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Clinical Conditions and Prescription Drug Utilization among Early Medical Marijuana Registrants in Florida

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ABSTRACT

Initial legalization of medical marijuana (MM) in Florida required providers to submit initial and follow-up treatment plan forms to the University of Florida to support research on MM safety and efficacy. This study retrospectively analyzed all treatment plan forms submitted between program inception (August 2016) through July 2017 and describes early Florida MM registrants by clinical conditions and prescription drug utilization. Among 7,548 unique treatment plans, the initial visit was characterized by registrants who were mostly white (83.7%), 52.3 (SD 16.4) years of age on average, and who were assessed by the provider as at least moderately ill (79.6%). Musculoskeletal and spasticity-related conditions (44.8%), chronic pain (41.9%), and mental health disorders (17.0%) were the most frequent medical complaints for seeking MM treatment with more than one condition per patient possible. One in four (25.9%) patients reported use of prescription opioids and over one-fifth of patients frequently utilized at least one psychotropic medication as well as cardiovascular agents. There were 2,075 unique follow-up plans available which were mostly characterized by clinical improvement and reported reductions in utilization of some drug classes. Further research is needed to guide clinicians on the risks and benefits of MM used concomitantly with prescription drugs.

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Medical marijuana; cannabis; cannabinoid; Florida; drug utilization

Introduction

The use of medical cannabis has been increasing with two-thirds of states in the United States (U.S.) permitting use via medical marijuana (MM) programs or recreational legalization. Existing studies on MM registry patients have described demographic information and the conditions for which they have sought treatment with cannabis. These studies have found that MM is most often recommended for chronic pain, spasticity-related symptoms, and mental health disorders (predominantly anxiety and depression) across the U.S. (Boehnke et al. 2019a; Bonn-Miller et al. 2014; Freisthler and Gruenewald 2014; Ilgen et al. 2013; Nunberg et al. 2011; Nussbaum, Boyer, and Kondrad 2011; Reiman 2007; Reinarman et al. 2011; Troutt and DiDonato 2015; Walsh et al. 2013; Zaller et al. 2015). It is expected that patients with these conditions will also use prescription drugs and may desire to reduce the use of prescription drugs through MM. Indeed, some surveys report that MM use can impact prescription drug use patterns and may reduce the potential for harm reduction via decreased use of other substances (Boehnke et al. 2019b; Lucas, Baron, and Jikomes 2019; Lucas et al. 2016).

Past scientific literature on cannabis has focused on illicit use which is not necessarily generalizable to cannabis as a medicinal product. More recent literature has addressed the effects of MM policies and scientific evaluations of cannabinoid compounds (Di Forti et al. 2019; Klieger et al. 2017; Whiting et al. 2015). Only within the last few years has evidence on the safety and efficacy of medical cannabis begun to emerge, but practical information for healthcare providers is still lacking and will foreseeably be limited due to regulatory constraints (National Academy of Sciences 2017). A particular area of concern are drug-drug interactions (DDIs) between cannabis and prescription drugs due to common metabolic pathways, but the clinical consequences of concurrent use of such combinations are lacking in harmonization. The most common cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD), have known interactions with drug-metabolizing enzymes and certain drugs (or their metabolites) that depend most prominently on CYP2C19, CYP2C9, and CYP1A2 enzymes appear to be susceptible to DDIs with cannabinoid compounds (Brown and Winterstein 2019; Qian, Gurley, and Markowitz 2019). Bioavailability is

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further complicated by routes of administration (ROAs) that affect absorption and elimination differently while cannabis' known biological effects (e.g., sedation and somnolence) impart differences in DDI potential (Brown 2020; Qian, Gurley, and Markowitz 2019). A comprehensive understanding of common prescription drugs used by the MM patient population can define clinicians' needs for information when treating patients and highlight priority areas for pharmacological and pharmacoepidemiological research.

Florida was the 22nd state in the U.S. to legalize access to MM with the Compassionate Medical Cannabis Act of 2014 (CCA) (Florida Legislature 2018; Florida Senate 2014). The CCA was informally known as Charlotte's Web law in response to legalization advocacy for a high-CBD strain that had demonstrated effectiveness for treatment-resistant forms of epilepsy in pediatric patients (Sweeney 2014). MM legalization in Florida has been sustained by broad support from a populous state census and a substantial proportion of older adults, a population that constitutes the largest growth in cannabis users overall (Lloyd and Striley 2018). The CCA legislation mandated that physicians submit patient treatment plans to the University of Florida quarterly to support research on the safety and efficacy of MM. Therefore, this study aimed to describe clinical characteristics and prescription drug utilization pattern of MM registry patients enrolled in Florida's MM program at the time of MM initiation, and to assess changes in prescription drug utilization for a subset of patients who had follow-up information available.

