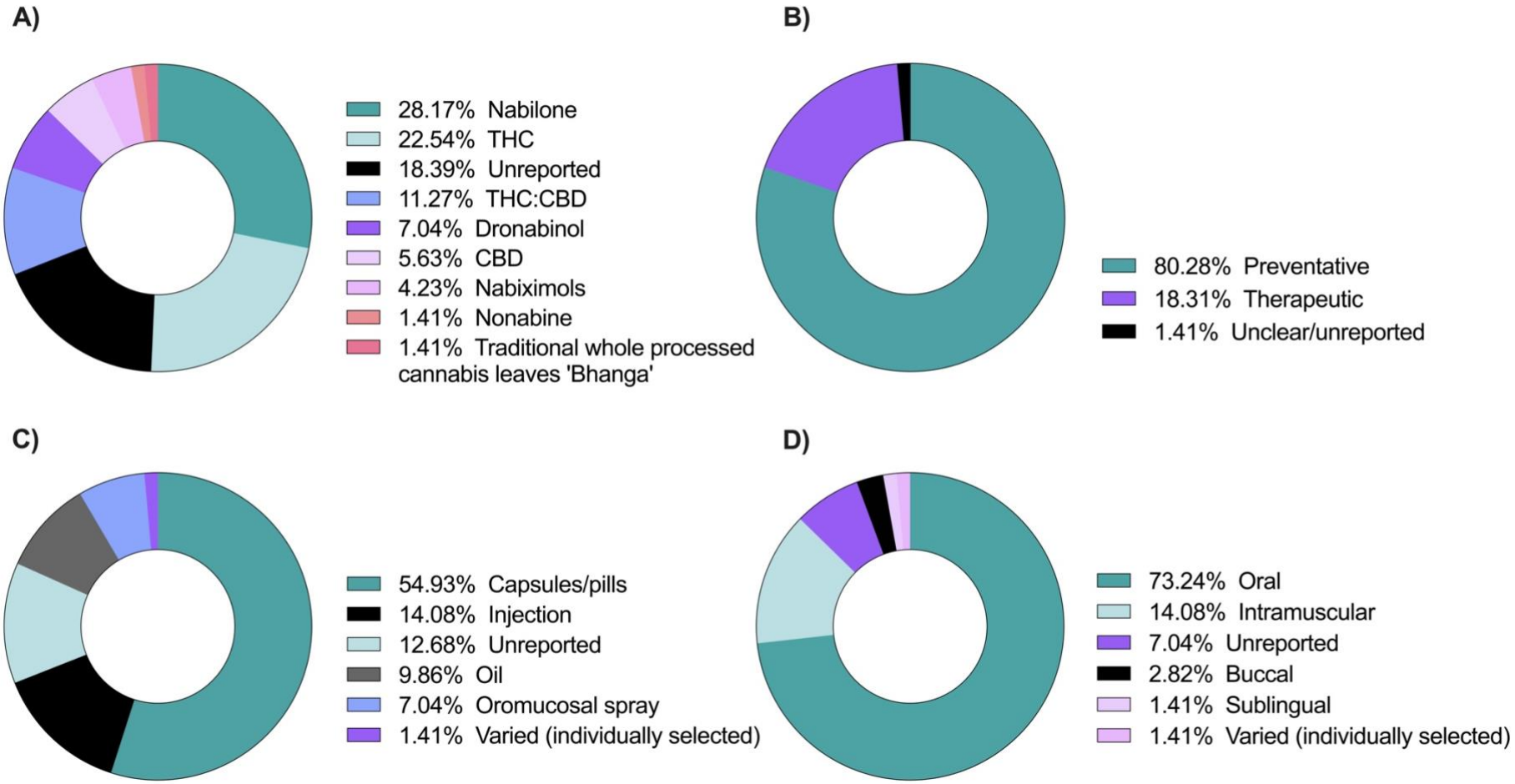


Figure 7: Cannabinoid-based intervention details (n = 71).
A) Type of cannabinoid-based medicine; **B)** Timing of intervention relative to symptom occurrence; **C)** Formulation of product; **D)** Route of administration.

Table 4: Cannabinoid intervention details classified by chemotype (n = 71 studies).

Chemotype	Cannabinoid-based medicine	Timing	Administration route & formulation	Single dose & frequency	Dose per day (mg/day)	Duration on cannabinoid
CBD dominant	CBD	Therapeutic	Oral, oil	100 mg, 3x Daily	300 mg/day	28 days
	CBD	Prophylactic	Oral, oil	150 mg, 2x Daily	300 mg/day	1 treatment cycle, 8 days
	CBD	Prophylactic	Oral, oil	150 mg, 2x Daily	300 mg/day	37 days
	CBD	Prophylactic	Oral, oil	150 mg, 2x Daily	300	3 treatment cycle, 8 days
Mixed THC:CBD	Nabiximols	Therapeutic	Oral, oromucosal spray	THC 2.7 mg: CBD 2.5 mg, 8.5x Daily	THC 22.95 mg/day: CBD: 21.25 mg/day	5 Weeks
	Nabiximols	Therapeutic	Oral, oromucosal spray	THC 2.7mg: CBD 2.5 mg, 8x Daily	THC 21.6 mg/day: CBD 20 mg/day	4 Weeks
	Nabiximols	Unclear/unreported	Oral, oromucosal spray	THC 2.7mg: CBD 2.5 mg, 7.5x Daily	THC 20.25 mg/day: CBD 18.75 mg/day	12 months
	THC:CBD	Therapeutic	Oral, capsules/pills	THC 2.5mg: CBD 1 mg, 2x Daily	THC 5 mg/day: CBD 2 mg/day	6 Weeks
	THC:CBD	Prophylactic	Buccal, oromucosal spray	THC 12.9 mg: CBD 12.0 mg, 4.81x Daily	THC 13.0 mg/day: CBD 12.0 mg/day	1 treatment cycle, 3 days
	THC:CBD	Therapeutic	Oral, capsules/pills	THC 9.5mg:CBD 0.5 mg, 2x Daily	THC 19 mg/day: CBD 1 mg/day	6 months
	THC:CBD	Prophylactic	Oral, capsules/pills	5 mg, 3x Daily	THC 15 mg/day: CBD 15 mg/day	1 treatment cycle, 5 days
	THC:CBD	Prophylactic	Oral, oil	THC 10.35mg: CBD 10.8 mg, 1x Daily	THC 10.35 mg/day: CBD 10.8 mg/day	12 Weeks
	THC:CBD	Therapeutic	Administration, formulation and dosage varied (individually selected)	Varied (individually selected), 4x Daily	THC 34.4 mg/day: CBD 16.6 mg/day	3 months

	THC:CBD	Therapeutic	Buccal, oromucosal spray	1.25 mg, 4x Daily	THC 5 mg/day: CBD 5 mg/day	6 days
	THC:CBD	Prophylactic	Sublingual, oil	THC 0.325mg: CBD 0.325 mg, 2.5x Daily	THC 0.8125 mg/day: CBD 0.8125 mg/day	1 treatment cycle, 5 days
THC dominant	Dronabinol	Prophylactic	Oral, Unreported	10 mg, 4x Daily	40 mg/day	1 treatment cycle, 4 days
	Dronabinol	Prophylactic	Oral, capsules/pills	10 mg, 4x Daily	40 mg/day	1 treatment cycle, 6 days
	Dronabinol	Therapeutic	Oral, capsules/pills	2.5 mg, 2x Daily	5 mg/day	Until symptoms resolved or AEs were deemed intolerable
	Dronabinol	Prophylactic	Oral, capsules/pills	2.5 mg, 4x Daily	10 mg/day	1 treatment cycle, 5 days
	Dronabinol	Therapeutic	Oral, capsules/pills	2.5 mg, 2x Daily	5 mg/day	18 days
	Levonantradol	Prophylactic	Intramuscular, injection	1 mg, 3.5x Daily	3.5 mg/day	1 treatment cycle, 1 day
	Levonantradol	Prophylactic	Oral, capsules/pills	3 dosage groups: 0.5mg, 1.0mg, 1.5 mg, 4.5x Daily	3 dosage arms: 2.25 mg/day, 4.5 mg/day, 6.75 mg/day	1 treatment cycle, 3 days
	Levonantradol	Prophylactic	Intramuscular, injection	1 mg, 3x Daily	3 mg/day	1 treatment cycle, 1 day
	Levonantradol	Prophylactic	Oral, capsules/pills	4 dosage groups: 0.5mg, 1.0mg, 1.5mg, 2.0 mg, 4x Times per cycle	4 dosage groups: 2.0 mg/day, 4.0 mg/day, 6.0 mg/day, 8.0 mg/day	Variable number of chemotherapy treatments, depending on patient. 1
	Levonantradol	Prophylactic	Intramuscular, injection	0.25 mg, 6x Daily	1.5 mg/day	1 treatment cycle, 1 day
	Levonantradol	Prophylactic	Unreported	Two dosage groups: 0.5mg, 0.75 mg, 1x Times per cycle	Two groups: 0.5 mg and 0.75mg, 1x before radiotherapy	1 treatment cycle, Not reported

Levonantradol	Prophylactic	Intramuscular, injection	0.75 mg, 1.5x Daily	1.125 mg/day	1 treatment cycle, 1 day
Levonantradol	Prophylactic	Intramuscular, injection	3 dosage groups: 0.5mg, 0.75 mg, 1 mg, 4x Daily	3 dosage groups: 2 mg/day, 3 mg/day, 4 mg/day	1 treatment cycle, 1 day
Levonantradol	Prophylactic	Intramuscular, injection	0.5 mg, 6x Daily	3 mg/day	1 treatment cycle, 2 days
Levonantradol	Prophylactic	Intramuscular, injection	0.5 mg, 3x Daily	1.5 mg/day	1 treatment cycle, 1 day
Levonantradol	Prophylactic	Intramuscular, injection	1 mg, 4x Daily	4 mg/day	2 treatment cycle, 1 day
Levonantradol	Prophylactic	Intramuscular, injection	4 dosage groups: 0.5mg, 1.0mg, 1.5mg, 2.0 mg, 4x Daily	4 dosage groups: 2.0 mg/day, 4.0 mg/day, 6.0 mg/day, 8.0 mg/day	1 treatment cycle, 1 day
Levonantradol	Prophylactic	Intramuscular, injection	1 mg, 7x Daily	7 mg/day	1 treatment cycle, 1 day
Nabilone	Prophylactic	Oral, capsules/pills	2 mg, 3x Daily	6 mg/day	1 treatment cycle, varied based on anticancer treatment. 5 1/2 days to 1 1/2 days
Nabilone	Prophylactic	Oral, capsules/pills	2 mg, 2x Daily	4 mg/day	1 treatment cycle, 2.5 days
Nabilone	Prophylactic	Oral, capsules/pills	2 mg, 4x Daily	8 mg/day	1 treatment cycle, 5 days
Nabilone	Prophylactic	Oral, capsules/pills	1.5 mg, 2x Daily	3 mg/day	3 days
Nabilone	Prophylactic	Oral, Unreported	2 mg, 2x Daily	4 mg/day	1 treatment cycle, 2 days
Nabilone	Prophylactic	Unreported	2 mg, 2x Daily	4 mg/day	1 treatment cycle, 2 days
Nabilone	Prophylactic	Unreported	2 mg, 3x Daily	6 mg/day	1 treatment cycle, 2 days
Nabilone	Prophylactic	Oral, capsules/pills	2 mg, 3x Daily	6 mg/day	1 treatment cycle, 3 days
Nabilone	Prophylactic	Oral, capsules/pills	1 mg, 2x Daily	2 mg/day	1 treatment cycle, 4 days
Nabilone	Prophylactic	Oral, Unreported	1.5 mg, 2x Daily	3 mg/day	1 treatment cycle, 2 days
Nabilone	Prophylactic	Oral, capsules/pills	2 mg, 2x Daily	4 mg/day	1 treatment cycle, 2 days

Nabilone	Prophylactic	Oral, capsules/pills	1 mg, 3x Daily	3 mg/day	2 treatment cycle, 3 days
Nabilone	Prophylactic	Oral, Unreported	2 mg, 2x Daily	4 mg/day	1 treatment cycle, 5 days
Nabilone	Prophylactic	Oral, capsules/pills	1 mg, 3x Daily	3 mg/day	2 treatment cycle, 1 day
Nabilone	Prophylactic	Oral, capsules/pills	1 mg, 2x Daily	2.1 mg/day	1 treatment cycle, 3 days
Nabilone	Prophylactic	Oral, capsules/pills	1 mg, 2.5x Daily	2.5 mg/day	1 treatment cycle, started 1 day before, and continued for as long as emesis persisted
Nabilone	Therapeutic	Unreported route administration, capsules/pills	1 mg, 2x Daily	2 mg/day	7 days
Nabilone	Prophylactic	Oral, capsules/pills	2 mg, 3.5x Daily	7 mg/day	2 days
Nabilone	Prophylactic	Oral, capsules/pills	0.5 mg, 2.5x Daily	1.25 mg/day	1 treatment cycle, Variable, every day until end of radiotherapy
Nabilone	Therapeutic	Oral, capsules/pills	1 mg, 1x Daily	1 mg/day	8 Weeks
Nonabine	Prophylactic	Oral, Unreported	15 mg, 2x Times per cycle	1 x 15mg on days 1 and 8 chemotherapy	2 treatment cycle, 2 days
Processed whole cannabinoid leaves ‘Bhanga’	Therapeutic	Oral, capsules/pills	250 mg, 3x Daily	750 mg/day	4 Weeks
THC	Therapeutic	Oral, capsules/pills	10 mg, 1x Daily	10 mg/day	7 days
THC	Prophylactic	Oral, capsules/pills	10 mg/m^2, 3x Daily	30 mg/m^2	1.5 treatment cycle, 1 day
THC	Prophylactic	Oral, capsules/pills	10 mg/m^2, 5x Daily	50 mg/m^2 per day	3 treatment cycle, 1 day
THC	Prophylactic	Oral, capsules/pills	15 mg, 3x Daily	45 mg/day	1 treatment cycle, 4 days
THC	Prophylactic	Oral, capsules/pills	10 mg/m^2, 5x Daily	50 mg/m^2/day	1 treatment cycle, 1 day
THC	Prophylactic	Oral, capsules/pills	10 mg/m^2, 5x Daily	50 mg/m^2/day	1 treatment cycle, 1 day

THC	Prophylactic	Oral, capsules/pills	10 mg/m^2, 6x Times per cycle	30mg/m^2/day on days 1 and 8 of chemotherapy	3 treatment cycle, 2 days
THC	Prophylactic	Oral, capsules/pills	4 mg/0.33m2, 3x Daily	12 mg/0.33m^2 / day	2 treatment cycle, 1 day
THC	Prophylactic	Oral, capsules/pills	10 mg, 4x Daily	40 mg/day	2 treatment cycle, 2 days
THC	Prophylactic	Oral, oil	5 mg/m^2, 6x Daily	30mg/m^2/day	2 treatment cycle, 4 days
THC	Prophylactic	Oral, capsules/pills	10 mg/m^2, 3x Daily	30 mg/m^2	1.5 treatment cycle, 1 day
THC	Prophylactic	Oral, capsules/pills	7 mg/m^2, 4x Daily	28 mg/m^2/day	1 treatment cycle, 1 day
THC	Prophylactic	Oral, capsules/pills	10 mg/m^2, 5x Daily	50 mg/m^2/day	2 treatment cycle, 1 day
THC	Prophylactic	Oral, Unreported	10 mg/m^2, 4x Daily	40 mg/m^2/day	1 treatment cycle, 3 days
THC	Prophylactic	Unreported, capsules/pills	15 mg, 3x Daily	45 mg/day	2 treatment cycle, 1 day
THC	Prophylactic	Oral, capsules/pills	15 mg/m^2, 6x Daily	90 mg/m^2/day	1 treatment cycle, 1 day

Dosing schedules

Cannabinoid dosing schedules varied widely, especially across different products. The dose ranged from 0.5 to 43.2 mg/day for THC-dominant products, and from 2.5 to 600mg/day for CBD (Table 5, Table 6). Summary statistics for total daily doses for each type of cannabinoid-based medicine are presented in Table 5.

Table 5: Cannabinoid dosing schedules, reported as dose per day and grouped by cannabis-based medicine (n = 71).

Cannabinoid-based medicine	Minimum* (mg/day)	Maximum* (mg/day)	Mean (mg/day)	Median (mg/day)	Mode (mg/day)
CBD	300	600	300	300	300
Dronabinol	2.5	40	20	10	5, 40
Levonantradol	0.5	9	3.96	3	3, 4
Nabilone	0.5	8	3.7925	3.5	4
Nabiximols	CBD: 2.5 THC: 2.7 (1 sprays)	CBD: 40 THC: 43.2 (16 sprays)	THC: 21.6 CBD: 20 (8 sprays)	THC: 21.6 CBD: 20 (8 sprays)	N/A
THC*	10mg/day 12 mg/m^2/day	45 mg/day 90 mg/m^2/day	35 mg/day 41.82 mg/m^2/day	42.5 mg/day 40 mg/m^2/day	45 mg/day 50 mg/m^2/day
THC:CBD	THC: 0.81 CBD: 0.81	THC: 40 CBD: 40	THC: 12.82 CBD: 7.90	THC: 11.68 CBD: 7.9	THC: 5 CBD: N/A

Note* Minimum and maximum values included titrated interventions that reported dosing in ranges, and were directly extracted from papers, differing from the averaged dosing extraction synthesis approach outlined in methods. Mean, median and mode were calculated according to the averaged dosing extraction synthesis approach, and did not include titrated values. Most THC studies (12 out of 16) reported dosage units as mg/m^2 for body surface area, while the remaining 4 studies reported units as mg, thus results have been presented separately for studies using mg and mg/m^2.

Frequency

Frequency of administration varied by product and indication. The most commonly reported frequency schedule was twice per day (n = 17; 23.9%), followed by three times per day (n = 15; 21.1%), four times per day (n = 12; 16.9%), and six times per day (n = 4; 5.6%).

Dose titration

Fifteen studies (21.1%) titrated their cannabinoids, tailoring the dosing to individual participant needs to optimise therapeutic effects. Details regarding titration are presented in Table 6.

Table 6: Minimum and maximum titration values for each type of cannabinoid-based medicine (n = 15).

Cannabinoid-based medicine	Minimum (mg/day)	Maximum (mg/day)
CBD	50.0	600.0
Dronabinol	2.5	20.0
Levonantradol	0.5	9.0
Nabilone	0.5	2.0
Nabiximols	CBD: 2.5 THC: 2.7	CBD: 40.0 THC: 43.2
THC	No titrations	No titrations
THC:CBD	CBD: 0.96 THC: 0.92	CBD: 40 THC: 40

Dosage justification

Only 16 out of 71 interventional studies (22.5%) provided justification for their cannabinoid dosage. Table 7 summarises the rationale and cited studies behind the chosen dosage schedules in the 16 reporting studies. Most dosage decisions were influenced by studies outside the cancer setting or were tailored to specific cancer populations, often lacking a systematic rationale (Table 7).

Table 7: Justification for cannabinoid dosage schedules (n = 16).

Overall reasoning	Specific reasoning from included studies (n = 16)
Previous preclinical studies	• Dominiak et al.[161], citing Peters et al.[234], chose a CBD dosing schedule extended until day 7 after chemotherapy infusion. This decision was based on animal models suggesting neuroinflammatory changes in nerve cell ganglia occur within the first 24 hours to 6 days after injection of classical chemotherapeutic agents. This approach aimed to ensure a reasonable margin of safety for a potential effect, given the complete elimination of paclitaxel and oxaliplatin within 3–5 days following infusion. • Garb et al.[166] prescribed doses of 10mg each of THC and a phenothiazine, justifying that higher THC doses were safe because "phenothiazines block most of the undesirable effects of THC." Supporting references were not provided. • Lynch et al.[185] stated that the terminal elimination half-lives of cannabinoids in nabiximols are 24-36 hours or longer, justifying a 2-week washout period to prevent carry-over effects between study arms. Supporting references were not provided.
Previous clinical studies	• Einhorn[163], Jones [175],Levitt [182], and Wada [206] et al. influenced the dosage schedule based on "data generated in earlier clinical studies"[235]. References to supporting studies were not provided. • Yeshurun et al.[88] determined the dose and duration of CBD administration based on doses previously safely used in several clinical trials in the nontransplant setting [236-242]. • Frytak et al.[165] selected a THC dosage to duplicate that previously used by Sallan and colleagues [197].

	• Sallan et al.[196] administered 10 mg of THC to five patients with body surface areas of less than 1m2 based on the variability of response observed in their previous study [197]. • Twelves et al. [205] chose their individualized the dosing regimen of 3–12 sprays/day for nabiximols due to the high degree of interpatient pharmacokinetic variability. This approach was informed by dose-ranging trials that demonstrated a favourable risk/benefit profile in patients with chronic pain [243-245]
Regulatory indication/ guidance	• Sukpiriyagul et al.[63] based their dosage schedule according to the CINV prophylaxis guidelines in the National Comprehensive Cancer Network Antiemesis Version 1.2022[246]. • Zylla et al. [115] cited the "Review of Medical Cannabis Studies Relating to Chemical Compositions and Dosages for Qualifying Medical Conditions" document[247]. • Turcott et al.[90] chose a dosage schedule of 0.5 mg daily of nabilone or placebo for 2 weeks, stating that "administration of this agent must initiate with an induction dose as per regulatory indication," although the specific regulatory indication was not cited.
Subjective author decisions	• Three studies stated that their dosage decisions were "somewhat arbitrary," and were based on what "the authors 'felt' would be optimal for maximal therapeutic efficacy with minimal side effects and activity impairment" [153, 159, 193].

Duration of intervention

The most reported duration for cannabinoids was one treatment cycle, spanning 1 to 8 days (n = 38; 53.5%). Fourteen studies (19.7%) followed participants over 2-3 treatment cycles, each lasting 1-8 days. Reporting units varied, with eight studies specifying days, six reporting in weeks, and three in months (Table 4).

Risk of bias (RoB) assessments

Most studies (76/87; 87.4%) were assessed to have a 'high' overall risk of bias, and the remaining 11 (12.6%) studies were assessed to have 'some concerns'. No studies demonstrated an overall low risk of bias (Figure 8). Individual study assessments are provided in Appendix 2.

1. Bias arising from the randomisation process

All non-RCT studies (n = 34; 39.1%) were automatically assigned a high bias rating due to the absence of randomisation. Most RCTs (32/53, 60.4%) were assessed to have 'some concerns' in this domain, 18 RCTs (34.0%) were assessed as 'low' risk, and four (7.5%) were judged as 'high' risk of bias. Although randomisation and blinding were adequately reported, allocation sequence and concealment was poorly reported, especially in older RCTs (Figure 8).

2. Bias due to deviations from intended interventions

Bias due to deviations from intended interventions was a major concern. The majority of studies (n = 69; 79.3%) were rated 'high' risk, 14 (16.1%) had 'some concerns', and only three (3.4%) studies were considered low risk for this domain. The prevalence of high risk studies was largely due to the poor-reporting of analyses used to estimate the effect of assignment to intervention, as well as details regarding deviations (Figure 8).

3. Bias due to missing outcome data

Missing outcome data was poorly reported, with only eight out of 87 studies (9.2%) considered low risk. Most studies (n = 59; 67.8%) were rated high risk, and 22 (25.3%) had some concerns, mainly due to inadequate reporting on dropout numbers, particularly in older RCTs (Figure 8).

4. Bias in measurement of the outcome

This domain was assessed to have 'some concerns' in 41 studies (47.1%), low risk in 35 (40.2%) studies, and high risk in 10 (11.5%) studies. A low-risk rating was assigned when studies were double-blinded, measures were validated with clear parameters, and there was a minimal chance of intervention knowledge influencing assessments. The prevalence of 'some concerns' resulted from the use of non-validated PROMs, as well as the lack of clear definitions and parameters in studies focusing on observed episodes of CINV (i.e. identity of assessor, definition of vomiting episodes, time frame etc.) (Figure 8).

5. Bias in selection of the reported result

Most studies were at risk of selective reporting bias, with 49 out of 87 (56.3%) studies having 'some concerns', 37 (42.5%) at 'high risk', and none at 'low risk.' While some studies provided a protocol or trial registration, none provided a pre-specified statistical analysis plan. Despite all studies using multiple outcome measurements, only 19 (21.8%) studies clearly stated a primary outcome and there was insufficient reporting on multiple data analyses (Figure 8).

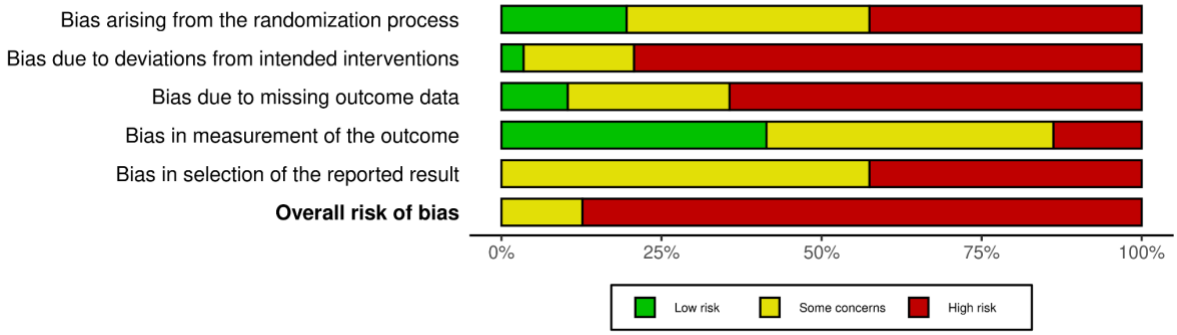


Figure 8: Cochrane risk of bias scores (low, some concerns and high risk) across 5 bias domains (n = 87).

Bar chart is unweighted. Summary plot generated using Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments[248].

Primary outcomes: Effects of cannabinoids on cancer treatment-related symptoms

This section includes data on all reported primary outcomes, which can be >1 per study as outlined in Extraction Synthesis decisions 5c. Multiple comparators. Hence, the total number of "studies" in this section is N = 93. For ease of interpretation, Table 8 broadly categorises primary outcomes alongside associated measurement tools. For a more detailed summary of primary outcomes including time frames and comparator, refer to Table 2.

Table 8: Frequency of primary outcomes and measurement tools (N = 93)

Time frames for primary outcomes were not recorded in this table due to inconsistent reporting, with many studies omitting them or providing arbitrary values. Including time frames would have resulted in an excessive number of similar outcomes with minor time variations.

