Characteristics of Older Adults Who Were Early Adopters of Medical Cannabis in the Florida Medical Marijuana Use Registry

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Abstract: Use of medical marijuana is increasing in the United States and older adults are the fastest growing user group. There is little information about the characteristics and outcomes related to medical marijuana use. This study is a descriptive analysis of older adults (aged ≥50 years old) who were early adopters of a medical marijuana program in the U.S. state of Florida. Per state legislation, initial and follow-up treatment plans were submitted to the University of Florida College of Pharmacy. Data collection included demographics, clinical history, medical conditions, substance use history, prescription history, and health status. Follow-up treatment plans noted changes in the chief complaint and actions taken since the initial visit. Of the state’s 7548 registered users between August 2016 and July 2017, \( N = 4447 \) (58.9%) were older adults. Patients utilized cannabidiol (CBD)-only preparations (45%), preparations that had both tetrahydrocannabinol (THC) and CBD (33.3%) or were recorded to use both CBD-only and THC + CBD products (21.7%). The chief complaints indicating medical cannabis treatment were musculoskeletal disorders and spasms (48.4%) and chronic pain (45.4%). Among other prescription medications, patients utilized antidepressants (23.8%), anxiolytics and benzodiazepines (23.5%), opioids (28.6%), and cardiovascular agents (27.9%). Among all drug classes with potential sedating effects, 44.8% of the cohort were exposed to at least one. Patients with follow-up visits (27.5%) exhibited marked improvement as assessed by the authorizing physicians. However, the patient registry lacked detailed records and linkable information to other data resources to achieve complete follow up in order to assess safety or efficacy. Future improvements to registries are needed to more adequately capture patient information to fill knowledge gaps related to the safety and effectiveness of medical marijuana, particularly in the older adult population.

Keywords: medical marijuana; cannabis; cannabidiol; CBD; THC; tetrahydrocannabinol; older adults; safety; effectiveness

1. Introduction

Cannabis use is increasing among medically complex individuals. The vast majority of cannabis use is recreational; however, there is an increasing number of adults who use cannabis and cannabis-derived substances for medical and complementary health purposes. Increased use corresponds with expanding
access through state medical cannabis programs, broad consumer marketing and use of cannabidiol (CBD) products. There is a continued increase in public support of legalization at the individual state level, whereas cannabis remains illegal (i.e., Schedule 1) at the national level [1–3]. State programs range from what is deemed a “comprehensive” program that allows both CBD and tetrahydrocannabinol (THC) use (N = 33 states), programs that restrict the amount of THC allowed and promote CBD-only products (N = 13 states), and four states (ID, SD, NE, KS) which have no program in place [1]. Currently, 11 states have also legalized recreational cannabis for use by adults [1]. Florida was the 22nd state in the U.S. to legalize access to medical marijuana—the third largest state with one of the largest and fastest growing populations of older adults.

In 2018, state-based medical cannabis programs were estimated to include over 2.1 million legal medical cannabis patients. Enrollment in these programs varies by state, with a range of 1 to >38 patients per 1000 residents [4]. Medical cannabis users represent approximately 10% of adult cannabis users [5]. Practically all state programs have specified conditions for which medical cannabis can be used. These conditions include epilepsy/seizures, chronic pain, nausea/vomiting, muscle spasms, inflammatory conditions, Alzheimer’s disease, Parkinson’s disease, and cancer [1]. These conditions are highly prevalent among older adults who are likely to have complex medical profiles and pharmacotherapeutic regimens [6–10]. A recent national survey reported increased odds of about 50% for past year marijuana use among patients with history of stroke, heart disease, asthma, chronic pulmonary disease, diabetes, arthritis, renal disease, cancer, and depression among medical cannabis users [11].

The Baby Boomer generation (~55–75 years old), which represents the fastest growing segment of the population in terms of substance use and abuse in general, are more likely to be comfortable with cannabis use compared to their parents’ generation due to social or personal exposure earlier in life [12,13]. Data from the period 2006–2013 suggest a 250% increase in cannabis use among those 65+ and nearly a 60% increase among those 50–64 years old—numbers that are likely to have increased as more states legalize medical and recreational cannabis programs [9]. Prevalence estimates of cannabis use in the past year for these age groups are approximately 3% and 9%, respectively [14]. Among older adults, 75% consider cannabis use to have no or only slight health risks if used once or twice a week [14]. Thus, it appears that older adults regard cannabis as generally safe and are rapidly adopting cannabis into their health and medical regimens.

This study described the characteristics of older adult patients, aged ≥50 years old, who were licensed to use medical marijuana during the early implementation period of the Florida medical marijuana program between 2016 and 2017 and followed these individuals from treatment initiation to the point of a follow-up encounter.

2. Methods

This was a retrospective analysis of initial and follow-up treatment plan forms electronically submitted by providers to the University of Florida College of Pharmacy (UF-COP) between 01 August 2016 and 31 July 2017. The forms were created to meet the Compassionate Medical Cannabis Act (CCA) statutory requirements by a team of outcomes researchers, health policy experts and physicians and pharmacists with expertise in psychiatry, neurology, and pain medicine. The authorizing physician completed the initial and follow-up treatment plans and submitted the forms electronically via a secured portal maintained by the UF-COP. The forms received covered visit dates during the period in which CBD-only cannabis was available associated with the 2014 CCA legislation as well as a period of time when the Amendment 2 legislation was approved, but not yet fully implemented.