Methods

Data source

This study analyzed treatment plans that were mandated by the initial version of the CCA legislation. MM treatment was initially limited to low-THC cannabis (i.e., CBD-dominant cannabis or CBD), defined as containing no more than 0.8% of THC and at least 10% of CBD (Florida Legislature 2018). Low-THC cannabis was permissible in extract or concentrate (resin) form in oral, sublingual, pulmonary, and topical ROAs. Due to delays in rulemaking implementation, low-THC cannabis was not available for ordering until July 2016. In March of 2016, legislation was passed permitting "medical cannabis" with no defined limit on THC content in the same forms and ROAs (Florida Senate 2017). In June 2017, further legislation was passed which included the removal of the language requiring treatment plan submissions to the University of Florida. The initial CCA legislation approved MM use for qualifying conditions of either cancer or conditions that chronically produce symptoms of seizures or severe and persistent muscle spasms (Florida Senate 2014). In contrast, the legislation enacted by Amendment 2 permitted MM use for a much broader range of conditions and addition of two ROAs (Florida Legislature 2018). A summary of the qualifying medical conditions, cannabis type, and ROAs permitted by each law are presented in Table 1.

Under the former and latter MM laws, eligible patients must be a permanent or seasonal Florida resident and all ages are allowed but with specific requirements for individuals under the age of 18. The amount of cannabis that may be ordered and purchased is limited to a 70-day window. Patients are responsible for the costs associated with physician visit fees, obtainment of a required registry identification care, and the purchase of MM products. Detailed information on the methodology and data elements have been previously described by Brown and authors which analyzed a subset of the dataset (Brown et al. 2020). The Initial Treatment (IT) plan and Follow-Up Treatment (FUT) plan forms can be found at https://figshare.com/projects/Supplementary_Materials_Initial_Treatment_IT_plan_and_Follow-Up_Treatment_FUT_plan_forms/93653.

Data analysis

This was a retrospective analysis of all IT and FUT plan forms of MM registry patients electronically submitted by providers to the University of Florida's College of Pharmacy (UF COP) between August 1st, 2016 and July 31st, 2017. Forms were excluded when providers submitted blank forms and when data entries were clearly erroneous or invalid. We calculated descriptive statistics of patient and treatment characteristics and examined frequency counts, sample means, and proportions. Chi-squared tests and ANOVA tests were used to calculate *p*-values for categorical variables and continuous variables as appropriate for differences between patients stratified by cannabis type ordered. Analyses were conducted with SAS version 9.4 statistical software (SAS Institute Inc, Cary, NC). This study was approved by the institutional review and privacy board of the University of Florida with a waiver of informed consent and HIPAA authorization.

Results

Treatment forms

A total of 9,888 IT plan forms and 2,916 FUT plan forms were submitted with the earliest treatment plan submission date being July 22, 2016. Of the forms received,

Table 1. Florida medical marijuana laws.

Florida law and approval dates	Qualifying medical conditions	Cannabis type and route of administration (ROA) permissible
Compassionate Medical Cannabis Act of 2014 ("CCA") June 2014 Approval date for orders: July 2016[†]	Cancer A physical medical condition that chronically produces symptoms of seizure or severe and persistent muscle spasms	Low-THC cannabis ROAs: extracts or concentrates (resin) via oral (capsules); sublingual (oils, tinctures); pulmonary (vaporization); and transdermal (topicals) routes
House Bill 307 March 2016 Approval date for orders: July 2016[†]	N/A	Medical cannabis ROAs: *routes permitted for low-THC*
Florida Medical Marijuana Legalization Initiative ("Amendment 2") November 2016 Approval date for orders: June 2017[‡]	*A patient must be diagnosed with at least one of the following conditions to qualify*: Cancer Epilepsy Glaucoma HIV/AIDS Post-traumatic stress disorder (PTSD) Amyotrophic lateral sclerosis (ALS) Crohn's disease Parkinson's disease Multiple sclerosis (MS) "Medical conditions of the same kind or class as or comparable to those enumerated" "A terminal condition diagnosed by a physician other than the qualified physician issuing the physician certification" "Chronic nonmalignant pain caused by a qualifying medical condition or that originates from a qualifying medical condition and persists beyond the usual course of that qualifying medical condition"	Low-THC cannabis Medical cannabis A combination of both ROAs: *routes permitted for low-THC;* oral (edibles) and pulmonary (cannabis flower in a sealed, tamper-proof receptable for vaping)

