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Dronabinol Prescribing and Exposure Among Children and Young Adults Diagnosed with Cancer

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Purpose: The therapeutic utility of *Cannabis* in cancer is a topic of intense interest. Dronabinol is synthetic Δ^9-tetrahydrocannabinol (THC), the primary psychoactive component of *Cannabis sativa*, and is approved for treating refractory chemotherapy-induced nausea and vomiting. Little is known about dronabinol prescribing in children and young adults, and no published concentration data are available. This study evaluated national level dronabinol use and assessed concentrations of THC and its primary metabolites in patients with cancer <27 years of age prescribed dronabinol.

Methods: Observational review of records from the Pediatric Health Information System (PHIS) and a regional network of hospitals in the Intermountain West, including a tertiary care children's hospital, Primary Children's Hospital (PCH), for inpatients <27 years of age prescribed dronabinol. Prospective blood samples were collected from children with cancer at PCH.

Results: Across PHIS institutions, overall dronabinol prescribing aligned with the pharmacy records for those with cancer ($p < 0.0001$), and of these, 10.4% received dronabinol as inpatients. Blood collected within 72 hours of dronabinol administration was available from 10 children with a median age of 12.5 (range 6–17) years. Quantifiable concentrations were found in 4 (13%), 6 (20%), and 1 (3%) samples assayed for THC, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (COOH-THC), and 11-hydroxy-Δ^9-tetrahydrocannabinol (OH-THC), respectively. THC concentrations ranged between 0.100 and 0.128 ng/mL and were not associated with dose.

Conclusion: Dronabinol prescribing appears exclusive to patients diagnosed with cancer, and its use has increased steadily in the past decade. In a small sample of children administered dronabinol, THC and metabolite concentrations were consistently low or undetectable.

Keywords: dronabinol, tetrahydrocannabinol, orexigenic, chemotherapy-induced nausea and vomiting (CINV)

Introduction

Interest surrounding the use of medical marijuana (*Cannabis*) to treat patients with cancer has dramatically increased in recent years.[1–3] Dronabinol is synthetic Δ^9-tetrahydrocannabinol (THC), the primary psychoactive component of *Cannabis sativa*. Marketed as oral capsules (Marinol®), dronabinol was approved for use by the U.S. Food and Drug Administration (FDA) in 1985 as an adjuvant for the control and management of chemotherapy-induced nausea and vomiting (CINV) and as an appetite stimulant for adult patients with AIDS-related weight loss.[4] An orally administered liquid formulation of dronabinol (Syndros®) was U.S. FDA approved in 2016.[5,6] Although available for more than 30 years, little is known about dronabinol prescribing patterns, and no specific pharmacokinetic (PK) data have been published for children.

Both indications for which dronabinol has been approved, management of refractory CINV and as an appetite stimulant to treat anorexia/cachexia, remain urgent medical needs for children and young adults with cancer.[7–9] Currently, no pediatric studies evaluating the efficacy of dronabinol for cancer-related anorexia/cachexia have been published. A recent retrospective study by Elder and

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Knoderer evaluated the efficacy of dronabinol for the management of CINV in children.[10] They reported that vomiting episodes were reduced in 60% of children but also discovered a pattern of chronic underdosing for this indication. Lower doses may profoundly impact the likelihood of attaining the intended therapeutic effect with dronabinol. This is because dronabinol undergoes extensive first-pass metabolism limiting systemic bioavailability to 5%–20% of the administered dose while introducing large interindividual variations in exposure.[5,6] As THC is presented to the liver, through hepatic-portal circulation, cytochrome P450 enzymes (CYP) catalyze its biotransformation. Primarily, THC is hydroxylated to 11-hydroxy-Δ^9-tetrahydrocannabinol (OH-THC) by CYP2C9, followed by rapid second oxidation to 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (COOH-THC). CYP3A4 catalyzes the formation of 8β-hydroxy-Δ^9-tetrahydrocannabinol (8β-OH-THC). The THC metabolites, but not THC itself, are predominantly eliminated from the body as glucuronide acid conjugates.[11]

PK and pharmacodynamic data crucial to safe and effective dronabinol use for disease-related weight loss and CINV afflicting younger patients with cancer are lacking. Moreover, the number of therapeutic modalities for THC (dronabinol) relevant to patients with cancer will likely expand beyond its current indications.[12] Investigations are ongoing for THC use in the treatment of pain, anxiety, sleep disorders, depression, and various cancers.[1,13] Although THC has established a reasonably robust drug safety profile, there may be distinct risks or toxicities associated with THC use in children, such as an association with neurodevelopmental deficits in adolescence.[1,6,14] Addressing knowledge gaps regarding the therapeutic use of THC is essential to ensure treatment efficacy and diminish the risk for adverse effects in current, as well as for potential future, indications. This study uses national and regional level health system databases to characterize dronabinol prescribing among pediatric and young adult patients diagnosed with cancer. In addition, dronabinol and metabolite exposures were evaluated using plasma samples collected from pediatric inpatients diagnosed with cancer receiving care at a tertiary children's hospital.

Methods

Study design and setting

A multicenter retrospective analysis was conducted utilizing electronic medical records collected from two sources (Fig. 1) with IRB approval from the University of Utah, Intermountain Healthcare (IH) and Primary Children's Hospital (PCH). IH is composed of 23 hospitals, serving $\sim$1.5 million people within the Intermountain West region (Utah, Idaho, Wyoming, Nevada, and Montana).

Specimen collection and data from IH/PCH

Data were extracted from the enterprise data warehouse of IH, which includes PCH, for patients diagnosed with cancer from whom scavenged blood samples (residual blood from standard-of-care collections) were collected (August 1, 2016–January 30, 2018). This included demographics and vital statistics, diagnoses, laboratory values, microbiologic information, pharmacy records, and anthropomorphic measurements. Cancer diagnosis was derived from a validated registry.[15]

Among a subset of patients receiving dronabinol, scavenge blood samples were available, collected under IRB#80686. Briefly, at the central clinical laboratory, excess blood (having been obtained for routine clinical care and drawn into heparinized or EDTA tubes) was kept on ice and fractionated by centrifugation. Plasma was aliquoted into cryovials and refrigerated. A study coordinator coded (deidentified) the