The data elements collected on the initial treatment plan forms are the date of treatment plan submission and information on the patient, provider, and the cannabis order. All treatment forms were automatically de-identified upon electronic submission. For each patient, a unique registry identification number was generated for longitudinal tracking. Patient data collected were demographics (i.e., age, race/ethnicity), clinical history, medical conditions, history of substance use (i.e., alcohol, tobacco, illicit
drugs), prescription medication history, and a patient’s health condition score assessed by the provider on a scale of 1–7 which is based on the Clinical Global Impression Severity Scale [15]. The clinical history included the indication or indications for cannabis treatment, herein referred to as the chief complaint. For the cannabis order, information covered the date of order, the dosing regimen, the type of cannabis (CBD-only, THC + CBD, or both types of products), the planned duration, the treatment plan goal and the plan for monitoring of patient’s symptoms, and a planned follow-up encounter date.

Data collected on the follow-up treatment form include the patient’s registry identification number, the date of treatment plan submission, the date of last patient encounter, changes in the cannabis order since last treatment plan, changes in the chief complaint, hospitalization history since last treatment plan, changes in the patient’s comorbidities or current medications since last treatment plan, indicators of tolerance or reaction to cannabis, discontinuation of cannabis use during the last quarter, and the provider’s assessed patient condition score compared with the initial condition on a scale of 1–7.

We analyzed all electronically submitted forms of registry patients aged 50 to 100 years who attended at least an initial visit. Forms were excluded when providers submitted blank forms and when data entries were erroneous or invalid. Free-text data entries, such as chief complaints, medical treatments, and planned treatment duration were manually reviewed and summarized into clinically meaningful categories. Chief complaint categories were based on the medical conditions listed in the current law and on broader disease categories found to be prominent. Categories for medications were determined by therapeutic classifications that were found to be prominent. The planned treatment duration was categorized into appropriate time intervals determined by all possible entries.

Data Analysis

We calculated descriptive statistics of patient and treatment characteristics and examined frequency counts, sample means, and proportions. Analyses were conducted with SAS version 9.4 statistical software (SAS Institute Inc, Cary, NC, USA). 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.

3. Results

There were $N = 4447$ older adults registered in Florida’s medical marijuana treatment registry of a total of 7548 registered (Table 1). Of these, 2662 (59.9%) were 50–64, 1238 (27.8%) were 65–74, and 547 (12.3%) were 75 years old or older. Registered users were predominantly of white race (87.5%). Physician-assessed conditions indicated that most patients were moderately ill or worse and low-THC cannabis (i.e., CBD) was the most common treatment choice (45%) compared to medical cannabis (33.3%) or a combination of the two (21.7%). Most patients were given a planned duration of treatment of 12 months or less.

Chief complaints indicating medical marijuana use were primarily related to pain including musculoskeletal disorders, spasms, and chronic pain (Table 2). Cancer was indicated for 15.5% of all patients. Non-pain-related conditions included epilepsy or seizures (2.9%), glaucoma (2%), autoimmune disorders (3.2%) post-traumatic stress disorder (10%), multiple sclerosis (2.7%), Parkinson’s disease (4.5%), amyotrophic lateral sclerosis (ALS; 0.5%) and Crohn’s disease (1.2%). Psychological disorders were prevalent in 13.2% of patients and post-traumatic stress disorder in an additional 10%. These chief complaints were not mutually exclusive, and providers could have identified more than one per patient. Other conditions, such as sleep disorders (7%) and headaches or migraines (10.4%), were also common.
Table 1. Characteristics of Florida medical marijuana registry patients at the initial treatment visit by cannabis type ordered.