[†]Approval enacted by Senate Bill 1030 in 2014. Effective date June 16, 2014. Laws of Florida, Ch. 2014–157. Retrieved from http://laws.flrules.org/2014/157. Due to delays in rulemaking implementation, low-THC cannabis was not available for ordering until July 2016.
[‡]Approval enacted by Senate Bill 8-A in 2017. Effective date June 23, 2017. Laws of Florida, Ch. 2017–232. Retrieved from http://laws.flrules.org/2017/232.
The ROA of oral inhalation of smoke (i.e., burning or igniting cannabis flower and inhaling the smoke) for medical use was not approved until March 2019 per Senate Bill 182.

2,334 IT and 841 FUT plan forms were excluded due to missing information for demographics, clinical characteristics, the cannabis order, or provider information. The final sample consisted of 7,548 unique patient-level IT plans and 2,075 unique patient-level FUT plans that were available for analysis. Follow-up visits may have been conducted for the remaining sample of patients with IT plans after the change in legislation in 2017 that removed the requirements for treatment plan submissions to UF COP.

Patient characteristics and chief complaints

Characteristics of registry patients seeking MM treatment at the initial visit are provided for the total sample and stratified by cannabis type ordered for low-THC cannabis (low-THC), medical cannabis (MC), and both low-THC and medical cannabis (LTHC+MC) (Table 2).

Patients (N = 7,548) were mostly white (83.7%) and between the ages of 50 to 69 years (45.9%). Most patients receiving MM were assessed as moderately ill (43.3%) by the physician. For social histories, 14.6% reported to be alcohol users, 10.5% reported to be tobacco smokers, and 4.8% reported to be illicit drug users. The cannabis type order at the initial visit was: 43.2% low-THC (n = 3,222), 34.9% MC (n = 2,600), and 21.9% LTHC+MC (n = 1,636). The most frequent planned duration of therapy ordered was one to three months (42.8%). The majority of MM providers were specialized or board certified in primary care (45.2%) followed by pain medicine and anesthesiology (19.0%) with more than one specialization reported per provider possible. Patient characteristics were similar across cannabis-type strata except for a larger proportion of patients in the MC group who self-identified as Hispanic (9.6%) or who were assessed as severely ill (11.5%). Patients in the LTHC+MC group differed by social history of alcohol use with the highest frequency reported (21.5%) and were more likely to receive a planned duration of therapy for 12 months or indefinitely (48.4%) compared with the other two groups.

The chief complaints indicated as qualifying medical conditions by the provider are summarized in Table 3. The specific medical conditions in each category are provided in the online Supplementary Table 1. Overall, the most frequent identified chief complaint was musculoskeletal disorders including spasms (44.8%), chronic

Table 2. Characteristics of Florida medical marijuana registry patients at the initial treatment visit by cannabis type ordered.