Symptom	Primary outcome (broad)	Frequency of primary outcome (n =)	Name measurement tool	Frequency of measurement tool (n =)	Type of measure
Chemotherapy induced nausea and vomiting (CINV) (n = 54)	Proportion of patients with a "complete" response (i.e. no vomiting)	14	Self-administered questionnaire and compared with nurses' notes	9	Objective measure
			Combined 'Visual Analog Scale' (VAS) 0-10 self-rated nausea (no nausea vs extreme nausea), and observed episodes vomiting	2	PROM
			Observed and recorded with digital counter	1	Objective measure
	Total number of vomiting and retching episodes	10	Observed by nursing staff and patient	10	Objective measure
	Mean number of vomiting episodes	7	Observed and recorded on a case report by patients	7	Objective measure
	Median frequency of vomiting episodes	6	Observed, patients recorded on daily questionnaires	6	Objective measure
	Graded antiemetic response	5	Assessed by physician and categorised into grades: Complete response (absence nausea vomiting), Partial response (50% reduction), No response (<50% reduction). Expressed as numerical 'mean physician rating' score.	5	CROM
	Mean combined nausea and vomiting score	3	Unnamed questionnaire	3	PROM

	Mean combined nausea/vomiting severity score	3	Assessed by staff after each chemotherapy cycle	3	CROM
	Number of participants expressing preference for cannabis over previous antiemetic treatment experience	2	Unnamed self-assessed questionnaire	2	PROM
	Self-graded antiemetic response to nabilone (excellent, good, fair, poor)	1	Self-reported experience	1	PROM
	Number of patients with a >50% reduction in number of emetic episodes	1	Number of emetic episodes reported by patients, then compared to prior experience	1	PROM
	Total number of chemotherapy cycles (among all participants) accompanied by vomiting	1	Number of vomits recorded by patients in self-administered questionnaire 24h following chemotherapy	1	PROM
	Number of participants expressing preference for cannabis over comparator	1	Recorded in patient diary	1	PROM
Quality of life/ total symptom burden (n = 15)	Change in cancer symptom severity score from baseline to follow-up	13	European Organisation for Research and Treatment of Cancer Quality of Life for Cancer Patients Questionnaire (EORTC QLQ-C30-v3), Global Health domain (n = 6)	6	PROM
			Memorial Symptom Assessment Scale (MSAS) total score (n = 1)	1	PROM
			Edmonton Symptom Assessment Scale (ESAS), Total Symptom Distress Score (TSDS) (n = 1)	1	PROM

			Functional Assessment of Cancer Therapy- Brain (FACT-Br) questionnaire, Total Fact Br domain score (n = 1)	1	PROM
			Rotterdam Symptom Checklist (RSCL), Overall Valuation of Life domain (n = 1)	1	PROM
			Baseline composite symptom score (n = 1)	1	PROM
			Measured via "online patient self-evaluation", tool name not provided (n = 1)	1	PROM
			Self-reported as grades: without symptom (0), minimal (1-2), or severe (3-4), aggregated as sum (n = 1)	1	PROM
	"Treatment success" change in % of patients reporting good quality of life from baseline to 6 months	1	Self-reported quality of life assessed on Likert scales ranging from very poor, neither poor nor good, good, to very good	1	PROM
	Quality of life in THC-positive vs. THC-negative oncology patients	1	Measured by Total ESAS domain on Edmonton Symptom Assessment Scale (ESAS)	1	PROM
Pain (n = 7)	Change in weekly average pain score from baseline to follow up	5	Measured by 11-point Numeric Rating Scale for Pain Intensity (NRS-PI) from baseline (average pain score over seven days pretreatment) to the final week of stable dose treatment	2	PROM
			Wong-Baker Faces Pain Rating Scale (FACES)	1	PROM
			Assessed by self-reported pain log (documenting average daily pain scores over a 7 day period using a 0-19 ‘visual analog scale’ rating)	1	PROM
			Assessed by average pain domain of Brief Pain Inventory (BPI)	1	PROM

	Difference in vibration perception threshold (VPT) from baseline to day 4±1 after initiation of first chemotherapy cycle	1	Measured by multi-frequency vibrometry (MF-V) with the VibroSense Meter® II medical device, extracted for first reported data: merged VPT model at Dig-32Hz	1	Objective measure
	Proportion of participants with minimal clinically important difference (MCID) in ESAS pain score at most recent palliative care visit	1	Pain domain, Edmonton Symptom Assessment System (ESAS). Established MCID improvement score for an individual ESAS category is ≥1/10.	1	PROM
Anorexia/ cachexia/ chemosensory perception (n = 7)	Proportion of patients reporting appetite improvement from baseline at “some point” during study period	1	Assessed by the North Central Cancer Treatment Group questionnaires for appetite and weight	1	PROM
	Mean daily appetite change (VAS score) from baseline to week 6	2	Assessed via Visual analogue scale (VAS; 0mm worst; 100mm = best)	1	PROM
	Total chemosensory complaints score on day 18	1	Measured on Taste and Smell Survey	1	PROM
	Mean change in appetite from baseline to 8 weeks	1	Measured by the anorexia/cachexia subscale (A/CS) of the Functional Assessment of Anorexia-Cachexia Therapy (FAACT) questionnaire	1	PROM
	Number of participants with weight increase of ≥10% from baseline to 6 months	1	Weighed by scales and physical examination	1	Objective measure
	5% change in Lean Body Mass (LBM) from baseline (before first round of	1	Bioelectrical impedance analysis (BIA) using the medical Body Composition Analyzer Seca 515/514	1	Objective measure

	chemotherapy), to after 3 rounds of chemotherapy (n = 7)				
Radiotherapy induced nausea and vomiting (RINV) (n = 2)	Total number of patients who vomited within 0-4 hour period following radiotherapy	1	Patient interviewed within a few days of treatment	1	PROM
	Mean daily scores for nausea, vomiting episodes, and appetite	1	Self-assessed and recorded in patient diary	1	PROM
Chemotherapy induced peripheral neuropathy (CIPN) (n = 2)	Median functionally disturbing (grade 2-3) neuropathy survival (FdNFS) defined as the time from the first cannabis treatment to the time of first appearance of Fd neuropathy among cannabis-treated patients compared to the control group	1	CTCAE grade for neuropathy as evaluated by treating oncologist	1	CROM
	Change in neuropathic pain score	1	Measured by 11-point Numeric Rating Scale for Pain Intensity (NRS-PI) from baseline (average pain score over seven days pretreatment) to the final week of stable dose treatment. 0 (no pain) - 10 (pain as bad as you can imagine) n = 2	1	PROM
Safety (n = 2)	Tolerability defined as the % of patients that developed an adverse event	1	Recorded in patient diary and daily telephone interviews	1	Objective measure
	Proportion of patients with incidence of treatment-emergent adverse events	1	Assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)	1	CROM

	(TEAEs) leading to discontinuation				
GVHD (n = 1)	Cumulative incidence rates (%) of patients with grades II to IV acute GVHD at day 100 post-transplant	1	Assessed by Consensus grading system with histological confirmation	1	CROM
Anxiety/depression (n = 1)	Self-assessed effects of THC on tension-anxiety and depression at 6 hours after administration	1	Self-rated "Mood scales, McNair & Lorr 1964"	1	PROM
Sleep (n = 1)	Change in sleep quality score from baseline to follow-up	1	Measured by Pittsburgh sleep Quality Index (PSQI), modified single item to ask about last 2 weeks (sleep quality rated on scale from 0 "very good" to 3 "very bad"	1	PROM

Chemotherapy-induced nausea and vomiting (CINV)

CINV was assessed in 50 studies (n = 54 separately extracted primary outcomes; 2379 participants)[63, 84, 136, 151, 154, 157, 162, 164, 166, 167, 171, 175, 177, 180, 182-184, 188, 193, 195, 203].

Seventeen studies assessed nabilone[136, 138, 148, 154, 157, 158, 163, 172, 174, 175, 182, 189, 190, 192, 194, 195, 202], and there were 15 for THC[63, 149, 151, 153, 165, 166, 177, 178, 183, 187, 193, 196, 197, 200], 12 for levonantradol[151, 156, 160, 167, 170, 171, 173, 176, 181, 184, 199, 201, 203], three for dronabinol[179, 180, 188], two mixed THC:CBD[63, 84], and one for nonabine[140]. In two studies, cannabinoids were administered in addition to prochlorperazine, with one using nabilone[157] and one using THC[177]. Four studies had three arms, where the third study arm was a combination therapy group[82, 138, 179, 180, 188]. Two of these studies had combined dronabinol and prochlorperazine[179, 180], one had combined dronabinol and megestrol acetate[82], and one had combined dronabinol and ondansetron[188]. Sixteen studies included a placebo control[63, 84, 149, 162, 165, 175, 177-180, 182, 188, 193, 197, 200, 201], and three of these also included an active comparator[153, 165, 188, 193]. Twenty-four studies included only an active comparator. The most common active comparators were prochlorperazine (16 studies)[138, 148, 163-165, 172, 174, 177, 179, 180, 187, 192, 193, 196, 199, 202] and metoclopramide (5 studies)[136, 153, 157, 170, 195], with one of the metoclopramide studies delivered in combination with dexamethasone[157]. Chlorpromazine[140, 173] and domperidone[158, 194]each had two studies, while other comparators like Alizapride[190], ondansetron[188] and natural THC[151] (compared to synthetic) were evaluated in single studies. One study had two active comparators (metoclopramide and thiethylperazine)[153]. 10 studies compared cannabinoids to previous experience with an active comparator prior to the study[144, 154, 156, 160, 167, 171, 176, 181, 183, 189, 203].

Of the 50 studies, 46 (92.2%) had a high overall risk of bias, and four (7.8%) had some concerns.

Out of 54 separately extracted primary outcomes for CINV, 38 (70.3%) of these suggested a greater benefit of cannabinoids compared to comparator[63, 84, 138, 148, 149, 151, 153, 158, 163-167, 170-175, 177-179, 182, 187, 190, 192-194, 196, 197, 200-203, 206]. Of these, 23 were statistically significantly superior[63, 84, 138, 148, 149, 158, 163, 164, 166, 170, 172-175, 178, 179, 182, 187, 190, 192, 194, 197, 201, 206], nine were non-significantly superior[136, 140, 151, 153, 165, 167, 177, 180, 188, 200, 203], and six were reported as superior but did not report significance[171, 187, 193, 196, 202]. Two (3.6%) studies reported no effect[179]. Five (13.2%) studies found that cannabinoids were worse than comparator, none were significantly worse, four were non-significantly worse[136, 140, 153, 157], and 1 was worse with no significance reported[188]. Nine studies were not extractable[120, 154, 156, 160, 176, 181, 183, 189, 199]. Overall, there was a significantly higher proportion of CINV studies reporting significantly positive outcomes compared to those reporting non-significantly positive, negative, or no effect outcomes (p = 0.004) (Table 2; Figure 9).

Quality of life and/or total symptom burden

The effect of cannabinoids on quality of life and/or total symptom burden was assessed in 15 studies (n = 15 primary outcomes; 10,414 participants)[64, 70, 112, 139, 141, 143-145, 147, 150, 152, 155, 168, 186, 198]. Of these, 11 were observational case series with cross-sectional or pre-test/post-test outcomes, while the remaining four were interventional studies. Among the 11 observational studies, six were based on registry data from medicinal cannabis license programs[112, 139, 141, 144, 145, 147], two involved recreational cannabis users[64, 70], one focused on licensed medical cannabis users (outside registry setting)[186], and one included a mixed population of both licensed and recreational users[143]. Among the four interventional studies, two assessed mixed THC:CBD[152, 198], and CBD[168] and nabilone[155] were each evaluated in single studies. Seven studies compared cannabinoids to a concurrent cohort of non-users[64, 70, 143, 145, 147, 150, 186], six

studies compared cannabinoids to baseline before cannabinoid treatment[112, 139, 141, 144, 152, 168], and one trial compared a 1:1 ratio of THC:CBD with a 4:1 ratio[198].

Among the 15 studies, 13 (86.7%) were rated as high risk of bias, with two (13.3%) having some concerns. Eight (53.3%) studies suggested a greater benefit of cannabinoids compared to comparator. Of these, five were statistically significantly superior[64, 112, 139, 141, 144], and three were non-significantly superior[152, 168, 198]. Five (33.3%) studies indicated that cannabinoids were worse than comparator[70, 143], with three being significantly worse[147, 150, 186]. Overall, there was no significant difference in the proportion of QoL studies reporting positive outcomes compared to those reporting negative or no effect outcomes (Table 2; Figure 9).

Five out of 11 (45%) observational studies reported a significant benefit, while three out of four (75%) interventional studies found a non-significant benefit[152, 168, 198]. However, the remaining 5/11 (45%) observational studies reported that cannabinoids were worse than comparator, with three of these being significant[70, 143, 147, 150, 186]. Data was not extractable for one observational[145] and one interventional study[155] each (Table 2).

Pain

Pain was assessed in seven studies (n = 7 primary outcomes; 1328 participants), consisting of four interventional[115, 169, 185, 204] and three observational studies[85, 87, 142]. Among the interventional studies, two examined nabiximols[169, 185], two focused on mixed THC:CBD[115], and two on traditional processed whole cannabis 'Bhanga'[204]. Out of the four interventional studies, two compared cannabinoids with placebo[169, 185], one compared cannabinoids to standard care[115], and one compared to baseline before cannabinoid treatment[87, 204].

All seven studies (100%) were considered high risk of bias. Five (71.4%) studies suggested that cannabinoids were more effective than the comparator in reducing pain. Among these, three were statistically significant[85, 142, 204], and two were non-significantly superior[169, 185]. One study (12.5%) reported no effect[115] (identical scores for cannabinoids and comparator), and one study (12.5%) reported cannabinoids to be non-significantly worse than the comparator[87]. Overall, there were no significant differences in the proportion of pain studies (Table 2; Figure 9).

Anorexia/cachexia/chemosensory perception

The effect of cannabinoids on anorexia, cachexia and chemosensory perception was assessed in six studies (n = 7 primary outcomes; 877 participants)[81-83, 90, 146, 161]. There were four RCTs[81-83, 90], one comparative study without concurrent controls[161], and one case series with pre/post outcomes[146]. All studies were interventional. Dronabinol[81, 82] and mixed THC:CBD[83, 146] were assessed in two trials each, while CBD[161] and nabilone[90] were evaluated in single studies. Three studies compared cannabinoids to placebo[81, 83, 90], with one of these having a third study arm with natural THC as the comparator[83]. One study compared cannabinoids to active comparator megestrol acetate[82], and one pre-post study compared to baseline before cannabinoids[146].
Of the six studies, four (66.7%) were at high risk of bias, and two (33.3%%) were assessed to have some concerns. Of the seven primary outcomes, three (42.9%) studies[81, 83, 90] reported that cannabinoids were better than comparator at improving chemosensory perception and appetite, although none were statistically significant. Two (28.6%) studies reported that cannabinoids were worse[82, 83], with one being significant[82], and two (28.6%) studies[146, 161] were not extractable. Overall, there were no significant differences (Table 2; Figure 9).

Radiotherapy induced nausea and vomiting (RINV)

RINV was assessed in two studies (n = 3 primary outcomes; 83 participants)[184, 195]. Both trials were RCTs, with one having a parallel design[184] and the other having an unclear design[195]. In one trial, nabilone was compared with the active comparator metoclopramide[195]. The other trial, with three arms, assessed two dosages of levonantradol (0.5mg and 0.75mg) compared with the active comparator chlorpromazine[184].

Both studies (100%) had an overall high risk of bias. The levonantradol study[184] reported that both dosages were less effective at controlling RINV than chlorpromazine, though significance was not reported. The nabilone study[195] results were not extractable (Table 2; Figure 9).

Chemotherapy-induced peripheral neuropathy (CIPN)

CIPN was assessed in two studies (n = 2 primary outcomes, 567 participants)[191, 207]. One was a large, retrospective observational registry study comparing the median functionally disturbing (grade 2-3) neuropathy survival (FdNFS) between cannabis-treated patients and a concurrent cohort of non-users [207]. The other was an interventional study comparing vibration perception threshold as a measure of early CIPN between patients receiving CBD and a historical control group[191].

Both studies (100%) had a high risk of bias. Both studies reported cannabinoid superiority over controls, with the observational study being significant[207]. (Table 2; Figure 9).

Safety

Two studies assessed safety as their primary outcome (2 primary outcomes; 37 participants[162, 205]. Both trials were pilot RCTs with parallel designs. Both trials were

placebo-controlled; one trial assessed nabiximols[205], and the other assessed mixed THC:CBD[162].

Both studies (100%) had overall 'some concerns' for risk of bias. The THC:CBD study reported worse safety outcomes[162], as the proportion of patients experiencing adverse events was higher than placebo. In contrast, the nabiximols study had fewer treatment-emergent adverse events than placebo[205]. However, neither study was statistically significant (Table 2; Figure 9).

Graft-versus-host disease (GVHD)

A small interventional phase II comparative study, without concurrent controls, investigated the effects of CBD in preventing graft-versus-host disease (GVHD) in 48 patients undergoing allogeneic haematopoietic cell transplantation [88]. The study compared the cumulative incidence rate (%) of grades II to IV acute GVHD at day 100 post-transplant in the CBD cohort to historical data [88].

The study was judged to have a high risk of bias [88]. The study reported significant superiority of the CBD cohort over historical controls. There was a significantly smaller proportion of patients receiving CBD who developed grades II to IV GVHD at day 100 post-transplant (12.1%) compared to historical controls (46%), with a hazard ratio of 0.3 [95% CI, 0.2 to 0.6, $p = 0.0002$][88] (Table 2; Figure 9).

Anxiety/depression

One pilot pseudorandomised placebo-controlled trial with crossover design assessed the effects of THC on improving 'mood' in 12 patients undergoing radiotherapy, and anxiety and depression were included as subscales within the Mood Scales from MacNair and Lorr questionnaire[159].

The study was judged to have a high risk of bias. Results were not extractable as no values were provided, but it was stated that there was “nil” effect for both anxiety and depression domains compared to placebo[159] (Table 2) (Figure 9).

Sleep

One observational pre-post case-series assessing QoL using multiple PROMs, included sleep assessed by the Pittsburgh Sleep Quality Index (PSQI) as one of its primary outcomes[86]. This outcome was presented as the first reported data and was extracted according to the extraction synthesis decisions. The study compared participants receiving a cannabis license to their baseline first appointment to 2 weeks after cannabinoid use.

The study was judged to have a high risk of bias. It was reported that sleep quality when treated with cannabinoids was significantly superior to baseline (mean difference from baseline -0.33 PSQI score, $p = 0.020$)[86] (Table 2) (Figure 9).

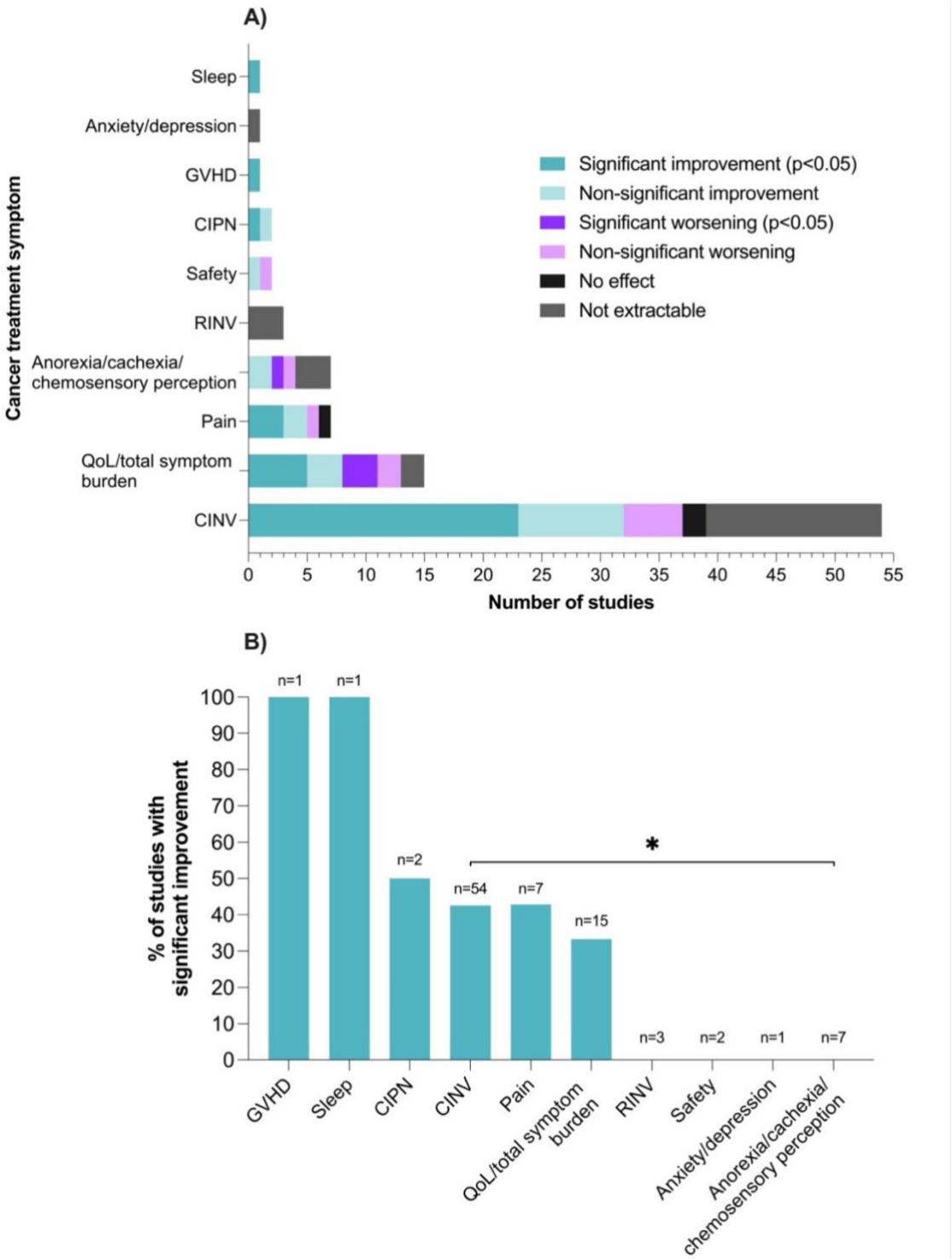


Figure 9: Effectiveness of cannabinoids at improving cancer-treatment related symptoms and side effects (N = 93 primary outcomes).

A) Number of studies categorised by significance outcomes (significant improvement ($p < 0.05$), non-significant improvement, significant worsening ($p < 0.05$), non-significant worsening, no effect, and not extractable). Improvement and worsening reported relative to study comparator. *Studies not reporting significance were categorised as 'Not Extractable.'* **B) Proportion of studies with significant improvement**. A significant difference between CINV and anorexia/cachexia/chemosensory perception was observed (Fisher's exact test, $p = 0.038$, two-tailed).

Adverse events (AEs) and dropouts

Adverse events (AEs) were reported for 76 (87.4%) studies, with an overall dropout rate of 33.3% (across all study arms). Although there was a higher incidence of AEs in participants taking cannabinoids compared to placebo/active comparators (Table 9), and a higher rate of dropouts (36.1%, compared to 26.71%), this was not significant. Commonly reported side effects included dizziness, drowsiness/somnolence, fatigue, dysphoria, dry mouth, blurred vision, anxiety, confusion, hypertension, and tachycardia. In general, these side effects were reported to be mild to moderate. Although few studies reported severe side effects, most occurrences of severe side effects resulted in participant withdrawal. Reported severe side effects included memory lessening [112], sedation[84, 165], coordination problems[165], hallucinations[183], and anxiety[84].

Table 9: Dropouts among cannabinoid trials (N = 87).

N = and % of cannabinoid and comparator arms calculated as outlined in extraction synthesis decisions.

Reference	Total N = dropouts (% total sample size)	Dropouts in cannabinoid arm (% of arm)	Dropouts in comparator arm (% of arm)
Ahmedzai et al., 1983	8 (24%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Anderson et al., 2019	377 (34%)	N/A - observational	N/A - observational
Aviram et al., 2020	185 (63%)	N/A - observational	N/A - observational
Aviram et al., 2022	278 (86%)	N/A - observational	N/A - observational
Bar-LevSchleider et al., 2018	1675 (57%)	N/A - observational	N/A - observational
Bar-Sela et al., 2013	105 (50%)	N/A - observational	N/A - observational
Bar-Sela et al., 2019	18 (75%)	N/A - single arm intervention	N/A - single arm intervention
Brisbois et al., 2011	30 (65%)	16 (67%)	14 (64%)

Chan et al., 1987	10 (25%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Chang et al., 1979	0	0.00%	0
Chang et al., 2019	N/A - cross-sectional study	N/A - cross-sectional study	N/A - cross-sectional study
Citron et al., 1985	20 (43%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Clarke et al., 2022	4 (16%)	N/A - single arm intervention	N/A - single arm intervention
Colls et al., 1980	Not reported	Not reported	Not reported
Cone et al., 1982	Not reported	Not reported	Not reported
Cote et al., 2016	24 (43%)	9 (32%)	15 (54%)
Crawford et al., 1986	25 (78%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Cronin et al., 1981	3 (10%)	N/A - single arm intervention	N/A - single arm intervention
Cunningham et al., 1988	10 (13%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Davies et al., 1974	Not reported	Not reported	Not reported
Duran et al., 2010	1 (6%)	1 (14%)	0
Einhorn et al., 1981	20 (25%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Frytak et al., 1979	32 (27%)	22 (58%)	Prochlorperazine = 6 (9.76%) Placebo = 4 (10.1%)
Garb et al., 1980	12 (55%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Gerhartz et al., 1983	Not reported	Not reported	Not reported

Good et al., 2019	13 (62%)	N/A - single arm intervention	N/A - single arm intervention
Grimison et al., 2020	9 (11%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Guy et al., 2010	Not reported	122.4 (High dose group = 22% Middle dose = 7% Low dose = 5%)	36 (10%)
Heim et al., 1984	12 (21%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Herman et al., 1979	39 (26%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Hutcheon et al., 1983	36 (33%)	Not reported	Not reported
Jatoi et al., 2002	345 (71%)	116 (73%)	107 (67%)
Johansson, et al., 1982	9 (33%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Jones et al., 1982	30 (56%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Kenny, J. B. et al., 1982	Not reported	N/A - single arm intervention	N/A - single arm intervention
Kleinman, S. et al., 1983	2 (13%)	2 (13%)	0
Lane et al., 1990	6 (32%)	3 (43%)	0
Lane et al., 1991	23 (37%)	14 (67%)	Prochlorperazine alone = 4 (19%)
Levitt et al., 1982	20 (34%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Lucas et al., 1980	4 (7%)	N/A - single arm intervention	N/A - single arm intervention
Lucraft et al., 1982	Not reported	Not reported	Not reported

Lynch et al., 2014	2 (11%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
McCabe et al., 1988	Not reported	Not reported	Not reported
Meiri et al., 2007	15 (23%)	4 (24%)	Ondansetron alone = 4 (25%) Placebo = 3 (21%)
Niamatali et al., 1984	Not reported	Not reported	Not reported
Niederle et al., 1986	Not reported	Not reported	Not reported
Nielsen et al., 2022	Not reported	Not reported	6 (25%)
Niiranen et al., 1985	8 (25%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Orr et al., 1981	24 (30%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Pawasarat et al., 2020	N/A - retrospective chart review	N/A - retrospective chart review	N/A - retrospective chart review
Pomeroy et al., 1986	7 (18%)	3 (16%)	4 (21%)
Sallan et al., 1980	35 (42%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Sallan et al., 1975	11 (50%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Schloss et al., 2021	27 (31%)	16 (36%)	11 (26%)
Sheidler et al., 1984	4 (20%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Shiling et al., 1981	1 (11%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Stambaugh et al., 1984	8 (40%)	Not reported	Not reported
Steele et al., 1980	18 (33%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group

Strasser et al., 2006	79 (33%)	29 (31%)	THC = 35 (35%) Placebo = 15 (31.5%)
Stuart Harris et al., 1983	1 (4%)	N/A - single arm intervention	N/A - single arm intervention
Tavhare et al., 2019	14 (38%)	N/A - single arm intervention	N/A - single arm intervention
Turcott et al., 2018	25 (53%)	13 (59%)	12 (48%)
Twelves et al., 2021	17 (81%)	11 (92%)	6 (67%)
Ungerleider et al., 1982	75 (35%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Wada et al., 1982	30 (26%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Yeshurun et al., 2015	2 (4%)	2 (4%)	N/A - historical control
Zhang et al., 2018	Not reported	Not reported	Not reported
Zylla et al., 2021	12 (40%)	6 (40%)	6 (40%)
Aprikian et al., 2023	197 (55%)	N/A - observational	N/A - observational
Archer et al., 1983	Not reported	Not reported	Not reported
Azizoddin et al., 2023	3 (1%)	N/A observational	N/A observational
Bar-Sela, et al., 2019	51 (60%)	28 (63%)	16 (37%)
Calcaterra et al., 2020	N/A - cross-sectional study	N/A - cross-sectional study	N/A - cross-sectional study
Dalzell et al., 1986	5 (22%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Diasio et al., 1981	5 (19%)	N/A - single arm intervention	N/A - single arm intervention
Dominiak et al., 2023	Not reported	Not reported	Not reported
Ekert et al., 1979	11 (58%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Ekert et al., 1979	7 (50%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group

Giordano et al., 2023	3 (11%)	N/A - observational	N/A - observational
Heim et al., 1981	3 (25%)	N/A - single arm intervention	N/A - single arm intervention
Kluin-Neleman et al., 1979	2 (18%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Laszlo et al., 1981	2 (6%)	N/A - single arm intervention	N/A - single arm intervention
Macari et al., 2020	N/A cross-sectional study	N/A cross-sectional study	N/A cross-sectional study
Nielsen et al., 2022	N/A cross-sectional study	N/A cross-sectional study	N/A cross-sectional study
Priestman et al., 1987	8 (20%)	6 (30%)	1 (5%)
Sukpiriyagul et al., 2023	6 (10%)	N/A - crossover, dropouts could not be assigned specific group	N/A - crossover, dropouts could not be assigned specific group
Waissengrin et al., 2021	N/A - observational	N/A - observational	N/A - observational

Secondary outcomes: Tumour response and survival outcomes

Tumour response

Four studies assessed tumour response as a secondary outcome[88, 146, 198, 205]. Of these, two studies used magnetic resonance imaging (MRI) scans and Response Assessment in Neuro-oncology (RANO) criteria to compare tumours at baseline and endpoint[198, 205]. One study assessed tumour progression through the cumulative incidence of relapse at 1-year post allogeneic-HSCT transplantation[88], and the final study reported tumour progression, partial response, and stable disease without specifying the assessment method[146].

Twelves et al.[205] reported that RANO assessments of MRI images showed no discernible difference between nabiximols and placebo, and both groups had an equal proportion of patients (33%) remaining progression-free at 6 months. Similarly, Schloss et al.[198] found no significant difference in MRI tumour burden/control ($p = 0.751$) or reduction ($p = 1.000$) between 1:1 and 4:1 ratios of THC:CBD. Yeshurun et al.[88] reported a 41% cumulative incidence of relapse at 1 year post-transplantation among participants receiving CBD, although relapse data for historical controls were not provided. Bar-Sela reported that out of the 11 participants receiving cannabinoids for more than 2 weeks, two (18.2%) experienced tumour progression, seven (63.6%) had a partial response, and two (18.2%) showed stable disease[146].

Survival

Overall survival (OS)

Seventeen studies assessed survival as a secondary outcome[82, 83, 88, 90, 112, 115, 141, 142, 144, 166, 168, 182, 196, 197, 202, 205, 206]. In all 17 studies, overall survival was evaluated over study duration, a period ranging from 1 to 24 months. Overall survival (at the defined follow up time point, which varied between studies) ranged from 66.7% to 98.2%. The average OS was 86.4%, and the median OS was 86.1%. Only two out of the 17 studies differentiated OS between participants receiving cannabinoids and the comparator[83, 205]. Strasser et al. found slightly worse OS on cannabinoids (98.4%) compared to placebo (99.58%) at 6 weeks, although this study was not powered for survival[83]. Twelves et al. reported significantly better OS on cannabinoids (83.0%) compared to placebo (44.0%) at 12 months[205].

Median survival time (days)

Two studies reported median survival time [82, 168]. Good et al.[168] reported 143 days as the median survival time on cannabinoids but did not have a comparator. Jatoi et al.[82] reported a higher median survival time on the cannabinoid dronabinol (141 days) than the comparator megestrol acetate (123 days), although this difference was not statistically significant (log-rank $p = 0.66$).

Non-relapse mortality

One study reported that the cumulative incidence rate of non-relapse mortality at 12 months post allogeneic-HSCT transplantation was lower for participants receiving CBD (13.4%) compared to historical controls (20%)[88]. However, this difference was not statistically significant ($p = 0.950$)[88].