| Characteristic, N (%) | Total (N = 4447) | 50–64 Years (N = 2662) | 65–74 Years (N = 1238) | 75+ Years (N = 547) |
|-----------------------|------------------|------------------------|------------------------|---------------------|
| **Age, mean (SD)**    |                  |                        |                        |                     |
| 50–64 Years (N = 2662)| 63.4 (9.17)      | 57.3 (4.17)            | 68.8 (2.71)            | 80.9 (5.37)         |
| 65–74 Years (N = 1238)|                  |                        |                        |                     |
| 75+ Years (N = 547)   |                  |                        |                        |                     |
| **Race**              |                  |                        |                        |                     |
| White                 | 3893 (87.5)      | 2290 (86.0)            | 1115 (90.1)            | 488 (89.2)          |
| Black                 | 157 (3.5)        | 118 (4.4)              | 29 (2.3)               | ***                 |
| Hispanic, Latino or Spanish | 203 (4.6)  | 121 (4.6)              | 52 (4.2)               | 30 (5.5)            |
| Other/Unknown †       | 194 (4.4)        | 133 (5.0)              | 42 (3.4)               | 19 (3.5)            |
| **Patient condition assessed by provider** |                  |                        |                        |                     |
| Normal, not at all ill| 195 (4.4)        | 111 (4.1)              | 61 (4.9)               | 23 (4.2)            |
| Borderline ill        | 99 (2.2)         | 59 (2.2)               | 20 (1.6)               | 20 (3.7)            |
| Mildly ill            | 588 (13.2)       | 359 (13.5)             | 167 (13.5)             | 60 (13.4)           |
| Moderately ill        | 1909 (42.9)      | 1150 (43.2)            | 512 (41.4)             | 247 (45.1)          |
| Markedly ill          | 1156 (26.0)      | 715 (26.9)             | 317 (25.6)             | 124 (22.7)          |
| Severely ill          | 412 (9.3)        | 224 (8.4)              | 130 (10.5)             | 58 (10.6)           |
| Among the most extremely ill | 88 (2.0) | 44 (1.7)               | 31 (2.5)               | 13 (2.4)            |
| **History of substance use** |                  |                        |                        |                     |
| Alcohol               | 628 (14.1)       | 406 (15.3)             | 160 (12.9)             | 62 (11.3)           |
| Smoking               | 444 (10.0)       | 323 (12.1)             | 202 (8.2)              | 20 (3.7)            |
| Illicit drugs         | 162 (3.6)        | 118 (4.4)              | 42 (3.4)               | ***                 |
| **Cannabis type ordered ‡** |                  |                        |                        |                     |
| Medical cannabis      | 1481 (33.3)      | 926 (34.8)             | 409 (33.1)             | 146 (26.7)          |
| Low-THC cannabis      | 2000 (45.0)      | 1172 (44.0)            | 534 (43.1)             | 294 (53.7)          |
| Both low-THC and medical cannabis | 966 (21.7) | 564 (21.2)             | 295 (23.8)             | 107 (19.6)          |
| **Planned order duration** |                  |                        |                        |                     |
| <1 month              | 469 (10.6)       | 288 (10.8)             | 110 (8.9)              | 71 (13.0)           |
| 1–3 months            | 1919 (43.2)      | 1209 (45.4)            | 515 (41.6)             | 195 (35.7)          |
| 3–12 months           | 382 (8.6)        | 238 (8.9)              | 109 (8.8)              | 35 (6.4)            |
| >12 months or indefinitely | 1343 (30.2) | 739 (27.8)             | 406 (32.8)             | 198 (36.2)          |
| Not specified         | 334 (7.5)        | 188 (7.1)              | 98 (7.9)               | 48 (8.8)            |

† Includes Asian, Native Hawaiian, Pacific Islander, American Indian, or Alaska Native. SD = standard deviation. ‡ Medical cannabis not explicitly defined by Florida law. Low-THC cannabis defined by Florida law as “containing no more than 0.8 percent of tetrahydrocannabinol (THC) and at least 10 percent of cannabidiol (CBD)”. *** cell count ≤ 10.
Table 2. Characteristics of Florida medical marijuana registry patients at the initial treatment visit by cannabis type ordered.

| Chief Complaint†, N (%) | Age Group |
|-------------------------|-----------|
|                         | Total (N = 7548) | 50–64 Years (N = 2662) | 65–74 Years (N = 1238) | 75+ Years (N = 547) |
| **Musculoskeletal disorders and spasms** | 2154 (48.4) | 1348 (50.6) | 534 (43.1) | 272 (49.7) |
| **Cancer** | 691 (15.5) | 350 (13.2) | 235 (19.0) | 106 (19.4) |
| **Epilepsy or seizures** | 130 (2.9) | 93 (3.5) | 30 (2.4) | *** |
| **Glaucoma** | 87 (2.0) | 41 (1.5) | 30 (2.4) | 16 (2.9) |
| **Autoimmune or immune disorders±** | 142 (3.2) | 104 (3.9) | 29 (2.3) | *** |
| **Post-traumatic stress disorder (PTSD)** | 444 (10.0) | 298 (11.2) | 136 (11.0) | *** |
| **Amyotrophic lateral sclerosis (ALS)** | 24 (0.5) | *** | *** | *** |
| **Crohn’s disease** | 52 (1.2) | 33 (1.2) | 15 (1.2) | *** |
| **Parkinson’s disease** | 201 (4.5) | 51 (1.9) | 92 (7.4) | 58 (10.6) |
| **Multiple sclerosis (MS)** | 121 (2.7) | *** | *** | *** |
| **Chronic pain** | 2019 (45.4) | 1242 (46.7) | 520 (42.0) | 257 (47.0) |
| **Back, spine, or neck conditions** | 696 (15.7) | 475 (17.8) | 147 (11.9) | 74 (13.5) |
| **Major brain and head injuries** | 149 (3.4) | *** | *** | *** |
| **Gastrointestinal conditions** | 225 (5.1) | 137 (5.2) | 69 (5.6) | 19 (3.5) |
| **Headaches or migraines** | 461 (10.4) | 318 (12.0) | 93 (7.5) | 50 (9.1) |
| **Other nervous system and neurological disorders** | 486 (10.9) | 269 (10.1) | 123 (9.9) | 94 (17.2) |
| **Psychological disorders (excl. PTSD)** | 589 (13.2) | 376 (14.1) | 158 (12.8) | 55 (10.1) |
| **Sleep disorders** | 310 (7.0) | 199 (7.5) | 82 (6.6) | 29 (5.3) |
| **Others** | 35 (0.8) | *** | *** | *** |

† Chief complaints are not mutually exclusive; more than one condition per patient possible. ± Including HIV/AIDS; excluding MS and Crohn’s disease. *** Data suppressed due to low cell count < 11.