Characteristic, n (%)	Total	Cannabis type ordered: Low-THC cannabis	Medical cannabis (MC)	Both (LTHC+MC)	*p* value[†]
	(N = 7,548)	(n = 3,222)	(n = 2,600)	(n = 1,636)	
Age, *m* (SD)	52.3 (16.4)	53.1 (17.1)	51.5 (15.3)	52.0 (16.6)	.0009
< 18 years	128 (1.7)	80 (2.5)	***	38 (2.3)	
18–29 years	576 (7.7)	225 (6.9)	227 (8.7)	124 (7.6)	
30–49 years	2,307 (31.0)	225 (6.9)	227 (8.7)	124 (7.6)	
50–69 years	3,425 (45.9)	1,495 (46.4)	1,192 (45.9)	738 (45.1)	
≥ 70 years	1,022 (13.7)	505 (15.7)	289 (11.1)	228 (13.9)	
Race					<.0001
White	6,241 (83.7)	2,763 (85.8)	2,080 (80.0)	1,398 (85.5)	
Hispanic, Latino or Spanish	495 (6.6)	172 (5.3)	250 (9.6)	73 (4.5)	
Black	354 (4.8)	160 (5.0)	119 (4.6)	75 (4.6)	
Other/Unknown[‡]	368 (4.9)	127 (3.9)	151 (5.8)	90 (5.4)	
Patient condition assessed by provider					<.0001
Normal, not at all ill	331 (4.4)	156 (4.8)	155 (5.9)	20 (1.2)	
Borderline ill	171 (2.3)	84 (2.6)	67 (2.6)	20 (1.2)	
Mildly ill	1,019 (13.7)	449 (13.9)	464 (17.9)	106 (6.5)	
Moderately ill	3,226 (43.3)	1,576 (48.9)	863 (33.2)	787 (48.1)	
Markedly ill	1,934 (25.9)	738 (22.9)	689 (26.5)	507 (31.0)	
Severely ill	644 (8.6)	186 (5.8)	307 (11.8)	151 (9.2)	
Among the most extremely ill	133 (1.8)	33 (1.1)	55 (2.1)	45 (2.8)	
Social histories (Yes)					
Alcohol	1,090 (14.6)	401 (12.5)	337 (13.0)	352 (21.5)	<.0001
Smoking	783 (10.5)	337 (10.5)	255 (19.8)	191 (11.7)	.1545
Illicit drugs	360 (4.8)	145 (4.5)	123 (4.7)	92 (5.6)	.2165
Medical marijuana provider specialty (≥ 1 specialty per provider possible)					
Primary care[±]	3,369 (45.2)	1,136 (35.3)	1,177 (45.3)	1,056 (64.6)	<.0001
Pain medicine & anesthesiology	1,419 (19.0)	750 (23.3)	401 (15.4)	268 (16.4)	<.0001
Neurology & psychiatry	1,300 (17.4)	578 (17.9)	593 (22.8)	129 (7.9)	<.0001
Physical medicine & rehabilitation	284 (3.8)	219 (6.8)	41 (1.6)	24 (1.5)	<.0001
Other specialty[††]	1,132 (15.2)	452 (14.0)	368 (14.2)	312 (19.1)	<.0001
Not specified	544 (7.3)	313 (9.7)	175 (6.7)	56 (3.4)	<.0001
Planned treatment duration					
≤ 1 month	766 (10.3)	519 (16.1)	223 (8.9)	24 (1.5)	<.0001
1 to 3 months	3,194 (42.8)	1,232 (38.2)	1,363 (52.4)	599 (36.6)	
3 to 12 months	662 (8.9)	337 (10.5)	181 (7.0)	144 (8.8)	
> 12 months or indefinite	2,281 (30.6)	828 (25.7)	662 (35.5)	791 (48.4)	
Not specified	555 (7.4)	306 (9.5)	171 (6.6)	78 (4.8)	

MC = medical cannabis; LTHC+MC = both low-THC and medical cannabis
[†]Chi-squared tests used to calculate *p* values for categorical variables, ANOVA used to calculate *p* values for continuous variables
[‡]Includes Asian, Native Hawaiian, Pacific Islander, American Indian, and Alaska Native
[±]Includes family medicine, internal medicine, pediatrics, and osteopathic medicine
[††]Addiction medicine, age management medicine, emergency/critical care medicine, dermatology, gastroenterology, hematology, hospice and palliative care, infectious disease, obstetrics and gynecology, occupational therapy or medicine, oncology, ophthalmology, otolaryngology, pulmonary medicine, radiology, regenerative medicine, rheumatology, surgery, venous and lymphatic medicine
*** *low cell count < 11*

pain (41.9%), and mental health disorders excluding post-traumatic stress disorder (PTSD) (17.0%). These chief complaints were also the most frequently reported for the MC and LTHC+MC groups. However, the low-THC group had significantly lower prevalence of mental health disorders. Other frequently identified chief complaints for the total sample that were found to be prominent were spinal or neck conditions (14.9%), PTSD (14.1%), and cancer (11.7%).

Prescription medications

A summary of all prescription drug classes reported as concomitant medications by patients at the initial treatment visit is shown in Table 4 for the total sample. On average, all patients were reported to take 2.16 (interquartile range [IQR], 0–3) medications at the time of MM initiation. About one in four patients had concurrent use of prescription opioids including opioid-combination products (25.9%), which was the most frequently used drug class overall. A significant percentage were using psychiatric medications concurrently with anxiolytics including benzodiazepines (23.1%) and antidepressants (22.6%) accounting for the second and third most frequently used drug classes overall, respectively. Between the cannabis type groups, the top three most frequent concomitant medications were the same as the total sample for the low-THC and MC groups. However, the LTHC-MC group's

Table 3. Chief complaints reported by Florida medical marijuana registry patients at the initial treatment visit by cannabis type ordered.