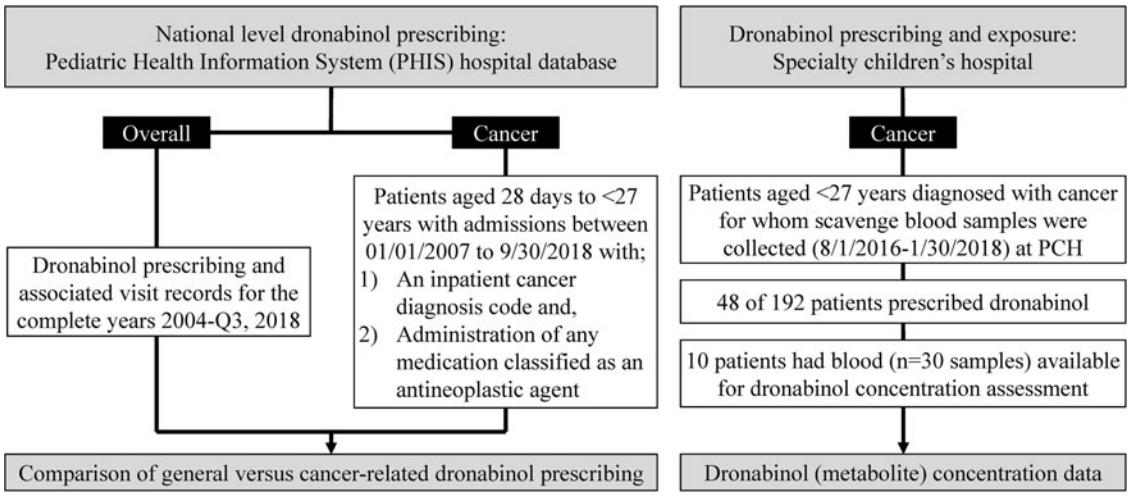

FIG. 1. Flow chart of data and sample collection used to assess dronabinol prescribing patterns and exposure among hospitalized children and young adults diagnosed with cancer. Left: Medical records were obtained in two independent extractions from the PHIS hospital database to create a nationally representative sample of dronabinol prescribing. First, all billing records for dronabinol were collected (''Overall'') and compared to the medication billing records for patients diagnosed with cancer (''Cancer''). Right: Scavenge blood samples were collected from patients with cancer receiving care at PCH. A subset of these patients received dronabinol. Of these patients, available blood samples were used to assess THC (and metabolite) concentrations. PCH, Primary Children's Hospital; PHIS, Pediatric Health Information System; THC, Δ^9-tetrahydrocannabinol.

samples and transferred them to a secured −80°C freezer within 24 hours of blood collection. All samples were independently verified and cataloged for volume.

Pediatric Health Information System data extraction

Records related to dronabinol prescribing were extracted from the Pediatric Health Information System (PHIS) hospital database for the years 2004 through the third quarter (Q3) of 2018.[16] Independent of the dronabinol prescribing record extraction, PHIS data were extracted for patients aged 28 days to <27 years discharged between January1, 2007 and September 30, 2018. Inclusion criteria were as follows: (1) an inpatient cancer diagnosis code and (2) administration of any medication classified as an antineoplastic agent.[17] Data included International Classification of Diseases Clinical Modification (ICD; i.e., ICD-9-CM and ICD-10-CM) discharge diagnoses, Current Procedures Terminology codes, day-to-day medication, laboratory billing records, and unique patient identifiers. Medication exposures can be tracked through multiple ''visits'' (i.e., hospital encounters) using patient identifiers.

Sample bioanalysis

Concentrations of THC, OH-THC, and COOH-THC in plasma were determined using a previously validated gas chromatography–tandem mass spectrometry (GC-MS/MS) method (Fig. 2).[18] This assay can also simultaneously determine cannabidiol (CBD) concentrations in plasma. Briefly, analytes were extracted from 100 μL of plasma using acetonitrile precipitation followed by liquid–liquid extraction (9:1 hexane:ethyl acetate). Samples were derivatized using N-methyl-N-(trimethylsilyl) trifluoroacetamide and injected onto an instrument consisting of an Agilent 7890A GC interfaced with an Agilent 7000 MS/MS by electronic ionization. A lower limit of quantitation (LLOQ) of 0.1 ng/mL and an upper limit of quantitation of 100 ng/mL were achieved for THC and OH-THC, while the assay's dynamic range for COOH-THC was 0.5 to 500 ng/mL.

Clinical variables and statistical methods

Age stages were defined using National Institute of Child Health and Human Development (NICHD) pediatric terminology.[19] Body surface area was as per DuBois.[20] Cancer subtypes were defined as per the International Classification of Childhood Cancer (ICCC), International Classification of Diseases for Oncology, 3rd Ed., and WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ICD-O-3/WHO 2008). Analyses performed based on episodes of care (admit to discharge) are designated as ''hospitalizations'' or ''visits.'' Analyses at the patient level were inclusive of all individual episodes of care in the study period. As appropriate, chi-square or Fisher's exact test was used to compare categorical variables, while continuous variables with normal distributions were expressed as the mean (±standard deviation [SD]) and compared using Student's *t*-test (with or without a prior transformation based on a Box-Cox test) or the Wilcoxon log-rank test. Statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) or Prism version 6 (GraphPad Software, La Jolla, CA).

Results

Dronabinol prescribing at children's hospitals

For the years 2004-Q3 2018, dronabinol was prescribed in 30,986 hospital visits based on data available across 52 contributing children's hospitals (Fig. 1, ''Overall''). Among patients diagnosed with cancer and discharged from a PHIS hospital (Fig. 1, ''Cancer'') between January 1, 2007 and September 30, 2018, there were 72,486 unique patients (i.e., distinct Medical Record Number entries) and 1,377,797 visits (i.e., distinct ''Billing Number'' entries). Of these, dronabinol was prescribed to 10.4% ($n=7510$) of patients within 24,811 (1.8%) visits (Table 1 and Fig. 3). Nabilone, a congener of THC (dronabinol), was approved for adult use as an antiemetic for managing refractory CINV at the same time as dronabinol (1985). However, it only became available in the United States after the year 2006.[21] Nabilone was not