On average, registered patients used approximately 2.5 other medications with medians of 3 (interquartile range 0–4) for all age groups (Table 3). With regards to concomitant medication use, more than 20% of all patients utilized antidepressants (23.8%), anxiolytics and benzodiazepines (23.5%), opioids (28.6%), and cardiovascular agents (27.9%). Among all drug classes with potential sedating effects, 44.8% of the cohort were exposed to at least one.
Table 3. All concomitant prescription medication classes reported to be used by Florida medical marijuana registry patients at the initial treatment visit †.

| Medication Class, N (%) | Total (N = 4447) | 50–64 Years (N = 2662) | 65–74 Years (N = 1238) | 75+ Years (N = 547) |
|------------------------|-----------------|------------------------|------------------------|-------------------|
| Number of medications per patient, mean (SD), IQR | 2.4 (2.54), 3 (0–4) | 2.4 (2.52), 3 (0–4) | 2.4 (2.57), 3 (0–4) | 2.3 (2.58), 3 (0–4) |
| Antidepressants | 1060 (23.8) | 670 (25.2) | 289 (23.4) | 101 (18.5) |
| Antipsychotics | 128 (2.9) | 82 (3.1) | 35 (2.8) | 11 (2.0) |
| Anxiolytics and benzodiazepines | 1046 (23.5) | 674 (25.3) | 285 (23.0) | 87 (15.9) |
| Mood stabilizers | 37 (0.8) | *** | *** | *** |
| Stimulants and amphetamines | 124 (2.8) | *** | *** | *** |
| Hypnotics and sedatives | 292 (6.6) | 168 (6.3) | 98 (7.9) | 26 (4.8) |
| Opioids § | 1271 (28.6) | 863 (32.4) | 296 (23.9) | 112 (20.5) |
| Non-opioid analgesics | 861 (19.4) | 512 (19.2) | 229 (18.5) | 120 (21.9) |
| Skeletal muscle relaxants | 611 (13.7) | 458 (17.2) | 127 (10.3) | 26 (4.8) |
| Other musculoskeletal agents †† | 133 (3.0) | 73 (2.7) | 38 (3.1) | 22 (4.0) |
| Anticonvulsants and antiepileptics | 760 (17.1) | 496 (18.6) | 176 (14.2) | 88 (16.1) |
| Anti-Parkinson | 162 (3.6) | 58 (2.2) | 69 (5.6) | 35 (6.4) |
| Other neurological agents ±± | 71 (1.6) | 39 (1.5) | 21 (1.7) | 11 (2.0) |
| Antiemetics | 200 (4.5) | 128 (4.8) | 56 (4.5) | 16 (2.9) |
| Other GI agents | 217 (4.9) | 135 (5.1) | 58 (4.7) | 24 (4.4) |
| Cardiovascular agents | 1241 (27.9) | 623 (23.4) | 417 (33.7) | 201 (36.8) |
| Antidiabetic agents | 271 (6.1) | 147 (5.5) | 92 (7.4) | 32 (5.9) |
| Hematologic agents | 126 (2.8) | 52 (2.0) | 51 (4.1) | 23 (4.2) |
| Hormonal agents and steroids | 596 (13.4) | 319 (12.0) | 198 (16.0) | 79 (14.4) |
| Genitourinary agents | 264 (5.9) | 99 (3.7) | 100 (8.1) | 65 (11.9) |
| Respiratory agents | 181 (4.1) | 90 (3.4) | 60 (4.9) | 31 (5.7) |
| Chemotherapeutic agents | 102 (2.3) | *** | *** | *** |
| Autoimmune agents | 75 (1.7) | *** | *** | *** |
| Antivirals incl. HIV medications | 40 (0.9) | *** | *** | *** |
| Anti-infective agents | 50 (1.1) | *** | *** | *** |
| Ophthalmic and glaucoma medications | 51 (1.2) | 17 (0.6) | 18 (1.5) | 16 (2.9) |
| OTC medications, vitamins, supplements and others | 348 (8.2) | 204 (7.6) | 111 (9.0) | 48 (8.8) |

SD = standard deviation; IQR = interquartile range. † Medications are not mutually exclusive, more than one medication per patient possible. § Includes combination products containing an opioid; †† Includes medications for multiple sclerosis. ±± Includes triptans and medications for Alzheimer’s disease. *** Data suppressed due to low cell count < 11.