Interplay between study design components and outcomes

To identify key elements in study design that may be associated with optimal cannabinoid effectiveness, the interplay between study design and outcomes was investigated. Given the heterogeneous nature of this dataset, conducting meta-analyses was not feasible. Additionally, recent recommendations highlighting the overreliance on null-hypothesis-testing were considered and used to inform our approach to this section of our investigations[137]. Data are presented as descriptive statistics (as outlined in Extraction Synthesis Decisions 5e: Significance) alongside statistical tests. This approach was adopted with the aim of moving beyond the binary categorisation of trials as 'significantly positive' or otherwise 'negative', and to instead acknowledge the continuum of trial effectiveness in a more transparent assessment. This section includes data on all reported primary outcomes, which can be >1 per study as outlined in Extraction Synthesis decisions 5c. Multiple comparators. Hence, the total number of "studies" in this section is N = 93.

Study type

Among the 59 included RCTs, the majority (n = 37; 62.7%) reported improvement with cannabinoids over the comparator, with 23/37 achieving statistical significance. Three RCTs (5.1%) reported no effect, and seven RCTs (11.9%) reported that cannabinoids were less effective than the comparator, with 1/7 demonstrating significant worsening. Of the four comparative studies with concurrent controls, two (50%) reported cannabinoids to be significantly superior to the comparator, one (25%) indicated non-significant worsening, and one (25%) was not extractable. In the four comparative

studies without concurrent controls, most (n = 3; 75%) reported that cannabinoids were superior to the comparator, with 1/3 being statistically significant; the remaining study (25%) was not extractable. Out of the eight post-test only case series, only one (12.5%) was extractable, and it was non-significantly superior to the comparator. Among the 13 pre-post case series, 10 (77.0%) showed superiority, with 8/10 being statistically significant; one (7.7%) demonstrated non-significant worsening, and two (15.4%) were not extractable. All four cross-sectional studies (100%) found that cannabinoids were worse than the comparator, with 3/4 being statistically significant (Figure 10a). Among study designs, pre-post case series were associated with a higher proportion of significant benefits (defined as a significant and positive effect on the primary outcome); compared to post-test only case series (Figure 10b).

Out of 77 interventional studies using cannabinoid-based medicines, 44 (57%) reported benefits over the comparator (25/44 significant); three reported no effect; and seven reported worsening (1/7 significant). The primary outcomes for 23/77 (30.0%) interventional studies were not extractable. Observational studies exhibited a more balanced distribution: nine studies reported improvements, 9/9 were significant; six reported worsening, with 3/6 being significant, and one study was not extractable. Although observational studies had a higher proportion of significantly positive outcomes than interventional studies (56.3% vs 32.5%), this was not significant.

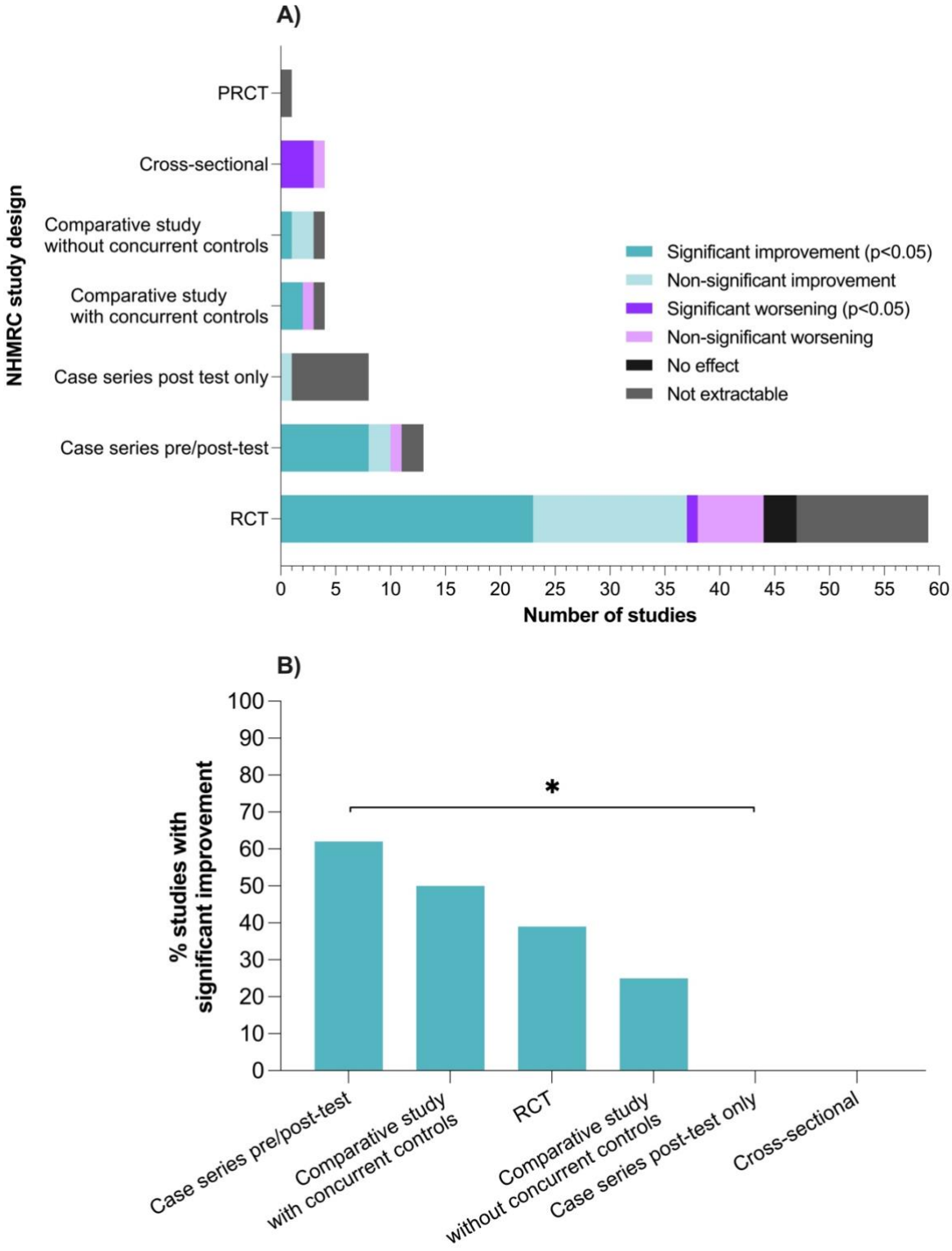


Figure 10: NHMRC Study design compared to outcomes (N = 93).

A) Number of studies categorised by significance outcomes (significant improvement ($p < 0.05$), non-significant improvement, significant worsening ($p < 0.05$), non-significant worsening, no effect, and not extractable). **B) Proportion of studies with significant improvement.** A significant difference between case series with pre/post-test and post-test only was observed (Fisher's exact test, $p = 0.007$, two-tailed).

Participants

Tumour groups

Out of the 35 studies focusing on solid tumour populations, 20 (57.1%) reported superiority, with 14/20 being statistically significant; six (17.1%) showed worsening, with 2/6 being significant; and one (2.9%) reported no effect. Among the 33 studies with a mixed population of participants with both solid tumours and haematologic cancers, 17 (51.5%) reported superiority, with 10/17 being statistically significant; five (15.2%) showed worsening, with 2/5 being significant; two (6.1%) had no effect, and nine (27.3%) were not extractable. Out of the three studies focusing on haematological cancers, two (66.7%) reported significant improvement, and one (33.3%) reported non-significant worsening. There was no significant difference in the proportion of significantly positive outcomes across tumour groups.

Cancer type

Among the 64 studies with a heterogeneous cancer population, 33 (51.6%) reported the superiority of cannabinoids over the comparator, with 23/33 being statistically significant; two (3.1%) reported no effect; nine (14.1%) reported worsening, with 3/9 being significant; and 20 (31.3%) were not extractable. Out of the four studies focusing on lung cancer patients, three (75%) were superior, with 2/3 being significantly superior, and one (25%) was not extractable. In the four studies focusing on gastrointestinal cancer patients, two (50%) were superior, with 1/2 being significant; one (25%) was significantly worse; and one (25%) had no effect. Out of three genitourinary cancer studies, two (66.7%) were significantly superior, and one (33.3%) was non-significantly worse. Among the two studies focused on head and neck cancer, one (50%) was significantly superior, and one (50%) was not extractable. Both glioblastoma-focused studies were non-significantly superior (100%). Among the two

lymphoma-focused studies, one (50%) reported significant superiority, while the other (50%) reported non-significant worsening. The single bone cancer-focused study was significantly superior (100%) (Figure 11a). There were no significant differences in the proportion of significantly positive studies across cancer types (Figure 11b).

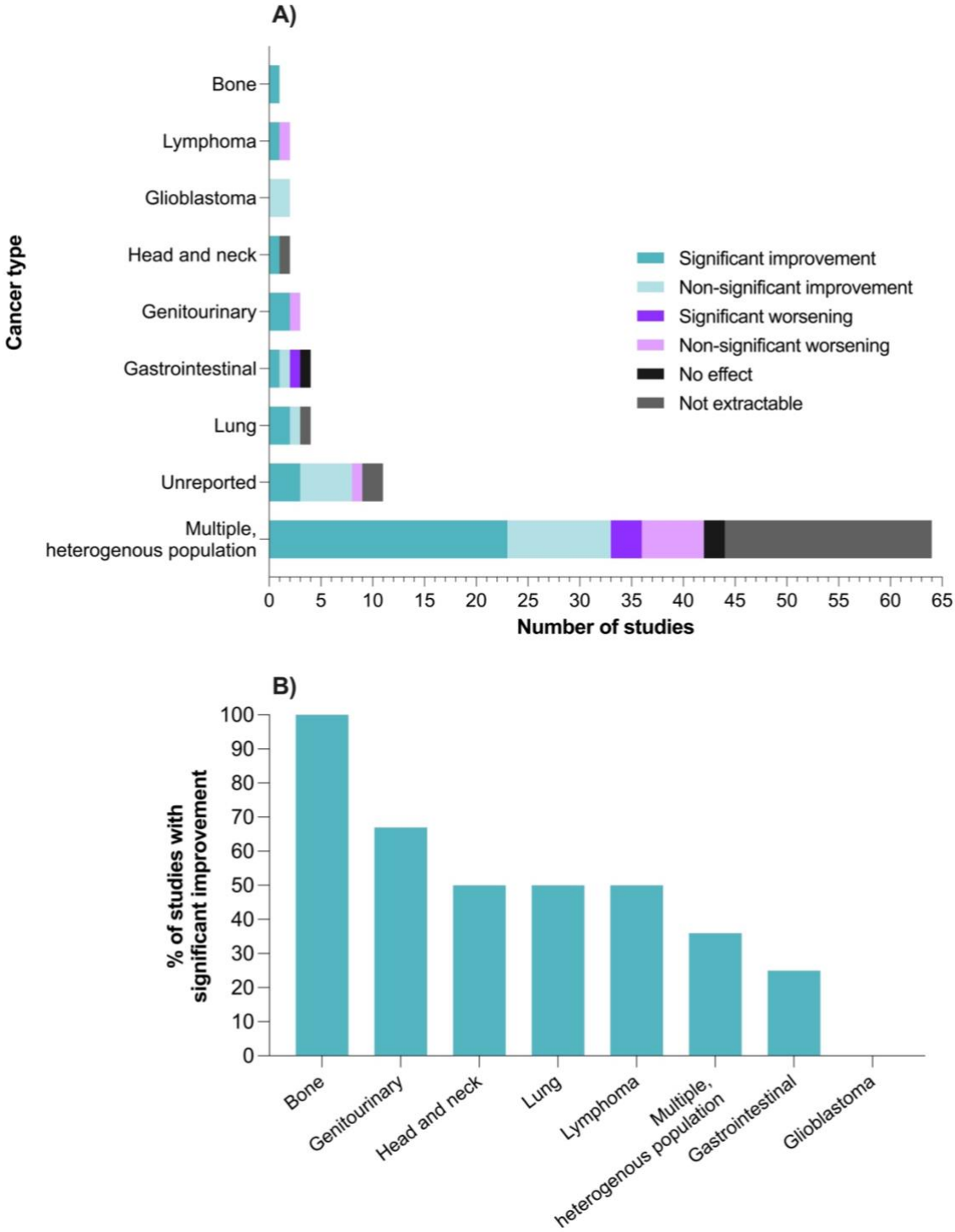


Figure 11: Cancer type compared to outcomes (N = 93).

A) Number of studies categorised by significance outcomes (significant improvement ($p < 0.05$), non-significant improvement, significant worsening ($p < 0.05$), non-significant worsening, no effect, and not extractable). **B) Proportion of studies with significant improvement.** No significant differences were observed across groups (Chi-square test and Fisher's exact test, $p > 0.05$).

Cancer treatment

Cannabinoids were evaluated in a range of clinical contexts, with participants undergoing varying cancer treatment modalities. Among the 62 studies focusing on people undergoing chemotherapy, 37 (59.7%) reported cannabinoids as superior to the comparator, with 24/37 achieving statistical significance. Six studies (9.7%) were non-significantly worse, two (3.2%) showed no effect. In the 11 studies with a heterogeneous population undergoing all types of cancer treatment, seven (63.6%) reported superiority, with 5/7 being significant; three studies (27.3%) reported worsening, with 1/3 being significant. In the seven studies with participants undergoing combined chemoradiotherapy, three (42.9%) reported superiority, with 1/3 being significant; two studies (28.6%) reported worsening, with 1/2 being significant; and two (28.6%) were not extractable. The single study focused on people undergoing combined allogeneic-HSCT and chemotherapy, as well as the single study focused on immunotherapy with chemotherapy, were both significantly superior (100%) (Figure 12a). Overall, there was no significant difference in the proportion of significantly positive outcomes across any cancer treatment group (Figure 12b).

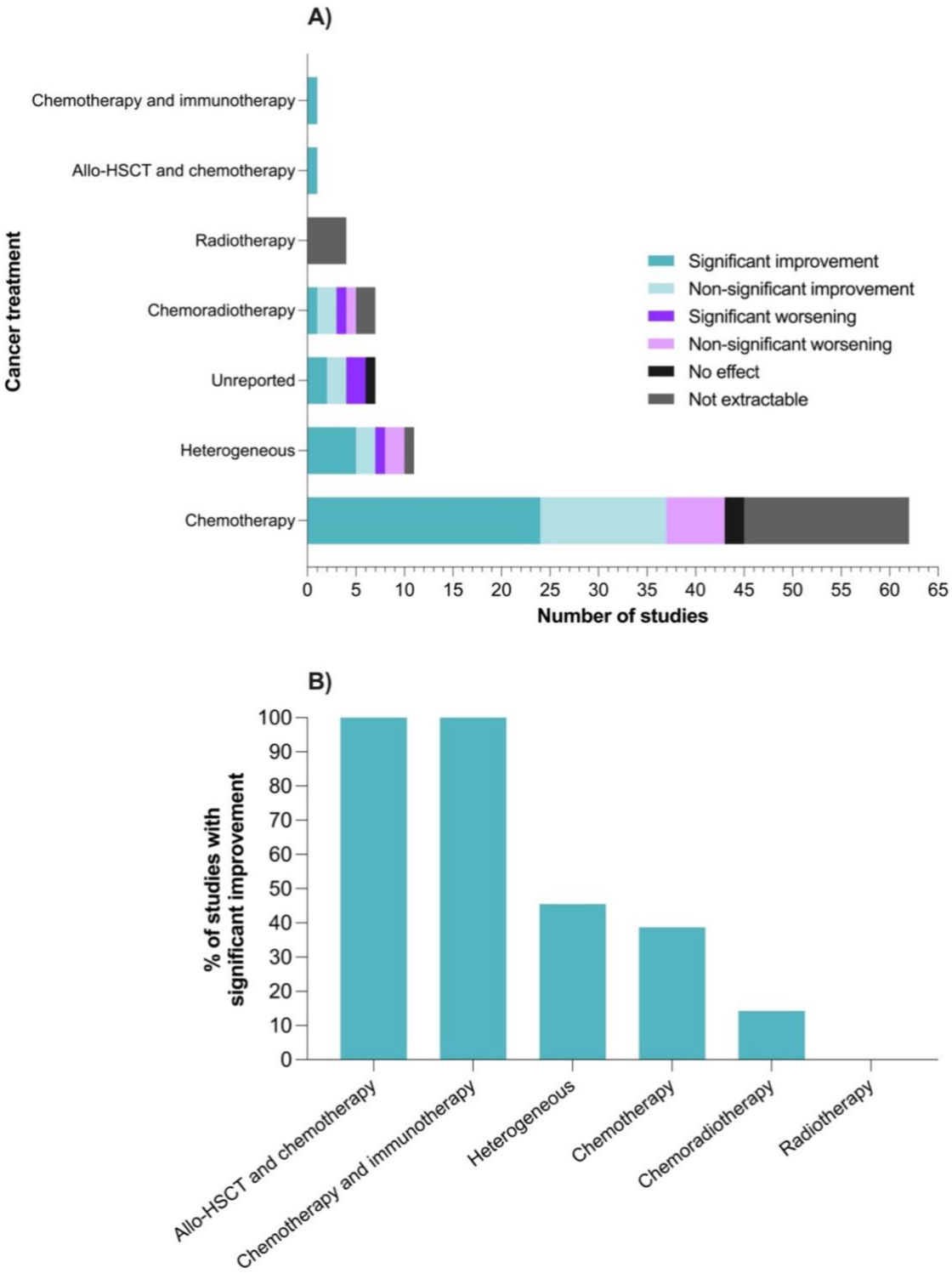


Figure 12: Type of cancer treatment compared to outcomes (N = 93).

A) Number of studies categorised by significance outcomes (significant improvement ($p < 0.05$), non-significant improvement, significant worsening ($p < 0.05$), non-significant worsening, no effect, and not extractable). **B) Proportion of studies with significant improvement.** No significant differences were observed across treatment groups (Chi-square test and Fisher's exact test, $p > 0.05$).

Intervention & comparator

Chemotype

Among the 61 studies focused on THC-dominant interventions, 33 (54.1%) reported the superiority of cannabinoids over the comparator, with 22/33 being statistically significant; five (8.2%) reported worsening, with 1/5 being significant; two (3.3%) reported no effect, and 21 (34.4%) were not extractable. Out of the four CBD-dominant intervention studies, three (75%) were superior, with 1/3 being statistically significant, and one (25%) was not extractable. Out of the 12 studies investigating mixed THC:CBD interventions, eight (66.7%) were superior, with 2/8 being statistically significant; two (16.7%) were inferior, both non-significant; one had no effect, and the remainder (8.3%) was not extractable (Figure 13a). There were no significant differences in the number of studies reporting a significant benefit when compared across different chemotypes (Figure 13b). However, for specific cannabinoid-based medicines, there was a higher proportion of studies reporting a significant improvement in outcomes for nabilone compared to dronabinol ($p = 0.017$).

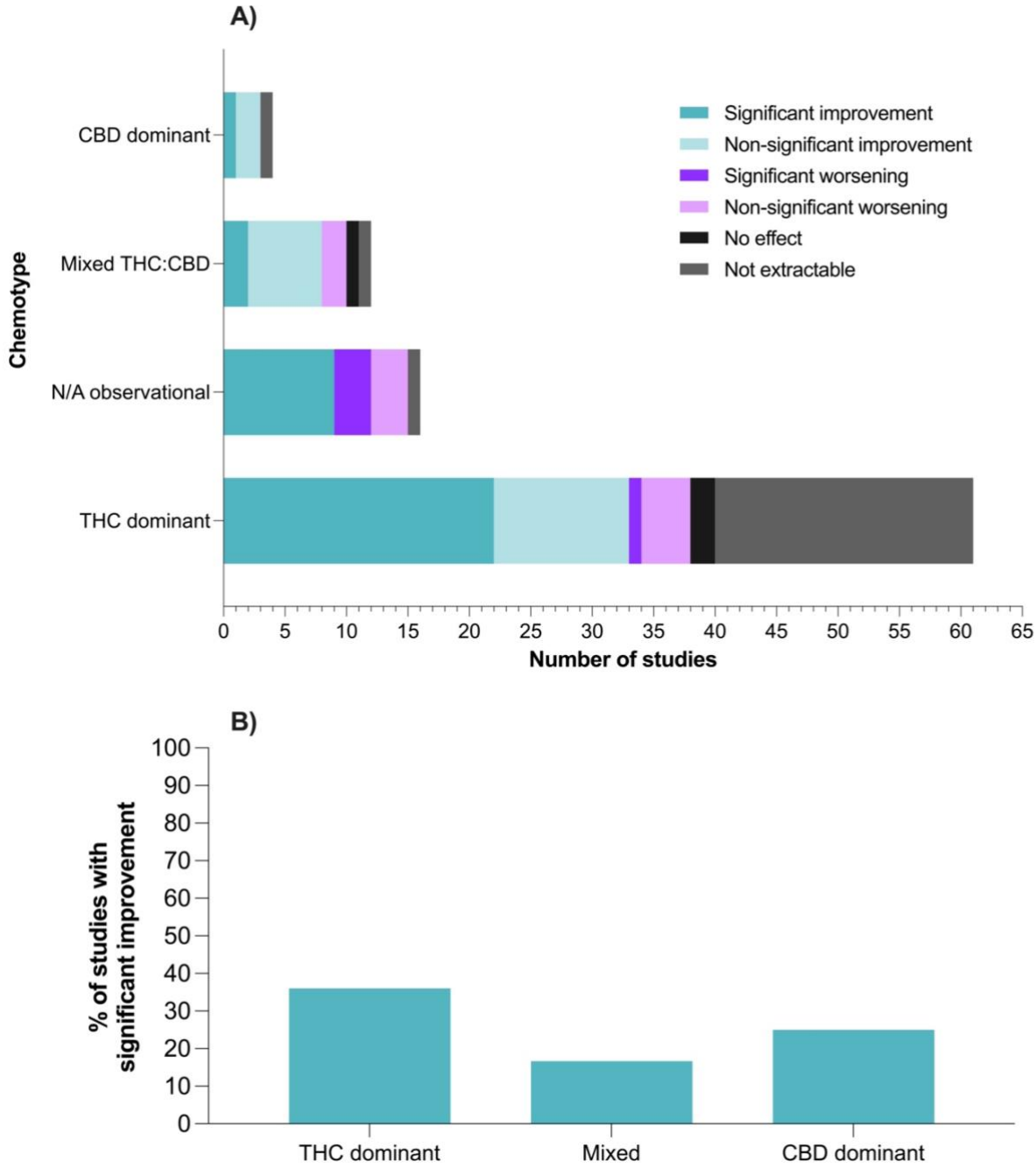


Figure 13: Chemotype compared to outcomes (N = 93).

A) Number of studies categorised by significance outcomes (significant improvement ($p < 0.05$), non-significant improvement, significant worsening ($p < 0.05$), non-significant worsening, no effect, and not extractable). **B) Proportion of studies with significant improvement.** No significant differences were observed across chemotypes (Chi-square test and Fisher's exact test, $p > 0.05$).

Timing

Out of 62 studies that administered cannabinoids prophylactically, 35 (56.5%) reported superiority to the comparator, with 24/35 being statistically significant; five (8.1%) reported worsening, with 1/5 being significant; two (3.2%) reported no effect, and 20 (32.3%) were not extractable. Out of 14 studies that administered cannabinoids therapeutically, eight (57.1%) were superior, with 1/8 being statistically significant; two (14.3%) were worse, with 1/2 being significant; one (7.1%) had no effect, and three (21.4%) were not extractable. 17 studies were observational or unreported (Figure 14a). Overall, there was a significantly higher proportion of studies reporting a significant benefit when cannabinoids were administered prophylactically compared to therapeutically (p = 0.028, two-tailed) (Figure 14b).

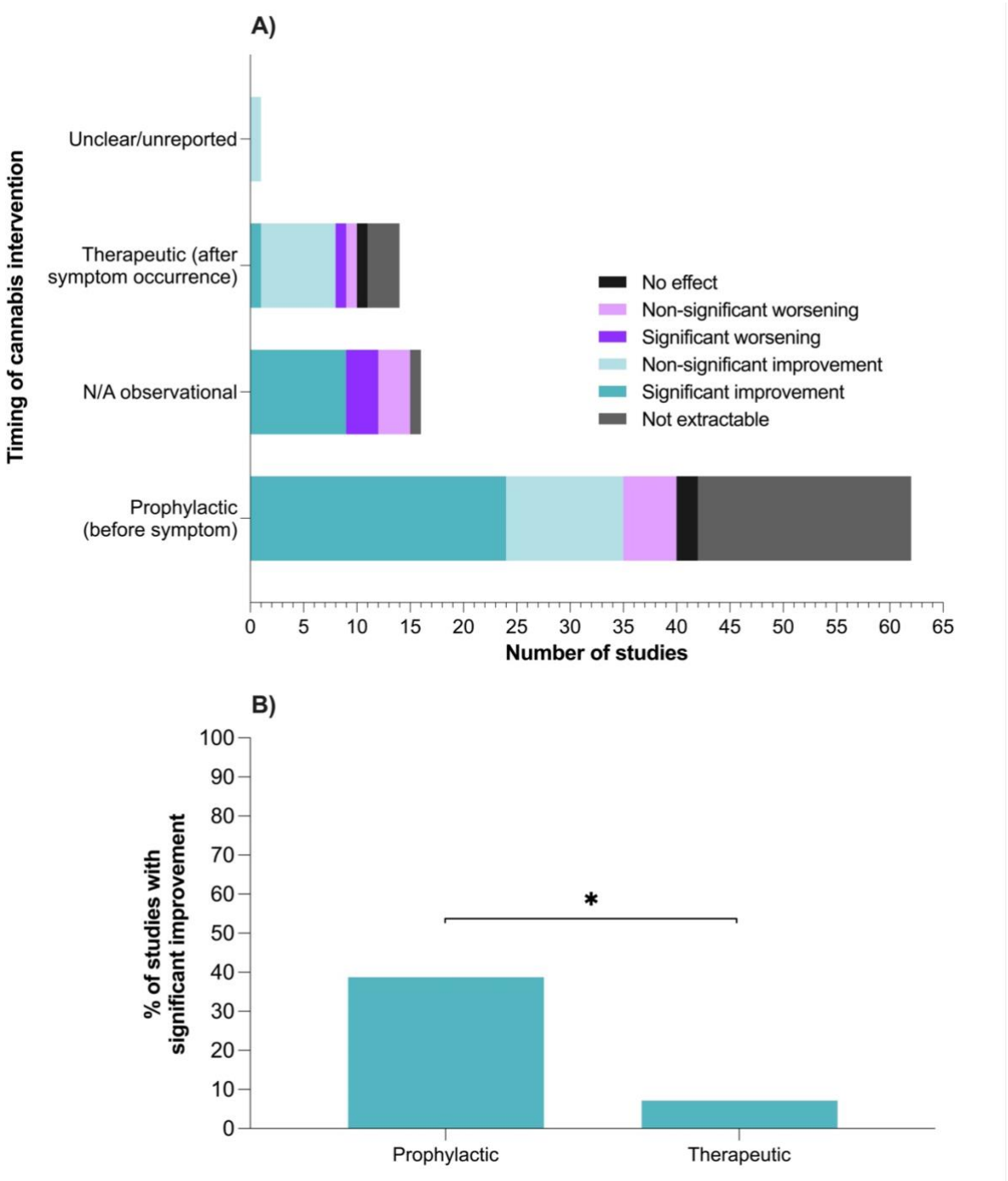


Figure 14: Timing of intervention compared to outcomes (N = 93).

A) Number of studies categorised by significance outcomes (significant improvement ($p < 0.05$), non-significant improvement, significant worsening ($p < 0.05$), non-significant worsening, no effect, and not extractable). **B) Proportion of studies with significant improvement.** Significant difference between prophylactic and therapeutic timing ($\chi^2(1) = 5.156$, $p = 0.023$, Fisher's exact test, $p = 0.028$, two-tailed).

Comparator

Cannabinoid effects were compared to various controls, including active comparator (active medication used as standard care for the indication), placebo, baseline before cannabinoids (participants' pre-treatment symptom score), a concurrent cohort of non-cannabinoid users, prior experience with an active comparator, and standard care.

Among the 32 studies comparing cannabinoids to an active comparator, 15 (46.9%) reported superiority, with 13/15 being statistically significant; five (15.6%) were inferior, with 1/5 being significant; two (6.3%) reported no effect, and 10 (31.3%) were not extractable. Out of 24 studies comparing cannabinoids to placebo, 19 (79.2%) reported cannabinoid superiority, with 10/19 being significant; two (8.3%) were worse, with both being non-significant, and three (12.5%) were not extractable. In 11 pre-post studies comparing cannabinoids to baseline, 10 (90.9%) reported improvement, with 8/10 being significant, and 1 (9.1%) was not extractable. Among the nine studies comparing cannabinoid users to a concurrent cohort of nonusers, two (22.2%) were superior, with none being significant; six (66.7%) were worse, with 3/6 being significant; and one (11.1%) was not extractable. Non-significant improvements were observed in all studies (n = 3; 100%) comparing types of cannabinoids. One study indicated CBD superiority over THC, another favoured synthetic THC levonantradol over natural THC, and the third study reported that a 1:1 ratio THC:CBD was superior to 4:1 THC:CBD. Out of 10 studies comparing cannabinoids to prior experience with an active comparator, two (20%) were non-significantly superior, while eight (80%) were not extractable. Out of three studies comparing cannabinoids to historical data, two (66.7%) reported superiority, with 1/2 being statistically significant, and one (33.3%) was not extractable. The single study comparing cannabinoids to standard care (absence of cannabinoids in a control chemotherapy cycle immediately prior to the study) found

no effect (100%) (Figure 15a). Overall, studies comparing cannabinoids to active comparators (p = 0.018), placebo (p = 0.017), or baseline (p = 0.001) reported a significantly higher proportion of significantly positive outcomes compared to 'previous experience on an active comparator' (Figure 15b); However, caution is warranted due to a large proportion of studies with non-extractable results.