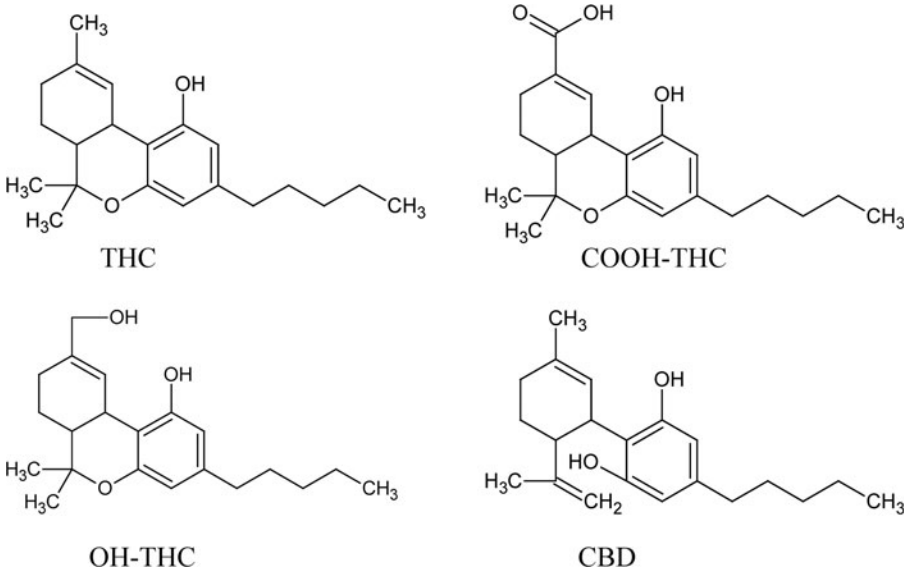

FIG. 2. Chemical structures of the cannabinoids assayed from blood collected among children receiving dronabinol. OH-THC and COOH-THC are metabolic products of THC. Synthetic THC is dronabinol. THC undergoes phase I metabolism, generating OH-THC and COOH-THC. The presence of CBD was additionally monitored in the assay. CBD, cannabidiol; COOH-THC, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; OH-THC, 11-hydroxy-Δ^9-tetrahydrocannabinol.

Table 1. Demographics and Clinical Characteristics of National and Regional Cohorts

	PHIS (cancer)	*PCH*
	n = *7510*	n = *41*[a]
Patient level	n *(%)*	n *(%)*
Sex		
Female	3047 (40.6)	17 (41.5)
Male	4463 (59.4)	24 (58.5)
Race		
American Indian	33 (0.4)	1 (2.4)
Asian	198 (2.6)	0 (0.0)
Black Hispanic	21 (0.3)	0 (0.0)
Black Non-Hispanic	656 (8.7)	0 (0.0)
Multiple	606 (8.1)	0 (0.0)
Other	446 (5.9)	0 (0.0)
Pacific Islander	17 (0.2)	1 (2.4)
Unknown	211 (2.8)	0 (0.0)
White Hispanic	1036 (13.8)	7 (17.1)
White Non-Hispanic	4286 (57.1)	32 (78.0)
Cancer type[b]		
Leukemia/lymphoma		26 (63.4)
CNS neoplasm		1 (2.4)
Neuroblastoma		1 (2.4)
Sarcoma		2 (4.9)
Renal		2 (4.9)
Bone		9 (22.0)
	n = *24,811*	n = *162*
Visit level	n *(%)*	n *(%)*
Age category at admission (years)		
Infant (<1)	7 (0.03)	0 (0.00)
Toddler (1–<2)	47 (0.19)	1 (0.6)
Child (2–<12)	6139 (24.7)	57 (35.2)
Adolescent (12–<19)	14,825 (59.8)	90 (55.6)
Young adult (19–<27)	3793 (15.3)	14 (8.6)
Clinical characteristics[c]		
Total parenteral nutrition	5269 (21.2)	20 (12.4)
Operating room charge	4570 (18.4)	39 (24.1)
Transplant procedure	2574 (10.4)	4 (2.5)
Infection	8642 (34.8)	16 (9.9)
Mechanical ventilation	818 (3.3)	5 (3.1)
Dronabinol prescribing relative to initiation of induction chemotherapy		
Before first year	325 (1.3)	1 (0.6)
During first year	20,069 (80.9)	131 (80.9)
After first year	4417 (17.8)	30 (18.5)
Outpatient dronabinol prescription	NA	155 (95.7)
Dose amount[d] (mg)		
2.5	16,931 (68.2)	106 (65.4)
5	9761 (39.3)	55 (34.0)
10	209 (0.8)	12 (7.4)
Unknown	7 (0.03)	0 (0.00)
		Median *IQR*
Dose amount[e] (mg/m^2)		2.5 1.8–3.6

[a]Patients administered dronabinol within a hospital visit are described.
[b]As per International Classification of Childhood Cancer (ICCC) classification.
[c]Factors identified within PHIS billing records and the IH EMR are not exactly analogous, complicating direct comparisons. Infection flag for PCH cohort was based on any culture being positive for growth in a visit. Total parenteral nutrition for a PCH visit was determined by pharmacy records.
[d]More than one dose amount could be prescribed per visit.
[e]For patients with height and weight recorded at time of dose administration.
IQR, interquartile range; PCH, Primary Children's Hospital; PHIS, Pediatric Health Information System; NA, not available.

prescribed to patients diagnosed with cancer at any contributing hospitals during the study period.

Trends in dronabinol prescribing were assessed using pharmacy records from those hospitals consistently contributing data over the 15-year (60 quarters) study period. Among the 21 PHIS institutions providing data for $\geq 90\%$ of quarters, the frequency of visits in which dronabinol was prescribed (Fig. 4, left), as well as the number of doses administered per visit (Fig. 4, right), increased over time ($p < 0.0001$). These trends in dronabinol use did not differ from dronabinol use among patients diagnosed with cancer (Fig. 4, left, data in gray). While the number of dronabinol doses administered per visit significantly increased over time, the amount per dose (e.g., 2.5 vs. 5 mg) did not. For patients with cancer, the median (interquartile range [IQR]) number of visits per patient where dronabinol was prescribed was 2 (1–4) with 7 (3–17) doses administered per visit. The median (IQR) age was 15 (12–17) years and ranged from 46 days to 29 years. The number and amount of dronabinol doses prescribed were similar for males and females. The liquid formulation of dronabinol was used, at two institutions, to treat seven patients, accounting for 0.026% ($n = 116$) of total doses administered.

Demographic and clinical characteristics for the PHIS patient cohort (''PHIS cancer''), as well as those for patients receiving dronabinol as inpatients admitted to the tertiary children's hospital (PCH) from which scavenge blood samples were collected, are listed in the Table 1. The PCH cohort was younger with a median age of 12 years (IQR 8.8–15; $p < 0.0001$), received fewer doses of dronabinol per visit (median [IQR], 6 [3.8–9]; $p = 0.01$), and had a shorter length of hospital stay (LOS; $p = 0.0004$). The median (IQR) LOS was 4 (3–5) at PCH compared to 5 (3–11) days for the PHIS cohort with a cancer diagnosis.