Chief complaint†, n (%)	Total	Cannabis type ordered: Low-THC cannabis	Medical cannabis (MC)	Both (LTHC+MC)	*p* value‡
	(N = 7,548)	(n = 3,222)	(n = 2,600)	(n = 1,636)	
Musculoskeletal disorders & spasms	3,338 (44.8)	1,875 (58.2)	826 (31.8)	637 (38.9)	<.0001
Chronic pain	3,121 (41.9)	1,222 (37.9)	1,239 (47.7)	60 (40.3)	<.0001
Post-traumatic stress disorder (PTSD)	1,049 (14.1)	262 (8.1)	515 (19.8)	272 (16.6)	<.0001
Cancer	873 (11.7)	265 (8.2)	378 (14.5)	230 (14.1)	<.0001
Epilepsy or seizures	456 (6.1)	286 (8.9)	99 (3.8)	71 (4.3)	<.0001
Autoimmune disorders±	229 (3.1)	78 (2.4)	94 (3.6)	57 (3.5)	.0174
Multiple sclerosis (MS)	209 (2.8)	91 (2.8)	54 (2.1)	64 (3.9)	.0020
Parkinson's disease	209 (2.8)	105 (3.3)	54 (2.1)	50 (3.1)	.0195
Crohn's disease	135 (1.8)	40 (1.2)	42 (1.6)	53 (3.2)	<.0001
Glaucoma	101 (1.4)	27 (0.8)	49 (1.9)	25 (1.5)	.0022
Amyotrophic lateral sclerosis (ALS)	26 (0.4)	15 (0.5)	***	***	.2110
Other medical conditions indicated as a qualifying chief complaint					
Mental health disorders (excl. PTSD)	1,264 (17.0)	369 (11.5)	529 (20.4)	366 (22.4)	<.0001
Spinal or neck conditions	1,108 (14.9)	612 (19.0)	342 (13.2)	154 (9.4)	<.0001
Headaches or migraines	780 (10.5)	358 (11.1)	291 (11.2)	131 (8.0)	.0012
Nervous system & neurological disorders	701 (9.4)	255 (7.9)	243 (9.4)	203 (12.4)	<.0001
Sleep disorders	554 (7.4)	156 (4.8)	216 (8.3)	182 (11.1)	<.0001
Gastrointestinal conditions	380 (5.1)	112 (3.5)	169 (6.5)	99 (6.1)	<.0001
Major brain & head injuries	330 (4.4)	122 (3.8)	128 (4.9)	80 (4.9)	.0650
Others	79 (1.1)	19 (0.6)	41 (1.6)	19 (1.2)	.011

MC = medical cannabis; LTHC+MC = both low-THC and medical cannabis
†Chief complaints are not mutually exclusive; more than one condition per patient possible
‡Chi-squared tests used to calculate *p* values
±Including HIV/AIDS; excluding MS and Crohn's disease
*** *low cell count < 11*

most frequent medications were anxiolytics/benzodiazepines (24.5%), antidepressants (24.2%), and cardiovascular agents (23.5%). For the total sample, other prescription drugs that were reported with high frequencies were: cardiovascular agents (20.5%), non-opioid analgesics (17.4%), anticonvulsants (17.2%), skeletal muscle relaxants (14.5%), and hormonal agents and steroids (10.8%).

Follow-up data

At the first follow-up encounter for 2,075 patients, the 50–69 years age group remained the most frequent (46.9%) while white race increased to 88.9%. Compared to the patient condition assessed at the initial visit, over 40% were assessed by the provider with a condition score of much improved or very much improved. There were 25.8% patients assessed as unchanged and less than 3.0% were worse following initiation of MM. The majority of MM providers remained as most likely to be specialized in primary care (44.1%) followed by pain medicine and anesthesiology (17.2%). Almost 10% of patients reported changes in their chief complaint and 9.8% reported changes in concomitant medication use. A summary of the follow-up data is provided in the online Supplementary Table 2 for the total sample as cannabis type ordered was not collected at follow-up. In free-text entries recorded by the physician, there were notable instances of reported reductions in prescription drug use since the IT visit. In particular, reductions or complete cessation of opioid medications were reported as well as reductions of anxiolytics/benzodiazepines and hypnotics/sedatives, although we were unable to quantify the explicit number of patients who experienced these specific changes as providers inconsistently reported this information. A 10% sample of quotations of provider entries describing changes in medication use and changes in chief complaint at follow-up are provided in the online Supplementary Table 3. We found 5.0% of patients had reported discontinuation of MM use and 1.7% reported indicators of a reaction to cannabis. Indicators of reaction to cannabis was defined on the FUT form as adverse drug reactions, patient-reported problems, medication holds, emergency room visits, or hospitalizations associated with use of cannabis. There were 3.1% reported hospitalizations since last visit, but we were unable to

Table 4. All concomitant prescription medication classes reported to be used by Florida medical marijuana registry patients at the initial treatment visit.