Among the active comparators, prochlorperazine was the most common, appearing in 16 studies. Compared to prochlorperazine, cannabinoids were superior in eight (50%) studies, with 7/8 being significant; two (12.5%) studies found no effect; the remaining six (37.5%) were not extractable. Both (2/2; 100%) synthetic cannabinoid levonantradol studies reported non-significant improvement compared to natural THC. When compared to metoclopramide, cannabinoids were significantly better in two (40%) studies, non-significantly worse in two (40%), and not extractable in one (20%). In the single study comparing cannabinoids to thiethylperazine, cannabinoids were non-significantly better (100%). However, in the study comparing cannabinoids to the combination of metoclopramide and dexamethasone, cannabinoids were non-significantly worse (100%). Out of three chlorpromazine studies, cannabinoids were significantly better in one (33.3%), non-significantly worse in one (33.3%), and not extractable for the remaining study (33.3%). In the single study comparing cannabinoids to megestrol acetate for anorexia, cannabinoids were significantly worse (100%). Cannabinoids were significantly better than Alizapride (n = 1, 100%) and domperidone (n = 2, 100%). No significant differences were reported between any active comparator.

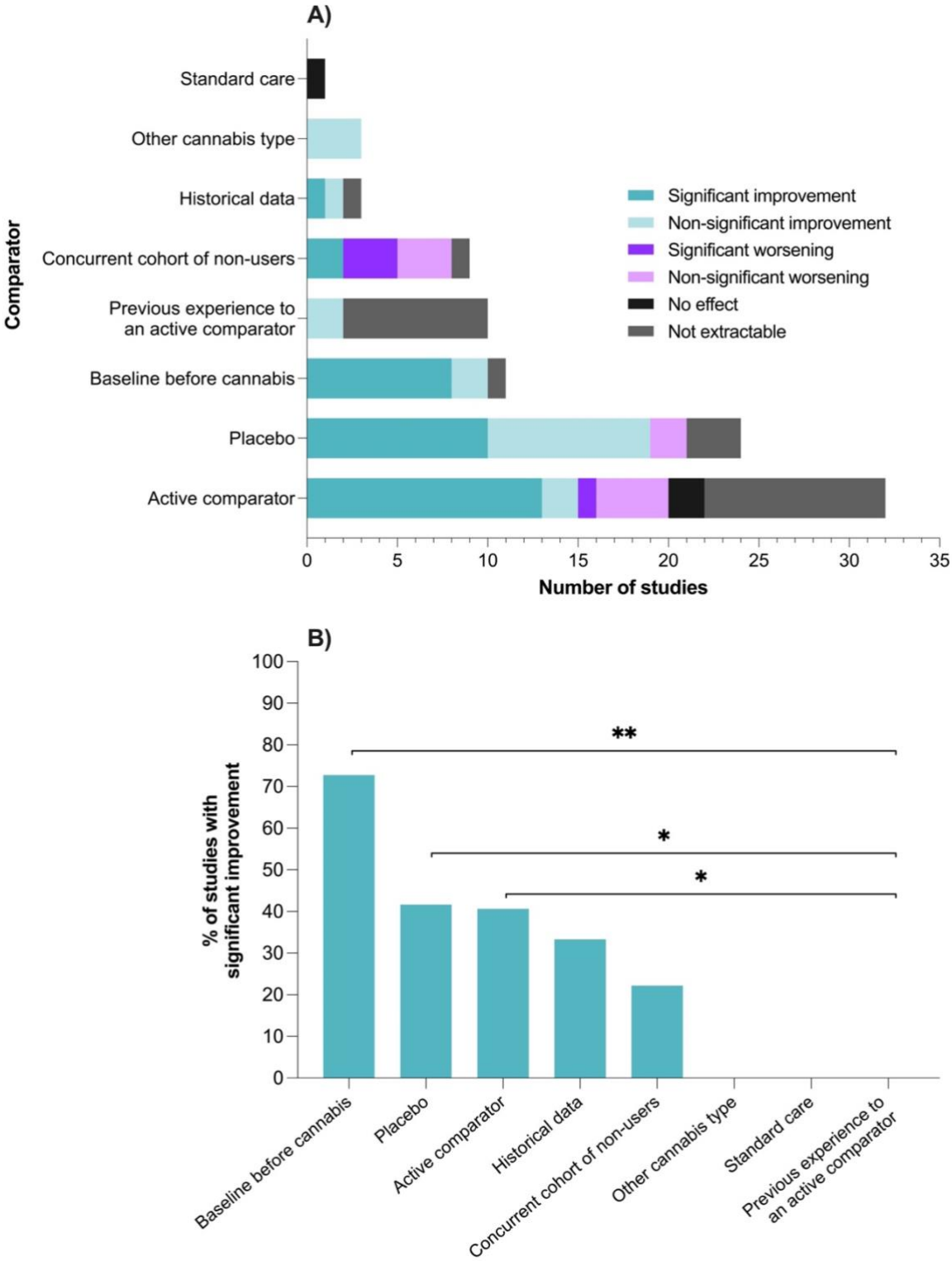


Figure 15: Comparator compared to outcomes (N = 93).

A) Number of studies categorised by significance outcomes (significant improvement ($p < 0.05$), non-significant improvement, significant worsening ($p < 0.05$), non-significant worsening, no effect, and not extractable). **B) Proportion of studies with significant improvement.** Significant difference between baseline, placebo, active comparator, and previous experience to an active comparator (Fisher's exact test, two-tailed $p = 0.001$, $p = 0.017$, and $p = 0.018$, respectively).

Outcome measure: symptom assessment methodology

Symptom assessment methodology is commonly categorised as clinician- or patient-reported outcome measures (CROMs/PROMs) or objective measures (such as biomarkers or quantifiable numbers of events like vomiting). Given the growing body of evidence supporting the use of PROMs in clinical trials[249-253], and the recognition that CROMs often underestimate the true symptom burden[118, 127, 129], the impact of different assessment methods was investigated.

Among the 45 studies utilising PROMs, 27 (60%) reported cannabinoid superiority, with 16/27 being statistically significant; eight (17.8%) found cannabinoids to be worse than the comparator, with 4/8 being significant; one (2.2%) had no effect, and nine (20%) were not extractable. Out of the nine studies employing CROMs, six (66.7%) were superior, with 4/6 being significant; 1 (11.1%) reported non-significant worsening; and two (22.2%) were not extractable. Among the 36 studies utilising the observed number of events of interest as a measure (i.e. observed number of vomits for CINV), 19 (52.8%) reported superiority, with 14/19 being significant; four (11.1%) found non-significant inferiority; two (5.6%) found no effect, and 11 (30.6%) were not extractable. In the three studies using objective measures, one (33.3%) was not significantly superior, and two (66.7%) were not extractable (Figure 16a). There was no significant difference in the proportion of significantly positive outcomes across any outcome measure (Figure 16b).

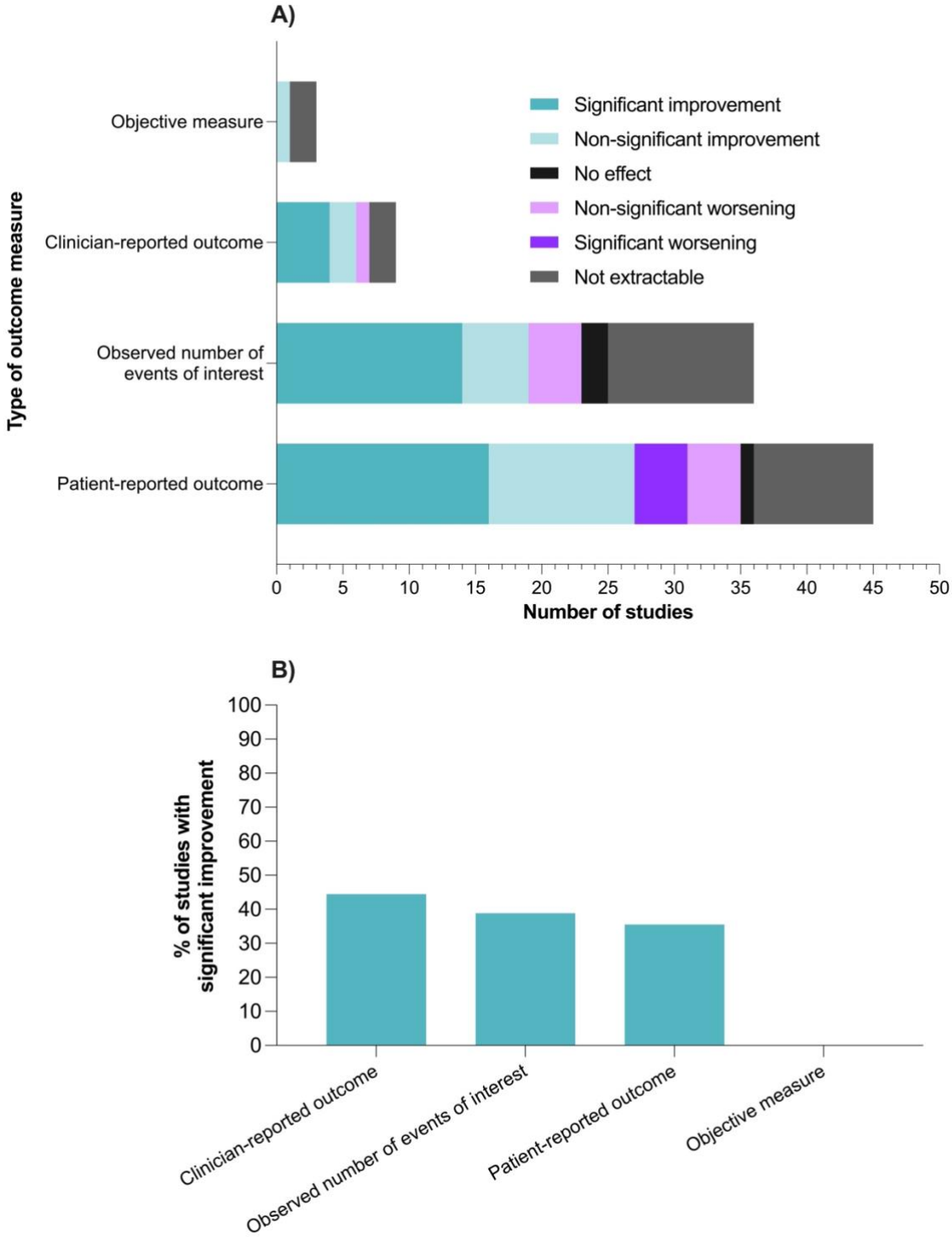


Figure 16: Outcome measure compared to outcomes (N = 93).

A) Number of studies categorised by significance outcomes (significant improvement ($p < 0.05$), non-significant improvement, significant worsening ($p < 0.05$), non-significant worsening, no effect, and not extractable). **B) Proportion of studies with significant improvement.** No significant differences were observed ($\chi^2(3) = 2.074$, $p = 0.5572$).

Chapter 4: Discussion, limitations, conclusion, and future directions

Discussion

Summary of main results

Although cannabinoids are becoming increasingly popular for managing cancer treatment-related symptoms, clinicians remain ill-equipped to guide their patients due to a lack of clear and useful evidence. Current guidelines are hindered by methodological inconsistencies in the existing evidence base, limiting their ability to draw conclusions. We conducted a systematic review to evaluate the evidence on cannabinoids in supportive oncology, with a focus on identifying clinical contexts and methodological considerations. Our primary objective was to synthesise all existing, relevant cannabinoid research to date to generate insights to inform a standardised and evidence-based approach for the next generation of cannabinoid trials.

In our review of 87 studies involving 15,773 participants, cannabinoids were mainly investigated for the management of CINV, quality of life, pain, cancer-related anorexia-cachexia/chemosensory perception, RINV, CIPN, safety, GVHD, anxiety/depression, and sleep. Despite a greater number of studies indicating the benefits of cannabinoids across all symptoms, caution is advised due to the high risk of bias in most studies and the absence of a formal meta-analysis in our review. While some systematic reviews have reported low-quality evidence supporting the benefits of cannabinoids for CINV[99, 100, 102, 103], pain[102, 103], anorexia-cachexia and chemosensory perception[102], anxiety[103], and sleep[103, 104, 107, 108, 110], it should be noted that several others[104-106] and international

guidelines from the Multinational Association of Supportive Care in Cancer (MASCC)[101, 106, 110] and American Society for Clinical Oncology (ASCO)[98] recommend that there is insufficient evidence to support the use of cannabinoids. This caution is due to insufficient evidence on effectiveness and potential harm alongside the availability of other evidence-based therapeutic options. Our findings that participants receiving cannabinoids were more likely to experience adverse events and withdraw, although not significantly different compared to controls, were supported by other systematic reviews[99-101, 111]. Moreover, the MASCC guidelines also highlight that AEs related to cannabinoids may resemble other symptoms associated with cancer and its treatment[106], further complicating the assessment of their effects. However, numerous studies have indicated that despite experiencing AEs, participants generally prefer cannabinoids over placebo[84, 254] and active comparators, specifically standard antiemetics[99, 138, 148, 158, 167, 170, 174, 175, 192, 231, 255]. This preference remains even when participants are blinded, although it is important to note that these findings are limited to the context of CINV and the effectiveness of the antiemetics available during the time of these studies. Overall, while several systematic reviews advise against cannabinoids due to safety concerns[98, 101, 106, 110], others suggest that AEs may be more acceptable compared to the potential benefits[111]; the consensus was that further research is needed to accurately assess cannabinoid effectiveness and safety.

Interplay between study design and outcomes

Given the heterogeneity of included studies, we explored the interplay between design decisions and outcomes. The most prevalent study attributes were:

- **Study design/setting:** Crossover RCTs, conducted during the 1970s and 1980s, in the US, funded by Pfizer or the National Institute on Drug Abuse (NIDA)
- **Population:** Solid tumour patients undergoing chemotherapy

- **Intervention:** Prophylactically administered THC-dominant products (particularly nabilone)
- **Comparator:** Antiemetic active comparator (prochlorperazine or chlorpromazine), or placebo
- **Outcome:** Antiemetic effect on CINV, determined by number of vomiting episodes.

Notably, these attributes were consistently found in studies that reported significant positive outcomes. The predominance of these CINV trials has likely contributed to previous challenges in synthesising evidence on cannabinoids, especially due to the lack of guidelines for both study conduct and reporting during that period[121, 256]. Therefore, we present our findings considering this context, and provide comparisons with existing PICOS recommendations for cannabinoids in supportive oncology.

Population

The higher proportion of significantly positive studies among people with mixed cancer diagnoses and treatments suggests that cannabinoids may be effective in managing symptoms across diverse cancer populations. This suggests that their effectiveness may not be limited to a specific mechanism in a particular clinical setting. However, upon closer examination of specific cancer types and treatments, cannabinoids were found to be more effective in people receiving active chemotherapy for solid tumours, such as lung, bone, head, and neck cancers, compared to those with haematological malignancies. This may be attributed to the predominance of CINV-focused studies, where emetogenic chemotherapy was the main treatment for solid tumour patients. However, there were still instances of symptom worsening, highlighting the need for further investigation into the interaction between cannabinoids, cancer types, and therapies.

While these data suggest that cannabinoid trials should prioritise broad inclusion criteria for generalisability to a wider range of patients, careful consideration is necessary. Working with heterogeneous patient populations introduces variability and complexity, which may require a larger study cohort to ensure sufficient statistical power, while also allowing for specific investigations into subgroups. With this in mind, strategies to unify heterogeneous patient populations, such as focusing on specific classes of anti-cancer treatments, should be considered. Additionally, when designing these trials, it is crucial to assess the suitability for any sub-cohorts who may be at greater risk. Targeted recruitment, or well-powered secondary analyses, should be considered for these sub-cohorts. This is particularly important in the context of immunotherapy, where emerging evidence suggests that cannabinoids may potentially reduce the effectiveness of certain immunotherapies[88, 89, 125, 257, 258]. However, there is conflicting evidence regarding this potentially harmful interaction[259]. Interestingly, one of the studies included in our review, which involved participants undergoing combined chemotherapy and/or immunotherapy, did not observe any significant impacts[86]. Whether this study had adequate statistical power remains unclear.

Eligibility criteria should also consider participant history of cannabinoid use, screen for polypharmacy, and assess if there are any specific contraindications for cannabinoids such as substance misuse. Surprisingly, only a small number of studies in our systematic review reported using any tools to identify and potentially exclude recreational users or those with dependency issues. Participant screening should incorporate a standardised combination of qualitative and biological testing, and accordingly, any contraindications, such as substance abuse and hypersensitivity to cannabinoids, should be evaluated. Among the few studies that did evaluate recreational or cannabis misuse, variable methods were reported including review of the

participant's medical history, and standardised tools such as the Cannabis Use Disorders Identification Test-Revised (CUDIT-R)[233]. Recent studies have also conducted urine drug testing to identify existing cannabis use, or the presence of other drugs that may interact with the study medication. These measures should be integrated into workflow during the consent and intake interview, as well as the participant's initial appointment to receive the medicinal cannabinoid intervention. In addition to the risk of self-medication in trial participants, trials should also consider evidence suggesting that people who self-medicate or seek cannabinoids may already experience more severe symptoms or a lower quality of life, and the validity of outcomes that can be drawn from these populations[145].

Intervention

Cannabinoid products

The variability of cannabinoid products, administration routes, and dosing schedules adds complexity to the reproducibility of trial results. THC-dominant products were the most extensively studied, particularly the synthetic cannabinoid nabilone. The prevalence of nabilone is attributed to the focus on CINV studies, although its investigation extends to other symptoms such as anorexia-cachexia and RINV. Despite demonstrating superiority over placebo and older antiemetics[260], nabilone lacks sufficient evidence to support its effectiveness over modern treatments[101], reflecting decreased research interest since the 1990s. Although cannabis research has historically focused on synthetic cannabinoids, there is increasing advocacy suggesting that these isolated extracts may lose some synergistic therapeutic potential[2, 3]. Recently, there has been a shift in interest towards mixed THC:CBD products, particularly in a 1:1 ratio, due to potential evidence of synergistic therapeutic benefits, improved effectiveness and fewer side effects compared to historical THC-dominant formulations[154, 198, 261].

Additionally, there is some evidence supporting the 'entourage effect', which suggests that full-spectrum medicinal cannabis products containing other phytocannabinoids and terpenes alongside THC and CBD, may be more effective and tolerable than isolated extracts[2-4, 114]. Our review did not find any notable associations between chemotypes or cannabinoid products being more beneficial for specific therapeutic indications or symptoms. It remains unclear whether this reflects the effectiveness of cannabinoids or if a lack of product standardisation and quality has impacted outcomes. Further research is needed, particularly in regard to the 'entourage effect' on outcomes.

Delivery, formulation, and administration route

Our findings suggest that administering cannabinoids as a prophylactic measure is more effective than therapeutic timing, aligning with growing recommendations for preventative symptom management[39]. While this can be attributed to the predominance of CINV studies, the use of cannabinoids as a prophylactic treatment for all CINV studies may explain its relative "success" compared to other symptoms. However, further research is needed to determine the mechanisms of prevention in this context. Achieving prevention can be challenging due to the variable nature of treatment side effects, as many participants may never experience the symptom of interest. Therefore, efforts should be made to enrich trial populations and increase the number of participants who develop the symptom of interest. Although current strategies for predicting side effects have limitations, there is evidence that many symptoms that develop during cancer treatment tend to recur during subsequent treatments[262-264], supporting the use of preventative measures. For example, experiencing CINV in a previous cycle is a significant predictor for recurrence[262, 263], and a recent study leveraged the refractory nature of CINV to demonstrate the effectiveness of cannabinoids in preventing CINV[84]. Additionally, there is growing evidence that

response expectancies, such as the anticipation of involuntary nausea and vomiting, can also predict subsequent side effects[262, 264]. Therefore, trial efficiency can be improved by using interim analyses to increase the number of patients who experience the symptom of interest and adaptively excluding those who do not[265, 266]. These surrogate methods could involve recruiting participants who develop the side effect of interest in the first cycle of chemotherapy for participation in the second cycle[265, 266] and/or screening for response expectancies during the consent process[264].

Regarding formulation of cannabinoid-based medications, oral capsules and oils were the most commonly studied. This may be attributed to their ease of administration as a study drug, participants' preference for their convenience, and long-lasting effects[125, 261, 267, 268]. However, this preference is challenged by recommendations against its use, with data indicating that oral administration (with intestinal absorption) is highly variable in absorption, has relatively low bioavailability, and is subject to first-pass metabolism, making it difficult to achieve stable concentrations and potentially increasing the risk of adverse events[52, 125, 154, 261, 267, 269]. The second most commonly studied method, intramuscular injection, was used only for the administration of Dronabinol and has limited relevance in modern medicine due to pain, inconvenience for outpatients, and additional adverse effects. No studies in this review used the inhalation route, aligning with recommendations cautioning against its highly variable bioavailability, which is influenced by inhalation depth, timing, and duration, and is associated with respiratory damage and inflammation[52, 125, 267]. However, recent research on novel inhaled vaporiser products, which offer precise dosing and rapid systemic absorption with a reduced first-pass effect compared to oral and oromucosal administration, suggests potential in this area.[270, 271]. Only one study utilised the sublingual route, which involves placing cannabinoid oil or other formulation (e.g.

wafer) under the tongue, despite evidence suggesting its benefits in bypassing first-pass metabolism for more accurate dose delivery[52, 125, 272, 273]. However, there is conflicting evidence regarding the effectiveness of the sublingual route, with one study reporting increased side effects and less pain relief [274], indicating the need for further investigation.

In general, different symptoms and patient goals may require different formulations and routes of administration. The inclusion of heterogeneous patient populations can be challenging because individuals may benefit from different cannabinoid products and delivery methods. Additionally, there is a lack of standardisation even within each route; for example, oral administration can include capsules, tablets, and oils; inhalation can refer to smoking or vaping; and sublingual administration can refer to oil droplets or sprays, with each subcategory associated with their own advantages and disadvantages[125]. These inconsistencies further contribute to varying levels of effectiveness across trials, impacting the ability to generate guidelines. Therefore, it is important to consider intervention administration on an individual basis[261, 267, 274], and further research is needed to establish standardised delivery methods for each route.

Dosing schedules and self-titrations

A major challenge to developing cannabinoid guidelines is the wide variation in THC and CBD dosing across studies[274]. While our study found a dosing range of 0.5 to 43.2 mg/day for THC and 2.5 to 600mg/day for CBD, other studies have reported differing ranges. One study reported that dose recommendations ranged from 0.5 to 40 mg/day for THC and 40 to 1280 mg/day for CBD[274], while another study recommended a common therapeutic dose for most indications of 5-30mg of THC and CBD divided to 2-3 doses[52]. Few studies included in this systematic review provided justification for

their chosen dosage, and among these, most referenced preclinical studies[161, 166, 185, 234], clinical studies in non-cancer populations[88, 236-245], or subjective decisions made by the authors[153, 159, 193]. Only two studies cited regulatory guidelines[63, 115, 246], although neither guideline provided clear guidance for cannabinoids in the supportive oncology setting.

Given this vast heterogeneity, does coming up with a standardised dose even matter? Presently, only four cannabinoid-based medicines - Nabiximols (Sativex®), Nabilone (Cesamet®), Dronabinol (Marinol®), and EPIDIOLEX - are marketed with specific dosing guidelines[274]. Beyond these specific products, the only widely accepted approach is to start treatment with a low dose and gradually titrate upward[52, 267]. While there is no universally accepted titration protocol at present, several studies have emphasised the need to tailor doses considering interpatient variability in pharmacokinetics and pharmacodynamics[52, 115, 267]. Previous research has recommended to individually titrate doses based on factors such as weight, patient-reported efficacy, and tolerability[52, 115, 267, 274]. Therefore, it is likely that this field would benefit from guidance on how to approach self-titrations and other personalised dosing strategies in the context of clinical trials.

These self-titrated dosing strategies should consider individual variation across the ECS and gut microbiota, as well as the impact of cancer treatment on cannabinoid pharmacokinetics and pharmacodynamics. A key challenge in developing dosing guidelines is the significant genetic variability in ECS receptor expression across individuals, leading to wide variations in the effectiveness and safety of cannabinoids [39, 275, 276]. Adding to the complexity of this ECS variability, there is also emerging evidence suggesting a bidirectional relationship between the ECS and gut microbiota[39, 67, 277-279], with a recent study reporting that germ-free mice (without a microbiota) are

deficient in a several ECS components[278]. Furthermore, with the growing understanding of this ECS-microbiota interaction, there are unanswered questions regarding the effects of chemotherapy-related microbiota dysbiosis on cannabinoid availability. Since cancer therapy is well-known known to negatively impact the diversity and composition of the gut microbiota, this dysbiosis may affect the effectiveness and tolerability of cannabinoids as a supportive care intervention[39].

In addition to these ECS-microbiota interactions, individuals undergoing cancer treatment likely have pharmacokinetic and pharmacodynamic differences that impact the effectiveness and toxicity of cannabinoids. For example, oral and gastrointestinal mucositis, a common side effect of cancer treatment, heavily impacts oral and gastrointestinal absorption[280, 281]. The structural changes in the gastrointestinal lining can result in a paradoxical combination of both malabsorption and increased permeability, and it remains unclear how this would affect the oral absorption of cannabinoids[280, 281]. Moreover, the impact of cancer treatment on the metabolism and elimination of cannabinoids is not well understood. Despite these concerns, there have been limited pharmacokinetic studies conducted in people with cancer, with most of these studies focusing on healthy patients[269, 272, 273]. However, there has been a recent increase in pilot trials with pharmacokinetic sub-studies[152, 282], which may be a valuable aspect to consider in future research. These emerging challenges underscore the need for further investigation into the complex interplay of ECS variability, gut microbiota interactions, and cancer treatment-induced pharmacokinetic changes, as well as the development of personalised dosing guidelines that take these factors into account.

Comparator

Cannabinoid effectiveness was most commonly assessed through comparison with an active comparator, a placebo, baseline, or non-users. The most frequently used active comparator was prochlorperazine (an outdated antiemetic used in the 1970s and 1980s), which raises concerns about potential bias since cannabinoids may appear to be disproportionately effective due to the ineffectiveness of prochlorperazine[99, 100, 260]. Additionally, while most comparisons favoured cannabinoids over placebo, inadequate reporting on provision of standard supportive care raises concerns about their potential impact on cannabinoid effects, translatability to real-world setting, and ethical considerations in care provision[283]. Furthermore, while comparisons to baseline consistently demonstrated the benefits of cannabinoids, studies measuring outcomes over time should consider the confounding effects of cancer progression, treatment completion, and response-shift (i.e. patient perception of symptom severity changes)[284], contributing to perceptions of overall improvement. Given that most observational studies employed a pre/post design, careful consideration is warranted regarding the impact of these factors.

Outcome measures

Patient-reported outcome measures (PROMs) were the most commonly used outcome measure, which is consistent with recommendations for their inclusion in clinical trials[128, 249-253, 285-288]. Interestingly, despite PROMs being better positioned to capture the nuances of symptom burden due to clinicians' tendencies to underestimate symptom severity in trial settings[283, 289], clinician assessment seemed to favour the benefits of cannabinoids, although this was not significant. This may be due to the use of non-validated PROMs, inadequate consideration of PROM implementation, and the need for enhanced statistical considerations to address the inherent subjectivity of PROMs, with

78 out of 87 studies (89.7%) published before the COSMIN reporting guidelines on PROMs[256]. Given the increased popularity of PROMs, it was concerning that while nearly half (48.4%) of the included studies used PROMs, 38.7% of these studies used non-validated questionnaires. Non-validated and poorly designed PROMs are subject to many issues such as sampling and recall bias, raising concerns regarding the external validity of these trial results[251-253, 285-288, 290-293]. Additionally, none of the studies reported any modifications or translations of their PROMs. This is problematic because including participants from diverse ethnic backgrounds is important for generalisability, and the lack of appropriately translated PROMs introduces selection bias in favour of English speakers[128, 129, 294]. Furthermore, PROMs can be administratively burdensome[292, 295]. Studies that use multiple PROMs to assess numerous symptoms increase the risk of overburdening participants, potentially leading to attrition and missing data if participants are unable to complete questionnaires[252, 287, 288, 291, 292, 295]. Electronic PROMs (ePROMs) may lessen this burden through offering participants the flexibility of reporting from home, automated reminders, and branching logic questions to exclude unnecessary items based on previous responses[250, 285, 286, 296]. Despite these benefits, there are still barriers to ePROM uptake, including workflow integration, variability between platform providers, and software accessibility. Importantly, factors such as PROM timing, frequency, most effective combinations, mode of delivery, and completion logistics must be carefully considered to ensure efficient and meaningful data collection and synthesis across trials[292].

Overall, despite the value of PROMs, both our results and previous research indicate that their validation and implementation in trials have been subpar, compromising the ability to compare trial results[287, 288, 292]. Further research is required regarding the

selection, validation, and delivery of PROMs in supportive oncology trials, particularly in regard to the assessment of cannabinoid effectiveness.

Studies measuring outcomes through observed events (e.g., vomiting episodes for CINV) inadequately reported crucial details such as assessor identity, oversight during patient unattended periods, time points, episode definitions, and whether conditions were similar between intervention and comparator arms. As a result, we faced numerous challenges when extracting data from studies using objective measures, with a significant number of non-extractable studies. Collectively, these findings limited opportunities for meta-analyses, highlighting the necessity of rigorous outcome measure validation and standardisation, consideration of confounding factors, and transparent reporting.

