APPENDIX

Supplementary Table 1. Cannabis and urologic cancer symptom management

Author	Symptom	Cancer type (s)	Methods	Participants and setting	Intervention	Outcome measures	Results
Brisbois et al[34]	Anorexia	Bladder, renal, prostate, testicular	– Randomized, double-blind placebo-controlled pilot study – N=21 total – n=5 UC	– Advanced cancer patients with a score of 2 or more on Taste and Smell Survey – Two arms: THC or placebo – Canada	– Patients were given 2.5 mg 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 20 mg/day for 18 days	– Assessment at baseline and 18 days after treatment using multiple questionnaires	– 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]	CIN	Bladder, testicular	– Randomized, double-blind	– Patients receiving combination	– Patients received either 10 mg of	– Severity of nausea and	– Nausea was experienced in both study arms

			crossover study – N=80 total – n=73 UC	chemo-therapy for neoplastic disease – U.S.	prochlor-perazine or 2 mg of nabilone (identically prepared capsules) every six hours as needed, as well as 30 minutes prior to chemotherapy (majority was cisplatin combination chemotherapy)	frequency of vomiting	but was not as severe and prolonged on nabilone ($p<0.001$) – 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 GU (unspec-ified)	– Double-blind, randomized, placebo-controlled phase 3 trial – N=399 total	– Patients were adults with advanced incurable stage of cancer and a clinical	– Patients were randomized to Sativex (THC (27 mg/mL): CBD (25 mg/mL) or placebo for an	– Efficacy was measured in the percent improvement in average pain NRS score between	– Median percent improvement in average pain NRS of 7.2% in Sativex group compared to 9.5% in placebo

			– n=61 UC	diagnosis of cancer-related pain that was not alleviated by opioid therapy – Austria, Bulgaria, Germany, Hungary, India, Israel, Italy, Lithuania, Poland, Romania, Spain, Taiwan, U.K.	initial titration period up to 14 days – Patients started with one spray and gradually increased by one additional spray per day for 10 days, followed by stable 4-day dose	baseline to the end of treatment – Safety and tolerability	(mean difference -1.84%, CI 6.19, 1.50,p=0.274) – 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 GU (unspec-ified)	– Double-blind, randomized, placebo-controlled phase 3 trial, two-part withdrawal design – N=206 total – n=45 UC	– Patients from the parent study who demonstrated an improvement of 15% or more on NRS pain scale – Belgium, Bulgaria, Czech	– Patients were randomized to Sativex (THC (27 mg/mL): CBD (25 mg/mL) or placebo for 5 weeks	– Mean change from the randomized baseline to the end of treatment in average pain NRS score – Safety and tolerability	– 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

				Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, U.K., U.S.			score, average pain NRS
Heim et al[30]	CIN	Testicular, prostate	– Randomized crossover study – N=57 total – n=5 UC	– Patients with various advanced cancers without primary chemo-therapy; had high emetic potential – Germany	– Either 10 mg of metoclopramide or 0.5 mg of levonantradol an hour before chemotherapy and 2 and 6 hours after	– Efficacy was evaluated by a standard questionnaire before chemotherapy and 2, 6, and 24 hours after	– 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	– Followup RCT – N=43 total – n=7 PCa	– Patients who were previously in the two-week parent RCT – In 21 study sites in the U.K. and 1 in Belgium	– Patients were randomized to self-titrating a spray of THC: CBD(2.7 mg:2.5 mg) or THC (2.7 mg). – A maximum of 8 sprays in a three-hour period, and a maximum of 48 sprays/day	– Efficacy and safety of the oromucosal spray	– 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
Johnson et al[22]	Pain	Prostate	– Double-blind, placebo-controlled RCT – N=177 – n=24 PCa	– 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	– Patients were randomized to self-titrating a spray of THC: CBD (2.7 mg:2.5 mg) or THC (2.7 mg) for 2 weeks. – A maximum of 8 sprays in a three-hour period, and a maximum of 48 sprays/day	– 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	– 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) – 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 GU (unspec-ified)	– Double-blind, RCT – N=397 – n=72 UC	– Adults with advanced incurable stage of cancer and a clinical diagnosis of cancer-related pain that was not alleviated by opioid therapy – U.S., Belgium, Bulgaria, Czech Republic, Estonia,	– Patients were randomized to receive Sativex (THC [27 mg/mL]:CBD [25 mg/mL]) or matching placebo – Self-titrate for 14 days and then continue at stable dose for 3 weeks	– Percent improvement between baseline and end of treatment in average pain on NRS score – Average pain score, worst pain score, and sleep disruption	– 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