Of the 4447 with an initial visit, only 1225 (27.5%) of patients had a second visit treatment plan recorded (Table 4). The majority (72.7%) of patients were recorded to have an improved chief complaint with less than 3% with a worsened complaint. In open response feedback, available for only 85 visits, physicians noted several instances of reduced medication use since initiation of medical marijuana. Noteworthy, were mentions of reduced or stopped opioid medications, improved sleep quality, reduction of medications for sleep, and reduced anxiety medications. Adverse effects were also noted in 16 entries, which included hallucinations, respiratory side effects due to vaped products, sedation or “loopy” feelings, and worsened insomnia. Further, 33 entries were noted in patients who discontinued medical marijuana, which primarily noted inability to afford treatment, preference to not travel with a potentially illegal product, and ineffective treatment. Free text submissions are shown in the Appendix A Figures A1–A4.
Table 4. Summary of the follow-up information reported by Florida medical marijuana registry patients at a follow-up visit after treatment initiation for total follow-up sample.

| Follow-Up Question Since Last Treatment Visit | Yes (%) |
|----------------------------------------------|---------|
| Changes in chief complaint since last visit? | 10.0%   |
| Changes in alcohol, smoking, or illicit drug use since last visit? † | 1.4%    |
| Changes in comorbidities since last visit? | 1.7%    |
| Hospitalizations since last visit? | 2.9%    |
| Changes in current medications since last visit? | 10.0%   |
| Were there indicators of reaction to cannabis since last visit? ‡ | 2.0%    |
| Did the patient discontinue cannabis use? | 4.6%    |

| Patient Condition Since the Initiation of Treatment Compared to Condition Initially Assessed |
|-----------------------------------------------|
| Very much improved | 10.8% |
| Much improved | 31.4% |
| Minimally improved | 30.5% |
| No change from baseline | 24.7% |
| Minimally worse | 1.4% |
| Much worse | 0.9% |
| Very much worse | 0.4% |

† Missing N = 62. ‡ Adverse drug reactions, patient-reported problems, medications holds, ER visits, or hospitalizations.

4. Discussion

In the state of Florida, there were relatively few initiators of medical marijuana in the first years of implementation but more than one-half were older adults aged ≥50 years. The chief complaints indicating medical marijuana use were primarily related to pain conditions. Other recorded medication use was common and, notably, nearly one-half of registered patients use other potentially sedating medications. Adherence to treatment appeared low, with approximately 1 in 4 patients having a recorded follow-up visit, though the brief treatment plan collection window may not have captured all follow-up visits.

Early adopters may not be completely generalizable to more contemporary late adopters in lifestyle and clinical factors. Nevertheless, several noteworthy concerns are evident even in this sample. Both THC and CBD containing products have high potential to induce side effects of sedation, lethargy, or other altered mental states. In our cohort, nearly one-half used at least one medication such as antidepressants, anti-anxiety, and other classes known to cause sedation. In older adults, this is particularly troubling due to increased sensitivity and higher incidence of negative sequelae that are related to sedation (e.g., falls and fractures). Further, THC-containing pharmaceutical products in other non-U.S. countries are contraindicated in patients with heart disease [16]. In our sample, nearly 1 in 3 patients used cardiovascular medications and may be at risk for additional complications with medical marijuana treatment. Improvements noted in this cohort for the chief complaints as well as reductions in other medications deserve additional research to understand if this is causal. Alternative reasons these improvements were observed may include natural disease progression or attrition of those who did not experience benefit.
The public seems to assume the safety of cannabis and its constituents from a long history of recreational use in mostly younger persons or personal use earlier in life [17,18]. Cannabis is generally viewed as a safer alternative to prescription drugs due to its natural origin and because it has become ubiquitous throughout the U.S. via medical and recreational legalization [19]. Safety is further assumed given that consumer CBD-based products are widely available over the counter for recreational and complementary health uses. However, cannabis has been found to have low-quality evidence for any benefit in a myriad of conditions but has been associated with up to 3-fold higher odds of experiencing adverse drug effects [20,21].

Cannabis is a complex botanical product with broad pharmacologic activity and effects on other medications. Whole cannabis and hemp (with low THC composition) plants contain more than 500 phytoconstituents including, but not limited to, approximately 120 cannabinoids [22,23]. Cannabis-derived substances like CBD are delivered as a purified product, cannabinoid combinations (e.g., CBD:THC) or consumed as part of the whole cannabis or hemp plant [22,23]. Alone, the main cannabinoids CBD and THC have established metabolic routes, absorption/elimination characteristics, and known interactions with drug metabolizing enzymes. Thus, cannabis has potential to cause pharmacokinetic drug–drug interactions as either an inhibitor or inducer of these enzymes [24,25]. Cannabinoids have similar pharmacodynamic properties as many common medications. Constituents in cannabis have significant biological effects, e.g., sedation and somnolence, which can be potentiated with concomitant medications with similar effects (e.g., opioids or benzodiazepines), specifically referred to as pharmacodynamic drug–drug interactions [26,27]. These effects are characterized as both the target effects (e.g., pain relief) that drive patients to seek therapy with cannabis as well as adverse drug events (ADEs) related to cannabis and its components (e.g., psychiatric events). These have included somnolence, sedation, acute psychiatric events (paranoia, hallucination, euphoria), cognitive and memory impairment, insomnia, gait disturbances, suicidal thoughts or behaviors, tachycardia, vertigo, and anorexia [16,21,28,29].