Quality of the evidence

The evidence for all outcomes was of very low quality. There was a high risk of bias in most included studies due to poor reporting of randomisation, blinding, missing outcome data, and the use of non-validated outcome measures. While the inclusion of observational studies and older studies published before the CONSORT and COSMIN guidelines contributed to these findings[121, 256], even recent RCTs had significant issues. These included poor reporting of analyses used to estimate the effect of assignment to intervention, inadequate reporting of primary outcomes, and a high risk of selective reporting bias. Although the assessment of publication bias was not within the scope of this thesis, previous systematic reviews have reported high publication bias, and that the majority of published cannabinoid studies are funded by the drug manufacturer[104, 105].

Limitations of our review

While this review provides practical strategies and areas for advancing the field, these must be interpreted with caution due to the limitations of our approach. Firstly, the lack of meta-analyses and GRADE assessments limited our ability to draw definitive conclusions on effectiveness, safety, or relationships between variables. We also did not analyse specific adverse events or evaluate long-term effects beyond a narrative collation of survival outcomes (OS/PFS). These in-depth analyses were beyond the scope of this thesis due to the vast heterogeneity of adverse events, as well as the poor reporting on the parameters of these AEs and whether they were attributed to cannabinoids. Additionally, our approach to assessing RoB should be considered appropriately. Although our systematic review included many study types, the RoB-2 tool was used to assess all studies, which may have overestimated bias, particularly since all non-RCT studies (39.1%) were automatically assigned a high rating. While this conservative approach aimed to reduce type 1 error and provide a consistent approach to bias assessment, we almost certainly over-estimated bias in studies that were not RCTs.

Although we intentionally included older studies for their historical value, the wide timeframe of eligible studies limited the quality and applicability of our findings, with 49 out of 87 studies (56.3%) published before the CONSORT guidelines[121]. A considerable amount of data could not be extracted, reflecting inconsistency and a lack of oversight in reporting standards. We did not contact authors for missing data to maintain a consistent approach across the large number of older studies included. Moreover, most of these older studies focused on synthetic cannabinoids, such as Nabilone and Dronabinol, primarily within the context of CINV. However, CINV is now well-managed with modern anti-emetics[23], and synthetic cannabinoids are less

relevant to the current research landscape, which is trending towards plant-based, full-spectrum cannabis[2-4, 114, 154, 198].

Another important consideration in our analysis was the difficulty of synthesising even quantifiable data from the eligible studies. There was significant variation in the units used to report cannabinoid dosing schedules. Although we used techniques to adapt the reported dosing units into a consistent dataset for our analyses, as outlined in Extraction synthesis: Dosing Schedules, this was challenging and negatively impacted by the lack of reporting. Furthermore, the variation in cancer treatment modalities among the included studies made it exceptionally difficult to compare the duration of the interventions. Given the suggestions to test cannabinoids in heterogeneous patient groups, both the duration of the intervention and the evaluation of its effectiveness are likely to remain challenging to synthesise. Based on our experience, in the context of chemotherapy, which is typically administered in cycles, it may be helpful to consider a "cycle" as a unit of time. Symptoms typically occur episodically with each cycle, so evaluating the progression of a symptom over the course of a cycle and potentially calculating the area under the curve (AUC) for longitudinal assessments could facilitate comparisons among participants with different treatment regimens.

In addition to the limitations inherent in the data, our methodology for extracting and synthesising the data (see section Extraction synthesis: Primary outcome) may have been subject to bias, particularly our approach of extracting first-reported data when primary outcomes were unclearly reported, and our assessment of parameters that determined a study as 'not extractable'. It is important to note that all statistical tests performed were based on the categorisation of studies (see section Extraction synthesis: Primary outcomes - significance), and thus were limited by these assumptions. Our

approach of grouping symptoms such as nausea and vomiting as CINV, and anorexia, cachexia, and chemosensory perception as a single category, limited our ability to identify any differences in cannabinoid effects and underlying mechanisms for each symptom. Additionally, we did not differentiate between curative and palliative treatment goals, which may have affected outcomes, especially in advanced cancer patients. In these cases, the primary focus on managing symptoms rather than treating the disease itself could have influenced the perceived effectiveness of cannabinoids in relieving symptoms.

Finally, the calculation of dropouts associated with cannabinoids versus comparators (see section Extraction synthesis: Dropouts) was limited by the small number of studies (22 out of 87; 25.3%) that explicitly reported withdrawals within each arm. The calculation of dropouts is also limited by the broad synthesis of all comparator arms as if they were uniform, despite some being placebo and others being active comparators.

Conclusions

The enthusiasm for cannabinoid trials has outpaced our understanding on how to conduct them effectively, and the inconsistency in approaches has resulted in a heterogeneous body of evidence that is limited in scope and scientific validity. We should not continue to conduct trials that fail to translate into meaningful clinical practice. It is time for the field to establish a unified approach and prioritise trials that are applicable to diverse populations and real-world settings. Therefore, we propose the following considerations for trial design (Table 10) and suggest the following areas of research (Table 11) to support the integration of cannabinoids into clinical practice.

Table 10: Considerations for cannabinoid trial designs

Design:	• Design studies that adhere to Helsinki Requirements of the World Medical Association[297] and Consolidated Standards of Reporting Trials (CONSORT)[121] reporting standards. • Incorporate qualitative sub-studies within trials to gain insights from participants. Areas of focus could include identifying challenges to participation, which can inform revisions to study design and recruitment practices, as well as the eventual implementation of the intervention into clinical practice. • Incorporate pharmacokinetic and mechanistic sub-studies to understand cannabinoids in the context of cancer and its treatment, and to identify suitable dosing strategies. • Integrate cannabinoids into existing care plans and ensure participants have access to cannabinoids even after the study concludes, possibly through collaborations with licensed cannabinoid dispensaries. • Integrate with multidisciplinary care resources, including palliative care specialists, and ensure all participants have access to standard care that would have been available without trial participation. • Address challenges in blinding THC treatment by administering low doses at timed intervals more frequently, and consider alternatives to placebo control (e.g., designing studies with three arms including an active comparator).

	• Implement longitudinal studies to assess the long-term effectiveness and safety of cannabinoids. • Design studies to assess clusters of multiple symptoms, considering evidence that sequelae are interconnected. Reducing the number of narrow-scope trials focused on isolated symptoms may help streamline research efforts, reduce costs, and lessen the participant burden.
Participants	• Broaden participant criteria to include populations representative of real-world oncology settings. This should include individuals at any stage of their disease and symptom severity (particularly the under-represented early stages), those with comorbidities (if possible and not contraindicated), those undergoing active treatment or participating in chemoradiotherapy trials, and both cannabinoid-naïve and experienced individuals. Participants should also be allowed to receive other forms of supportive care. These populations, along with any other potentially confounding factors, can be carefully documented and stratified, rather than excluded. Considering the statistical implications of working with heterogeneous groups, it is important to consider this early in the trial design process. • Consider enrichment strategies with interim analyses to adaptively increase the number of participants who develop the symptom of interest[265, 266], such as recruiting participants who develop the side effect of interest in the first cycle of chemotherapy for trial participation in the second cycle[265, 266] and/or screening for response expectancies during screening and consent processes[264]. • When recruiting and obtaining consent, screen for polypharmacy and assess if there are any specific contraindications for cannabinoids, such as substance misuse, severe cardiovascular diseases, neurodegenerative diseases, and psychotic comorbidities. Clearly communicate patient goals and the risk-benefit profile of cannabinoids. • Ensure that publications and protocols demonstrate that recruitment was accessible to diverse populations through trial design and recruitment strategies. • Clearly specify the inclusion of self-medicators and provide justification for their inclusion, especially for observational studies. • Provide appropriate support to participants who are unable to drive during the trial if taking THC.
Intervention	• Facilitate patient collaboration with an interdisciplinary team well-versed in cannabinoid pharmacokinetics and side effects to assist them in selecting products (e.g., THC-dominant, CBD-dominant, mixed THC/CBD), and administration

	routes (e.g., oral, sublingual, inhaled, topical). This process should also ensure that cost does not influence patients' product choices. • When determining dosing strategies, rely on guidance from relevant studies conducted on the target patient group rather than relying on dosing strategies published for other indications. • Allow patients to individually titrate their dosing schedules to optimise symptom control and minimise side effects. • Consider administering cannabinoids prophylactically (i.e., prior to the occurrence of symptoms). • Standardise reporting units, such as dosing in mg/day, to address the inconsistent reporting of frequency, duration, and dosing units, which can make synthesis challenging.
Outcomes	• Use a combination of objective, clinician- and patient-reported measures to assess the symptom(s) of interest, including disease-specific endpoints, quality of life, and adverse events. • Select validated PROMs to ensure they capture the intended measures. • Ensure that the reporting of PROMs adheres to COSMIN guidelines[256]. • Take measures to minimise burden on patients and staff. Reduce the need for in-person appointments where possible. Consider using electronic PROMs (ePROMs) if feasible. • Explicitly report any modifications made to existing validated PROMs, including translations. • Clearly define a single primary outcome that can be expressed as a single, comparable value alongside its measurement methods in both the protocol and the paper reporting results. The reported parameters should include recording methods and time points to ensure inclusion in future meta-analyses. • Consider outcome measures that can capture dynamic changes in symptom severity over time, across heterogeneous study populations with different treatment regimens, and while accounting for response-shift. Examples include the area under the curve (AUC) of a PROM assessed over multiple time points, or the proportion of days where the symptom of interest has met a defined threshold of severity. • Monitor titration closely, as adverse events are often dose-related, and conduct frequent assessments for both efficacy and adverse events following a risk-benefit analysis for each patient. • Consider assessing tumour response and survival as secondary outcomes

- Ensure publications and protocols report the provision of other lines of supportive care, including details on the type of intervention, timing, dosage, and potential confounding effects.
- Clearly report and compare different outcomes between the cannabinoid and comparator arms (e.g., number of withdrawals) to facilitate future synthesis.

Future directions

Table 11: Future research areas

Trial-specific	• Establish global leadership guidelines to standardise trial design and reporting specific to the cannabinoids in supportive oncology setting. • Establish guidelines on outcome assessment of cannabinoids, with a focus on validation of PROMs and outcome measures that can capture dynamic changes in symptom severity across heterogenous populations.
Therapeutic effectiveness	• Investigate the clinical effectiveness of cannabinoids for global symptom burden rather than specific symptoms/side effects. Studies should also be designed appropriately for secondary analyses. • Determine the mechanism of action and role of the endocannabinoid system for cancer treatment-related symptoms such as CINV, pain, anorexia-cachexia, RINV, CIPN, GVHD, psychosocial symptoms, and sleep disturbances. • Investigate both short and long-term effects of cannabinoids on cancer progression, tumour response and survival. • Elucidate the mechanisms of other cannabis compounds, such as terpenes, flavonoids, and phytocannabinoids. Rather than treating these as an undefined 'entourage' to THC and CBD, they should be isolated in standardised formulations with known compositions, and their individual and collective mechanisms of action determined through preclinical and clinical studies[(2)]. • Investigate the ‘entourage effect’ in full-spectrum, mixed THC:CBD cannabis products, and determine whether the presence of these compounds results in a more effective supportive care intervention compared to isolated THC and CBD.

	• Investigate the interaction between the ECS and the gut microbiome and determine factors in this bidirectional relationship that can predict the effectiveness and safety of cannabinoids.

Safety	• Conclusively determine the benefit-risk ratio of cannabinoids and develop clear guidelines and recommendations.
	• Investigate the safety profile of cannabinoids, including potential adverse effects and long-term outcomes throughout the cancer continuum.
	• Examine potential interactions between cannabinoids and:
	  o Types of cancers, particularly haematological cancers.
	  o Cancer treatments, particularly immunotherapy
	  o Other supportive care drugs, particularly cardiovascular drugs and antidepressants.

Optimisation of usage	• Determine which patients may benefit most from cannabinoids and optimal products for symptoms. • Determine most effective administration route(s) and standardise delivery methods, with a focus on the sublingual route. • Establish a protocol for titrating cannabinoid doses based on individual patient needs and responses.

Improving cannabinoid studies will require attention to several areas. These include diversifying populations, tailoring product selection and dosing, implementing robust blinding, selecting appropriate comparators, carefully monitoring adverse events, and ensuring that symptom clusters and patient experiences are captured using validated outcome measures. Additionally, it is crucial to integrate multidisciplinary care and minimise logistical challenges where feasible. Further research is required to determine the effect of individual variations in ECS expression and gut microbiota, as well as the impact of the "entourage effect," on the effectiveness of cannabinoids in supportive care. By improving the design and execution of studies, we can improve the clinical translatability of future research. This will not only optimise the allocation of resources, but also deepen our understanding of the benefits and risks of cannabinoids. In turn, this will provide the much-needed evidence-based guidance for both clinicians and patients.

The CANCAN trial: putting considerations into practice

In light of these considerations, we have designed a clinical trial incorporating some of these recommendations. The CANnabinoids in CANcer therapy trial (CANCAN) has been designed with a strong focus on patients. It is based on the hypothesis that the breakdown of the gastrointestinal environment following chemotherapy serves as a catalyst for a constellation of secondary side effects. As detailed in our publication (Appendix 3)[39], we propose that medicinal cannabinoids are well-positioned to address the numerous pathological mechanisms underlying acute mucositis and its associated symptom clusters.

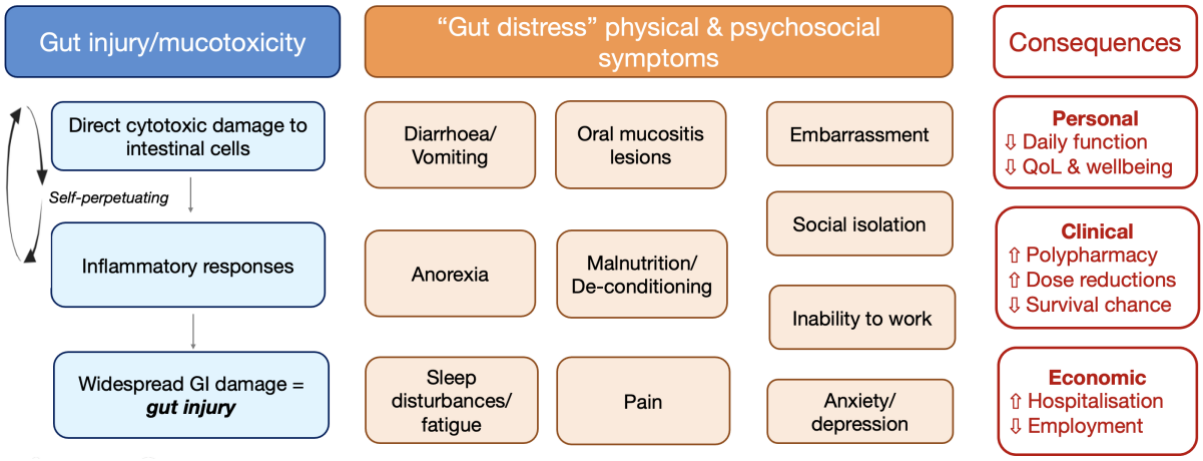


Figure 17: Gastrointestinal mucositis presents as gut distress symptom clusters with severe clinical, economic, and personal consequences.

Gastrointestinal mucositis pathology is an underlying mechanism to physical and psychological symptoms commonly reported in people with advanced cancer undergoing chemotherapy. This positions gastrointestinal mucositis as an ideal therapeutic target[39].

The CANCAN trial is a Phase II, double-blind, placebo controlled RCT (Appendix 4). The trial aims to investigate the effectiveness and safety of combined CBD and THC in managing gastrointestinal symptoms caused by cancer therapy. The CANCAN trial has been designed with broad inclusion criteria, focusing on people scheduled to undergo mucotoxic, systemic cancer therapy for advanced solid or haematological cancers.

Participants will undergo rigorous screening using qualitative and quantitative measures, including the standardised Cannabis Use Disorder Identification Test Revised (CUDIT-R). To avoid randomising participants who may not develop gastrointestinal mucositis and its associated symptoms, the trial will use a tiered enrichment strategy for enrolment and randomisation of participants undergoing chemotherapy. Eligible participants will undergo screening and enrolment into the CANCAN trial without randomisation, during which their first cycle of chemotherapy will be monitored. Only participants who experience gastrointestinal mucositis (defined as the Mucositis Daily Questionnaire Score, MDQ > 1) during the first round of chemotherapy will be randomised, with participants then provided the investigational product as soon as possible. This allows for a near-prophylactic, "early" provision of the medication but also still allows for people that do not develop mucositis to be excluded from the study, thus increasing efficiency. The intervention group will receive a daily standardised dose of 300 mg of CBD and a patient-titrated dose of 5-20 mg of THC, both in the form of separately administered sublingual wafers. These cannabinoids will be administered prophylactically from the day of admission for the duration of their cancer therapy (i.e. 3 full cycles of chemotherapy or day 35 for HSCT recipients).

Importantly, the trial will use a patient-centred approach to assess the effectiveness of medicinal cannabis in relieving gastrointestinal mucositis and associated symptoms. The primary outcome measure will be the MDQ PROM, represented as the AUC of the MDQ per treatment cycle. Gastrointestinal mucositis will also be assessed objectively using the biomarker citrulline, as well as through clinician assessment using the NCI-CTCAE. Other PROMs, such as the ESAS-r-CS, FAACT, EORTC-Q-CLC30, HADS, and FACT-COST, will be used to assess a range of symptoms as well as financial burden (see Appendix 4 for full abbreviations). All PROMs will be collected using an

ePROM tool to minimise administrative burden and streamline data collection, with the platform allowing irrelevant questions to be removed based on the participant's previous answers. Additionally, participants will be monitored for supportive care service utilisation, hospitalisation, treatment completion or cessation, and response to chemotherapy. Biospecimens (saliva, blood, faeces) will be collected for ancillary studies on interactions between the host, gut microbiome, and cannabinoids.

Finally, all participants, including those in the placebo group, will be invited to participate in a pharmacokinetic sub-study after completing the main CANCAN trial. The purpose of this sub-study is to facilitate the development of a predictive population pharmacokinetic model and identify patient-specific physiological and demographic characteristics that can predict differences in exposure and response among participants. The ultimate objective is to aid in the development of personalized treatment plans for cannabinoids in the field of supportive oncology.

Appendix 1: PROSPERO protocol

Cannabis as an adjunctive supportive care strategy for cancer – PROSPERO protocol for a systematic review

Ms Katrina Cao. School of Public Health, University of Adelaide, Precision Medicine Theme (Cancer Program) South Australian Health and Medical Research Institute

Associate Professor Amy Salter. School of Public Health, University of Adelaide

Dr Jessica Stanhope. School of Allied Health Science and Practice, University of Adelaide

Dr Hannah Wardill. School of Biomedicine, University of Adelaide, Precision Medicine Theme (Cancer Program) South Australian Health and Medical Research Institute

PROSPERO 2022 CRD42022373000

Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42022373000

Review question

What are the effects of cannabis on people undergoing anti-cancer therapy?

Context

Through this systematic review, we hope to not only answer the primary research question regarding the effectiveness of cannabis as an adjunctive cancer care strategy, but to also explore the way(s) in which it has been investigated to date. This will identify and inform areas for future research, provide basis for conflicting results, and ultimately guide future decision-making regarding cannabis in supportive oncology.

Searches

Sources: MEDLINE (Ovid), PubMed, Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science Core Collection. The reference and citation lists from included studies and relevant systematic reviews (Boland et al. 2020; Doppen et al. 2022; Hanganu et al. 2022; Hauser et al. 2019; and Whiting et al. 2015 https://doi.org/10.1001/jama.2015.6358) will be manually screened. Citation lists will be obtained from PubMed, Scopus, Web of Science Core Collection, and Google Scholar.

Search strategy: Will include only terms relating to the intervention, cannabis, and the condition being studied, cancer. To retrieve human studies, the search will filter animal studies through strategies adapted for each database and guided by a librarian.

Restrictions: None

Search dates: Studies published between database inception and the date searches are run.

Search strategy

Ovid Medline

1. Exp Cannabinoids OR cannabis.sh OR medical marijuana.sh OR (Cannab* OR Marijuana OR Marihuana OR delta-9-tetrahydrocannabinol OR THC OR CBD OR Tetrahydrocannabinolic Acid or THCA or dronabinol or nabilone or nabiximols).ti,ab,kw
2. Exp neoplasms OR (Neoplas* OR Cancer* OR Malignan* OR Tumour* OR tumor* OR Oncolog* OR metasta*).ti,ab,kw
3. #1 AND #2
4. Exp Animals NOT (Exp Animals AND exp Humans)
5. 3 NOT 4

PubMed

1. "Cannabinoids"[mh] OR "cannabis"[mh:noexp] OR "medical marijuana"[mh:noexp] OR Cannab*[tiab] OR Marijuana[tiab] OR Marihuana[tiab] OR delta-9- tetrahydrocannabinol[tiab] OR THC[tiab] OR CBD[tiab] OR Tetrahydrocannabinolic Acid[tiab] or THCA[tiab] or dronabinol[tiab] or nabilone[tiab] or nabiximols[tiab]
2. "Neoplasms"[mh] OR Neoplas*[tiab] OR Cancer*[tiab] OR Malignan*[tiab] OR Tumour*[tiab] OR *[tiab] OR Oncolog*[tiab] OR metasta*[tiab]
3. #1 AND #2
4. "Animals"[Mh] NOT ("Animals"[Mh] AND "Humans"[Mh])
5. 3 NOT 4

Embase (Ovid)

1. Exp Cannabinoid OR cannabis.sh OR medical cannabis.sh OR (Cannab* OR Marijuana OR Marihuana OR delta-9-tetrahydrocannabinol OR THC OR CBD OR Tetrahydrocannabinolic Acid or THCA or dronabinol or nabilone or nabiximols).ti,ab,kw
2. Exp neoplasm OR (Neoplas* OR Cancer* OR Malignan* OR Tumour* OR tumor* OR Oncolog* OR metasta*).ti,ab,kw
3. #1 AND #2
4. (exp animal/ or animal experiment/ or nonhuman/) not (exp human/ or human experiment/)
5. 3 NOT 4

Cochrane Central Register of Controlled Trials (CENTRAL)

1. [mh “Cannabinoids”] OR [mh ^”cannabis”] OR [mh ^”medical marijuana”] OR (Cannab* OR Marijuana OR Marihuana OR delta 9 tetrahydrocannabinol OR THC OR CBD OR Tetrahydrocannabinolic Acid OR THCA OR dronabinol OR nabilone OR nabiximols):ti,ab,kw
2. [mh neoplasms] OR (Neoplas* OR Cancer* OR Malignan* OR Tumour* OR tumor* OR Oncolog* OR metasta*):ti,ab,kw
3. #1 AND #2

Scopus

Note: searched within title, Abstract, Keywords

1. Cannab* OR Marijuana OR Marihuana OR “delta-9-tetrahydrocannabinol” OR THC OR CBD OR “Tetrahydrocannabinolic Acid” OR THCA OR dronabinol OR nabilone OR nabiximols
2. Neoplas* OR Cancer* OR Malignan* OR Tumour* OR tumor* OR Oncolog* OR metasta*
3. #1 AND #2

Web of Science Core Collection

Note: search within ‘Topic’ (searches title, abstract, author keywords, and Keywords Plus)

1. Cannab* OR Marijuana OR Marihuana OR “delta-9-tetrahydrocannabinol” OR THC OR CBD OR “Tetrahydrocannabinolic Acid” OR THCA OR dronabinol OR nabilone OR nabiximols
2. Neoplas* OR Cancer* OR Malignan* OR Tumour* OR tumor* OR Oncolog* OR metasta*
3. #1 AND #2

Eligibility Criteria

Types of study to be included

To be eligible for inclusion, studies must be primary research in humans, with a comparison group (e.g. RCT) or a pre-post study design. Studies must also be published in full-text, in English language, and peer-reviewed.

Condition or domain being studied

The condition being studied is cancer, of any type, at any stage of malignancy, treated with systemic and/or localised anti-cancer therapy. Specifically, any symptom, side effect or outcome attributed to anti-cancer therapy.

Participants/population

Studies including participants undergoing any anti-cancer therapy (such as, but not limited to, chemotherapy, radiotherapy, immunotherapy, and hormonal therapy) will be eligible for inclusion. Anti-cancer therapy may be ongoing or finished. Studies where participants are receiving surgery only (i.e., no anti-cancer medication) will be excluded. All ages and sexes will be included.

Intervention(s), exposure(s)

Cannabis, also known as marijuana, is defined as any compound extracted from the Cannabis plant genus, obtained legally or illegally. Medicinal cannabis (MC) refers to prescribed cannabis. This systematic review will include any form of cannabis obtained in any manner, including all cannabinoids, isolates, ratios, formulations, doses, and routes of administration.

Comparator(s)/control

All comparison groups must be undergoing/have undergone anti-cancer therapy. Studies comparing cannabis to standard care, placebo, or before cannabis (pre-post studies) will be considered for inclusion. Studies comparing different cannabis formulations (e.g., THC vs CBD) will also be considered.

Standard care: any supportive care intervention given to alleviate any anti-cancer treatment-related symptom.

Placebo: inactive or inert vehicle carriers, or interventional comparators that do not contain any cannabis compound. Placebo may be given alongside supportive care.

Pre-post studies: studies comparing anti-cancer therapy-related outcomes before and after cannabis intervention. For pre-post studies, the baseline data must be collected after cancer treatment has commenced, and prior to cannabis intervention.

Main outcome(s)

Effects (beneficial and adverse) of cannabis on:

1. Anti-cancer treatment-related symptoms or side effects. Symptoms/side effects may include, but are not limited to, diarrhoea, oral mucositis, pain, nausea and vomiting, anorexia/loss of appetite, cachexia, sleep disturbances, depression, and anxiety.
2. Quality of life

Additional outcome(s)

For studies that include the main outcomes, effect of cannabis on the following outcomes will also be reported:

1. Other indications of cancer treatment-induced morbidity (e.g., incidence in hospitalisation, use of supportive care interventions/rescue medications, cancer treatment dose modifications)

2. Anti-cancer treatment response (including tumour response, progression-free survival, and overall survival)

Data extraction (selection and coding)

All stages of study screening and selection will be conducted independently by two reviewers, with any uncertainty resolved through discussion, and a third reviewer consulted where consensus is not reached. Search results will be imported into Covidence Systematic Review management software for de-duplication. Titles and abstracts will undergo initial screening against eligibility criteria above. The full text of studies that pass initial screening will be assessed for eligibility against the same criteria. Studies that pass full-text screening will be included and will undergo data extraction.

Data extraction will be conducted manually and independently by two reviewers, with a third reviewer consulted if there are discrepancies that cannot be resolved through discussion. A standardised, pre-piloted form will be used to manually extract data from included studies. Extracted information will include: (a) Citation details, (b) study characteristics (country, setting/site(s), study design, month(s)/year(s) of data collection), (c) population and sample characteristics (sample size, cancer type/s, anti-cancer treatment regimen, demographics), (d) intervention and comparator details (cannabis isolate, formulation, administration, dose, duration, timing), (e) methodology (tools used to assess cannabis effect), (f) outcomes, (g) outcome measures, (h) statistical approaches, and (i) findings.

Risk of bias (quality) assessment

Two reviewers will independently assess risk of bias, and any disagreements will be resolved through discussion, with involvement of a third reviewer where necessary.

The risk of bias for each included study will be assessed using the Cochrane Risk of Bias 2 (RoB 2) (https://methods.cochrane.org/file/rob-2-starter-pack-cochrane-reviewspdf). Study designs will also be allocated to the NHMRC Hierarchy of Evidence for intervention studies (https://www.nhmrc.gov.au/sites/default/files/images/NHMRC%20Levels%20and%20Grades%20(2009).pdf).

The certainty of the evidence overall will be assessed using The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (https://training.cochrane.org/grade-approach).

Strategy for data synthesis

A qualitative narrative synthesis of the findings from the included studies, structured around the type of cancer treatment-related symptom, cannabis intervention, target population characteristics, and type of outcome will be conducted. We will provide summaries of intervention effects on outcomes of interest for each study.

If the included studies are sufficiently homogenous (i.e., at least three studies comparing the same interventions using the same outcomes), quantitative meta-analyses will be performed. We anticipate there will be limited scope for meta-analyses because of the variation in cannabis products, the large number of cancer treatment-related symptoms studied, and the range of different outcomes measured across heterogeneous study designs. Where possible, we will pool results using a random-effects meta-analysis (with standardised mean differences for continuous outcomes and risk ratios

for binary outcomes) and calculate 95% confidence intervals and two-sided P values for each outcome. In studies where the effects of clustering have not been considered, we will adjust the standard deviations for the design effect. Heterogeneity will be assessed using both the χ^2 test and the I^2 statistic. An I^2 value greater than 50% will be considered substantial heterogeneity. We will conduct sensitivity analyses based on study quality. We will also use stratified meta-analyses to explore heterogeneity in effect estimates where possible according to study quality; study populations; the logistics of intervention provision; and intervention content.

If meta-analyses are not feasible, statements will be made to justify this decision and qualitative synthesis will be performed alone.

Where possible, we will also assess evidence of publication bias by the creation and interpretation of funnel plots.