				Germany, Hungary, Latvia, Lithuania, Poland, Romania, U.K.			improved sleep NRS score (p=0.027)
Niederle et al[31]	CIN	Testicular	– Crossover study – N=20	– 20 non-semi-noma testicular cancer patients undergoing cisplatin therapy were given nabilone or alizapride during the first or second course of chemo-therapy – Germany	– On days 1–5, hospitalized patients were given nabilone (2 mg) or alizapride (150 mg) 2 hours before chemotherapy and at intervals in the afternoon and evening and observed	– Therapeutic and adverse effects of both drugs were evaluated in daily questionnaires	– 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
Pawasarat et al[21]	Pain	UC (unspec-ified)	– Retrospec-tive chart review – N=232 total – n=49 UC	– 2 arms: cannabis users (n=137 [22 UC]) and non-cannabis users (n=95 [27 UC]) – NJ, U.S.	– This study did not capture the frequency and dosing of cannabis or the time frame of evaluation	– Assessed pain through daily opiate consumption and ESAS scores in sections of pain, physical, and emotions	– 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	– Randomized, placebo-controlled, graded-dose trial – N=263 – n=44 PCa	– Patients had to have active and chronic pain that was moderate or severe	– Sativex (THC (27 mg/mL): CBD (25mg/mL) 1-week titration, and 4 weeks of	– Assessed average pain and worst pain in the last 24 hours, pain disruption in sleeping	– Low (1–4 sprays) and medium (6–10 sprays) led to a significant improvement in average daily

				despite the lack of a stable opioid regimen – Randomized into three different dose ranges of oromucosal spray – North America, Europe, Latin America, South Africa	stable dosing based on 1 of 3 dose groups (low, medium, high)	patterns, and doses of breakthrough pain killers – Assessed quality of life through selected questionnaires	pain compared to placebo from 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 (unspec-ified)	– Multicenter, phase 3, double-blind, placebo-controlled RCT 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	– After baseline assessment, patients received either THC:CBD (2.5 mg:1 mg), 2. of THC, or placebo for 6 weeks – Patients received a two-week supply of capsules to take twice before lunch and	– Appetite change from baseline to week 6, measured through a visual analog scale and Anorexia-Cachexia EORTC QLQ-C30 module – Change in QOL from	– 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%

				three arms: THC:CBD, THC, or placebo. – Germany	dinner	baseline to week 6	improvement 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 – U.S.	– Nabilone (1–2 mg) 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 – 70% of patients preferred nabilone over placebo ($p<0.001$) (22% favored placebo and 8% had no preference)

CBD: cannabidiol; CI: confidence interval; CIN: chemotherapy-induced nausea; EORTC: European Organisation for Research and Treatment of Cancer; ESAS: Edmonton Symptom Assessment System; GI: gastrointestinal; GU: genitourinary; NRS: numerical rating scale; OR: odds ratio; PCa: prostate cancer; RCT: randomized controlled trial; THC: Delta-9-tetrahydrocannabinol; UC: urological cancer; QOL: quality of life.

Search strategy

The search strategy contained the following keywords and combinations: “testicular cancer OR germ cell tumor OR prostate cancer OR penile cancer OR bladder cancer OR kidney cancer OR renal carcinoma OR prostatic neoplasms OR urinary bladder neoplasms OR testicular neoplasms OR ureteral neoplasms OR kidney neoplasms OR urological neoplasms” AND “cannabis OR marijuana OR marihuana OR cannabinoids OR cannabidiol OR delta-9-tetrahydrocannabinol OR dronabinol OR nabilone OR nabiximols OR tetrahydrocannabinol”. A second search was completed for the use of cannabis for urologic cancer-related symptom management and utilized the above keywords AND “cancer pain OR chemotherapy induced nausea OR cachexia OR anorexia OR nausea OR vomiting”.