Dronabinol concentration assessment: inpatient administration

Scavenge blood was available for a subset of patients who had been prescribed dronabinol ($n = 48$). Seven of the 48 patients only received dronabinol on an outpatient basis, while 41 children were administered dronabinol as inpatients ($n = 162$ hospital visits; see Table 1, ''PCH''). Of those who received dronabinol within a hospital visit, 34 (83%) were also prescribed dronabinol on an outpatient basis. The median (IQR) doses per patient (inpatient administration) were 18 (7.5–54), comprising a total of 1579 doses. Ten patients (median age of 12.5 (range 6–17) years) had blood collected within 72 hours of inpatient dronabinol administration. Table 2 describes patient details for whom samples were collected and assayed. Samples that met selection criteria of: (1) reliable data on the timing of dronabinol administration and sample collection, (2) were within 72 hours postdose, and (3) volume ≥ 0.4 mL, were assayed.

A majority of analyzed samples, regardless of time postdose or dose administered, were below the assay LLOQ for all analytes (Fig. 5). Out of the 30 samples analyzed, concentrations were quantifiable in 4 (13%), 6 (20%), and 1 (3%) for THC, COOH-THC, and OH-THC, respectively. Detectable, but not quantifiable (i.e., between ½ LLOQ and the LLOQ), concentrations were observed in 18 (60%), 3 (10%), and 3 (10%) samples for THC, COOH-THC, and OH-THC,

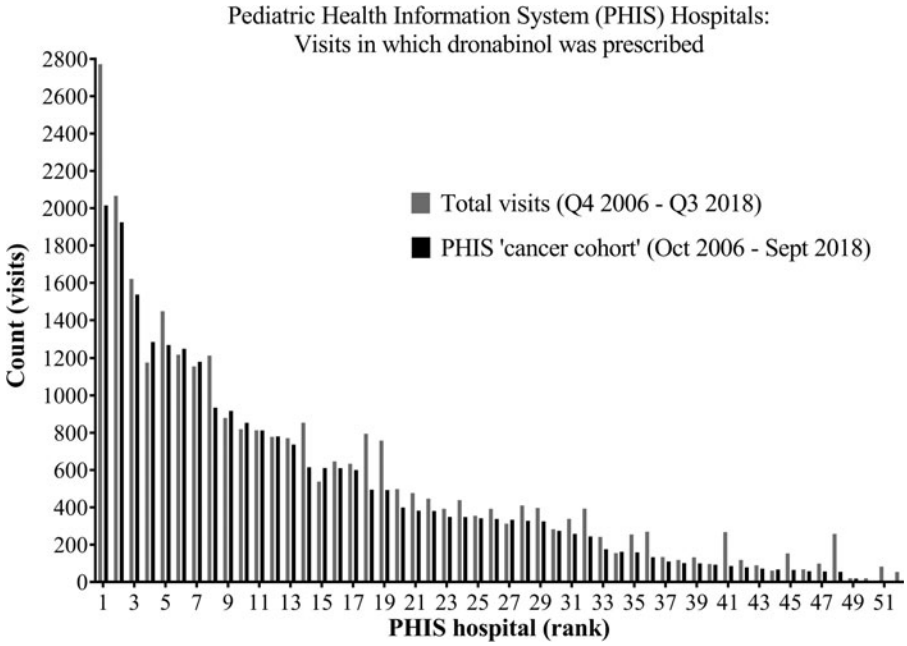

FIG. 3. Rank order of the 52 PHIS hospitals by number of visits for which dronabinol was prescribed. ''Total visits'' represents only dronabinol prescribing data collected in the same timeframe as that available for the ''PHIS Cancer cohort.''

respectively. Quantifiable THC concentrations ranged between 0.100 and 0.128 ng/mL and were not associated with dose amount. The median (range) COOH-THC concentration at the 2.5 mg dose was 1.19 (0.40–16.0) ng/mL and at the 5 mg dose was 0.42 (0.33–1.2). A single quantifiable OH-THC concentration of 0.407 ng/mL after a 5 mg dose was observed. While CBD was not prescribed as an inpatient medication for the PCH cohort, 5 (17%) of the samples, from four patients, had detectable CBD concentrations.

Dronabinol concentration assessment: outpatient prescribing

For three patients prescribed dronabinol on an outpatient basis, scavenge blood samples were collected at times between hospital visits in which dronabinol was administered (Fig. 6). A minimum of 194 days had passed since the last recorded inpatient dose. Two patients (one prescribed 2.5 mg and the other 2.5 and 5 mg capsules) had one blood

