

Use of cannabis in urological cancer patients: A review to evaluate risk for cancer development, therapeutic use, and symptom management

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Abstract

Introduction: Recent recreational legalization of cannabis has resulted in an increased interest in the therapeutic effects of cannabis use in cancer patients, with reports of its use in symptom management and as a risk factor for cancer development. The objective of this review was to evaluate the literature on the association of cannabis use with the risk of cancer development, symptom management, and therapeutic management in the urological cancer (UC) patient population.

Methods: A systematic search of databases and trial registries for papers published to March 2020 on cannabis, symptom and therapeutic management, and cancer development in UC patients was conducted. After screening of full-text articles, data were extracted for evaluation. Studies were eligible if they were in the clinical setting, included ≥ 5 UC patients, reported use of any cannabis variant, and were written in English.

Results: The search retrieved 2456 abstracts, of which 48 full-text articles were reviewed and 21 included in the review. Low-level evidence suggested a correlation between cannabis use and risk for development of testicular cancer. Some support existed for using cannabis for cancer pain and chemotherapy-induced nausea. There was inadequate evidence to substantiate cannabis use as a therapeutic agent for management of UCs. A lack of high-level evidence and robust methodology of the studies limited evaluation of the findings.

Conclusions: Given the paucity of data on cannabis use for therapeutic purposes in UC, large, prospective trials with adequate followup times to observe the effect of cannabis use on UCs are warranted to improve the evidence base.

Introduction

The recent recreational legalization of and subsequent increase in access to cannabis in Canada and some regions of the United States has resulted in a growing interest in the therapeutic effects of cannabis use in cancer patients.¹ Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been shown to possess analgesic, anti-inflammatory, and other properties²⁻⁴ that may aid in symptom treatment for cancer patients; however, the effect of cannabis on cancer development and as a therapeutic agent is largely unknown.

Misleading claims, often arising from Internet articles, have suggested that cannabis may cure cancer despite a lack of clinical evidence.^{5,6} A study published in 2019 showed that, based on Google Trends' relative search volume tool, from 2011-2018 the online search volume for cannabis and cancer increased ten times the rate of standard cancer therapies, with the use of cannabis as a cancer cure representing the largest category (23.5%) of social media content on alternative treatments for cancer.⁵ The authors also reported that the search rate was highest in areas where medical or recreation cannabis is legal and that false news stories that claim cannabis can cure cancer received significantly more social media engagement than accurate news stories debunking this claim, finding also that legitimate cancer organizations infrequently addressed cannabis via online media.⁵ This assumption has led some patients to believe that cannabis possesses properties that cure malignancy, which can steer patients to self-prescribe without medical oversight.⁷ A recent survey of prostate cancer (PCa) patients reported that 31% of their sample believed cannabis can treat their cancer,⁸ while a 2017 systematic review showed no conclusive evidence to support starting cannabinoid therapy for anticancer benefit when other therapies for urologic cancers (UCs) have failed.⁹

While evidence is lacking with respect to cannabis as a cancer treatment, there have been increasing reports of its use in other clinical capacities such as symptom management and its potential as a risk factor for cancer development.¹⁰ As our group previously reviewed the potential role of antiproliferative effects of cannabinoids on urological tumour activity,⁹ our current aim was to evaluate the available evidence on the association of cannabis use and the risk for development of UC, its therapeutic use, management of symptoms in UC patients in the clinical setting.

Methods

Search strategy

We performed a systematic literature search using PubMed, Embase, Cochrane CENTRAL Trials Registry, and Google Scholar databases for studies published between January 1947 to March 1, 2020. References from review articles and those in our initial search were manually searched for additional sources, as well as abstracts, conference proceedings, and the grey literature. Attempts were made to contact authors of abstracts for which we could not locate full text articles. The complete search strategy and keywords used are in Appendix 1. Institutional research ethics board approval was not required for this review.

Selection of studies

Two authors (ST, JH) independently screened titles and abstracts for inclusion in the full text review. Studies were included if they met the following criteria: 1) included ≥ 5 UC patients and associated use of any variant of cannabis; and 2) written in or translated to English. We excluded *in vitro* studies, animal studies, review articles, expert opinion pieces, articles not available in full text, and studies that did not evaluate the use of cannabis in UC patients. There were no exclusions based on study design. The same two authors independently reviewed all full text articles using inclusion and exclusion criteria. Disagreements were resolved by consensus and a third investigator (AK) when necessary.

Data extraction and outcomes

After full text screening, two authors (ST, JH) reviewed all articles to extract relevant data, which included cancer type, study design, participants and setting, intervention(s), outcome measures, results, and symptoms. Outcomes included evidence relative to the association of cannabis with the risk for development of UC and its use for therapeutic and symptom management in UC patients. The results are presented as a narrative synthesis of the available literature.

Results

Literature search

The initial search across databases retrieved 3323 abstracts with 877 duplicates, leaving 2456 for screening. After title and abstract screening, 2408 were removed based on inclusion and exclusion criteria and 48 full text articles were assessed for eligibility. Twenty-seven articles were removed after full text review, as they did not include at least 5 UC patients and/or were not primary sources. An examination of reference lists of included studies identified 10 articles that were excluded after full text review. A total of 21 articles were included in this review (Figure 1). Extensive results are summarized in Tables 1 (Cannabis and risk for development of UC), 2 (Cannabis and therapeutic management of UC), and 3 (Cannabis and UC symptom management).