Analysis of subgroups or subsets

If sufficient quantitative data are available, exploratory sub-analyses will be guided by the study characteristics, and may include:

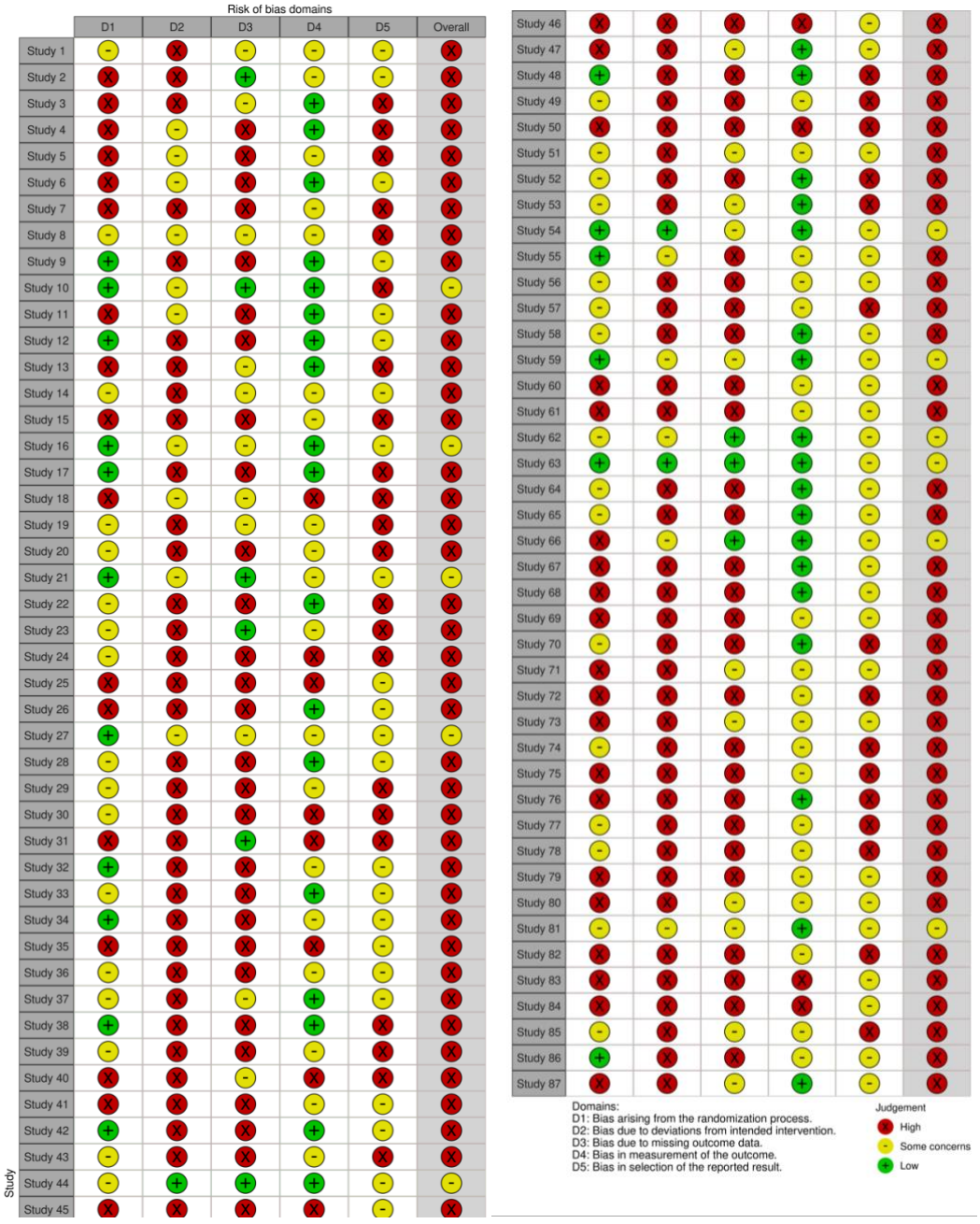
- Different cancer treatment-related symptoms (e.g., pain, nausea),
- Different types of cannabis intervention/cannabinoids (e.g., THC, CBD, CBG, nabiximols) to determine which has therapeutic potential in supportive cancer care (or for specific symptoms)
- Differences in intervention formulation and/or route of administration (e.g., oral oils, sprays, capsules, inhalational)
- Differences in interventional timing (e.g., prophylactic, therapeutic).
- Differences in population (type/s of cancer, type of anti-cancer treatment/regimen, adults, children)
- Different study designs based on level of evidence (NHMRC evidence hierarchy) and/or risk of bias,

- Different methodology/assessment tools/outcome measures used to assess cannabis effect (e.g., patient-reported outcome measures, clinician-reported outcome measures, biomarkers)

Other sub-analyses may also be performed depending on the available data, though these cannot be specified in advance.

Appendix 2: RoB 2 individual assessments

Cochrane RoB-2 individual bias assessments (n = 87). traffic light plot generated using *robvis* (McGuinness, LA, Higgins, JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1- 7. https://doi.org/10.1002/jrsm.1411)



Appendix 3: Review

Supporting gut health with medicinal cannabis in people with advanced cancer: potential benefits and challenges

Hannah R Wardill[1,2], Luke T Wooley[1], Olivia Bellas[1,2], **Katrina Cao**[2,3], Courtney B Cross[1,2], Madele vanDyk[4], Ganessan Kichenadasse[4,5], Joanne Bowen[1], Andrew Zannettino[1], Sepehr Shakib[1], Gregory B Crawford[5,6], Jaroslav Boublik[7], Mellar Davis[8], Scott Smid[1], Timothy Price[6,9].

1. The School of Biomedicine, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia
2. Supportive Oncology Research Group, Precision Cancer Medicine Theme, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia
3. School of Public Health, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia
4. Flinders Centre for Innovation in Cancer, Flinders Medical Centre/Flinders University, SA Health, Adelaide, Australia
5. Northern Adelaide Local Health Network South Australia, SA Health, Adelaide, Australia
6. Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia
7. LeafCann Group Pty Ltd
8. The Geisinger Commonwealth School of Medicine, Scranton, Pennsylvania. 100 North Academy Ave. Danville , Pennsylvania, USA.
9. Queen Elizabeth Hospital, Adelaide, Australia

Abstract

The side effects of cancer therapy continue to cause significant health and cost burden to the patient, their friends and family, and governments. A major barrier in the way in which these side effects are managed is the highly siloed mentality that results in a fragmented approach to symptom control. Increasingly, it is appreciated that many symptoms are manifestations of common underlying pathobiology, with changes in the gastrointestinal environment a key driver for many symptom sequelae. Breakdown of the mucosal barrier (mucositis) is a common and early side effect of many anti-cancer agents, known to contribute (in part) to a range of highly burdensome symptoms such as diarrhoea, nausea, vomiting, infection, malnutrition, fatigue, depression, and insomnia. Here, we outline a rationale for how, based on its already documented effects on the gastrointestinal microenvironment, medicinal cannabis could be used to control mucositis and prevent the constellation of symptoms with which it is associated. We will provide a brief update on the current state of evidence on medicinal cannabis in cancer care and outline the potential benefits (and challenges) of using medicinal cannabis during active cancer therapy.

Keywords: mucositis, gastrointestinal, inflammation, supportive cancer care, toxicity, medicinal cannabis, cannabinoid, endocannabinoid system, chemotherapy

Introduction

Despite the excitement that surrounds newer, more targeted agents, the reality for most people with advanced cancer is that chemotherapy will be used, and it will cause a degree of collateral damage to healthy tissues[(298)]. Clinically, this damage presents as a broad variety of diverse, individualised, and highly dynamic symptoms and side effects. Rarely do these side effects occur in isolation; instead, they often present as clusters of related symptoms that are united by common underlying mechanisms, as well as

physical and psychosocial/behavioural determinants[299]. With increased accessibility of "big," real-world data, these symptom clusters have been documented and characterised with greater precision[300]. This has prompted new initiatives to identify early drivers of chronic treatment-related morbidity, with the goal of halting the self-perpetuating nature of inter-related symptoms.

Of the many documented side effects of chemotherapy, breakdown of the mucosal barrier of the gastrointestinal tract ("mucositis") is one of the earliest and most common. Mucositis is initiated by rapid and extensive DNA damage in highly proliferative stem cells throughout the gastrointestinal mucosa[301]. The resulting apoptosis and inflammation degrade the mucosa, leading to the formation of ulcerative lesions in the mouth, oesophagus, intestines and rectum which severely impairs functional capacity. This dysfunction can lead to taste changes, dysphagia, pain and malabsorption; each of which drive anorexia, malnutrition, and dehydration [302]. On a cellular level, these breaches in the protective mucosa create an inhospitable environment for resident gut bacteria, leading to loss of commensal species and their protective metabolites including short chain fatty acids (SCFAs). These changes further weaken the mucosal barrier and permit unrestricted communication between the underlying immune system and luminal compounds (e.g., danger signals). This results in profound local and systemic inflammation which leads to numerous extra-intestinal consequences such as fever ("febrile mucositis")[303], cognitive impairment[304, 305] and fatigue[306]. As such, the destructive changes in the gastrointestinal microenvironment position mucositis as a catalyst for a range of secondary complications, and a key player in a range of symptom clusters.

Despite the impact of mucositis on patients and the healthcare system, it remains without effective intervention, and its range of secondary symptoms/consequences are managed reactively and in isolation[42]. Given the body of evidence that now suggests

many symptoms and treatment consequences may be influenced by mucositis, there is an opportunity to control mucositis to mitigate the constellation of impactful symptoms with which it is associated. This review aims to outline a rationale for how, based on its already documented effects on the gastrointestinal microenvironment, medicinal cannabis could be used to control mucositis and prevent its associated symptom cluster. We will provide a brief update on the current state of evidence on medicinal cannabis in cancer care and outline the potential benefits (and challenges) of using medicinal cannabis during active cancer therapy.

Medicinal cannabis: illicit drug, plant, or medicine?

Cannabis has been used medicinally for over 3,000 years, primarily for its analgesic properties. The predominant phytocannabinoids in cannabis by amount are Δ^9-tetrahydrocannabinol (Δ^9-THC or THC) and cannabidiol (CBD), with mainstay medicinal cannabis preparations containing either or both of these compounds in varying ratios as the active ingredients, either as isolates or whole extracts. However, there remains a vast phytochemical complexity to cannabis aside from just THC and CBD, whereby whole extracts may contain over one hundred different minor phytocannabinoids and terpenes, all of which may vary in their relative expression across a number of cannabis chemotypes and displaying variable retention via different extraction processes[307, 308]. Many of these compounds have been shown to exhibit selective bioactivities that may interact with the efficacy of THC and CBD in MC preparations and may be considerations particularly where full-spectrum botanical extracts are concerned, oft described through the popular term ‘entourage effect’ applied to medicinal cannabis [2, 309]. However, their contribution to the efficacy of most conventional MC formulations where THC and CBD predominate may only be

marginal, with a paucity of investigative studies on these cannabis phytochemicals compared to THC and CBD.

Today, over 40 countries have legalised medicinal cannabis (MC), with different access pathways depending on jurisdictional legislation[310]. Despite significant variation across jurisdictions, the medicinal use of cannabis is guided by the formulation (oil, sprays, tablets, and flowers). Typically, MC requires prescription for a pre-defined indication or with clear clinical justification for why a certain condition may respond positively to MC. This ambiguity often results in lengthy and administratively burdensome reporting requirements; hence, MC use continues to be a challenging medico-legal entity. The combination of its often-high cost, clinician hesitancy and logistic difficulties for supply compared to relative ease of access in the community, is a major driver of why people continue to self-medicate with uncontrolled and non-standardised cannabis products.

Canada was one of the first countries to introduce a MC access program in 1999. Between 2015 to 2019, the number of registered MC patients in Canada increased from 40,000 to nearly 400,000, an increase attributed to several policy changes that have gradually broadened access to a variety of medicinal cannabis formulations. In December 2015, the first cannabis oil product was launched in the Canadian market and in 2016, the Access to Cannabis for Medicinal Purposes Regulations allowed patients to grow cannabis for personal use[311].

The United States was another early adopter of medicinal cannabis, starting with state-level legalization in California in 1996. Now, as of February 2023, medicinal cannabis has been legalized in 37 states, 3 territories, and the District of Columbia[312]. In February 2019, Thailand became the first and only nation in Southeast Asia to legalize medicinal cannabis, offering 3 different categories of cannabis-based products: medicinal-grade cannabis-based medicines, Thai traditional medicine products that

contain cannabis as the active ingredient, and folk medicine products prepared by registered folk healers[313].

In 2016, cannabis was rescheduled in Australia to enable access for medicinal purposes. Currently, the majority of cannabis products are classified as "unapproved" therapeutic goods, with two exceptions: Sativex (nabiximols), an oromucosal spray containing equivalent amounts of THC and CBD, and Epidyolex (also known as Epidiolex), a CBD solution with a concentration of 100 mg/mL (Therapeutic Goods Administration, 2020a). The situation in the UK is similar; even though medicinal cannabis was legalized in 2018, it remains challenging for patients to obtain access, with only a limited number of National Health Service prescriptions issued to date[314]. Medicinal products that meet safety, quality and efficacy standards are registered on the Australian Register of Therapeutic Goods (ARTG), however additional pathways such as Special Access Schemes (SAS) and an Authorised Prescriber (AP) scheme facilitate patient access to "unapproved" therapeutic goods, including many other types of MC products currently. This scheme is being increasingly adopted in Australia, with the MC Therapeutic Goods Administration (TGA) dashboard showing an increase in AP applications and a levelling off of SAS-B approvals in the last two years.

The "endocannabinoidome" and its relevance to chemotherapy symptoms and side effects

The endocannabinoidome or, in its broader sense, the endocannabinoid system (ECS), is an endogenous network of receptors, enzymes, transporters and ligands, that has largely been recognized for its role in regulating of neurotransmitter release[53]. However, this original concept of the ECS is gradually being replaced by an increasingly sophisticated and complex network capable of regulating numerous biological pathways and functions across a range of organ systems. The interactions that exist within the ECS are

critical to central nervous system development, synaptic plasticity and the homeostatic maintenance of cognitive, behavioural, emotional, developmental and physiological processes[53, 55]. These diverse mechanisms are mediated by endogenous cannabinoids which are produced on demand, both physiologically and patho-physiologically, from membrane lipids and are metabolised by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively[315]. They include the main known endocannabinoids, N-arachidonoylethanolamine (AEA) or anandamide and 2-arachidonoylglycerol (2-AG) produced by phospholipid precursors through activity-dependent activation of specific phospholipase enzymes; N-acyl-phosphatidylethanolamine–selective phosphodiesterase and phospholipase C subsequent production of diacylglycerol via diacylglycerol lipase, respectively (Table 1)[53]. The broadly termed acylethanolamines and acylglycerols interact to a variable extent with cannabinoid receptors including the well described CB1 and CB2 receptors (CNR1/CNR2) as well as other G protein–coupled receptors such as GPR55, GPR18, GPR3, GPR6, GPR12, transient receptor potential channels such as TRP vanilloids TRPV1 to TRPV4, TRP ankyrin TRPA1, TRP M member TRPM8 and peroxisome proliferator-activated receptors such as PPAR2, and PPARγ[316]. Although there are diverse receptors with which endocannabinoids interact, CNR1 and CNR2 are functionally characterised both physiologically and with respect to ECS dysfunction. CNR1 is a G-protein coupled receptor that is highly abundant within the peripheral and central nervous system, largely present on axon terminals and pre-terminal axon segments[57] (Figure 1). It is highly abundant in medium spiny neurons in both the dorsal and ventral striatum, and is particularly high on the direct pathway axons as they enter the globus pallidus heading towards the substantia nigra[58]. However, the expression of CNR1 is increasingly diverse, with a range of immune cells (including glia) now understood to express CNR1[59, 60, 317] as well as the more immunologically

abundant, CNR2. Indeed, there remains debate about the expression of CNR2 which has historically been considered to be mainly expressed in the periphery[61]. Although emerging evidence suggests it is expressed on sensory nerve terminals and microglia in the brain[318].

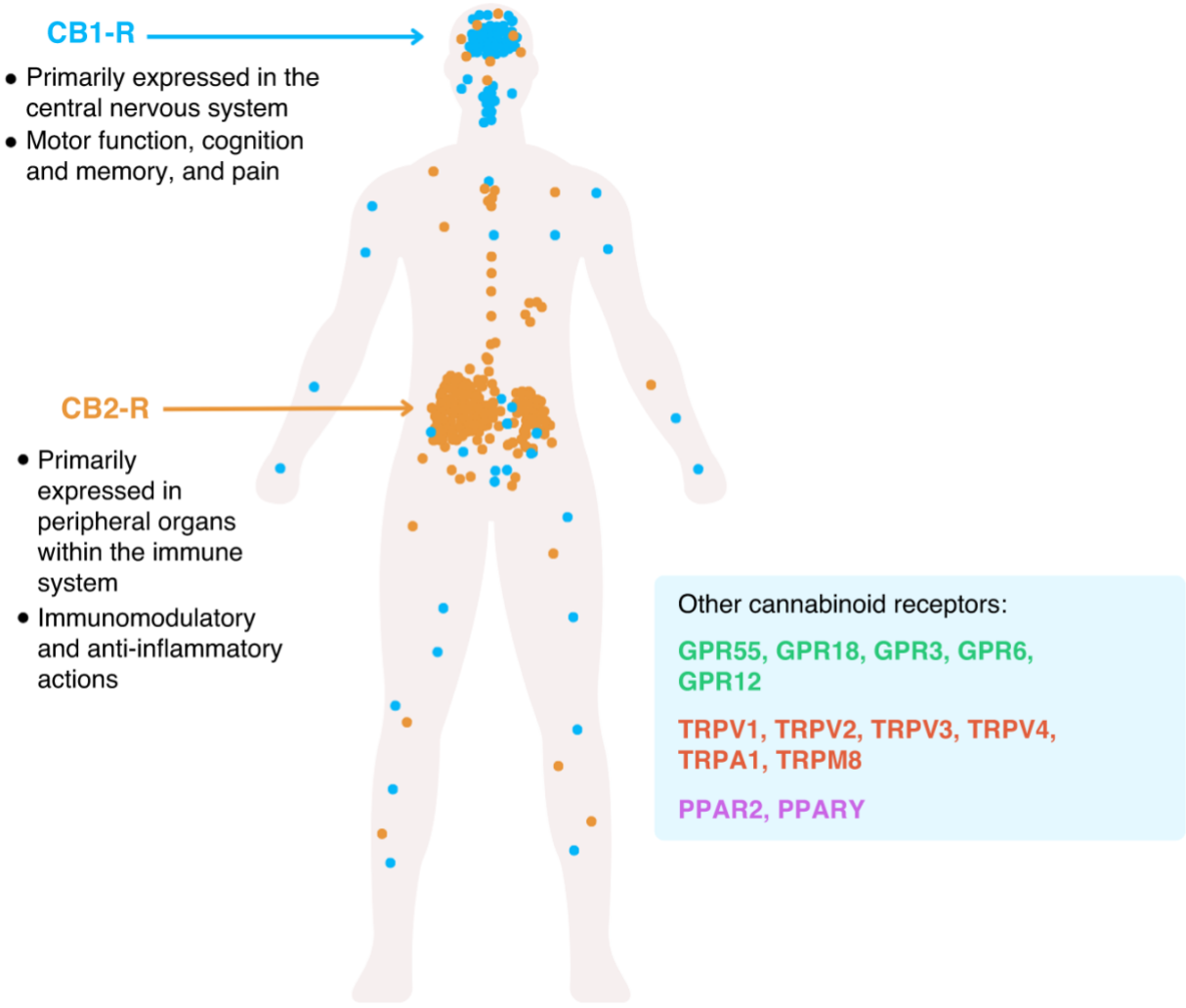


Fig. 1: Simplified scheme representing the expression pattern of the main cannabinoid receptors, CNR1 and CNR2.

In addition to CNR1 and CNR2, including GPCRs (GPR18, GPR55, GPR3, GPR6, and GPR12), the receptor potential (TRP) channels (TRPV1, TRPV2, TRPV3, TRPV4, TRPA1 and TRPM8) and peroxisome proliferator-activated receptors (PPAR2 and PPARγ).

Although not the only components of cannabis, the most commonly studied and clinically utilized components, THC and CBD, are highly lipid soluble and have a poor bioavailability when inhaled (10% to 35%) or orally ingested and 11% to 45%[319-321].

When THC is consumed by inhalation or mucosal sprays, it is absorbed through the lungs into the blood stream and concentrations in the plasma will typically peak in less than 10 minutes[319] and when it is orally congested, concentrations may peak at approximately 2 hours. THC is distributed into well vascularized organs as well as the brain. THC and CBD are highly protein bound and has a half-life of 25–36 and 18 to 32 hours, respectively[319, 322], with some of the metabolites (THCCOOH) having a very long half-life up to 52 hours[323]. Chronic users have much longer half-lives.

THC undergoes extensive first-pass metabolism in the liver by cytochrome P450 (CYP 450) isozymes; these enzymes are also responsible for the metabolism of many anti-cancer drugs and several other commonly used co-medication and are known to cause large inter-individual variability in plasma concentrations for majority of clinically used medications[324]. Therefore, it is particularly important to investigate any potential drug-drug interactions to avoid toxicity or therapeutic failure for any of the medications.

THC primarily is metabolised via oxidation by CYP2C9, CYP2C19 and CYP3A4 into several metabolites with 11-hydroxy-THC (11-OH-THC) and 11-carboxy-THC (11-COOH-THC) being the most abundant (Glaz-Sandberg 2007, Babayeva M 2023). 11-OH-THC is metabolized by the UGT1A9 and UGT1A10 enzymes and 11-COOH-THC is metabolized mostly by the UGT1A3 and UGT2B7enzyme (Babayeva M 2023; Dietz 2007). CBD is also metabolized in the liver via mostly CYP3A4, CYP2C19 and CYP2C9 and other CYPs to a lesser degree via hydroxylation to form metabolites, 7-OH-CBD and 7-COOH-CBD, which is then undergoes glucuronidation by UGT1A9 and UGT2B7[319, 322]. The remaining THC, CBD and metabolites can be taken up by fat tissue before it is redistributed into the circulation. More than 65% of THC and CBD will be excreted in faeces and approx. 20% in the urine [323, 325]. Metabolites excreted in urine has been observed to vary up to 5-fold between individuals when drug administration was controlled, demonstrating the variability in metabolism[323].

Appendices

Inter-individual differences in pharmacogenomics, pharmacokinetics, and pharmacodynamics may explain contradictory outcomes from previous studies and accounting for such difference will provide an opportunity for personalized medicine where efficacy can be maximized, and toxicity minimized for various conditions or diseases [326].

Reflecting the breadth of cells upon which ECS receptors are expressed, the ECS regulates a number of critical functions that are well known to contribute to the side effects of chemotherapy. Most notable is its psychotropic properties, modulating mood, anxiety, cognition, appetite, sleep and pain[327, 328]; all of which are well documented to be negatively impacted by chemotherapy[298]. Peripheral CB1 expression is also implicated in gastrointestinal inflammation, mucosal defences and gastric motility[65, 66, 329, 330], and thus by extension diarrhoea and constipation, due to its expression on presynaptic cell of sympathetic motor neurons innervating visceral organs leading to reduced noradrenalin release [331]. Further to this, given the immunomodulatory capacity of the ECS, its ability to influence numerous symptoms and side effects of chemotherapy of which many are underpinned by aberrant inflammation, is vast. It is for these reasons that medicinal cannabis, and strategies to augment the ECS, have gained considerable momentum for their potential benefits in people with cancer.

Medicinal cannabis use in cancer care: what is the evidence?

Cannabis use in people with cancer is not uncommon, although it remains difficult to determine exact prevalence based on heterogeneous results across numerous studies with varied designs. In a study published in 2018, 43% of respondents (at a Canadian cancer centre) reported using "illicit" cannabis for a variety of symptoms and side effects of their treatment[332]. This is similar to a large population-based analysis from 2005-14 in the US, which showed 40.3% of the 826 respondents with cancer having used cannabis in the last 12 months[333]. However, in a larger survey of more than 200,000 people, results indicated that less than 10% of people were using cannabis[94]. Irrespective of self-reported cannabis use, there is a high degree of interest in its potential benefits during cancer care, with 80% of healthcare professionals reporting that they have engaged in conversations with their patients about cannabis[95].

Unfortunately, less than 30% feel equipped to guide their patients citing a lack of clear evidence on its safety and efficacy[95]. This uncertainty undoubtedly stems from the inadequate and highly variable evidence base for cannabis in cancer care, which is dominated by largely observational studies that are subject to inherent biases, powerful placebo effects and diverse confounders, leading to a high rate of false positives[137, 334, 335]. Similarly, of the limited number of randomized control trials, few are considered high quality and they remain near impossible to compare/synthesize due to inherent differences in design, outcome measures and cannabis products/doses/delivery/formulations used[137]. This has prevented replication and meta-analyses, and the resulting evidence base is therefore inconsistent and largely uninformative.

Although challenging to compare studies, a large number of systematic reviews have been conducted in an attempt to synthesize data and determine its efficacy in symptom control. Notably, there have been few that have been able to perform meta-analysis, reflecting the heterogeneity of available data. The most recent review of cannabis in cancer care reviewed 42 studies (19 randomized, 23 non-randomized), focused on people with cancer receiving palliative care[336]. Among these studies, pain was the most commonly investigated symptom, with highly variable effects reported across the studies. This aligns with a recent systematic review and meta-analysis which investigated the effect of cannabis for pain management in people with cancer, which was unable to form any conclusive recommendation[337]. Accordingly, recent guidelines from the Multinational Association for Supportive Care in Cancer (MASCC) do not recommend the use of cannabinoids for cancer pain, although, it is unclear how this relates to chemotherapy-induced pain which is diverse in its origins[335].

While pain has dominated the landscape for cannabis research in cancer care, emerging evidence exists for its role in chemotherapy-induced nausea and vomiting (CINV),

anorexia, cachexia, sleep disturbance and psychological symptoms (depression/anxiety). Doppen and colleagues reviewed the evidence for CINV, reporting generally positive effects across multiple studies using various assessment tools[336]. This is consistent with recommendations from MASCC, which show THC and nabilone are both effective in controlling CINV, however, no more effective than current antiemetic medications[338]. Despite these positive findings, MASCC was unable to form any guideline due to insufficient, high-quality evidence. This is echoed by the American Society for Clinical Oncology (ASCO) who question the quality of current evidence[339]. Despite the lack of clinical recommendation from MASCC and ASCO, it appears that there is discordance between published clinical trial data and anecdotal reports of patient preferences, which tend to favour cannabis over existing antiemetic strategies, even when adverse effects were higher[340, 341].

MASCC maintains a similar stance with respect to anorexia and cachexia, with limited evidence available to inform relevant guidelines. Doppen et al. reviewed 15 studies for cannabis and appetite, with both objective and self-reported benefits reported for nabilone and Marinol, however, several studies reported no or inconsistent effects[336]. Given the heterogeneity in data and approaches, it remains difficult to draw robust conclusions despite the popularized effects of cannabis on appetite stimulation. Similarly, for psychological effects (e.g. on sleep, anxiety, depression), MASCC were unable to make any recommendations with most studies investigating these outcomes as secondary analyses with inconsistent data across studies[334].

While the systematic review by Doppen et al. has provided insight on the current state of evidence regarding cannabis use in cancer care, it has been scrutinized for its methodology and over-simplification of data as “positive” and “negative” effects based on the null hypothesis significance test[137, 336]. As cautioned by Davis and Soni (2022), our approach to cannabis research should be guided by effect sizes that are deemed

clinically significant, rather than *statistically* significant[137]. Furthermore, they highlight the need to be more holistic in our assessment of cannabis for symptom management, avoiding excessively large studies designed with highly restrictive outcomes guided by narrow-minded criteria[137]. With this in mind, and the growing appreciation for symptom clusters in people undergoing chemotherapy, there is a clear rationale to prioritize trial designs that address clusters of related symptoms, rather than single symptoms, to deliver meaningful impacts to the participant's physical or psychosocial wellbeing. Critical to these approaches is the inclusion of consumers in cannabis research, to ensure research methodologies are informed by, and consistent with, consumers behaviours and preferences. In line with ensuring consumer engagement, trials should include relevant patient reported outcome measures (PROMs) to ultimately determine if cannabis has a *meaningful* impact on people with cancer.

Gastrointestinal effects of cannabis: can they be adapted to control mucositis?

Cannabinoids, including both CBD and THC, are increasingly documented for their capacity to modulate gastrointestinal function, owing to the immense control that the ECS has on gastrointestinal homeostasis. Both CNR1 and CNR2 are present in the gastrointestinal tract, largely on enteric nerves and the epithelium, but also on enteroendocrine cells and immune cells[66]. This network of ECS receptors controls gastric motility, and as such, it is now understood that variants in the genes encoding for CNR1 are implicated in diseases characterised by altered motility including irritable bowel syndrome (IBS), particularly diarrhoea-predominant[342]. Both CNR1 and CNR2 are expressed in the gut at medium to high degrees, respectively. Accordingly, it has been shown that agonists of the cannabinoid receptors (CNR1 and CNR2)[343, 344], as well as targeting endocannabinoid degradation[345], minimises experimental colitis and associated visceral hypersensitivity[346]. Furthermore, preclinical investigations have

shown that potent agonists of CNR1 (without central nervous system effects) and CNR2 have been shown to control increased gastrointestinal motility caused by stress[347] and inflammation[330]. Similarly, inhibition of anti-diacylglycerol lipase (DAGL) and fatty acid amide hydrolase (FAAH) - two enzymes critical in endocannabinoid metabolism - has been shown to normalize transit time in the context of opioid-induced constipation[348]. Of particular interest to changes in the gastrointestinal microenvironment associated with mucositis is the ability of CNR2 activation[349] and FAAH inhibition[350] to control accelerated gastrointestinal motility induced by lipopolysaccharide - a bacterial product that is causally implicated in chemotherapy-induced diarrhoea.