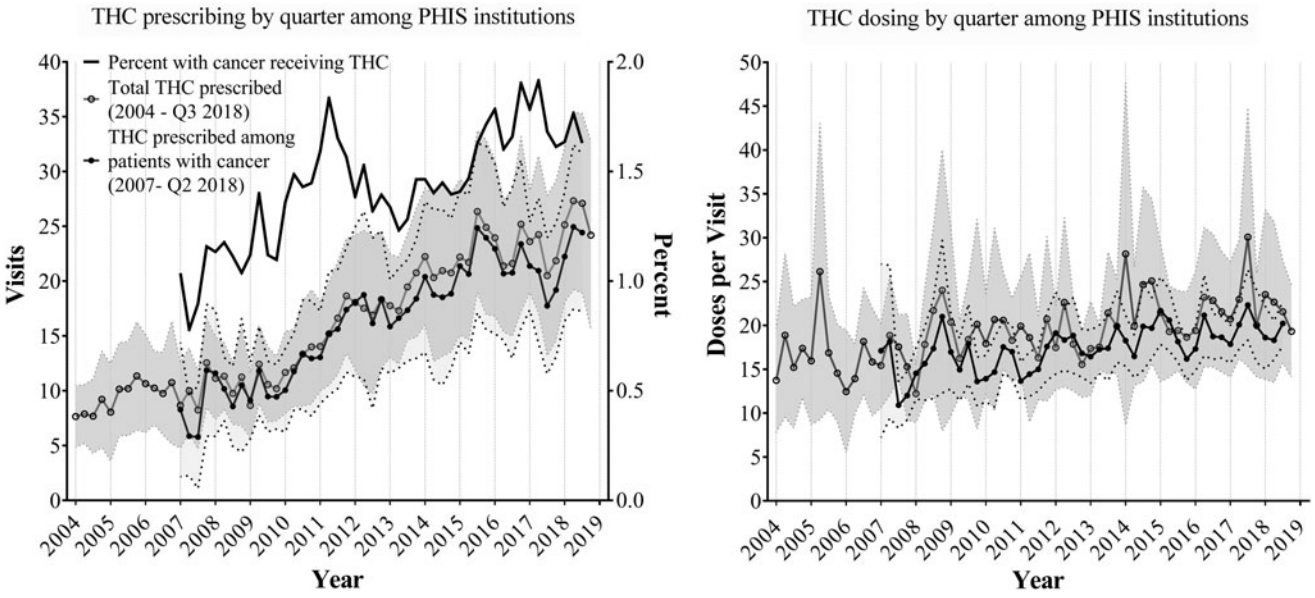

FIG. 4. National level pediatric dronabinol prescribing trends. The graph on the left contrasts the total number of hospital visits in which dronabinol was prescribed at PHIS institutions (''Total THC prescribed'') with visits by patients diagnosed with cancer administered dronabinol (''THC prescribed among patients with cancer''). The individual data points represent quarters within each year (x-axis). ''Percent with cancer receiving THC'' corresponds to the right y-axis. The graph on the right depicts the number of dronabinol doses administered per visit by quarter for each year for all PHIS inpatients (''Total THC prescribed'') and those diagnosed with cancer (''THC prescribed among patients with cancer''). Data are mean and 95% confidence interval with the exception of the percentiles. Dronabinol prescribing data shown represent pharmacy records from those hospitals providing data for $\geq$90% of quarters over the 15-year (60 quarters) study period ($n=21$). Analysis with data pooled from all 52 hospitals did not affect the results or conclusions (data not shown).

TABLE 2. DEMOGRAPHIC, CLINICAL, AND DRONABINOL DOSING FOR SUBJECTS WITH BLOOD COLLECTED FOR THC CONCENTRATION ASSESSMENT

Subject ID, sex	*Age (years)*		*Race*	*Malignancy type*	*Visits (n) dronabinol received; max dose (mg/m²)*	*Dronabinol dose before blood collection (mg; mg/m²)*	*Total inpatient doses*	*Plasma samples assayed (n)*	*Highest recorded concentration (ng/mL)*		
	At time of cancer diagnosis	*At time of blood draw*							*THC*	*COOH-THC*	*OH-THC*
Inpatient											
10, F	17	17	White	Lymphoma	4; 1.8	2.5; 1.7	115	3	0.128	16	*Detectable*
26, M	14	14	White	Bone tumors	8; 1.7	2.5; 1.6	43	1	*Detectable*	—	—
41, F	12	12	Native Hawaiian/Pacific Islander	Bone tumors	11; 4.2	5; 4.0	58	4	*Detectable*	*Detectable*	—
54, F	12	16	White	Leukemia	3; 1.8	2.5; 1.8	21	1	*Detectable*	*Detectable*	*Detectable*
67, F	15	16	White	Soft tissue sarcoma	10; 3.7	5; 3.6	72	5	0.1	1.21	0.407
71, M	8	8	White	Leukemia	2; 2.5	2.5; 2.5	10	1	—	3.67	—
73, M	2	6	White	Leukemia	6; 3.3	2.5; 3.0	19	3	*Detectable*	*Detectable*	—
74, M	6	6	White	CNS neoplasms	9; 3.4	2.5; 3.4	54	5	0.102	1.19	—
136, M	5	6	White	Neuroblastoma	7; 6.2	5; 5.8	45	6	0.101	*Detectable*	—
151, M	12	13	White	Bone tumors	12; 1.4	2.5; 1.3	54	2	*Detectable*	—	—
Outpatient[a]											
17, M	15	15	White	Leukemia	2; 2.6	5 mg	18	7	0.33	54.1	0.54
108, F	3	5	White	Renal tumors	7; 3.7	2.5 mg	54	1	—	—	—
136, M	5	6	White	Bone tumors	7; 6.2	5 mg	45	1	—	—	—

[a]*Dronabinol dose before blood collection* is unknown. Listed is the dose amount prescribed.
COOH-THC, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; OH-THC, 11-hydroxy-Δ^9-tetrahydrocannabinol; THC, Δ^9-tetrahydrocannabinol.

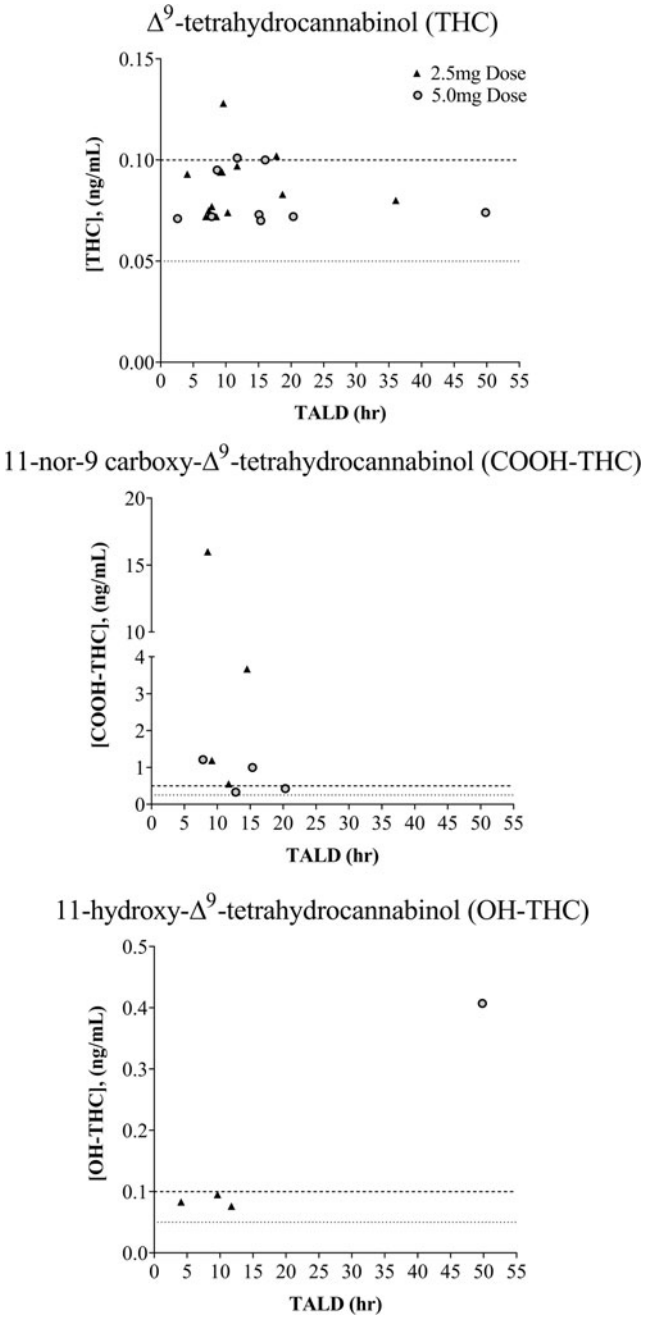

FIG. 5. Plasma concentrations of THC (top), COOH-THC (middle), and OH-THC (bottom) from scavenge blood samples collected from children diagnosed with cancer administered dronabinol as either a 2.5 mg (triangles) or 5 mg capsule (circles). Upper dashed line and lower dotted line represent the LLOQ and LLOD, respectively. TALD on the x-axis is the ''time after last dose.'' LLOD, lower limit of detection; LLOQ, lower limit of quantitation.