Cannabis and risk for development of UC

Bladder cancer

The search yielded two studies that evaluated the effects of cannabis use on the risk for developing bladder cancer. Chacko et al. conducted a prospective case-control study comparing 52 transitional cell carcinoma (TCC) patients with 104 age-matched cancer-free controls (patients <60 years old) to elicit participants' inhaled cannabis use.¹¹ Using the continuous variable "joint-years", 88.5% of the TCC patients and 69.2% of the controls reported habitual cannabis use (mean joint-years was 48.0 for TCC patients and 28.5 for controls; $p=0.008$). After adjusting for other TCC risk variables, increasing joint-years remained significantly associated with TCC ($p=0.01$).¹¹ These findings were limited by a large number of tobacco users (possible synergetic carcinogenic effect) and selection and recall bias.

Thomas et al. evaluated 82,050 men in the California Men's Health Study to determine whether inhaled cannabis was associated with bladder cancer development.¹² Baseline surveys completed in 2002-2003 were compared with the incidence of bladder cancer over the following 11 years as indicated in electronic medical records. Results showed that 0.3% of cannabis users developed bladder cancer compared to 0.4% of non-users ($p<0.001$). After adjusting for multiple variables, cannabis use alone was shown to be associated with a 45% reduction in bladder cancer risk ($HR=0.55$; 95% CI, 0.31-1.00).¹² Limitations included participation and response biases, lack of evaluation of other bladder cancer risk factors, lack of assessment of the time course between cannabis use and diagnosis, and no reported average cannabis use.¹⁰

Prostate cancer

One study on cannabis use and the risk for developing PCa was found. Sidney et al. reported current and ever use of inhaled cannabis by non-smokers of tobacco were associated with an increased risk of developing PCa ($RR=4.7$, 95% CI, 1.4-15.5 and $RR=3.1$, 95% CI, 1.0-9.5, respectively). Cannabis use of ≥ 1 time per week was associated with a two-fold increase in the risk of PCa compared to nonusers and experimenters, although this was not significant.¹³ PCa cases were relatively young compared to the general population (maximum age of 63).¹³ A systematic review evaluated this study, reporting a moderate level of bias, as well as insufficient evidence that is limited by a lack of adjustment of key confounders and quantification of cannabis exposure.¹⁰

Testicular cancer

Four studies examined the association between cannabis use and the development of testicular cancer.¹⁴⁻¹⁷ Pooled data of three case control studies showed a significant association between development of testicular germ cell tumour (TGCT) and current (at the reference point), frequent, and lengthy cannabis use.¹⁸ Two meta-analyses of these studies^{18,19} observed that current cannabis use increased TGCT risk by 62% ($OR=1.62$, 95% CI, 1.13-2.31), frequent use

almost doubled the risk of developing TGCT (OR=1.92, 95% CI, 1.35-2.72), and there was an association between duration of use (≥ 10 years vs. never use) and TGCT development (OR=1.50, 95% CI, 1.08-2.09). When compared to pure TGCT seminoma, current and frequent cannabis use doubled the odds of nonseminoma development (OR=2.09, 95% CI, 1.29-3.37 and OR=2.59, 95% CI, 1.60–4.19, respectively). No association with ever use of inhaled cannabis and TGCT risk was found.^{18,19} There was a high level of agreement between studies, with I^2 values of 0% for most exposure variables.¹⁸

The fourth study, Callaghan et al., retrospectively observed 119 men diagnosed with testicular cancer between 1970 and 2011, finding that heavy inhaled cannabis use (>50 times) was associated with testicular cancer (aHR=2.57, 95% CI, 1.02-6.50).¹⁷ This study was limited as the data collection point was between 1969-1970 via self-report with no follow-up data other than testicular cancer diagnosis, potentially causing spurious findings and misclassification bias. Histologic data were not reported.

Cannabis and therapeutic management of UC

Renal cancer

One retrospective chart review study²⁰ evaluated the clinical influence of cannabis use on clear cell renal cell carcinoma (ccRCC) and other cancers during immunotherapy with nivolumab. Findings showed that cannabis was not a significant predictor for progression-free survival but was a weak significant factor for overall survival (HR=1.58, 95% CI, 1.01-2.46; $p=0.045$).²⁰ The study was limited in that it was retrospective with a short follow-up period and used a nonrepresentative ccRCC patient population given the cohort size differences.

Prostate cancer

The therapeutic use of cannabis in PCa was identified in a prospective evaluation of the use of synthetic pharmaceutical-grade CBD oil in 119 advanced cancer patients.⁷ Six PCa patients received the oil in prescribed doses and a circulating tumour cell (CTC) test was conducted at baseline and after treatment. Results were provided in case report format only, where one PCa patient had reduced CTCs from an initial 8.1 cells/7.5ml, with steady reduction over 12 months of 4.8, 4.2, and 3.2 cells/7.5ml was shown. Results for the remaining five PCa patients were not reported. These data provide anecdotal information and do not account for potential confounders.