		Cannabis type ordered			
Medication class[†], n (%)	Total	Low-THC cannabis	Medical cannabis (MC)	Both (LTHC+MC)	*p* value[‡]
	(N = 7,548)	(n = 3,222)	(n = 2,600)	(n = 1,636)	
# of medications per patient, *m* (SD), IQR	2.16 (2.4), 0–3	2.47 (2.4), 1–4	1.78 (2.3), 0–3	2.18 (2.4), 0–4	<.0001
Psychiatric medications					
Antidepressants	1,684 (22.6)	814 (25.3)	474 (18.2)	396 (24.2)	<.0001
Anxiolytics/benzodiazepines	1,721 (23.1)	839 (26.0)	481 (18.5)	401 (24.5)	<.0001
Hypnotics/sedatives	443 (5.9)	223 (6.9)	104 (4.0)	116 (7.1)	<.0001
Antipsychotics	270 (3.6)	113 (3.5)	105 (4.0)	52 (3.2)	.1874
Stimulants	266 (3.6)	123 (3.8)	76 (2.9)	67 (4.1)	.1922
Mood stabilizers	121 (1.6)	62 (1.9)	37 (1.4)	37 (1.4)	.1943
Pain medications					
Opioids[±]	1,929 (25.9)	1,108 (34.4)	519 (20.0)	302 (18.5)	<.0001
Non-opioid analgesics	1,299 (17.4)	620 (19.2)	409 (15.7)	270 (16.5)	.0020
Musculoskeletal medications					
Skeletal muscle relaxants	1,079 (14.5)	585 (18.2)	302 (11.6)	192 (11.7)	<.0001
Other musculoskeletal agents[††]	195 (2.6)	87 (2.7)	54 (2.1)	54 (3.3)	.0481
Neurological medications					
Anticonvulsants	1,285 (17.2)	708 (22.0)	327 (12.6)	250 (15.3)	<.0001
Anti-Parkinson	180 (2.4)	99 (3.1)	44 (1.7)	32 (2.3)	.0133
Other neurological agents[±±]	111 (1.5)	61 (1.9)	29 (1.1)	21 (1.3)	.0381
Other classes					
Cardiovascular agents	1,525 (20.5)	694 (21.5)	447 (17.2)	384 (23.5)	<.0001
Hormonal agents & steroids	807 (10.8)	370 (11.5)	237 (9.1)	200 (12.2)	.0018
Others incl. over-the-counter medications	747 (7.5)	233 (7.2)	181 (7.0)	148 (9.1)	.0557
Antiemetics	345 (4.6)	181 (5.6)	92 (3.5)	72 (4.4)	.0020
Antidiabetic agents	340 (4.6)	149 (4.6)	100 (3.9)	91 (5.6	.0325
Other GI agents	317 (4.3)	153 (4.8)	91 (3.5)	73 (4.5)	.0566
Genitourinary agents	299 (4.0)	130 (4.0)	101 (3.9)	68 (4.2)	.9037
Vitamins & supplements	262 (3.5)	124 (3.9)	77 (3.0)	61 (3.7)	.1631
Respiratory agents	253 (3.4)	121 (3.8)	68 (2.6)	64 (3.9)	.0243
Chemotherapeutic agents	145 (1.9)	56 (1.7)	50 (1.9)	39 (2.4)	.3037
Hematologic agents	142 (1.9)	65 (2.0)	35 (1.4)	42 (2.6)	.0149
Autoimmune agents	111 (1.5)	44 (1.4	31 (1.2)	36 (2.2)	.0230
Antivirals incl. HIV medications	114 (1.5)	41 (1.3)	37 (1.4)	36 (2.2)	.3240
Anti-infective agents	98 (1.3)	36 (1.1)	31 (1.2)	31 (1.9)	.0635
Ophthalmic & glaucoma medications	58 (0.8)	28 (0.9)	19 (0.7)	11 (0.7)	.7198

SD = standard deviation, IQR = interquartile range; [†]Medications are not mutually exclusive, more than one medication per patient possible; [‡]Chi-squared tests used to calculate *p* values; [±]Includes combination products containing an opioid; [††]Includes medications for multiple sclerosis; [±±]Includes triptans and medications for Alzheimer's disease

determine if a hospitalization was due to MM use, the patient's chief complaint, or another medical event. There were 1.5% of patients who reported changes in comorbidities since the previous visit.