sample available each, and for these, THC and metabolites were not detected. A third patient (prescribed 5 mg capsules) had seven samples available (spanning 78 days), of which three were negative or below the limit of quantitation for all analytes. Two were positive for COOH-THC (6.2 and 8.7 ng/mL) only, one was positive for COOH-THC (13.3 ng/mL) and OH-THC (0.1 ng/mL), and one was positive for THC (0.33 ng/mL), COOH-THC (54.1 ng/mL), and OH-THC (0.54 ng/mL).

Discussion

Our findings confirm that among hospitalized children and young adults in the United States, dronabinol is primarily used in the treatment of patients with cancer and that its use has increased over time.[10] In this first report of dronabinol exposure in children, we found consistently low or no detectable plasma concentrations of THC, COOH-THC, or OH-THC within 72 hours of inpatient administration. As there is very little known about what to expect in the way of THC (and metabolite) concentrations among children receiving dronabinol, we assessed samples within the timeframe anticipated for; (1) detecting peak analyte concentrations and (2) beyond 24 hours to assess potential evidence of extra-clinical THC exposures. Based on the amount and frequency of inpatient dronabinol administration, we did not expect to see significant analyte concentrations out to 72 hours. Nonetheless, the results imply a risk of subtherapeutic exposures for children receiving dronabinol with current dosing practices. Further prospective studies will be necessary to confirm this finding because target exposure or concentration-based indices for CINV management or orexigenic effect for dronabinol have not been established for children (or adults).

Two studies have been conducted to assess dronabinol efficacy for managing CINV in children. Most recently, in a retrospective observational study, Elder and Knoderer reported that 60% (33 of 55 patients) of patients receiving dronabinol had improved CINV control among those receiving moderate to highly emetogenic chemotherapeutic regimens.[10] In 1976, Ekert et al. published a report comparing dronabinol versus metoclopramide and prochlorperazine for CINV control among patients <19 years of age. This study was used to support FDA approval of dronabinol for use in children with cancer.[4,22] In the blinded crossover study designs (THC:metoclopramide [eight patients] and THC:prochlorperazine [seven patients]) THC was superior to both antiemetics in decreasing bouts of nausea and episodes of vomiting, as reported by patients and family members. Drowsiness was common and significantly increased for those receiving THC. However, no difference in anorexia was found.

Current dronabinol dose amounts prescribed to children with cancer are lower than those used in the study by Ekert. In the Elder study, 95% of patients received doses at about half that was recommended (2.5 vs. 5 mg/m^2 based on product labeling),[5] whereas in the Ekert study, dosing of dronabinol was 10 mg/m^2 (with a maximum of 15 mg). Taken together, the threshold THC (plus active metabolite(s)) exposure necessary for adequate CINV control may be relatively low for some children.[23] While it has been judged that prescription cannabinoids in the United States are labeled with ''low initial doses,'' optimizing the therapeutic management of CINV will likely require adaptation by age and development in addition to chemotherapeutic regimen.[7,24,25] The dronabinol dosing (in mg/m^2) at our institution was similar to that reported by Elder and Knoderer.

Oral administration is a particular challenge for obtaining consistent THC exposures. Due to extensive first-pass metabolism, the estimated absolute bioavailability of oral THC

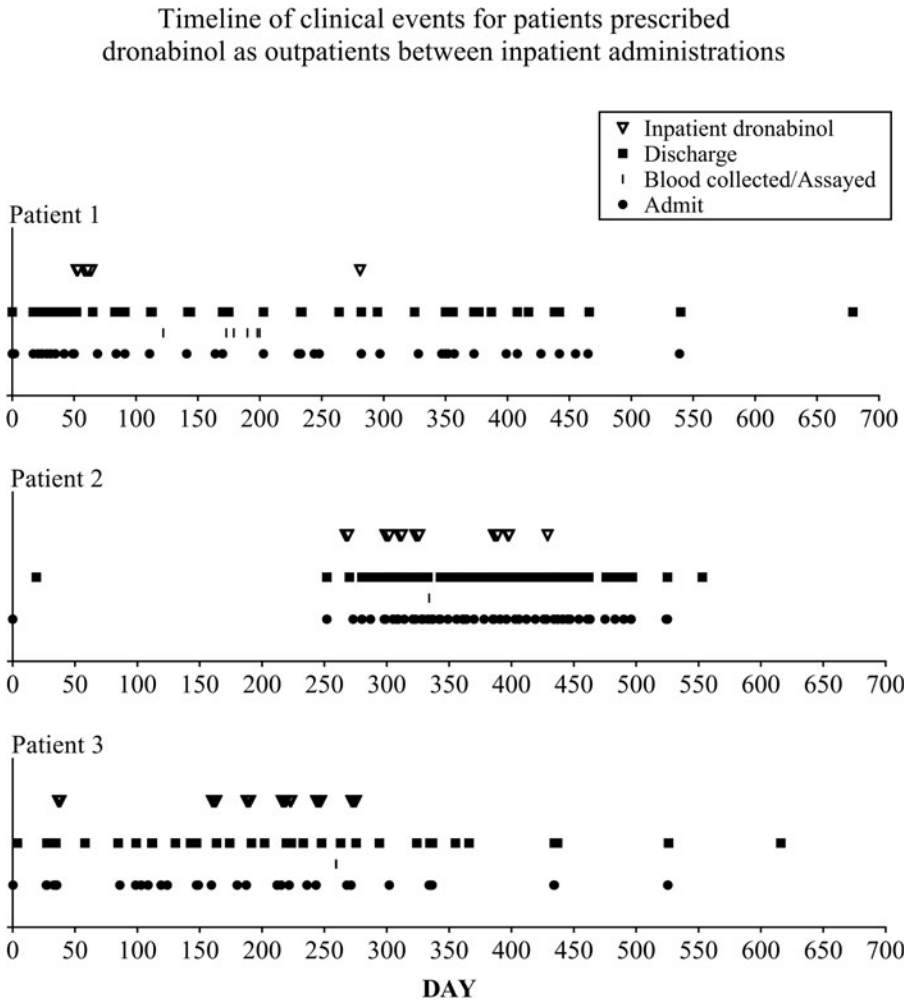

FIG. 6. Time to event for three patients with dronabinol outpatient prescriptions. Blood samples selected for concentration assessment were those obtained between bouts of clinical care in which dronabinol was administered in hospital. Day ''0'' represents the first record of hospitalization for a given patient.