ADEs are a major concern among older adults. Older adults are at an increased risk of ADEs due to pathophysiological changes (e.g., sarcopenia, renal/hepatic dysfunction), polypharmacy, and comorbid conditions [30,31]. The aging brain loses significant volume per decade and places older adults at more susceptibility to neurological ADEs as well as the effects of illicit drugs—including cannabis [32]. Older adults (>50 years) are the largest consumers of prescription medications with 67% using ≥5 prescription drugs, 40% using at least one over-the-counter drug, 60% using a dietary supplement—all numbers which increase throughout aging [33]. In older adults, the estimated prevalence of at least one potential drug–drug interactions in current regimens is 50% and is as high as 80% in certain clinical groups, with up to 1 in 4 patients at risk for ≥4 drug–drug interactions [34–37]. Many prescription drugs have unclear risk/benefit profiles in older users and have led to clinical tools (e.g., Beers Criteria, STOPP/START, anticholinergic burden scales) [38–41] to avoid certain medications or avoid specific drug–disease interactions in order to minimize ADEs. In older adults, ADEs disproportionately contribute to severe health outcomes. ADEs are associated with between 3% and 30% of all hospital admissions and ADEs increase the risk of emergency department visits, increased in-hospital morbidity and mortality, and increased health care expenditure [38,41–50]. It is estimated that up to 50% of all ADEs are avoidable, preventable, or ameliorable in that they can either be prevented through selecting alternative therapies to avoid drug–drug interactions or can be reduced through dose reductions or preventive measures against side effects [44,51–53]. The addition of medical cannabis to the armamentarium of treatments for a variety of conditions in older adults deserves further research not only for its potential benefits, but also to fully assess the risks associated with ADEs.
Limitations

This study included a convenience cohort of older adult medical cannabis users in Florida captured via a physician-provided treatment plan registry. The registry was discontinued due to statutory changes, which did not allow sufficient follow up of patients. Limited patient information was available such as comorbid conditions and medication use, which may have been underreported in the registry. Few follow-up treatment plans were submitted and, thus, assessment of patient outcomes including improvements or adverse effects was not thorough. A new patient registry will be developed in Florida by the Consortium of Medical Marijuana Clinical Outcomes Research, established by state legislature in 2019, to enable better data capture and linkage to other clinical outcome data to improve these limitations.

5. Conclusions

Older adults made up more than one-half of all early adopters of medical cannabis. Chronic pain was the most common treatment indication. Registered users were also prescribed several other medications which point to possibilities of drug–drug and drug–disease interactions. Follow up was limited and was likely due to a number of factors including a limited follow-up time, physician non-compliance submitting treatment plans, patients discontinuing medical cannabis, or patient death. Among patients with a follow-up treatment plan, most reported improved conditions and reductions of other medications but some reported side effects or lack of treatment effects. Further research is needed to fill knowledge gaps regarding the safety and effectiveness of medical cannabis for the myriad conditions for which it is being utilized by older patients.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Free-text entries of follow-up treatment plans indicating changes in chief complaints, medications, and patient experiences after an initial treatment with medical marijuana (Figures A1–A4).
Appendix A
Free-text entries of follow-up treatment plans indicating changes in chief complaints, medications, and patient experiences after an initial treatment with medical marijuana (Figures A1-A4).

Figure A1. Reasons for Change in Current Medication Noted During Follow-Up Visits; N = 85 entries.

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**current_medications_change_why**

- Added Atorvastatin 20mg QD, Amlodipine 5mg QD, Valsartan 80mg QD, Effient 10mg QD
- Added morphine and lorazepam by hospice prescription
- Began Chemotherapy
- Creon for stomach cramping and to aid digestion
- Currently taking lansoprazole and zofran for diarrhea. Suspect due to doubled magnesium dose
- DC’D LIGINOPRIL, CARVEDILOL INCREASED 10 19.5 MG BID, HUMULIN INCREASED TO 65 U HUMULIN R INCREASED NOON DOSE INCREASED TO 15 U AND PM DOSE INCREASED TO 25 U. ENTERETON 49-51 MG BID.
- SPIRONOLACTONE 25 MG DAILY
- DROSINABINOL 10MG DAILY PRN, OMEPRAZOLE 20 MG BID, NOSYNTA 50 MG PRN, MELATONIN DC’D, STOOL SOFTENER 100 MG X 2 DAILY, CEPHALAVER 200 MG PO TID FOR 5 DAYS, OXYDUDDIN 5 MG TID
- Decreased dose of pain medications
- Decreased pain medicine intake
- Decreased pain meds and patches by 50
- Decreased the Xanax dose
- Decreased the use of opiate medication.
- Decreased to 25 mcg fentanyl patches, oxycodone 10 mg bid instead of percocet q 6hrs. add xanax 0.5 mg q hs.
- Depakote ER 500mg x 2 tab bid changed to Depakote ER 500mg 3 qhs and patient is no longer on Clonazepam QD.
- Diazepam 10mg TID
- Gabapentin decreased from 600 tid to 300 TID. Morco between 3-5 doses per day (pre-cannabis always 5/day). Ativan prn use has decreased in frequency. Off abilify.