Cannabis and UC symptom management

Cancer pain

Six studies (5 RCTs and 1 chart review) on cannabis use and UC pain were evaluated (included prostate, bladder, kidney, and unspecified urogenital cancers). Across these studies, pain worsened in advanced cancer patients who were not using cannabis,²¹ while either reducing^{22–24} or remaining unchanged^{21,25} in those using any form of cannabis (THC: CBD or THC alone). The majority of cannabis users reduced their opioid doses, while most patients in placebo groups

increased their dosages.^{21,22} In assessing the safety of THC:CBD (27mg/ml:25mg/ml), one study found low (1-4 sprays) and medium (6-10 sprays) doses were well tolerated and improved pain compared to high dosages (11-16 sprays) that caused multiple side effects.²⁶ The long-term use of cannabis was found to be well-tolerated in patients, with continuation of pain improvement.²⁴

While the RCTs suggested that the use of oromucosal Sativex® may be a safe and effective adjunct to opioid treatment,^{22–26} they were limited as they relied on self-report with no objective evaluation component and used patient-administered dosing, which can cause protocol deviation. Results based on individual cancer sites were not always provided. Two systematic reviews and meta-analyses evaluated these RCTs, concluding that the evidence was poor while finding minimal changes in overall cancer pain.^{27,28}

Chemotherapy-induced nausea (CIN) and anorexia

Our search returned six studies on cannabis use for CIN and two for anorexia, each of which studied multiple types of cancer, including UC. In the CIN studies, nausea was rated as less severe and/or frequent with the use of cannabis (nabilone or levonantradol) prior to and/or after chemotherapy compared to placebo²⁹ or alternative treatment (prochlorperazine, metoclopramide, alizapride).^{30–32} Patients also reported significantly fewer vomiting episodes when using cannabis during chemotherapy.^{29–32} The majority of patients indicated that cannabis was their preferred choice of antiemetic treatment for future rounds of chemotherapy, despite side effect risk.^{29–32}

In the two RCTs on anorexia, patients reported increased appetite with cannabis (THC:CBD and THC alone) versus placebo.^{33,34} Brisbois et al. demonstrated that THC improved taste, smell perception, and appetite in cannabis-treated patients,³⁴ while Strasser et al. showed that THC patients reported an increase in appetite while the placebo group reported decreased appetite or no change.³³ Results for both studies were provided in aggregate without specification of UC patients and relied on patient dosing and self-report, introducing potential for bias. Previously reported studies in our review observed appetite as a secondary endpoint, with reports that levonantradol³⁰ and nabilone³¹ improved appetite, while others found that THC: CBD and THC²² and nabilone³² led to a slight reduction in appetite.

Discussion

As interest in the use of cannabis for its potential therapeutic benefits increases, an understanding of the available evidence is necessary to support informed clinical decision making for patients with UCs. Our review demonstrated an inconsistency in the literature evaluating the use of cannabis and its association with the risk for development of bladder and prostate cancer, while some low-level evidence supports an association between cannabis use and an elevated risk for development of TGCT.^{10,14–17} With respect to the data reported on TGCT, the findings from each study and the meta-analyses do not imply a causal relationship, although they suggest a positive relationship. Few data exist on the therapeutic effect(s) of cannabis in renal and prostate cancer patients, with no robust findings when used with immunotherapy or evaluation of CTCs. Our

review found some evidence to suggest cannabis use can alleviate UC-related pain and CIN, but contradictory findings existed for appetite improvement.

The recent recreational legalization and ease of accessibility of cannabis presents new challenges for clinicians, as patients may incorrectly believe that cannabis can “cure” their cancers and may be more willing to discuss cannabis as a treatment.³⁵ The limited data on antiproliferative agents⁹ and therapeutic properties of cannabis in UC precludes the provision of evidence-based recommendations to patients. Results of a 2016 survey showed that only 30% of medical oncologists felt knowledgeable enough to make recommendations to patients about cannabis use.³⁵ Several consensus statements are available to guide practitioners on the use of cannabis with certain cancer patient populations, largely indicating there is inconclusive evidence for the use of cannabis for treatment of cancer and related symptoms and that additional research is required.^{36–38}

Our findings demonstrate the need for large, randomized trials to evaluate cannabis use in UC patients with adequate follow-up time to evaluate cancer progression to improve the evidence base. Several clinical trials currently registered at clinicaltrials.gov are exploring the use of cannabis for UC-related symptom management. One is evaluating palliative patients with solid tumours taking cannabis for cancer treatment-related symptom management (NCT03617692),³⁹ another is assessing the use of cannabis oil for patients with poorly controlled cancer pain (NCT03522467),⁴⁰ and a RCT is evaluating the safety and efficacy of inhaled cannabis for uncontrolled pain in patients with advanced cancer (NCT04042545).⁴¹ In addition to symptom management, further study is required to determine whether there is an association between cannabis use and UC development, as well as its therapeutic use with UC patients in a clinical setting, especially with respect to progression-free and overall survival measures.

This review is not without limitations. We included clinical-based studies that contained at least 5 UC patients; and as such, we may have overlooked relevant studies that did not specifically state the number of UC patients. Most studies included multiple cancer types in their sample populations, with some only reporting results in aggregate, which at times did not allow us to parse out the specific findings for each type of cancer. In turn, this may have limited the generalizability of some results, while also making it difficult to discern the strength of the evidence of specific UC-related results. Many studies were limited by potential confounders (e.g., tobacco smoking), methodological flaws, and risk for biases, and we were unable to conduct any meta-analyses due to the aggregate reporting and there was no uniform reporting of GU-related results.

Conclusions

In this review, low-level evidence suggested a correlation between cannabis use and risk for development of testicular cancer, some support existed for using cannabis for cancer pain and CIN, and there was inadequate data to substantiate cannabis use as a therapeutic agent for UC. A lack of high-level evidence and robust methodology limited the evaluation of cannabis use in UC patients in the clinical setting. Large, high-quality prospective trials with adequate follow-up

time to observe the effects of cannabis use on UCs are needed to improve the evidence base, which in turn will provide data for clinicians who treat this patient population.