is low and highly variable.[25] Adding to the uncertainty of the dose–response relationship, therapeutic targets intended to achieve control in CINV or stimulate appetite are thought to differ, yet are poorly understood.[2] For instance, THC and metabolites are often described as being ''active'' or ''inactive,'' but this is typically regarding the psychoactive properties. CYP2C9 catalyzes the formation of the primary (*psycho*)active THC metabolite, OH-THC, which is subsequently oxidized to the (*psycho*)inactive COOH-THC, whereas CYP3A4 catalyzes the formation of a second primary, but (*psycho*)inactive metabolite, 8β-OH-THC.[11] For CINV control, in children, 8β-OH-THC has demonstrated potent activity.[26] Therefore, an individual's metabolic profile (and corresponding concentrations of entities generated) will dictate response (e.g., NV control, analgesia, and appetite stimulation), as well as the manifestation of unwanted psychotropic side effects.[5,27,28]

Other aspects of THC's pharmacology can also make dronabinol use challenging.[29] For example, after chronic use, tolerance develops to many of the effects of THC. A notable exception appears to be the orexigenic effect.[30] Currently, the use of dronabinol in the setting of anorexia-associated weight loss in patients with cancer is not an approved indication as it is for adults with HIV/AIDS.[5] Results for dronabinol efficacy in appetite stimulation, weight gain, or improved quality of life are mixed in cancer-related cachexia among adults.[31,32] However, data, other than anecdotal, are sparse for THC use as an appetite stimulant for cancer-related anorexia/cachexia in children. Elder and Knoderer cited the use of THC as an appetite stimulant among children with cancer (4 of 66) in their study, but only as it related to exclusion criteria.[10]

More than 80% of the PCH cohort administered dronabinol as inpatients also received outpatient prescriptions. Again, this finding was consistent with Elder and Knoderer's study, in which 62% of children received outpatient dronabinol prescriptions.[10] Indeed, the highest THC (0.33 ng/mL) and metabolite (COOH-THC; 54.1 ng/mL, OH-THC; 0.54 ng/mL) concentrations in our study were observed in a sample collected from a patient prescribed dronabinol on an outpatient basis between hospital visits in which dronabinol was administered.

While no studies have been published evaluating dronabinol disposition in children with cancer, a recent study by Wang et al. evaluated the PK of THC in children ($n=9$) administered oral *Cannabis* extracts to manage their epilepsy.[33] The authors reported high interindividual variability and a lack of correlation between THC exposure (peak concentrations; 0.8 to 3.6 ng/mL) and weight-based dosing. Peak concentrations were detected between 2 and 7 hours after administration. The metabolites, COOH-THC and COOH-THC-glucuronide remained at measurable concentrations over the 10–12 hour study period. Wang concluded that the

substantial interpatient variation might be a consequence of differences in bioavailability among children or that the three different formulations of *Cannabis* extracts provided were not sufficiently characterized for THC content.

As the majority of our patient derived samples exhibited concentrations that were not quantifiable, if not undetectable, it precluded us from performing any PK analyses beyond descriptive statistics. This circumstance also prevented the evaluation of dronabinol-associated effects or outcomes in our cohort. The reason behind the consistently low (or undetectable) concentrations of THC and primary metabolites following a dronabinol administration is unclear. One potential explanation is that the bioavailability of oral THC in this population is minimal. Notably, the bioavailability of dronabinol in adults is not high (5%–20%). Thus, any physiologic difference that reduces bioavailability in children (e.g., changes in gut pH and permeability) may result in dronabinol being largely excreted before systemic absorption. However, COOH-THC was observed in many samples that did not have detectable THC, indicating that metabolism of THC may occur at a rate that prevents observing the parent drug in systemic circulation. THC achieving systemic circulation in adults can undergo rapid clearance ($t_{1/2} \sim 1$ hour).[11] When quantifiable, the concentrations we observed were similar to those reported by Gustafson et al.[34] As the amount (mg or mg/m^2) of dronabinol per dose was similar between PCH, that reported by Elder, and among the pharmacy records of those with cancer collected from PHIS, there may be a substantial proportion of patients whose exposures are low enough to pose a risk for therapeutic failure. More study is needed to elucidate the PK of THC and its metabolites following oral dronabinol administration in children.

Our study used samples collected as part of a scavenge blood protocol, rather than for a specific prospective PK study protocol. Therefore, the handling and processing of samples could have increased the susceptibility to analyte loss (e.g., degradation of THC and metabolites).[35] However, the validation of the GC-MS method used to analyze these samples found that THC and metabolites were stable when held at room temperature for 25 hours or at −20°C for up to 207 days. Moreover, all blood specimens were initially collected for clinically indicated reasons and, therefore, would have been handled under standard procedures for a clinical laboratory before their storage at −80°C. Overall, attributing the pattern of low or undetectable concentrations of THC and its metabolites in our study to inappropriate sample handling seems unlikely. With regard to adherence, our inpatient data reflect known times of dronabinol administration. However, there is uncertainty for the subset of THC concentrations derived from patients receiving dronabinol on an outpatient basis.

Dronabinol prescribing at PCH is provider dependent but is considered an acceptable therapeutic option for patients with CINV not adequately controlled by standard institutional antiemetic regimen, which consists of ondansetron, diphenhydramine, and corticosteroids.[36] In addition, it will also occasionally be prescribed as a first-line or second-line agent for cancer-related anorexia/cachexia. While patient outcomes related to dronabinol use were not assessed in this study, our findings affirm the need for prospective studies to inform dronabinol use in children with cancer.

Conclusions

Dronabinol has made modest but sustained gains in use over time for the alleviation of chemotherapy-induced side effects in pediatric and young adult patients with cancer. However, we detected uniformly low exposures, except for a patient receiving dronabinol on an outpatient basis. In addition, despite not being prescribed, CBD was detected in 4 of 10 patients. We must work to better understand the pharmacology of cannabinoids as their use within, as well as outside, proper medical supervision continues to grow.