- Patient has stopped celebrex and gabapentin as not needing for pain. Patient is also checking with PCP about decreasing lisinopril as BP has been improved (patient thinks pain level was causing reactive MN which is now resolved)
- Patient is now on oxycodone, oxycodone, and baclofen! OFF Tramadol for sleep. Has not needed imitrex for breakthrough headaches, or zofran for nausea.
- Patient is now using less Xanax only 1 mg daily at bedtime when necessary, has completely discontinued baclofen 10 mg and tramadol 50 mg
- Patient reduced her need of opiates
- Patient stopped all opioids 2 months ago
- Patient stopped taking Ambien and decreased taking Seroquel
- Patient stopped taking Percocet and MS
- Prochlorperazine for nausea
- Pt no longer takes BP meds
- Reduced ibuprofen and pain meds
- Setraline increased to 150 mg bid. Abilify increased to 30mg
- Started new cancer treatments every 2 weeks.
- Stopped hydroxyzine (didn’t want to be on opiates any longer, took 2 weeks to wean off)
- Stopped librax and reglan.
- Stopped metformin. Off hydralazine.
- Stopped solmedrol premication of IVIG. Will be starting soriatane for psoriasis. Stopped grahamone for tremor.
- Taking 5 mg valium daily instead of 10 mg. Paxil is 10 mg instead of 20
- The patient has stopped taking fentanyl, methadone, serotonin inhibitor
- Was off lisinopril for low BP, now back on switching and intermittent lisinopril. Able to decrease alprazolam to 1-2 doses daily instead of 3. Was able to decrease opiate doses when using cannabis consistently, but has not been able to afford cannabis due to unexpected car and roof expenses, so b
d/c cymbalta, change to celetra, progesterone increased to 500
- decreased 2 mg Clonazepam to 1.5mg PBS 2.5 weeks ago with some insomnia relief felt on current therapy
- decreased his fentanyl patch from 75mcg to 50mcg
- decreased use of current prescribed medications, in half
dilaudid to xtabs due to a pt's pain angst physician changed medication
fioricet for headaches increased Lexapro to 20 mg daily
less narcotics
less pain medication
lisinopril-hctz changed to just lisinopril pcp removed hctz.
no longer taking oxycodone or fentanyl
no longer taking trazodone
off dekaphetone, switch to zyprexa
off marinol

- off morphine, decreased blood pressure and diabetic meds
- off phentermine and orphenadrine. Taking Norco S 2-3 times daily has HCTZ to take 3 times per week if BP elevated but has not needed on pap machine

**Figure A1.** Reasons for Change in Current Medication Noted During Follow-Up Visits; N = 85 entries.
Figure A2. Changes in the Original Chief Complain/Indicated Condition During Follow-Up Visits; N = 95 entries.