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Figures and Tables

Fig. 1. Study flow diagram.

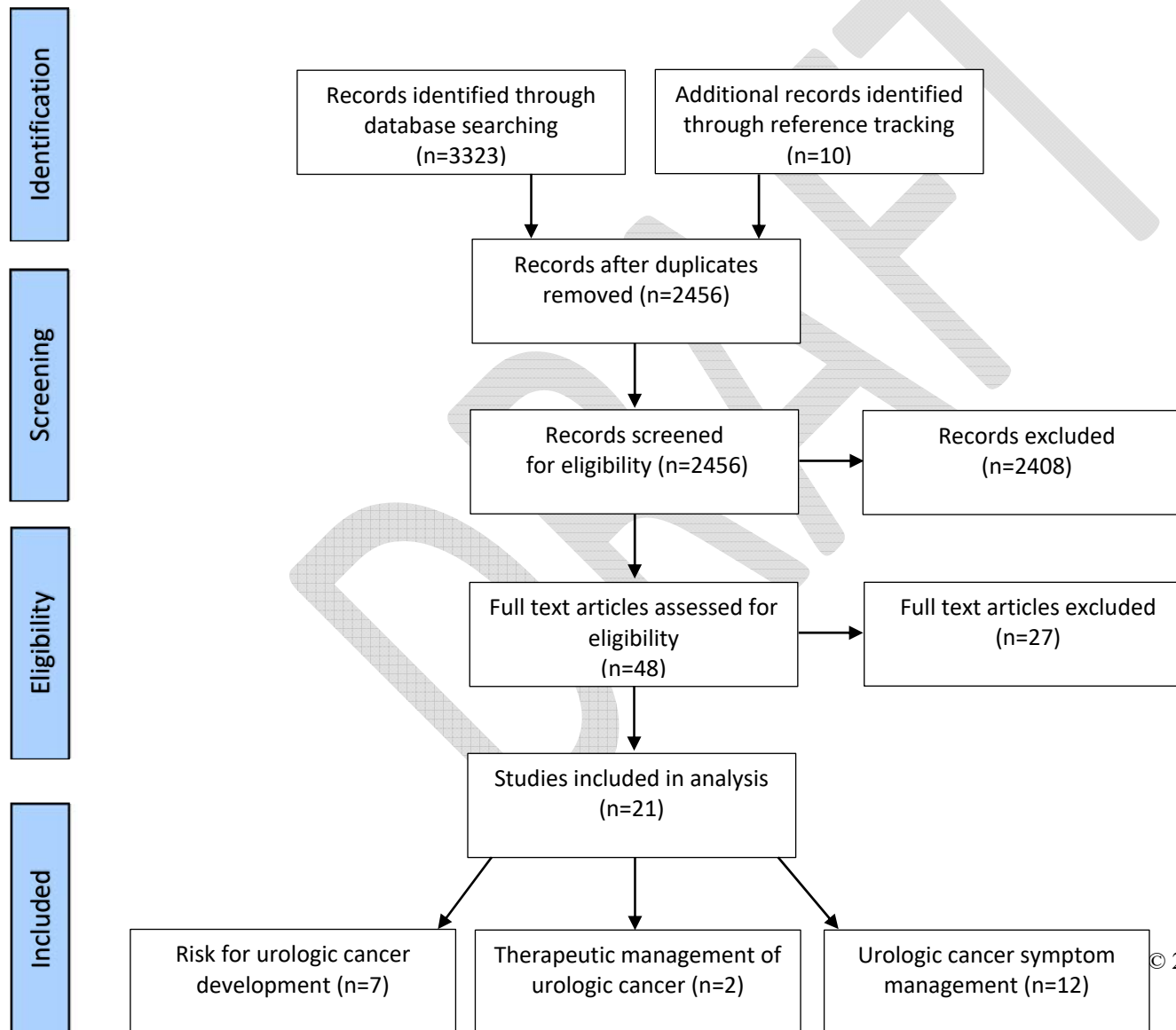


Table 1. Cannabis and risk for urologic cancer development					
Author	Cancer type(s)	Methods	Participants and setting	Intervention(s) and outcome measures	Results
Chacko et al. ¹¹	Bladder	<ul style="list-style-type: none"> • Case-control study • n=52 bladder cancer cases • n=104 controls 	<ul style="list-style-type: none"> • 52 transitional cell carcinoma patients and 104 age matched cancer-free controls • Males <60 years of age from two Veterans Affairs clinics in the USA 	<ul style="list-style-type: none"> • Assessed previous exposure to potential carcinogens (radiation, Agent Orange, dyes, intake of smoked or processed meats, tobacco, and marijuana) through self-administered questionnaires 	<ul style="list-style-type: none"> • 88.5% (n=46) of cases and 69.2% (n=72) of controls reported a history of habitual cannabis use (using the continuous variable joint-years) (p=0.008) • Increased joint-years was significantly associated with the incidence of bladder cancer (p=0.01) • Both cases and controls reported high rates of tobacco usage
Daling et al. ¹⁶	Testicular germ cell tumour (TGCT)	<ul style="list-style-type: none"> • Case-control study • n=369 TGCT cases • n=979 controls 	<ul style="list-style-type: none"> • Cases were men aged 18-44 years diagnosed with invasive TGCT between 1999 to 2006 • Controls were cancer-free men aged 18-44 years • Washington, USA 	<ul style="list-style-type: none"> • In-person interviews with a structured questionnaire to assess cigarette smoking, alcohol consumption, recreational drug use, and other known or suspected risk factors for TGCT 	<ul style="list-style-type: none"> • Cases (72.6%) were more likely to have ever smoked cannabis than controls (68%) (OR=1.3, 95% CI, 1.0-1.8). • Current cannabis use was identified more frequently in non-seminoma vs. pure seminoma TCGT cases (38.1% vs. 19%, p=0.08) • The risk for nonseminoma was higher in patients who smoked cannabis before 18 years of age (2.8, 95% CI, 1.6-5.1) compared to men who started smoking cannabis later in life (OR=1.3, 95% CI, 0.6-3.2) (p=0.08)