Discussion

This retrospective analysis of MM treatment forms covering the initial implementation phase of Florida's MM program provides characteristics and prescription drug utilization information on early registrants who sought treatment with medical cannabis. The majority of registry patients were aged 50 years and older and had a slightly higher representation of older adults compared to Florida's overall population (United States Census Bureau 2019). These findings differ from previous studies finding a lower mean age and age range of MM registry patients, although this may be attributable to demographic variations in the states studied (Boehnke et al. 2019a; Bonn-Miller et al. 2014; Freisthler and Gruenewald 2014; Ilgen et al. 2013; Nunberg et al. 2011; Nussbaum, Boyer, and Kondrad 2011; Reiman 2007; Reinarman et al. 2011; Troutt and DiDonato 2015; Walsh et al. 2013; Zaller et al. 2015). Our results are similar to other studies that found MM is used predominantly among white Americans and less likely among minority groups (Bonn-Miller et al. 2014; Ilgen et al. 2013; Nunberg et al. 2011; Reiman 2007; Walsh et al. 2013; Zaller et al. 2015). However, we recognize that our sample had high proportions of patients with chronic pain, a condition that tends to be more prevalent in healthcare settings among whites compared with minorities (Dahlhamer et al. 2018).

The most frequent chief complaints for seeking MM indicate that the majority of patients presented with musculoskeletal and spasticity-related conditions followed by chronic pain and mental health disorders. This is consistent with previous studies of MM registrants that have found chronic pain is the most common medical condition, followed by musculoskeletal conditions, spasticity-related symptoms, anxiety, depression, and PTSD (Ilgen et al. 2013; Nunberg et al. 2011; Reiman 2007; Reinarman et al. 2011; Troutt and DiDonato 2015; Zaller et al. 2015). Most recently, an analysis of over 20 MM state registries found that chronic pain, multiple sclerosis spasticity symptoms, chemotherapy-induced nausea and vomiting, PTSD, and cancer have historically been the most common qualifying conditions (Boehnke et al. 2019a). In contrast, Florida registry patients had a lower representation of cancer and gastrointestinal-related chief complaints. Collectively, the reported frequency of mental health disorders combined with PTSD represents almost one-third of our overall sample (31.1%). Given the limited evidence on both safety and efficacy of MM for psychiatric conditions, reports of varying treatment responses and reports of severe psychosis, there is an urgent need for research examining the effect of cannabis on prevalent mental health conditions (Hindocha et al. 2019; Kansagara et al. 2017; Lim, See, and Lee 2017; O'neil et al. 2017).

We observed frequent utilization of prescription opioids, anxiolytics including benzodiazepines, and antidepressants at the time of MM initiation, consistent with the most frequent medical complaints. A study in Canada by Lucas and Walsh found that MM patients reported using medical cannabis to replace medications with the highest reported drugs being opioids, benzodiazepines, and antidepressants (Lucas and Walsh 2017). While our study did not investigate medication substitution, our findings on the top three most frequently reported drug classes used by our sample were identical to those reported by the Canadian study and other studies (Boehnke et al. 2019b; Corroon, Mischley, and Sexton 2017; Piper et al. 2017). Furthermore, our findings show opioids were used the most frequently by our sample, which raises the possibility that switching to MM is an attempt to decrease use of these medications as suggested by some providers' responses to medication changes at follow-up. This is supported by studies finding that patients can decrease opioid, anxiolytic, and hypnotic utilization when using MM (Piper et al. 2017; Reiman, Welty, and Solomon 2017; Stith et al. 2018). The high usage of opioids echoes the responses by several states in changing MM laws to allow cannabis as a substitute for opioids (IL), for a qualifying condition of opioid use disorder (NJ, NM, NY, PA) or for a qualifying condition of a substance use disorder (ME) (Maine Legislature 2019; New Mexico Department of Health 2020; Shover et al. 2020; Voelker 2018). However, recent systematic reviews have concluded that there is insufficient evidence for the appropriateness of cannabis as a substitute for opioids (Hill et al. 2017; Mücke et al. 2018; National Academy of Sciences 2017).