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References

1. Abrams DI, Guzman M. Cannabis in cancer care. Clin Pharmacol Ther. 2015;97(6):575–86.
2. Kleckner AS, Kleckner IR, Kamen CS, et al. Opportunities for cannabis in supportive care in cancer. Ther Adv Med Oncol. 2019;11:1758835919866362.
3. Hinz B, Ramer R. Anti-tumour actions of cannabinoids. Br J Pharmacol. 2019;176(10):1384–94.
4. FDA. Marinol Label, NDA 18-651. 1985. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018651 (accessed July 9, 2020).
5. Marinol (dronabinol capsules) [package insert]. North Chicago, IL: AbbVie, Inc.; 2017.
6. Campbell CT, Phillips MS, Manasco K. Cannabinoids in pediatrics. J Pediatr Pharmacol Ther. 2017;22(3):176–85.
7. Ruggiero A, Rizzo D, Catalano M, et al. Acute chemotherapy-induced nausea and vomiting in children with cancer: still waiting for a common consensus on treatment. J Int Med Res. 2018;46(6):2149–56.
8. Patel P, Robinson PD, Thackray J, et al. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: a focused update. Pediatr Blood Cancer. 2017;64(10). DOI: 10.1002/pbc.26542.
9. Escobar Y, Cajaraville G, Virizuela JA, et al. Incidence of chemotherapy-induced nausea and vomiting with moderately emetogenic chemotherapy: ADVICE (Actual Data of Vomiting Incidence by Chemotherapy Evaluation) study. Support Care Cancer. 2015;23(9):2833–40.
10. Elder JJ, Knoderer HM. Characterization of dronabinol usage in a pediatric oncology population. J Pediatr Pharmacol Ther. 2015;20(6):462–7.

11. Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers. 2007;4(8):1770–804.
12. DeVane CL. Critical appraisals of cannabis and related compounds in pharmacotherapy. Pharmacotherapy. 2020; 40(2):100–1.
13. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78(5–6):320–9.
14. Rieder MJ, Canadian Paediatric Society, Drug Therapy and Hazardous Substances Committee. Is the medical use of cannabis a therapeutic option for children? Paediatr Child Health. 2016;21(1):31–4.
15. Kaul S, Korgenski EK, Ying J, et al. A retrospective analysis of treatment-related hospitalization costs of pediatric, adolescent, and young adult acute lymphoblastic leukemia. Cancer Med. 2016;5(2):221–9.
16. Balch A, Wilkes J, Thorell E, et al. Changing trends in IVIG use in pediatric patients: a retrospective review of practices in a network of major USA pediatric hospitals. Int Immunopharmacol. 2019;76:105868.
17. Fisher BT, Harris T, Torp K, et al. Establishment of an 11-year cohort of 8733 pediatric patients hospitalized at United States free-standing children's hospitals with de novo acute lymphoblastic leukemia from health care administrative data. Med Care. 2014;52(1):e1–6.
18. Andrenyak DM, Moody DE, Slawson MH, et al. Determination of -9-tetrahydrocannabinol (THC), 11-hydroxy-THC, 11-nor-9-carboxy-THC and cannabidiol in human plasma using gas chromatography-tandem mass spectrometry. J Anal Toxicol. 2017;41(4):277–88.
19. National Cancer Institute. Pediatric Terminology. Published 2018. Accessed November 27, 2018 from: https://www.cancer.gov/research/resources/terminology/pediatric
20. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989;5(5):303–11; discussion 312–3.
21. Polito S, MacDonald T, Romanick M, et al. Safety and efficacy of nabilone for acute chemotherapy-induced vomiting prophylaxis in pediatric patients: a multicenter, retrospective review. Pediatr Blood Cancer. 2018;65(12): e27374.
22. Ekert H, Waters KD, Jurk IH, et al. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. Med J Aust. 1979;2(12):657–9.
23. Wong SS, Wilens TE. Medical cannabinoids in children and adolescents: a systematic review. Pediatrics. 2017; 140(5):e20171818.
24. Freedman JL, Faerber J, Kang TI, et al. Predictors of antiemetic alteration in pediatric acute myeloid leukemia. Pediatr Blood Cancer. 2014;61(10):1798–805.
25. Cox EJ, Maharao N, Patilea-Vrana G, et al. A marijuana-drug interaction primer: precipitants, pharmacology, and pharmacokinetics. Pharmacol Ther. 2019;201:25–38.
26. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci. 1995;56(23–24):2097–102.
27. Wolowich WR, Greif R, Kleine-Brueggeney M, et al. Minimal physiologically based pharmacokinetic model of intravenously and orally administered delta-9-tetrahydrocannabinol in healthy volunteers. Eur J Drug Metab Pharmacokinet. 2019;44(5):691–711.
28. Milman G, Bergamaschi MM, Lee D, et al. Plasma cannabinoid concentrations during dronabinol pharmacotherapy for cannabis dependence. Ther Drug Monit. 2014; 36(2):218–24.
29. Hryhorowicz S, Walczak M, Zakerska-Banaszak O, Slomski et al. Pharmacogenetics of cannabinoids. Eur J Drug Metab Pharmacokinet. 2018;43(1):1–12.
30. Badowski ME, Perez SE. Clinical utility of dronabinol in the treatment of weight loss associated with HIV and AIDS. HIV AIDS (Auckl). 2016;8:37–45.
31. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J Clin Oncol. 2002;20(2):567–73.
32. Advani SM, Advani PG, VonVille HM, Jafri SH. Pharmacological management of cachexia in adult cancer patients: a systematic review of clinical trials. BMC Cancer. 2018;18(1):1174.
33. Wang GS, Bourne DWA, Klawitter J, et al. Disposition of oral delta-9 tetrahydrocannabinol (THC) in children receiving cannabis extracts for epilepsy. Clin Toxicol (Phila). 2020;58(2):124–8.
34. Gustafson RA, Moolchan ET, Barnes A, Levine et al. Validated method for the simultaneous determination of Delta 9-tetrahydrocannabinol (THC), 11-hydroxy-THC and 11-nor-9-carboxy-THC in human plasma using solid phase extraction and gas chromatography-mass spectrometry with positive chemical ionization. J Chromatogr B Analyt Technol Biomed Life Sci. 2003;798(1):145–54.
35. Molnar A, Lewis J, Fu S. Recovery of spiked Delta9-tetrahydrocannabinol in oral fluid from polypropylene containers. Forensic Sci Int. 2013;227(1–3):69–73.
36. Biltaji E, Enioutina EY, Yellepeddi V, et al. Supportive care medications coinciding with chemotherapy among children with hematologic malignancy. Leuk Lymphoma. 2020 [Epub ahead of print]; DOI: 10.1080/10428194.2020.1749604.

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