					<ul style="list-style-type: none"> • A 70% increased risk of TGCT was associated with current cannabis use (OR=2.3, 95% CI, 1.3-4.0); this was elevated when used daily or weekly vs. less than once per week (ORs=3.0 vs. 1.8)
Lacson et al. ¹⁴	Testicular germ cell tumour (TGCT)	<ul style="list-style-type: none"> • Case-control study • n=163 TGCT cases • n=292 controls 	<ul style="list-style-type: none"> • Men between 18-35 years of age who were diagnosed with TGCT between December 1986 and April 1991 • Controls were men matched by race, ethnicity, date of birth and neighbourhood of residence • California, USA 	<ul style="list-style-type: none"> • Interviews using structured questionnaires to identify personal use and duration of tobacco, alcohol, and multiple types of recreational drugs 	<ul style="list-style-type: none"> • Self-reported ever use of inhaled cannabis led to a two-fold increase in risk for TGCT compared to never use (OR=1.94, 95% CI, 1.02-3.68) • Former inhaled cannabis users had a greater than two-fold risk of TGCT compared to never users (OR=2.28, 95% CI: 1.17-4.43) • Current inhaled cannabis users had a non-significant increase in TGCT risk compared to never users (OR=1.38, 95% CI, 0.67-2.87)
Sidney et al. ¹³	Prostate	<ul style="list-style-type: none"> • Retrospective cohort study 	<ul style="list-style-type: none"> • Participants from Kaiser Permanente Medical Care Program 	<ul style="list-style-type: none"> • Participants completed self-administered research questionnaires between 1979 - 1985 	<ul style="list-style-type: none"> • Current and ever use of inhaled cannabis by non-smokers of tobacco were associated with an increased risk of developing prostate cancer (RR=4.7, CI, 1.4-15.5 and RR= 3.1, 95% CI, 1.0-9.5)

		<ul style="list-style-type: none"> • N=64 855 	<ul style="list-style-type: none"> • between ages 15-49 • San Francisco, USA 	<ul style="list-style-type: none"> • about tobacco, marijuana, and alcohol 	<ul style="list-style-type: none"> • There was a two-fold increase in the risk of prostate cancer for participants who used cannabis one or more times per week compared to non-users
Thomas et al. ¹²	Bladder	<ul style="list-style-type: none"> • Prospective cohort study • n=82 050 • n=34 000 cannabis users 	<ul style="list-style-type: none"> • Men ages 45-69 years in the California Men's Health Study Database • California, USA 	<ul style="list-style-type: none"> • Questionnaires assessed the number of times cannabis was used over an 11-year period 	<ul style="list-style-type: none"> • 34,000 men reported using cannabis, with 17% using it over 500 times • 89 (0.3%) of cannabis users developed bladder cancer compared to 190 (0.4%) non-cannabis users (p<0.001) • Cannabis use was associated with a 45% reduction in bladder cancer risk after adjusting for multiple variables (HR=0.55; 95% CI, 0.31-1.00) • Men using cannabis over 500 times were 31% less likely to develop bladder cancer (adjusted HR=0.69; 95% CI, 0.38-1.27) • Older men using both cannabis and tobacco had non-statistically significant increased risk for developing bladder cancer (adjusted HR=1.28; 95% CI, 0.88-1.86)
Trabert et al. ¹⁵	Testicular germ cell tumour (TGCT)	<ul style="list-style-type: none"> • Case-control study • n=187 TGCT cases • n=148 controls 	<ul style="list-style-type: none"> • Participants were between the ages of 18 and 50 • Cases were men diagnosed with TGCT Between January 1990 	<ul style="list-style-type: none"> • Assessed lifestyle habits, drug use (duration), medical history, and diet using self-administered surveys 	<ul style="list-style-type: none"> • Cases were twice as likely to be frequent cannabis users than controls (18.2% vs 7.1%, OR=2.2, 95% CI, 1.0-5.1) • Nonseminoma TGCT was associated with more frequent cannabis use than pure seminoma TGCT (22.3% vs. 14.3%, OR = 3.1, 95% CI, 1.2-1.8) and long-term cannabis use of 10 or more years (21.5% vs. 10.2%, OR=2.4, 95% CI, 1.0-6.1)

			and October 1996 • Controls were a male adult friend of similar age and race of the case • USA		
Callaghan et al. ¹⁷	Testicular germ cell tumour (TGCT)	• Retrospective cohort study • n=119 cases • n=49 343 initial sample	• Participants were from a cohort of Swedish military service • Cases had been diagnosed with testicular cancer between 1970 and 2011	• Self-reported use of alcohol, drugs, and tobacco at time of military enlistment	• Heavy cannabis use (>50 times) was associated with a higher incidence of testicular cancer (adjusted HR=2.57, 95% CI, 1.02-6.50) • No significant association between ever use of cannabis and subsequent diagnosis of testicular cancer (adjusted HR=1.42, 95% CI, 0.83-2.45)