Concomitant prescription drug use was frequent and many of the medication classes frequently used by our sample are implicated in pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions (Macdonald and Adams 2019). For example, medications that were reported by patients that are implicated in DDIs with drug-metabolizing enzymes include amitriptyline, bupropion, buprenorphine, hydrocodone, montelukast, clopidogrel, propranolol, simvastatin, warfarin, and zonisamide (Brown 2020; Qian, Gurley, and Markowitz 2019). The large proportions of reported use of opioids and central nervous system (CNS) agents supports the need for more research on potential PK/PD interactions with cannabis, particularly among older adults for whom polypharmacy is common (Abuhasira et al. 2018). There is substantial evidence that THC has psychoactive properties and other studies have found that both THC and CBD are substrates and inhibitors of CYP450 enzymes which are directly related to the pathways of many psychotropic agents (Brown and Winterstein 2019; National Academy of Sciences 2017; Rong et al. 2018). The biological effects of cannabis can be potentiated when used concomitantly with medications that have similar effects, such as anxiolytics, which were used by more than one-fifth of our total sample (Brown and Winterstein 2019). Additionally, other medication classes that act on the CNS that were frequently reported, anticonvulsants and skeletal muscle relaxants, can influence PK and PD profiles of cannabinoids (Macdonald and Adams 2019). Lastly, the high frequency of cardiovascular agents presents potential clinical complications and drug-disease interactions including increased risk of cardiac toxicity (DeFilippis et al. 2020). While we were unable to evaluate patient comorbidities, the reported use of cardiovascular agents by one-fifth (20.5%) of the sample implies a large proportion of cardiovascular-related comorbidities. There is definitive evidence on how cannabinoids affect cardiovascular function and the available evidence discourages cannabis use by patients at high-risk for cardiovascular events (DeFilippis et al. 2020; Franz and Frishman 2016).

It is worth noting that most of the high-quality evidence available has been extrapolated from FDA-approved synthetic cannabinoids which cannot be generalized to that of vaporized cannabis, one of the most common ROAs employed by our sample at the time of data collection. Additionally, the current literature on DDIs is heterogenous in terms of the specific contents of

cannabinoid compounds analyzed, varying ROAs, and differences in clinical populations (Qian, Gurley, and Markowitz 2019). This is a significant research gap considering smoked cannabis can induce certain CYP450 enzymes while vaporized cannabis can yield a pronounced PD effect compared to smoked cannabis (Macdonald and Adams 2019). There is an urgent need for more research on therapeutic dosing of cannabinoid compounds, the magnitude and clinical significance of PK/PD interactions, and assessments of ROAs, particularly in light of the recent concerns about safety risks associated with vaping-related lung injuries as a result of limited requirements for compliance with good manufacturing practices as mandated for drug products (CDC 2020; Qian, Gurley, and Markowitz 2019).

Over one-fourth of FUT forms were available, which were mostly characterized by improvements in chief complaints and reported reductions in prescription drug use. There were small proportions of patients discontinuing cannabis use (5.0%) and reports of any type of reaction to cannabis (1.7%). It should be noted that the statutory-related discontinuation of treatment plan collection inhibited the distinction between patients who discontinued therapy and did not follow-up versus those who had their follow-up visit after the end of our study. Thus, positive results may not be generalizable to all MM initiators nor may the negative effects reported by the small proportion of patients. Moreover, given the lack of a comparison group, some changes in patients' conditions and prescription drug use would have occurred regardless of MM use, as a result of a placebo effect, or due to the natural course of the underlying disease (Russo 2016). Recent statutory changes have established the Consortium for Medical Marijuana Clinical Outcomes Research (Consortium) and include a mandate for the Florida Department of Health, which collects MM orders and dispensing information, to share such information with the Consortium for research purposes. Linkage of such information with medical record data will provide an excellent platform to provide critical evidence on MM use and outcomes, but provision of such data to the Consortium is pending. Given the limited evidence that is currently available on medical cannabis effectiveness and safety, controlled studies are needed to put treatment effects into appropriate context and to provide complete information for a risk-benefit assessment and clinical and policy decision-making.

The study was limited by some features of the dataset that may have affected the reliability and overall quality of the results. Many data elements were entered in a free text format which required extensive manual extraction. Some information was self-reported by the patient without verification with medical records, and the treatment form submission date provided was not necessarily the same as the visit date due to the legislation only requiring quarterly submission of the treatment plans. Uncertainty about the actual visit date precluded analyses in the context of active legislation considering the various expansions of permissible qualifying medical conditions and type of cannabis that could be ordered. Finally, positive findings must be interpreted with caution considering the lack of a control group and the possible dilution of our sample with individuals whose intent was to gain access to cannabis for recreational use rather than medicinal use.

Florida MM registry patients initiated MM for a broad range of conditions mainly characterized by musculoskeletal and spastic symptoms, pain, and mental health conditions. Almost one quarter used prescription opioids and other psychotropic medications, one-fifth used cardiovascular agents, and a considerable proportion used anticonvulsants and skeletal muscle relaxants. Though follow-up information was only available for a fraction of patients, follow-up was mostly characterized by clinical improvements and reported reductions in some prescription medication classes.

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Data availability statement

data are not available due to legal restrictions.

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