In addition to its effect on gastrointestinal motility, which has clear applications in controlling chemotherapy-induced diarrhoea, the ECS exerts potent immunomodulatory effects in the gastrointestinal tract controlling intestinal inflammation[65]. Both synthetic CB receptor agonists and endocannabinoids have been shown to impair cellular and humoral immunity by reducing inflammatory cell recruitment, inducing T cell apoptosis and suppressing the production of numerous pro-inflammatory cytokines and chemokines (*e.g*. TNF-α, IL-1β, IL-2, IL-6, IL-17, IFN-γ, CCL2 or CXCL10)[65, 351]. Therapeutically, both exogenous administration of cannabis and preventing endocannabinoid degradation by inhibiting FAAH have been shown to reduce colitis[343-346, 352]. In fact, FAAH inhibition and CB receptor activation have shown efficacy in mouse models of colitis and FAAH knockout mice are less susceptible to experimentally induced colitis compared to wild type mice[352]. The ability of endocannabinoids (or exogenous cannabis products) to accelerate wound healing in the gut points to their ability to promote intestinal/mucosal barrier function, that is, the bonding of intestinal epithelial cells to create a uniform and restrictive barrier. This mechanism has been confirmed *in vitro*, with cannabinoids improving or maintaining

paracellular permeability (i.e. leakiness) and tight junction protein expression in Caco-2 cells treated with *Clostridium difficile* toxin A and other barrier-directed insults (e.g. cytokines, EDTA)[65, 353]. These mucoprotective effects have also been reported preclinically, with cannabinoids reported to decrease intestinal permeability (and increase regulatory T cell recruitment) in experimental colitis induced by dextran sulfate sodium (DSS)[65]. It has also been suggested that cannabinoids can modulate secretory processes in the intestinal epithelium which, when dysregulated, lead to altered osmotic forces and potentially diarrhoea[354-357].

An emerging area of interest with respect to the gastrointestinal microenvironment is the interaction between the ECS, cannabis and the gut microbiota[329, 358, 359]. The gut microbiota is a collection of microorganisms (bacteria, viruses and fungi) that reside in the gastrointestinal lumen and mucosal niches, regulating host physiology and immune function. Importantly, these beneficial host-directed effects are best achieved when there is high microbial diversity and enrichment for commensal microbes. Chemotherapy indirectly impacts the diversity and composition of the gut microbiota, through the destruction of their mucosal niches and oxidative stress[360]. As such, a highly dysbiotic microbiota is a hallmark trait of chemotherapy, and an event documented to drive a range of adverse effects including fever, infection, diarrhoea, cachexia, weight loss, anxiety, cognitive impairment, cardiotoxicity and fatigue. Although a relatively new concept, emerging data suggests an interaction between the ECS and the gut microbiota. Most recently, cannabis extracts (CN1, CN2, CN6) were shown to increase microbial diversity and richness in a mouse model of metabolic disease whilst promoting enrichment of microbial taxa associated with health[361]. Further suggesting an ECS-microbiota interaction is the finding that germ-free mice (mice without a microbiota) are deficient in a number of ECS components, including the CNR1[278]. A microbial taxa of particular interest is *Akkermansia muciniphila*, a

mucus-degrading microbe implicated in gut inflammation[362] and chemotherapy side effects[363, 364]. This microbe is reportedly elevated in response to CNR1 antagonism with the compound SR141716A, although this was only demonstrated in obese mice[279, 365]. Despite this emerging evidence, it is unclear if medicinal cannabis influences the gut microbiota and if this mechanism underpins/delivers meaningful impacts for the host.

Collectively, this body of evidence strongly demonstrates the profound control that the ECS exerts on gastrointestinal function, regulating motility, barrier function and repair, immune function, secretion and potentially the microbiota. These data underscore the potential mucoprotective effects of exogenous cannabinoid administration or augmentation of the ECS. In the context of cancer care, this therefore supports strategies targeting ECS (via direct cannabinoid administration or inhibition of degradation) to control mucositis and promote a more resilient gastrointestinal microenvironment. Despite the scientific strength of this rationale, and the prevalence of mucositis (occurs in ~60% of patients treated with standard chemotherapy), there have been few attempts to explore the mucoprotective properties of medicinal cannabis in cancer care[338]. This may reflect the complexities of using/investigating medicinal cannabis during active cancer treatment.

Using medicinal cannabis during active cancer treatment: precautions, challenges and potential benefits

To minimise both the depth and duration of mucositis, supporting the gastrointestinal microenvironment and controlling the constellation of symptoms with which mucositis is associated, medicinal cannabis should be used *during active chemotherapy treatment*. Of course, this raises some concerns regarding the possibility of adverse drug interactions with anti-cancer therapies and potential loss of anti-tumour efficacy. There

has been limited investigation of how cannabis influences the anti-tumour efficacy of cancer treatment. Cannabis has been investigated for its effect on the pharmacokinetics of irinotecan and docetaxel, with no effects observed[366]. While some evidence suggests that cannabis may impair the anti-tumour efficacy of immunotherapy[367],[368], recent evidence suggests cannabis may actually have a synergistic effect with immunotherapy. This has been shown both preclinically and clinically, with median survival in CT26 tumour-bearing mice treated with THC and an anti-PD1 antibody having significantly higher overall survival compared to controls[369]. Authors also reported higher overall survival (numerical, failed to reach statistical significance) in 201 people with non-small cell lung cancer undergoing monotherapy with pembrolizumab who used medicinal cannabis. Although this does not confirm a synergistic effect, it does indicate no detrimental effect. The only study in which a definite synergy has been identified was preclinical, where a combination of cannabigerol and anti-PD-1 resulted in enhanced tumour clearance and increased survival compared to monotherapy in tumour-bearing mice[370].

In the context of chemotherapy, although there is no concrete evidence that suggests cannabis may impair its anti-tumor efficacy, given the increasing evidence for immune-mediated mechanisms enhancing chemoefficacy[371], this risk cannot be ignored and should be appropriately built into studies investigating medicinal cannabis in combination with standard chemotherapy. Although it remains exclusively experimental and prone to inflation, there is a growing body of evidence that suggests medicinal cannabis may in fact be a beneficial adjunct to standard chemotherapy, capable of inducing cell death or controlling proliferation by inducing endoplasmic reticulum (ER) stress[372, 373], proteosome inhibition[374], upregulation of matrix metalloproteinases[375] and reactive oxygen species activation[376]. In line with these findings, several studies have outlined the potential for cannabinoids to be used as anti-cancer agents either on

their own or in combination with other systemic cancer therapies or radiotherapy[377, 378]. A recent review summarised the anticancer effects of cannabinoids to be mediated through multiple pathways including anti-proliferative, pro-apoptotic, pro-autophagy, anti-invasion and metastasis, anti-angiogenesis, and immunomodulation[379]. However, it is important to note that the majority of these findings have only been explored *in vitro* or in preclinical (animal) models and are subject to inflation in the public domain. As a result, these benefits have not been robustly translated into the clinical setting. Three human clinical trials reported the results on the role of cannabinoids on patients with recurrent glioma[380-382]. Guzman et al. demonstrated that only two of nine patients with recurrent Glioblastoma (GBM) had reduced tumor proliferation when treated with intracranial Δ^9-THC alone as monotherapy[380]. Another trial that combined Nabiximols (a mixture of plant derived THC, CBD and non-cannabinoid compounds) with temozolomide (N = 27) resulted in a numerically higher 2-year overall survival (50% vs 22%, p = 0.130) when compared to placebo/TMZ[381]. Schloss et al. compared two different doses of THC/CBD combination as adjunct to standard treatment of recurrent high-grade gliomas (N = 88) and demonstrated an improved quality of life and an imaging assessed tumor response in 11% while 34% had stable disease when compared to historical controls[382]. These clinical trials highlight that a small proportion of people with recurrent GBM may have benefit with cannabinoids, however, there are no available predictive biomarkers that may identify responder and non-responders.

On the other hand, two recently reported observational studies indicate a negative impact of cannabinoids on immune checkpoint inhibitors (ICI) related cancer outcomes[383, 384]. Bar-Sela et al. highlighted in a prospective study that the concomitant use of prescribed cannabis was associated with lower response rates (39% vs 59%), median time to progression (3.4 months vs 13.1 months) and median overall survival (6.4 months vs 28.5 months) when compared to ICI therapy alone[383]. Another

retrospective observational study from the same research group reported inferior outcomes for cannabinoid use along with nivolumab (an ICI) when compared to nivolumab among selected solid cancers[384]. Given the evidence from low quality clinical trials, well conducted trials are required to assess the efficacy of cannabinoids as anti-cancer therapeutics either alone or in combination with other systemic cancer therapies.

In addition to the impact on anti-tumor efficacy, the other main risk associated with medicinal cannabis use in parallel to active treatment is drug-drug interactions. Given the predominant role of MC for pain control in cancer care, its interaction with other analgesics is of interest. Evidence suggests that cannabis may in fact enhance opioid-induced analgesia, with synergistic analgesia observed when opioid/cannabinoid ligands are co-administered. In animal studies, either morphine or codeine produces synergistic antinociception when combined with THC[385-388], and similar synergies have been documented in humans[389]. However, these benefits must be taken in light of evidence that suggests this combination may increase tolerance to both forms of analgesia and increase the risk of "drug-liking" effects[368, 390]. There is also evidence to suggest drug-drug interactions between CBD and the non-steroidal anti-inflammatory, naproxen, although this is limited to in vitro evidence[391]. However, both CBD and THC are metabolised by CYP2C9, suggesting possibility of impaired drug clearance[391] or renal/liver toxicity. Although, there are no data to suggest CBD and THC cause renal/liver toxicity, and in fact there is data to suggest hepatoprotective effects[392] and prevention of cisplatin-induced renal toxicity[393]. However safety profiles of MC in the context of cancer care remains superficially addressed, underscoring the importance of regular renal and liver function tests, appropriately titrated dosing, and studies with co-primary endpoints that address efficacy and safety[368]. These studies should also endeavour to capture the patient experience with respect to milder adverse events such

as dry mouth and fatigue/somnolence, given their association with both cancer therapy and MC.

While medicinal cannabis use during active chemotherapy presents some challenges, if approached carefully, there are a number of benefits that can be achieved. These benefits largely relate to the ability to control multiple symptoms early in their aetiology, rather than therapeutically targeting single symptoms that may have developed and persisted well after treatment ends. This holistic approach to controlling multiple symptoms is in line with recent suggestions by the MASCC, and also aligns with the scientific evidence that underpins the clinical phenomenon of symptom clustering[394-396].

We have outlined a clear rationale for how medicinal cannabis products, or augmentation of the ECS, modulates gastrointestinal function and exerts mucoprotective effects. It is therefore well positioned to target numerous mechanisms known to be involved in mucositis pathobiology and symptomatology. Given the documented role of mucositis and associated changes in the gastrointestinal microenvironment (e.g. gut microbiota dysbiosis) driving a range of intestinal and extraintestinal symptoms, medicinal cannabis in the active stages of chemotherapy may deliver broad reaching benefits. This is particularly compelling when considering that medicinal cannabis, and the ECS, will likely have paralleled effects on these associated symptoms. For example, mucositis can cause taste changes and pain, leading to reduced oral intake (anorexia) and therefore clinically impactful weight loss. As such, targeting mucositis with cannabis, whilst simultaneously promoting food enjoyment and behaviours, will likely deliver meaningful impacts of weight maintenance and nutritional status. Similarly, diarrhoea and pain due to mucositis is anecdotally thought to cause sleep disturbances[397]. Again, by addressing a biological cause and providing symptomatic relief, the potential for meaningful impacts on patient quality of life is

enhanced. This same framework can be applied to numerous, interacting consequences of mucositis and associated symptoms (Figure 2).

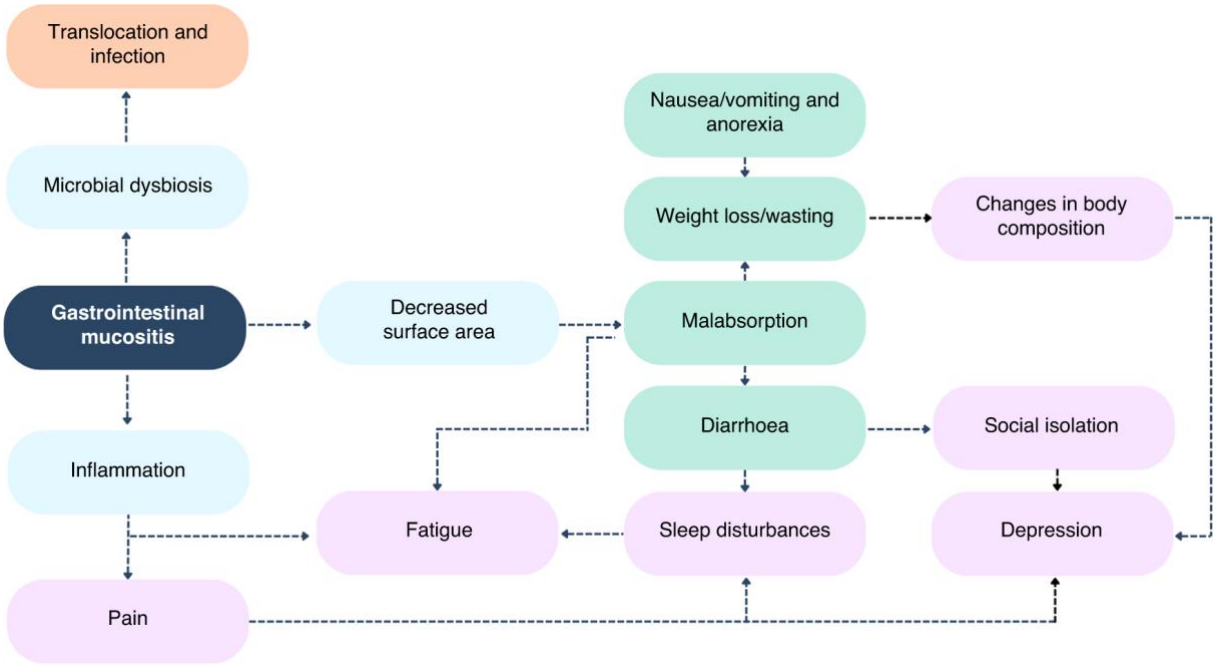


Figure 2: The centrality of gastrointestinal mucositis to infectious (orange), gastrointestinal (green) and neuropsychological (purple) symptoms commonly reported in people with advanced cancer undergoing chemotherapy.

This positions gastrointestinal mucositis as an ideal therapeutic target.

By approaching symptom management in this manner, the magnitude of benefit is likely to be larger, and thus the health and wellbeing of people undergoing chemotherapy better maintained. This will deliver knock-on effects to patients, ensuring they remain in the workforce, thus reducing personal financial toxicity, and remain willing/capable of receiving their intended chemotherapy dosing ensuring optimal tumor response and progression free/overall survival. This indirect effect on treatment efficacy is significant and should not be disregarded. For example, in a recent review of 874 women with advanced breast cancer, chemotherapy dose reductions of > 15% significantly increased the risk of mortality[398]. Similarly, a reduction in total cumulative dose of neoadjuvant FEC-D (where it is < 85% of intended dosing)

decreased the length of survival in women with breast cancer[399]. Similar effects have been reported in ovarian cancer and colon cancer[400-402].

When considering the causes of dose reductions or modifications, adverse effects (i.e. side effects) are the most common cause, accounting for 82% of all dose reductions in a recent audit of 584 people undergoing adjuvant chemotherapy for stage III colon cancer[401]. As such, the provision of proactive supportive care that tackles symptom clusters at multiple points in their aetiology and progression is critical. In fact, the provision of supportive care early in symptom aetiology is recommended, with evidence illustrating both quality of life and survival benefits when this approach is adopted[36]. Furthermore, by addressing multiple symptoms concurrently, or targeting common underlying mechanisms of multiple symptoms, polypharmacy (5+ medications) can be reduced. More than 80% of people with advanced care report polypharmacy[16]. This approach is fragmented, and places substantial burden on the patient who must navigate multiple medications, increasing their risk of adverse drug interactions and medical misadventure[48]. With recent calls to address the fragmented approach to supportive cancer care and symptom control[403], the ability of medicinal cannabis to transcend multiple symptoms is compelling, and advantageous.

In considering how medicinal cannabis can be used to deliver substantive impacts for people undergoing chemotherapy, a number of practical matters must be carefully considered. Firstly, there are a range of cannabis extracts that are available for consumption in a variety of formulations ranging from dry leaves/buds which can be smoked or vaporized, to highly purified and processed isolates[404, 405]. Typically, the more readily accessible cannabis products are in the community, the lower the degree of purification and quality assurance. In light of high rates of self-reported use[94, 311, 332], this underscores the need to deliver evidence that (if shown to be beneficial) will ensure patients can access medicinal cannabis in more appropriate and safe formulations.

Cannabis is commonly available as an oil, which contains or is enriched for CBD and THC, typically in combination with many other cannabinoids and phytochemicals (e.g. terpenes) at varying proportions. Oils are a convenient method of administration, and can be directly administered to the oral cavity for rapid mucosal absorption, however they do require a degree of dexterity and are prone to inaccurate dosing as people typically administer their dose as a number of "drops" [368]. Similarly, sublingual or oral-mucosal sprays can be used. While direct application to the oral mucosa is a common and easy method of administration, it is important to consider how factors like oral mucositis may influence tolerance, as some sprays are prepared in an ethanol diluent which would be painful to apply to an ulcerated oral cavity. Similarly, it is unclear how oral mucositis impacts the rate of absorption. Oils can also be encapsulated for ingestion; however, this method of administration must be considered in the context of dysphagia and nausea/vomiting, which may impact the patient's ability to swallow a capsule, or intestinal mucositis which may also influence the rate of absorption[406]. This underscores the need to conduct appropriate pharmacokinetic studies to determine how these unique factors associated with cancer, in particular active chemotherapy, impact the uptake and efficacy of cannabis. Further to this, there is evidence that suggests the presence of high-fat food impacts bioavailability of cannabis, and thus this should be carefully considered in the design of capsules and other formulation strategies[320, 407]. Importantly, these methods of administration result in different clinical effects, particularly with respect to the timing and duration of the response[368]. These should be considered when selecting the time of administration (i.e., time of day) and the symptom or side effect(s) of interest.

In addition to the method of administration, the selection of specific cannabinoids and their relevant doses is critical. This decision needs to be guided by the specific symptom or side effect(s) of interest, with a clear scientific rationale for their use. When

considering the medicinal cannabis intervention of interest, it is also important to acknowledge and respect the complexity of medicinal cannabis as an entire entity (i.e. a whole plant) in which the combination of numerous active compounds work cooperatively to elicit benefit. As such, while using synthesized isolates may be attractive from a pharmacological perspective, evidence suggests that the synergy of numerous cannabis compounds, a process referred to as the "entourage effect," outweighs the benefits that can be gained from a single isolate or molecule.

In the context of mucositis and its constellation of symptoms, the use of CBD and THC (with other cannabinoids and compounds such as terpenes) is likely to be best positioned to deliver meaningful benefits based on their unique yet synergistic effects[309, 408]. Of note, CBD is documented to counteract the *undesirable* psychotropic effects of THC[409] and may therefore improve adherence. This synergy is in addition to the ability of these compounds to address different but related symptoms. For example, CBD is hypothesised to control self-perpetuating inflammatory pathways that ultimately dictate the depth and duration of mucosal injury to deliver clinically meaningful benefits[345, 410-412]. In parallel, THC has the capacity to provide complementary effects to control anxiety, promote food intake/appetite and sleep quality[413-416]. However, it cannot be ignored that while THC provides potential benefits for the patient, it certainly introduces additional medico-legal complexity, with many countries enforcing strict no-tolerance laws with respect to operating heavy machinery or driving motor vehicles. This may negatively impact patient wellbeing by impacting their employment prospects, or ability to live independently. It also poses challenges for patients that may have caring duties. Further advice regarding dosing has been summarized by Cyr and colleagues[368].

The future of medicinal cannabis

The field of medicinal cannabis has been and continues to be difficult to navigate, reflecting the legislative challenges, variations in formulations and complexities of this emerging pharmacotherapy[321, 322, 326, 417]. To understand how to appropriately use this plant and its individual components in a therapeutic manner and avoid toxicity, well-designed in-vitro and in-vivo clinical pharmacology studies are required, particularly due to individual differences [417, 418]. Understanding the clinical pharmacology involved with MC will take the 'guesswork' out of the current largely uncontrolled and uncertain approach, which could provide the long wanting 'safeguard' for many vulnerable[419] individuals who are not benefiting from current practices and already suffering from poor quality of life due to undergoing cytotoxic chemotherapy and/or many other unpleasant conditions.

It is well-known that there are many cannabis species producing hundreds of compounds of which more than 100 chemicals are known as phytocannabinoids, with THC, CBD, terpenes and flavonoids being mostly abundant [319, 322]. Therefore, in order to provide this 'safeguard' with MC therapy, there are two key elements that need to be addressed. The first being, understanding the molecular mechanisms behind both the therapeutic and adverse effects of the various compounds within MC, and the second being, understanding the pharmacogenomics, pharmacokinetics and pharmacodynamics of the various products and formulations between individuals[322, 326, 418].

To achieve this, well established genetic approaches should be adopted in the field of MC to facilitate precision medicine ('selecting right drug')[326, 418] and pharmacokinetic guided approaches to facilitate precision dosing ('selecting the right dose')[319, 322, 420]. For the latter, specifically, exposure-response studies via therapeutic drug monitoring or pharmacogenomics may enable individualized therapy[326, 418], similar to how it has been done for anti-cancer therapeutics[421]. Additionally, to provide true individualized

or personalized dosing, population pharmacokinetic-pharmacodynamic (POP-PK/PD) models need to be developed to better understand how the population and individuals respond to these compounds, and which covariates (e.g. age, weight, gender, genotype, comedications, etc.) drive any variability in the pharmacokinetics and thus responses[419].

It has been well-documented that clinical trials are limited and of the available data, it is clear that varied design has resulted in the inability to compare and establish conclusive evidence. However, with *personalized medicine* currently in its peak in many research areas, such as antimicrobials, and anti-cancer drugs [422], it is an ideal time to build on current research and investigate which compounds should be isolated or combined in the appropriate formulations and administered to truly enable personalized MC therapy[322, 326, 418]. This will lead to a better understanding how exactly these compounds exert their effects and how this knowledge can be utilized to treat conditions such as mucositis which in turn has the potential to reduce symptom clustering and an array of treatments which cause additional challenges (polypharmacy, drug-drug interactions, adverse effects, poor quality of life and financial burden) for both the individuals and the healthcare systems. The need and opportunity to investigate how MC therapy can be personalized for individuals suffering from mucositis and other conditions is evident and brings on an exciting future for MC research.

While trial data remains inconclusive, it is likely that individual factors that dictate tolerance and efficacy have contributed to the variable and often contradictory results observed. For example, previous cannabis use is associated with lower anxiety after THC. Similarly genomic factors have been shown to predict efficacy and tolerability of CBD. In a recent genomic study of patients with treatment-resistant epilepsy, single-nucleotide polymorphisms in certain genes were identified which were associated with a lower response and greater side effects of CBD[420]. The study also revealed genetic

variants that were related to the likelihood of CBD-associated diarrhoea[420]. These findings present an opportunity for personalised pharmacogenomics-guided strategies for precise MC treatment that could be particularly advantageous for patients undergoing chemotherapy, already at risk of gastrointestinal side effects such as diarrhoea[420]. Understanding these factors will be critical in optimising the safe and effective use of cannabis in medical practice.

Conclusions

Soon after the discovery of its chemical structure and ability to obtain various compounds from the plant in the late 1900s and the description of the cannabinoid receptors and the endocannabinoid system in the 1990s, evidence has demonstrated that cannabis use for medical purposes has increased significantly with a steep rise in the last few years[319, 423]. It is evident that the majority of this use results from illegal access, however, this has been recognised and laws are in a fast-changing phase with several products approved and several others on a registered unapproved list. This at least provides new opportunities for users and prescribers to access MC products in a legal manner. In cancer care, self-reported cannabis use is prevalent, however the evidence base is lacking due to inconsistencies in study design and outcomes. Moving forward, it is critical that research efforts integrate appropriate pharmacokinetic and mechanistic sub studies to understand cannabis biology in the context of cancer and investigate its efficacy in a more holistic sense by considering its impact on clusters of related symptoms. In the context of mucositis, this is a compelling approach given the numerous symptoms that occur secondary to mucosal barrier injury and the already documented benefits medicinal cannabis has on gastrointestinal physiology, inflammation, and dysfunction.

Appendix 4: Trial protocol

Medicinal cannabis (CBD/THC) to prevent the symptoms and side effects of chemotherapy in people with advanced cancer: protocol for a phase II randomised, double-blind, placebo-controlled trial

Bellas OM[1,2*], **Cao K[1,2*]**, Bowen J[1], Smid S[1], Shakib S[1], Crawford G[3], Zannettino A[1], Kichenadasse G[4], Boublik J[5], Louise J[6], Marker J[7], Cambareri B[1,2], Price T[1,8], Wardill HR[1,2].

[1]The University of Adelaide, Adelaide, Australia; [2]Supportive Oncology Research Group, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia; [3]Northern Adelaide Local Health Network, SA Health, Adelaide, Australia; [4]Southern Adelaide Local Health Network, SA Health, Adelaide, Australia; [5]LeafCann Group Pty Ltd, Queensland, Australia; [6]South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia; [7]Cancer Voices South Australia (Consumer Representative); [8]Central Adelaide Local Health Network, Adelaide, Australia.

*Contributed equally to this work

Abstract

Introduction: Many chemotherapy agents used to treat advanced cancer are inherently mucotoxic, causing breakdown of the gastrointestinal mucosa (gastrointestinal mucositis, GI-M) and lead to a constellation of secondary complications including diarrhoea, malnutrition, anorexia, pain, fatigue, and sleep disturbances. These symptoms are typically managed in isolation, resulting in polypharmacy and its associated risks. The endocannabinoid system (ECS) is known to regulate numerous biological and behavioural processes relevant to chemotherapy side effects, hence suggesting a potential to control side effects via ECS modulation. In line with this concept, the CANnnabinoids in CANcer therapy (CANCAN) trial aims to determine the effectiveness of medicinal cannabis in minimising GI-M and its associated symptom burden.

Methods: Adults (N = 176) diagnosed with a solid tumour or a haematological cancer scheduled to receive mucotoxic chemotherapy will be eligible for the CANCAN trial. Eligible participants will be randomised 1:1 to receive the investigational product (IP) or placebo as a sublingual wafer. The active IP will include cannabidiol (CBD, 300mg/day) and △9-tetrahydrocannabinol (THC, 5-20mg/day titrated by the participant) administered as sublingual wafers. The primary outcome is GI-M burden, determined by the Mucositis Daily Questionnaire (MDQ). Secondary and tertiary outcomes include overall symptom burden (ESAS), anorexia (FAACT), depression/anxiety (HADS), financial toxicity (FACIT-COST), quality of life (EORTC-QLQ-C30), incidence of chemotherapy dose reductions/modifications, cumulative dose of chemotherapy administered, incidence/length of hospitalisation, the use of supportive care, and the cost-benefit of the IP.

Results: The CANCAN trial (ACTRN:12622000419763p) is scheduled to begin recruitment in Q2 2024.

Discussion: The CANCAN trial has been designed with the patient at its centre, prioritising PROMs and administering medicinal cannabis during active treatment to prevent the impactful symptoms that occur secondary to mucositis.

Ethics and dissemination: The protocol has been approved by Central Adelaide Local Health Network Human Research Ethics Committee (2022HRE00037). Trial results will be disseminated in peer-reviewed journals, at scientific conferences.

Trial registration: ANZCTR: ACTRN1262200041976

Strengths and limitations of this study

- Large, multi-site trial with rigorous design (e.g. placebo controlled, double-blind) addressing an area of unmet need.
- Prioritisation of patient-reported outcome measures (PROMs) capturing a broad range of symptoms.
- Evaluating synergistic effects of prophylactic CBD and THC, enabling participants to self-titrate to maximum tolerated THC dose.
- Inclusion of a pharmacokinetics study.
- Heterogeneous cohort of mixed tumour types
- High risk of drop-out/non-adherence due to long study duration and inability to drive during active trial period.

1. Introduction

Cancer therapy, including chemotherapy, causes a range of debilitating side effects that impact the quality of life (QoL) of people living with or beyond cancer. Currently, these side effects are managed reactively and in isolation [424, 425]. This approach is flawed for two major reasons: 1) it fails to acknowledge data that show early intervention with supportive care services is more effective and improves QoL [36], and 2) it increases the risk of polypharmacy (prescription of 5+ medications) and its associated risk of hospitalisation and death [48, 50, 426, 427]. Identifying streamlined strategies to proactively

control or prevent multiple symptoms is therefore an area of intense investigation in the field of supportive oncology.

A strong body of evidence shows that damage to the gastrointestinal microenvironment caused by chemotherapy (i.e. gastrointestinal mucositis, GI-M) is a major catalyst for secondary complications [281, 424, 428] (Figure 1). GI-M is initiated by direct cytotoxicity caused by chemotherapy and other cytotoxic agents which are unable to discriminate between the highly proliferative cells of the tumour and those that line the gastrointestinal tract [281]. This damage then initiates secondary events that perpetuate mucosal damage, including the production of reactive oxygen species, pattern recognition receptor activation, and the production of pro-inflammatory cytokines [281]. The extent and duration of this secondary inflammation ultimately then dictates the severity of mucosal injury, which presents as confluent, ulcerative lesions throughout the entire gastrointestinal tract and associated symptoms such as diarrhoea, bleeding, and pain [281]. In addition to pro-inflammatory mechanisms, damage to the mucosal also disrupts the delicate ecosystem of micro-organisms that reside in the gut (the gut microbiota), leading to dysbiosis. Dysbiosis, defined as a (typically pathogenic) change in the composition of the gut microbiota increases the production of microbially-produced danger signals (e.g. endotoxin/lipopolysaccharide, LPS) which further triggers pro-inflammatory responses via the activation of pattern recognition receptors, including toll like receptor 4. This, combined with a loss in the mucoprotective metabolites, short chain fatty acids (SCFAs), further contribute to mucosal barrier injury and systemic inflammatory responses.