Table 2. Therapeutic management of urologic cancer

Author	Cancer type(s)	Methods	Participants and setting	Intervention(s)	Outcomes	Results
Kenyon et al. ⁷	Bladder, prostate	• Case report • N=119 total • n=18 UC	• 28 of the 119 patients were given CBD as an only	• 1mg of CBD in neutral oil. Average dose 10mg twice a	• Circulating tumour cell test before and after treatment	• The results of one prostate cancer patient were reported, which showed a reduction in

		patients	treatment; of those, 6 were prostate cancer patients; bladder cancer patients were included but not described • London, UK	day; administered 3 days on, 3 days off for minimum of 6 months		circulating tumour cells with CBD alone from an initial 8.1cells/7.5mL to 5.9 cells/7.5mL, with a steady reduction over the course of 12 months of 4.8, 4.2, and 3.2/7.5mL • No data were provided for the other 5 prostate cancer patients in the study
Taha et al. ²⁰	Renal cell carcinoma (RCC)	<ul style="list-style-type: none"> • Retrospective chart review • N=140 total • n=42 RCC patients including melanomas (grouped together) 	<ul style="list-style-type: none"> • Two arms: nivolumab alone (n=89) and nivolumab plus cannabis (n=51) • Israel 	<ul style="list-style-type: none"> • 20-30 grams or more of cannabis per month, with cut-offs of 10% THC and 1% CBD 	<ul style="list-style-type: none"> • Clinical influence of cannabis use measured by response rate (RR), progression- free survival (PFS) and overall survival (OS) 	<ul style="list-style-type: none"> • Cannabis was not a significant for PFS, but was a weak significant factor for OS (HR=1.58, 5% CI, 1.01-2.46, p=0.045) • In the RCC and melanoma group, the RR was 10% for those with cannabis + nivolumab and 43.3% for nivolumab alone (OR=0.15, 95% CI 0.02-1.3, p=0.084)

Table 3. Cannabis and urologic cancer symptom management

Author	Symptom	Cancer type (s)	Methods	Participants and setting	Intervention	Outcome measures	Results
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Brisbois et al. ³⁴	Anorexia	Bladder, renal, prostate, testicular	<ul style="list-style-type: none"> • Randomized, double-blind placebo-controlled pilot study • N= 21 total • n=5 UC 	<ul style="list-style-type: none"> • Advanced cancer patients with a score of 2 or more on Taste and Smell Survey • Two arms: THC or placebo • Canada 	<ul style="list-style-type: none"> • Patients were given 2.5mg THC or placebo once daily for the first three days and twice daily on the fourth day, after which they could increase to a maximum of 20mg/day for 18 days 	<ul style="list-style-type: none"> • Assessment at baseline and 18 days after treatment using multiple questionnaires 	<ul style="list-style-type: none"> • 73% of THC patients reported an increase overall appreciation of food compared to placebo (30%) • 55% of patients said THC “made food taste better” compared to placebo (10%) (p=0.04) • 64% of THC treated patients had increased appetite, while 05% in the placebo group reported a decrease or no change (20%)
Einhorn et al. ³²	Chemotherapy-induced nausea (CIN)	Bladder, testicular	<ul style="list-style-type: none"> • Randomized, double-blind crossover study • N=80 total • n=73 UC 	<ul style="list-style-type: none"> • Patients receiving combination chemotherapy for neoplastic disease • USA 	<ul style="list-style-type: none"> • Patients received either 10mg of prochlorperazine or 2mg of nabilone (identically prepared capsules) every 	<ul style="list-style-type: none"> • Severity of nausea and frequency of vomiting 	<ul style="list-style-type: none"> • Nausea was experienced in both study arms but was not as severe and prolonged on nabilone (p<0.001)

					six hours as needed, as well as 30 minutes prior to chemotherapy (majority was cisplatin combination chemotherapy)		<ul style="list-style-type: none"> • 33% reduction of vomiting on chemotherapy days for patients taking nabilone • After completion of the crossover, 75% of patients indicated preference of nabilone as an antiemetic • Decreased appetite and reduced food intake in 80% of the nabilone group and 90% in prochlorperazine
Fallon et al. ²⁵	Pain	Prostate, bladder, kidney, other genito-urinary (unspecified)	<ul style="list-style-type: none"> • Double-blind, randomized, placebo-controlled phase 3 trial • N = 399 Total • n = 61 UC 	<ul style="list-style-type: none"> • Patients were adults with advanced incurable stage of cancer and a clinical diagnosis of cancer-related pain that was not alleviated by 	<ul style="list-style-type: none"> • Patients were randomized to Sativex (THC (27mg/mL): CBD (25mg/mL) or placebo for an initial titration period up to 14 days • Patients started with one spray 	<ul style="list-style-type: none"> • Efficacy was measured in the percent improvement in average pain numerical rating scale (NRS) score between baseline to the end of treatment 	<ul style="list-style-type: none"> • Median percent improvement in average pain NRS of 7.2% in Sativex group compared to 9.5% in placebo (mean difference = -1.84%; CI, 6.19, 1.50; p=0.274)

				<p>opioid therapy</p> <ul style="list-style-type: none"> • Austria, Bulgaria, Germany, Hungary, India, Israel, Italy, Lithuania, Poland, Romania, Spain, Taiwan, and UK. 	<p>and gradually increased by one additional spray per day for 10 days, followed by stable 4-day dose</p>	<ul style="list-style-type: none"> • Safety and tolerability 	<ul style="list-style-type: none"> • No significant treatment differences in worst pain NRS score, sleep disruption NRS score, percent improvement in average pain • Over 68% of Sativex patients reported an adverse effect
Fallon et al. ²⁵	Pain	Prostate, bladder, kidney, other genito-urinary (unspecified)	<ul style="list-style-type: none"> • Double-blind randomized, placebo-controlled phase 3 trial, two-part withdrawal design • N = 206 Total • n = 45 UC 	<ul style="list-style-type: none"> • Patients from the parent study who demonstrated an improvement of 15% or more on NRS pain scale • Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, 	<ul style="list-style-type: none"> • Patients were randomized to Sativex (THC (27mg/mL): CBD (25mg/mL) or placebo for 5 weeks 	<ul style="list-style-type: none"> • Mean change from the randomized baseline to the end of treatment in average pain NRS score • Safety and tolerability 	<ul style="list-style-type: none"> • Mean pain scores increased to 3.7 from 3.2 in the Sativex group and the placebo group • No significant treatment differences in worst pain NRS score, sleep disruption NRS score, average pain NRS

				Lithuania, Poland, Romania, UK, and USA			
Heim et al. ³⁰	CIN	Testicular, prostate	<ul style="list-style-type: none"> • Randomized crossover study • N=57 total • n=5 UC 	<ul style="list-style-type: none"> • Patients with various advanced cancers without primary chemotherapy; had high emetic potential • Germany 	<ul style="list-style-type: none"> • Either 10mg of metoclopramide or 0.5mg of levonantradol an hour before chemotherapy and 2 and 6 hours after 	<ul style="list-style-type: none"> • Efficacy was evaluated by a standard questionnaire before chemotherapy and 2, 6, and 24 hours after 	<ul style="list-style-type: none"> • 62% of patients had less nausea with levonantradol compared to 11% of metoclopramide therapy • 140 episodes of vomiting were reported in the levonantradol group and 301 in metoclopramide • 71% of patients complained of side-effects (somnolence, dizziness, “drunkenness”) with levonantradol • Appetite was found to be better in the levonantradol group

Johnson et al. ²⁴	Pain	Prostate	<ul style="list-style-type: none"> • Follow-up RCT • N=43 total • n=7 PCa 	<ul style="list-style-type: none"> • Patients who were previously in the two-week parent RCT • In 21 study sites in the UK and 1 in Belgium 	<ul style="list-style-type: none"> • Patients were randomized to self-titrating a spray of THC: CBD(2.7mg:2.5 mg) or THC (2.7mg). • A maximum of 8 sprays in a three-hour period, and a maximum of 48 sprays/day 	<ul style="list-style-type: none"> • Efficacy and safety of the oromucosal spray 	<ul style="list-style-type: none"> • Improvement in pain with time as there was a decrease in “pain severity” and “worst pain” scores from baseline • Commonly reported adverse effects with THC/CBD spray were dizziness, vomiting, nausea, dry mouth, somnolence, and confusion • 20 patients receiving THC/CBD combination spray experienced at least one serious adverse effect during the study, but only 3 were considered medication-related
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Johnson et al. ²²	Pain	Prostate	<ul style="list-style-type: none"> • Double-blind, placebo-controlled RCT • N=177 • n=24 PCa 	<ul style="list-style-type: none"> • Patients with moderate to severe cancer-related pain • Patients using strong opioids at least once a week • Patients with a pain severity score greater than 4 on a 0-10 NRS 	<ul style="list-style-type: none"> • Patients were randomized to self-titrating a spray of THC: CBD (2.7mg:2.5mg) or THC (2.7mg) for 2 weeks. • A maximum of 8 sprays in a three-hour period, and a maximum of 48 sprays/day 	<ul style="list-style-type: none"> • Change in pain from baseline measured on NRS • The use of breakthrough analgesia • Secondary endpoints: the use of opioid background medication, patient assessment of sleep quality, nausea, memory, concentration, and appetite over the previous 24 hours 	<ul style="list-style-type: none"> • Approximately twice as many patients in the THC: CBD group had an NRS reduction from baseline of at least 30% compared with THC (24%) and placebo (21%) and reduced breakthrough analgesics. ORs for THC: CBD vs. placebo were 2.81 (95% CI, 1.22, 6.50; p=0.006) and 1.10 for THC vs. placebo (95% CI, 0.44, 2.73; p=0.28) • More patients in the THC: CBD reduced breakthrough doses, while the placebo group increased their doses (p= 0.004)
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							<ul style="list-style-type: none"> • Reduction in appetite score for patients in both THC: CBD and THC groups (-0.59 vs. 0.24, $p=0.016$ and -0.59 vs. 0.06, $p=0.056$)
Lichtman et al. ²³	Pain	Prostate, bladder, kidney, other genito-urinary (unspecified)	<ul style="list-style-type: none"> • Double-blind, randomized, placebo-controlled trial • N=397 • n=72 UC 	<ul style="list-style-type: none"> • Adults with advanced incurable stage of cancer and a clinical diagnosis of cancer-related pain that was not alleviated by opioid therapy • USA, Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, 	<ul style="list-style-type: none"> • Patients were randomized to receive Sativex (THC (27mg/mL): CBD (25mg/mL) or matching placebo • Self- titrate for 14 days and then continue at stable dose for 3 weeks 	<ul style="list-style-type: none"> • Percent improvement between baseline and end of treatment in average pain on NRS score • Average pain score, worst pain score, and sleep disruption 	<ul style="list-style-type: none"> • Sativex patients had a median pain improvement of 10.7% while 4.5% in placebo, resulting in treatment difference of 3.41% (95% CI: 0.00-8.16; $p=0.0854$) • Sativex did not improve average pain NRS scores ($p=0.253$), worst pain NRS score ($p=0.678$), but improved sleep NRS score ($p=0.027$)