These secondary events related to GI-M lead to a constellation of symptoms, including infection, malnutrition/weight loss, anorexia, sleep disturbances, cognitive dysfunction, and fatigue [281]. Collectively, these cause profound distress and a debilitating loss of

QoL. When severe, these symptoms require intensive intervention (e.g. antibiotics, nutritional support) with hospital costs of up to $24,633 (USD) per episode [17]. In these cases, symptoms of gut distress may also necessitate dose-reductions, decreasing the depth of response and increasing disease progression and even risk of death [398, 429]. As such, whilst not universally recognised or defined as a "symptom cluster," the mechanisms of gut distress provide a compelling case that GI-M is a catalyst for number of inter-related symptoms, suggesting that targeting GI-M may deliver meaningful benefits to patients by addressing numerous symptoms.

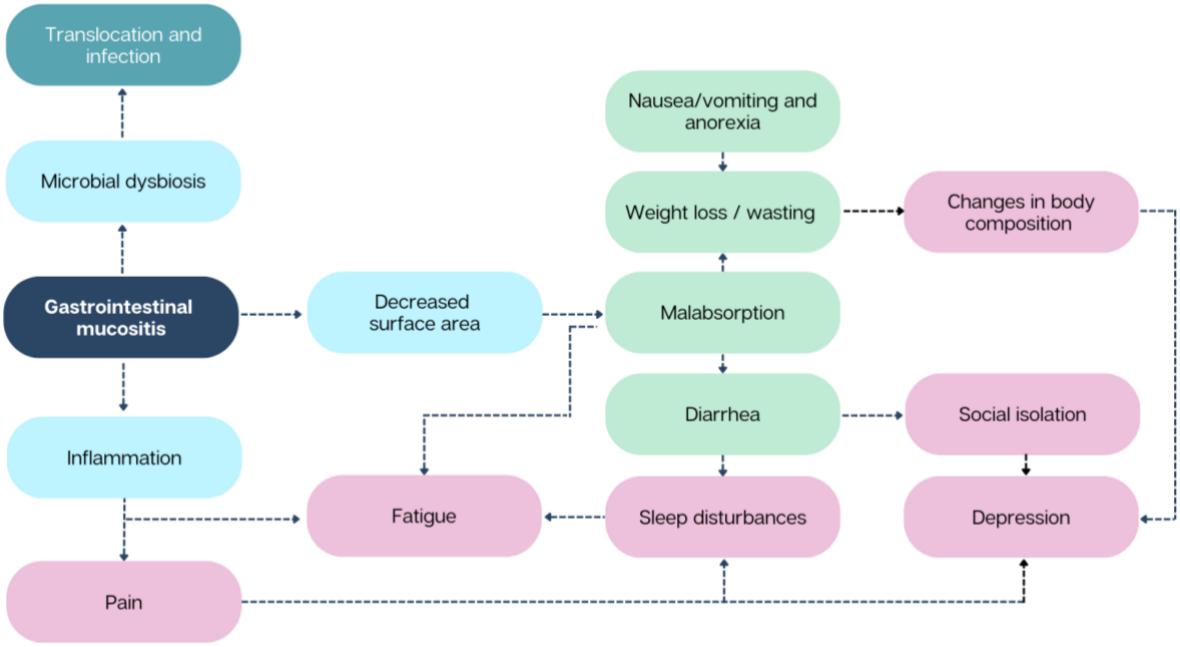


Figure 1. Centrality of gastrointestinal mucositis in intestinal and extra-intestinal symptoms

There are currently no effective interventions to prevent gastrointestinal symptom clusters in people undergoing cytotoxic cancer therapy. Considering its ability to modulate a variety of organ systems, biological and behavioural processes, medicinal cannabis has gained attention for its potential to control the symptoms and side effects of chemotherapy. Medicinal cannabis extracts are complex botanical mixtures

comprised primarily of $\triangle^9$-tetrahydrocannabinol ($\triangle^9$-THC or THC) and cannabidiol (CBD).

THC and CBD exert their effects through the endocannabinoid system (ECS), a widespread network composed of cannabinoid receptors, ligands, transporters, and enzymes. The ECS is a sophisticated and complex signalling network that spans multiple organ systems, including the nervous, cardiovascular, endocrine, and immune systems[39, 51, 53, 54]. There is strong supporting evidence for both a direct and indirect role of the endogenous cannabinoid system and exogenous compounds that interact with this system, in modulating gut functions in health and disease [430]. With respect to GI-M, CBD is a promising candidate to minimise its severity due to its documented anti-inflammatory properties, suppressing cytokine release and minimising inflammatory injury to the gut in colitis [431]. In the context of cancer therapy, CBD (300mg/day) has been shown to decrease graft-versus-host disease (phase II open-label testing), with a reduction in mucosal damage identified [432]. In addition to the anti-inflammatory benefits associated with CBD, THC has demonstrated varying levels of antiemetic[63, 99-103], analgesic[102-106], psychosocial[64, 109, 110], and appetite-improving properties[81-83, 101] in people with cancer.

Given the lack of interventions that effectively prevent gastrointestinal symptom clusters in people undergoing cytotoxic cancer therapy, cannabinoids are gaining popularity in cancer care due to their speculated ability to alleviate *multiple* symptoms through the widespread mechanisms of the ECS[69-80]. Therefore, the CANCAN trial will investigate the efficacy of medicinal cannabis in controlling GI-M and the constellation of impactful symptoms in people with advanced cancer. With CBD and THC administered concurrently, we anticipate synergistic benefits, with mechanistic

prevention of mucotoxicity and behaviour benefits that will minimise gastrointestinal distress symptoms and improve QoL (Figure 2).

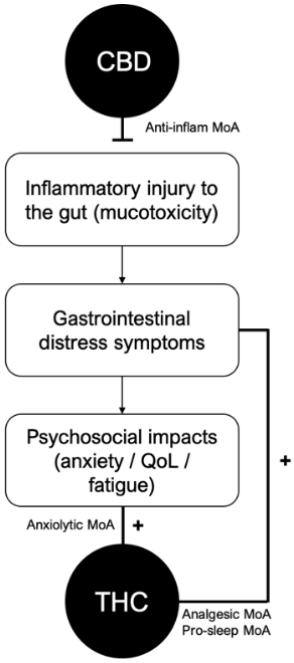


Figure 2. THC/CBD synergy with mechanism of action.

1.1 Hypothesis

Early intervention with CBD/THC will minimise the intensity and duration of GI-M, mitigating secondary physical and psychosocial symptoms, thus supporting adherence to anti-cancer therapy, and mitigating the economic burden of chemotherapy side effects.

2. Methods and analysis

2.1 Study objectives

- Determine the effectiveness of early intervention with the interventional product (IP) in mitigating GI-M caused by chemotherapy.
- Determine the flow-on effect of mitigating GI-M on secondary symptoms and QoL.
- Determine impact of the IP on incidence of dose-reductions or treatment delays.
- Quantify economic benefit of early intervention with the IP in reducing hospitalisation, supportive care utilisation and lost opportunity to the individual.

2.3 Eligibility criteria

Table 1. CANCAN trial inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria	
> 18 years of age Scheduled to receive mucotoxic, systemic cancer therapy for advanced solid and haematological cancers. Anticipated to undergo 3 cycles of chemotherapy (solid tumour cancer participants) OR autologous stem cell transplantation (haematological cancers – HSCT participants). Willing to commit to not taking cannabis in any other form during the clinical trial period. For randomisation of solid tumour participants: Gut distress symptoms related to their cancer therapy defined by a score of greater or equal to 1 in the MDQ and confirmed by a research nurse.	Cannabis dependence / misuse defined by the revised Cannabis Use Disorder Identification test score of 8 or above. History of unstable cardiovascular disease including myocardial infarction or cerebrovascular accident, crescendo history of angina or heart failure. Recreational or medicinal cannabis use defined as use > once/week in the month leading up to the clinical trial period. History of psychosis secondary to, or intolerance to cannabis products.	Presence of an active psychiatric disorder or concurrent disorder that may be exacerbated by cannabinoids, or which may interfere with clinical trial outcome determination (determined by the recruiting clinician). Pregnant or planning on becoming pregnant. Currently lactating. Involved in another clinical trial (except observational trials) or expected to start one soon after completion. Pre-existing oral disease or disability that would impair oral-administration or mucosal absorption. Presence of known impairment of hepatic synthetic dysfunction. Laboratory values suggestive of liver dysfunction.

Abbreviations. MDQ = Mucositis Daily Questionnaire

2.4 Intervention and placebo product

Eligible participants will be randomised 1:1, receiving the IP or placebo as a sublingual wafer over the course of 3 cycles of chemotherapy. The active IP will include CBD (300mg/day) and THC (5-20mg/day). CBD and THC will be packaged separately, and

as such, will be administered separately to ensure THC dose titrations can be easily achieved. CBD will be administered as a standard 300 mg/day dose (6 sublingual wafers, 3 BD) without opportunity for titration or modulation unless in the case of relevant adverse event (AE), see Section 2.7. THC will be administered at a starting dose 5 mg/day, increasing in 5 mg increments approximately twice weekly until the maximum tolerated dose is achieved (note: the maximum dose for participants is 20 mg/day). Packaging will be identical between placebo and medicinal cannabis, manufactured by iX Biopharma.

2.5 Randomisation, allocation concealment and double-blind conditions

Randomisation schedules have been developed by our trial statistician for each site centrally via an electronic platform using random number tables. These will be stratified for site, cancer type and chemotherapy type to ensure even distribution of participants across both arms. Solid tumour participants with a Mucositis Daily Questionnaire (MDQ) score of ≥1 and all haematological cancer participants scheduled to undergo HSCT will be randomised in a 1:1 ratio to intervention or placebo after their first dose of chemotherapy (C1) and at the time of enrolment (T0), respectively. This enables the participant cohort to be enriched, i.e. increasing the rate of GI-M, whilst also enabling early intervention with the IP. The randomisation schedule will be used by the hospital pharmacy staff to allocate the IP/placebo to participants. All staff and investigators involved in the trial will be blinded. Participants' data and notes will be referred to using their clinical trial ID number. The code will only be broken in cases of emergency as stipulated in the Data and Safety Monitoring Board Charter.

2.6 Recruitment and consent

Potentially eligible participants will be identified at multidisciplinary team meetings at each recruitment site and the treating clinician will discuss the clinical trial with the participant at their next consult/appointment. Participants will provide consent in either written or electronic form, with an eConsent module provided by Consentic™.

2.7 Discontinuation/modification and adherence

A participant may be discontinued from the study medication at any time if it is not in their best interest to continue.

2.7.1 *Adverse events that prompt dose modifications (in IP)*

CBD has been associated with liver toxicity and renal dysfunction. As such, at each chemotherapy visit, the most recent CBP/MBA20 results must be reviewed to identify any indicators of liver toxicity or renal dysfunction.

MBA20 results that require dose modifications to CBD include:

- INR: > 1.5
- ALT: > 5x upper limit of normal
- AST: > 5x upper limit of normal
- Bilirubin: > 3x upper limit of normal
- Creatinine: If > 5x upper limit of normal

Course of action: CBD to be stopped for 7 days. Liver function tests to be repeated and mode of action to be taken as per Stopping Criteria below (Table 3).

Table 2: IP dose modification and stopping criteria		
Parameter	**Dose modification criterion**	**Action to be taken**
INR	Grade 2 changes i.e. > 1.5 for patients not on anticoagulants	CBD held for 1 week then laboratory tests repeated - If abnormality resolves, **recommence dosing at previous dose** - If abnormality does not resolve and there is no other cause identified, **dose to be ceased**
Total bilirubin	Grade 3 changes (i.e. > 3.0 ULN)	
AST or ALT	Grade 3 changes in ALT or AST (i.e. > 5.0 ULN)	

Renal function	Creatinine values of Grade 3 changes (i.e. > 5.0 ULN)	- If there is uncertainty about the cause or the values fluctuating, the investigator has discretion to continue to hold the medication and repeat testing.
Somnolence	RASS score indicating significant impairment to participant's ability to perform daily tasks (as outlined by scores in Table below).	

THC may cause unwanted sedation or agitation/anxiety. This is to be assessed at each clinic visit or home nursing visit using the Richmond Agitation and Sedation Scale (RASS). The following RASS scores prompt the following actions:

+4	– Combative	THC to be stopped for 1 week & reduced to previous dose
+3	– Very agitated	
+2	– Agitated	Dose reduction to be discussed with participant
+1	– Restless	Dosing unchanged
0	– Alert and calm	
-1	– Drowsy	
-2	– Light sedation	Dose reduction to be discussed with participant
-3	– Moderate sedation	THC to be stopped for 1 week & reduced to previous dose

3. Study outcomes

3.1 Primary outcome

GI-M burden determined by the area under the curve (AUC) of the MDQ score/cycle.

Secondary outcomes

GI-M

- Number of days with MDQ≥1
- Maximum MDQ / cycle
- Average MDQ /cycle
- Plasma citrulline (biomarker of GI-M) assessed weekly through treatment
- AUC for hypocitrullinaemia (< 10µM)

Appendices

Body weight and nutrition

- Average body weight change / cycle
- Body weight change T1 and T2 follow up
- Average Functional Assessment of Anorexia/Cachexia Therapy (FAACT) score / cycle
- FAACT score at T1 and T2 follow up

Symptom burden

- Average Edmonton Symptom Assessment Scale (ESAS-r-SC) score / cycle
- ESAS-r-SC score T1 and T2 follow up

Depression, anxiety and QoL

- Hospital Anxiety and Depression (HADS) score at T1 and T2 follow up
- EORTC QLQ-C30 score at T1 and T2 follow up

Supportive care and hospitalisation

- Use of rescue medication (participant reported and clinically provided)
- Incidence of hospitalisation and/or emergency department presentations
- Duration of hospitalisation (days)

Chemotherapy adherence and survival outcomes

- Incidence of treatment breaks, delays, or dose reductions
- Cumulative dose of chemotherapy
- % of intended dose of chemotherapy achieved
- Response to treatment defined by RECIST criteria
- Progression free survival
- Overall survival

Adverse events

Appendices

- Incidence of Grade 3+ AEs (define by NCI CTCAE - National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0))
- Incidence of IP discontinuation
- Incidence of dose de-escalations (of IP) due to AEs

Economic impact

- Financial toxicity / cost analysis (FACIT-COST)
- Cost-benefit analysis

Tertiary/exploratory endpoints

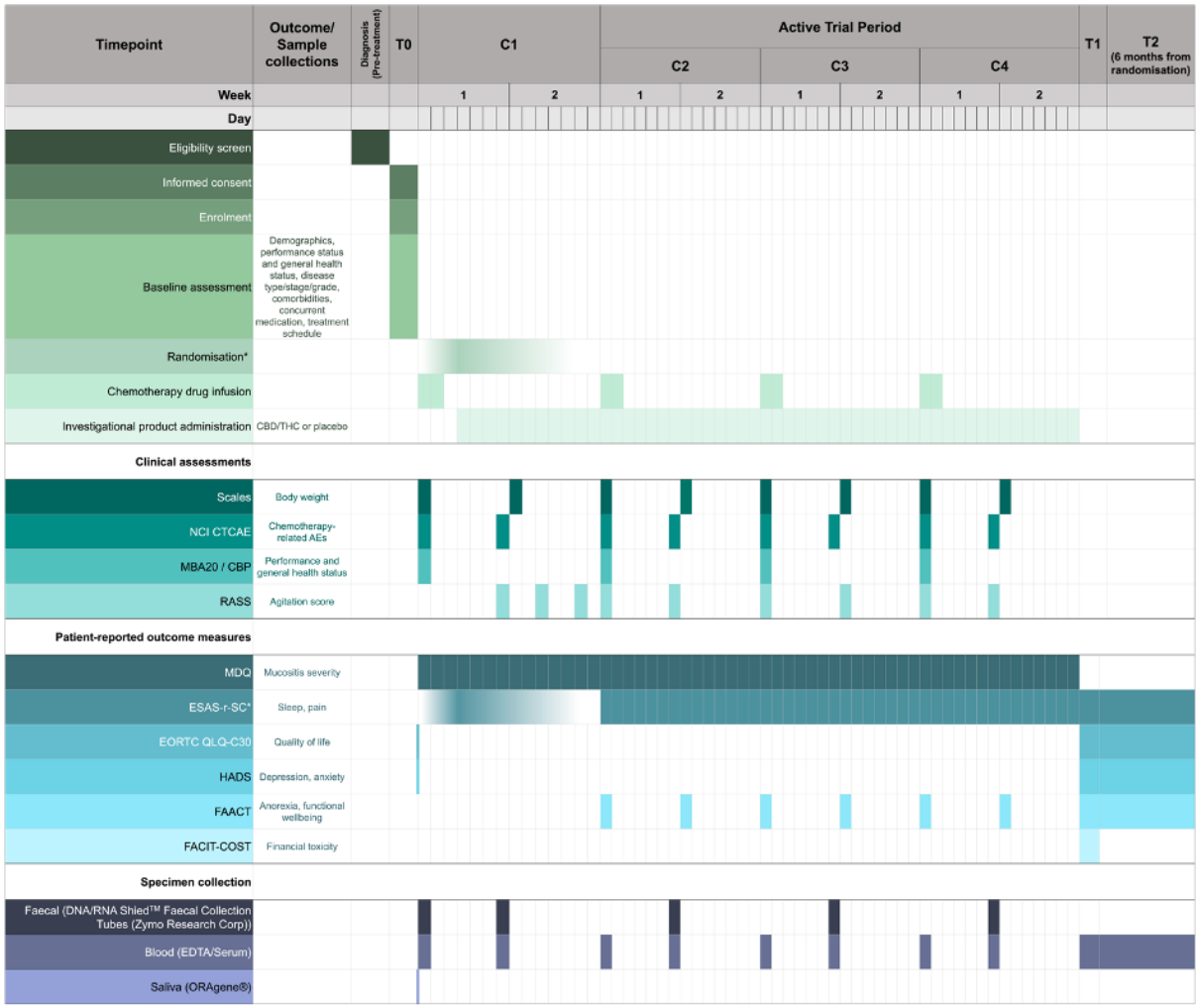
- Faecal microbiota composition
- Peripheral cytokine concentrations
- Population based pharmacokinetic – pharmacodynamic model

4. Participant timeline

Participants will be identified by their treating clinician and screened and enrolled if eligible by clinical trial and/or members of the investigator team. The intervention will be administered to people with solid tumour and haematological cancers using different approaches that reflect the differences in treatment protocols. All other components of the trial will remain the same for both participating cohorts. Timelines for solid tumour and haematological cancer participants are presented in Table 3 and 4, respectively.

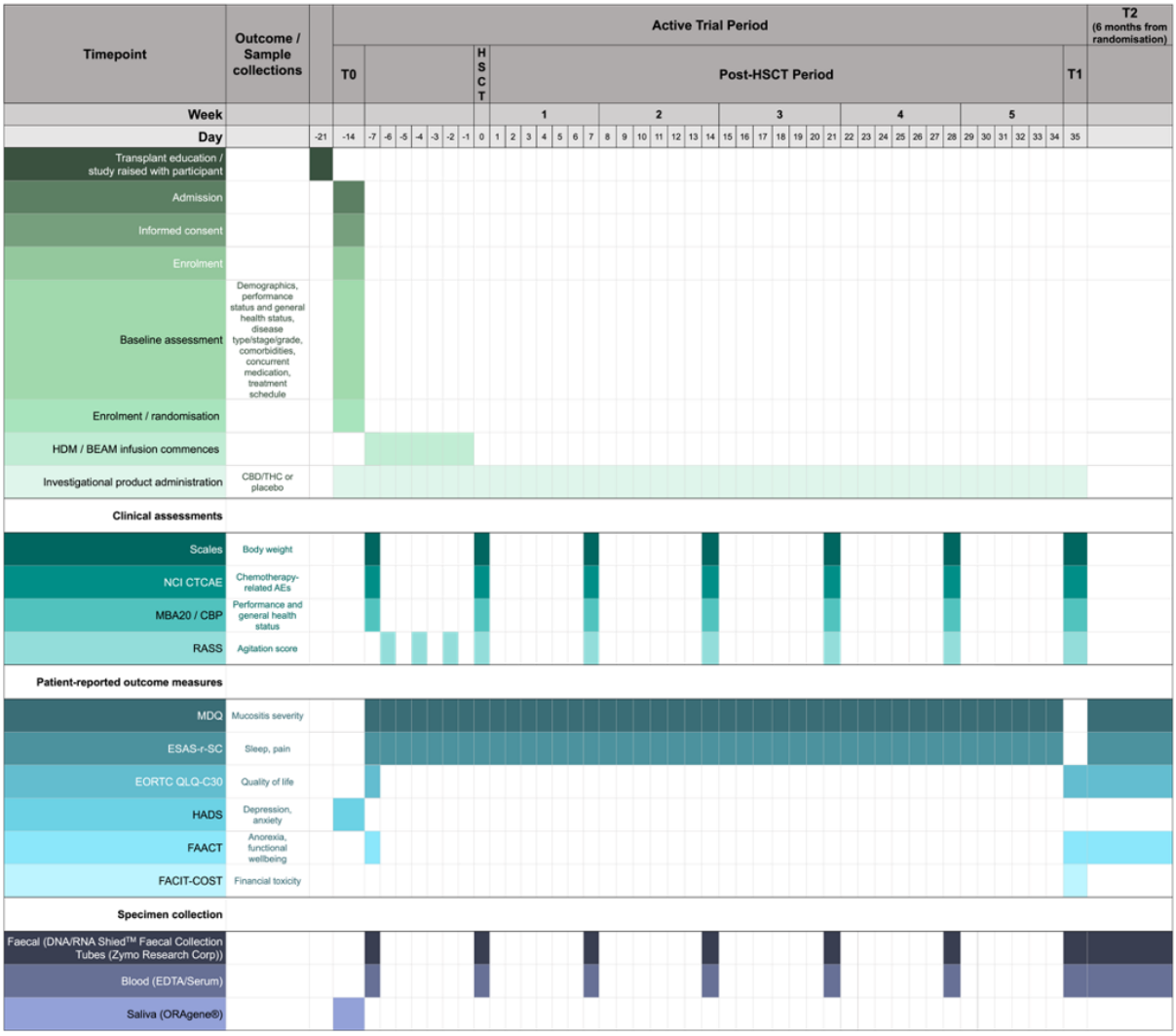
Appendices

Table 3. Timeline and summary of outcomes for solid tumour cancer participants.



Abbreviations. NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; MBA20 = multiple biochemistry analysis; CB*p* = complete blood picture; RASS = Richmond Agitation-Sedation Scale; MDQ = Mucositis Daily Questionnaire; ESAS-r-SC = Edmond Symptom Assessment System revised with Sleep Disturbance and Constipation Score; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; HADS = Hospital Anxiety and Depression; FAACT = Average Functional Assessment of Anorexia/Cachexia Therapy; FACIT-COST = Functional Assessment of Chronic Illness Therapy Comprehensive Score for financial toxicity.

Table 4. Timeline and summary of outcomes for haematological cancer participants.



Abbreviations. NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; MBA20 = multiple biochemistry analysis; CB*p* = complete blood picture; RASS = Richmond Agitation-Sedation Scale; MDQ = Mucositis Daily Questionnaire; ESAS-r-SC = Edmond Symptom Assessment System revised with Sleep Disturbance and Constipation Score; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; HADS = Hospital Anxiety and Depression; FAACT = Average Functional Assessment of Anorexia/Cachexia Therapy; FACIT-COST = Functional Assessment of Chronic Illness Therapy Comprehensive Score for financial toxicity.

5. Trial oversight, monitoring, and data management

The CANCAN trial is a collaboration by the University of Adelaide, the South Australian Health and Medical Research Institute (SAHMRI) and Central Adelaide Local Health Network (CALHN, study sponsor). The Medical Research Future Fund (MRFF) is the study sponsor. The Data and Safety Monitoring Board (DSMB) will be responsible for the safety of the clinical trial and data monitoring. The DSMB will meet on a monthly basis. Members and responsibilities of the board are summarised in Table 5.

Table 5. Responsibilities of the CANCAN trial's Data and Safety Monitoring Board (DSMB).

DSMB Members	Board Responsibilities
• DSMB chair with experience in clinical trials • Coordinating Principal Investigator • Chief Investigator • Clinical Investigator • Principal Investigator at each site (and named proxy) • Trial statistician • Independent clinician • Consumer	• Provide expert oversight of the trial. • Monitor and review participant safety in the trial. • Review participant recruitment, accrual, retention, treatment discontinuation, trial withdrawal, serious breaches, and protocol deviations that require exclusion of the participant from the per-protocol analysis. • Monitor planned sample size assumptions. • Monitor continuing appropriateness of participant information. • Monitor adherence with previous DSMB recommendations.

A data management plan has been prepared using the University of Adelaide's Research Data Planner Management System. All clinical trial data will be entered directly into REDCap in a de-identified manner and stored on a shared departmental drive with password protection. Any hard copy data will be stored in locked cabinets in secure

offices within the recruiting site clinical trial units and SAHMRI, Precision Cancer Medicine Theme, in accordance with international security standards and Australian laboratory accreditation requirements. Electronic files will be stored for 15 years.

6. Statistical considerations

6.1 Sample size

Data for sample size calculations were taken from Keefe et al. [22], reporting the incidence of GI-M using the MDQ in people undergoing FOLFOX/FOLFIRI multi-cycle chemotherapy. Calculations were based on the incidence of GI-M and worst diarrhoea. Assuming an overall incidence of gut distress in the placebo group of 70% (combining reported incidences in Keefe et al. for FOLFOX + FOLFIRI), a sample size of 176 participants gives 80% power, with two-sided alpha 0.05, to detect an absolute reduction of 21.7% in the incidence of GI-M (i.e. incidence in the CBD/THC group of 48.3%). Assuming a mean of 2 (worst diarrhoea) in the placebo group, and standard deviation of 1.5, a sample size of 176 participants gives 80% power, with two-sided alpha 0.05, to detect a reduction of 0.64 points (i.e. mean in the CBD/THC group of 1.36).

With this sample size, we are also sufficiently powered to detect changes in QoL (assessed using the EORTC-CLCQ30). Assumed means and standard deviations for the placebo group have been taken from the values reported for the FOLFOX group: the average of the 3 month and 6-month values was taken, along with the higher of the standard deviations (as this will provide conservative estimates).

6.2 Statistical analysis

No interim analyses are planned. Statistical analyses will be performed according to Intention-to-Treat principles, with all randomised participants analysed in the treatment

group to which they were allocated. All available data will be analysed, including incomplete data from participants who withdraw or do not complete all outcome assessments, unless consent for data use has also been withdrawn. See Appendix X for the complete Statistical Analysis Plan.

6.3 Harms

AEs will be identified during each visit using criteria established by the NCI CTCAE, version 5.0. Where parameters are not addressed within the criteria, severity of AEs should be graded as:

- Mild-Aware of sign or symptom, but easily tolerated
- Moderate-Discomfort enough to cause interference with usual activities
- Severe-Incapacitating with inability to work or perform usual activities
- Life-threatening- Participant is at immediate risk of death
- Fatal-Death

The Investigator and site staff are responsible for detection, recording and reporting of events that meet the criteria and definition of an AE or serious AE from time of trial registration until 30 days after the administration of the last dose of study medication. All adverse events that occur after the consent form is signed but before clinical trial treatment is administered will be reported by the investigator, if they cause the participant to be excluded from the trial or are the result of a protocol specific intervention.

7. Ethics and dissemination

This Protocol has been designed to comply with the Declaration of Helsinki and any subsequent amendments, the ICH Guidelines for Good Clinical Practice (CPMP/ICH/153/95) annotated with TGA comments (July 2000), the NHMRC National Statement on Ethical Conduct in Research involving Humans (2007, updated 2018), the

policies and procedures of any applicable local guidelines. At each trial site the trial will be conducted in adherence with the Protocol, International Conference on Harmonisation, Good Clinical Practice (ICH GCP R2) Guidelines in Australia, and applicable regulatory requirements.

Results of the trial will be published in appropriate peer-reviewed journals and presented at national and international scientific meetings. Clinically significant results from the trial will be disseminated amongst key stakeholders including: i) medical professionals involved in care of cancer patients, via leadership at peak representative bodies (AGITG/ALLG) and other organisations involved will include the Clinical Oncology Society of Australia, the Haematology Society of Australia and New Zealand (Yeung, Wardill) and the South Australian Comprehensive Cancer Consortium (Price, Wardill, Yeung, Zannettino), ii) consumer advocacy groups [433], iii) supportive care organisations (Wardill, Bowen, Crawford). Our team has a breadth of leadership positions across the public and private sectors with evidence of successful translation to clinical practice and policy, and the capacity to organise follow-up clinical trials to investigate hypotheses generated by CANCAN.

8. Funding statement

This work was supported by the MRFF (Grant Number: 2001877). The IP and placebo will be provided by iX Biopharma who have obtained all relevant licences for importation, distribution, and provision of the study medication. iX Biopharma have also performed all quality assurance tests of the product to confirm its stability at room temperature.

9. Competing interests statement

Jaroslav Boublik is CEO LeafCann Research & Advisory P/L & Chief Scientist LeafCann Group P/L. The remaining authors declare no competing interests.

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