				Lithuania, Poland, Romania, UK			
Niederle et al. ³¹	CIN	Testicular	<ul style="list-style-type: none"> • Crossover study • N=20 	<ul style="list-style-type: none"> • 20 nonseminoma testicular cancer patients undergoing cisplatin therapy were given nabilone or alizapride during the first or second course of chemotherapy • Germany 	<ul style="list-style-type: none"> • On days 1-5, hospitalized patients were given nabilone (2mg) or alizapride (150mg) 2 hours before chemotherapy and at intervals in the afternoon and evening and observed 	<ul style="list-style-type: none"> • Therapeutic and adverse effects of both drugs were evaluated in daily questionnaires 	<ul style="list-style-type: none"> • Frequency and severity of nausea were significantly reduced with nabilone compared to alizapride ($p<0.01$) • 50% of patients expressed preference for nabilone compared to 35% for alizapride • Nabilone patients experienced adverse effects of drowsiness, hypotension, and dry mouth • Patients reported food intake was slightly better with nabilone

Parasarat et al. ²¹	Pain	UC (unspecified)	<ul style="list-style-type: none"> • Retrospective chart review • N = 232 total • n = 49 UC 	<ul style="list-style-type: none"> • 2 arms: cannabis users (n=137 [22 UC]) and non-cannabis users (n=95 [27 UC]) • New Jersey, USA 	<ul style="list-style-type: none"> • This study did not capture the frequency and dosing of cannabis or the time frame of evaluation 	<ul style="list-style-type: none"> • Assessed pain through daily opiate consumption and Edmonton Symptom Assessment System (ESAS) scores in sections of pain, physical, and emotions 	<ul style="list-style-type: none"> • Opioid consumption increased by 23% for patients on opioids who were not prescribed cannabis (p=0.004), while remaining constant in patients taking opioids and using cannabis as adjunct therapy • ESAS pain scores worsened in the non-cannabis group while remaining unchanged in the cannabis group
Portenoy et al. ²⁶	Pain	Prostate	<ul style="list-style-type: none"> • Randomized, placebo-controlled, graded-dose trial • N=263 • n=44 PCa 	<ul style="list-style-type: none"> • Patients had to have active and chronic pain that was moderate or severe despite the 	<ul style="list-style-type: none"> • Sativex (THC (27mg/mL): CBD (25mg/mL) 1-week titration, and 4 weeks of stable dosing based on 1 of 3 	<ul style="list-style-type: none"> • Assessed average pain and worst pain in the last 24 hours, pain disruption in sleeping patterns, and doses of 	<ul style="list-style-type: none"> • Low (1-4 sprays) and medium (6-10 sprays) led to a significant improvement in average daily pain compared to placebo from

				lack of a stable opioid regimen • Randomized into three different dose ranges of oromucosal spray • North America, Europe, Latin America, South Africa	dose groups (low, medium, high)	breakthrough pain killers • Assessed quality of life through selected questionnaires	baseline to end of study (p=0.008 and p=0.0035) • The high dose (11-16 sprays) was not well-tolerated and had multiple side effects
Strasser et al. ³³	Anorexia	UC (unspecified)	• Multicenter, Phase III, randomized, double-blind, placebo-controlled study • N=243 • n=161 UC & GI	• Adult patients with advanced incurable cancer that were candidates for appetite stimulation and had involuntary weight loss of >5%. • Patients were split into three arms:	• After baseline assessment, patients received either THC: CBD (2.5mg:1mg), 2.5mg of THC, or placebo for 6 weeks • Patients received a two-week supply of capsules to take twice before lunch and dinner	• Appetite change from baseline to week 6, measured through a visual analog scale and Anorexia-Cachexia EORTC QLQ-C30 module • Change in QOL from baseline to week 6	• THC: CBD increased appetite by 75%, THC by 60% and placebo by 72% placebo (p=0.068) • All arms showed a 5% improvement on the EORTC QLQ-C30 score until week 2, followed by another 5% improvement

				THC: CBD, THC, or placebo. • Germany			until week 6 with placebo, steady state with THC and worsening by 2.5% with THC: CBD. • No differences between three groups for appetite, quality of life, mood, or nausea
Wada et al. ²⁹	CIN	Prostate, bladder, testicular	• Double-blind, randomized, crossover trial • N=114 • n=10 UC	• Patients were given a capsule the preceding evening of chemo- therapy, the morning of, and every 12 hours until the end of treatment • USA	• Nabilone (1-2mg) or matching placebo	• Safety and efficacy • Patients rated their nausea on a scale of 0 (none) to 3 (severe) daily	• Nabilone patients had 4.19 vomiting episodes per day compared to 7.08 on placebo (p<0.001) • Average nausea rating on nabilone vs. placebo was 1.22/3 and 1.96/3, (p<0.001); 61% of patients experienced less nausea while on nabilone

							<ul style="list-style-type: none">• 70% of patients preferred nabilone over placebo ($p < 0.001$) (22% favoured placebo and 8% had no preference)
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