marked improvement
improved
Symptoms improved
All symptoms improved
Symptoms decreased
decreased
75% relief of pain and muscle spasms, but continued issues with PTSD/anxiety causing insomnia
All symptoms have decreased
All symptoms the same but improved significantly
Cancer progressing
Doing better symptoms decreased
He had improvement with the low THC - CBD. His pain score 5/10. We will increase to get better capture. He has noted a significant decrease in headaches and decreased pain in neck. The headaches are still doing better. His current pain is 4/10. He is still off the clonazepam. He rates it at an 8 out of 10. He did better w/ the capsule over the tincture. He was able to decrease pain pill intake when he had 1mg capsule and slept better.
Her muscle spasms have decreased. She has been able to stop her amitriptyline.
Increased whole body pain
Inhalational 30mg twice, oral 20mg 3times. patient preferred route of administration
Less nausea after chemo, appetite has increased.
Doughing less, feeling stronger
Less pain/neuropathy. Less RA pain, no recurrence of squamous cell skin cancer
Marked improvement
PT symptoms have decreased. Patient does have a new symptom of tunnel vision.
Pain 6/10. She is decreasing morphine intake she is down to 45mg TID (from 60mg).
Pain decreased. Sleeping better.
Pain has improved since starting the low THC - however she still has pain at night with insomnia. But has helped her with her ANLS.
PT symptoms have persisted with minor issues with PTSD symptoms. reports CBD alone has been helpful for anxiety, but has not helped with sleep or nightmares. Additionally reports joint pain in knees and hands.
Patient diagnosed with Multiple Myelomas since last treatment plan. She is undergoing Chemotherapy. Patient did not want to follow protocol of increasing dosage after short time trials, complained the the bottles were the same when delivered and the strength was never correct. Patient did not want to come for appointments. Stated the pharmacy told her she should be given the strongest strength. Compromised of delivery charges and payment for office visits. Stated manjusma was helping her, but told the secretary it was not working at all. Patient requests sleeping improved and as well as anxiety.
Has noticed anti inflammatory effects of CBD, back pain not as severe and able to pick up dirty laundry and put on shoes and socks with ease.
Patient was able to open eyes fully without pain within 7 days of beginning the CBD.
REPORTS USING LESS INSULIN-LESS PRESERVATIVE-BETTER MOVEMENT-SLEEPY SIDE EFFECT REPORTED
Recent CT scan revealed no metabolically active tumors. Eating and sleeping better. Still taking chemo for lung CA.
Recent liver scan shows no tumors.
Same symptoms but all symptoms have improved
She has anxiety, muscle spasm, pain from hip fracture. trouble sleeping
Significant improvement, with cancer resolution
Skin cancers diminishing in size and healing
Skin lesions resolving with topical cannabis product
Spasms in extremities are rare now. Pain has decreased
Start of chemotherapy lead to severe nausea and loss of appetite
Still has a same symptoms but much less pain
Symptoms controlled
Symptoms are the same but controlled
Symptoms have improved with the CBD treatment. We are increasing to get better capture.
THERE WAS A SHORTAGE OF SUPPLY. PATIENT HAS BEEN OFF HER MEDICATION FOR A FEW WEEKS. SHE IS BACK TO HER ORIGINAL USE OF NARCOTICS AND IS NOT DOING WELL. SHE ALSO HAD A DETERIORATION IN HER MEDICAL CONDITION - HER CAVERN BONE GRAFT IS BEING REJECTED (IN WHICH IT FALLS). The severe nerve pain in left cheek has diminished and precancerous lesions on arms have resolved
add dx of glaucoma recently diagnosed by ophthalmologist.
Chronic pain
chronic pain and muscle spasm failed narcotics. cortisone spine injections and cervical fusion
decrease pain
decreased anxiety
decreased intensity and frequency of muscle spasm
her low back complaints have decreased. she feels more relaxed
improved symptoms of spasm
improvement in mood
increased due to disease progression
low THC ineffective for pain relief
marked improvement gave up methadone! and ativan! and quit smoking
marked improvement. decrease in spasms and shakes
marked improvement. no longer taking trazadone.
marked improvement. relaxes muscles, helps reduce headaches, reduces anxiety and depression
marked improvement. significantly relieves muscle and joint pain
marked improvement
more pain. less sleep
motor skills improved
neuropathy is better
off of oxycodone, reduced back pain
pain complaints
pain has decreased from 8 to 4 muscle spasms have decreased progression of CA
Pt has been diagnosed with breast cancer, would like to try THC for Breast cancer that has been slight improvement with increase of dosage.
Pt report that tremors have diminished since starting the cannabis products
worsening muscle spasms and uncontrolled by previous dose

Figure A2. Changes in the Original Chief Complain/Indicated Condition During Follow-Up Visits; N= 95 entries.
Documentation of Adverse Drug Reactions to Cannabis or Other Patient-Reported Problems with Treatment; N = 16 entries.

Figure A3. Documentation of Adverse Drug Reactions to Cannabis or Other Patient-Reported Problems with Treatment During Follow-Up Visits; N = 16 entries.

Figure A4. Reasons for Discontinuation of Cannabis During Follow-up Visits; N = 33 entries.

References

1. National Conference of State Legislatures (NCSL). State Medical Marijuana Laws. Available online: http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (accessed on 9 June 2019).
2. Denham, B.E. Attitudes toward legalization of marijuana in the United States, 1986–2016: Changes in determinants of public opinion. *Int. J. Drug Policy* 2019, 71, 78–90. [CrossRef] [PubMed]
3. Cerda, M.; Wall, M.; Keyes, K.M.; Galea, S.; Hasin, D. Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug Alcohol Depend.* 2012, 120, 22–27. [CrossRef]
4. Number of Legal Medical Marijuana Patients. Available online: https://medicalmarijuana.procon.org/view.resource.php?resourceID=005889 (accessed on 9 June 2019).

5. Compton, W.M.; Han, B.; Hughes, A.; Jones, C.M.; Blanco, C. Use of marijuana for medical purposes among adults in the United States. *JAMA* 2017, 317, 209–211. [CrossRef]

6. Wong, S.S.; Wilens, T.E. Medical Cannabinoids in children and adolescents: A systematic review. *Pediatrics* 2017, 140, 295. [CrossRef] [PubMed]

7. Sexton, M.; Cuttler, C.; Finnell, J.S.; Mischley, L.K. A Cross-sectional survey of medical cannabis users: Patterns of use and perceived efficacy. *Cannabis Cannabinoid Res.* 2016, 1, 131–138. [CrossRef] [PubMed]

8. Lucas, P.; Walsh, Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int. J. Drug Policy* 2017, 42, 30–35. [CrossRef] [PubMed]

9. Han, B.H.; Sherman, S.; Mauro, P.M.; Martins, S.S.; Rotenberg, J.; Palamar, J.J. Demographic trends among older cannabis users in the United States, 2006–2013. *Addiction* 2017, 112, 516–525. [CrossRef] [PubMed]

10. Lin, L.A.; Ilgen, M.A.; Jannausch, M.; Bohnert, K.M. Comparing adults who use cannabis medically with those who use recreationally: Results from a national sample. *Addict. Behav.* 2016, 61, 99–103. [CrossRef]

11. Dai, H.; Richter, K.P. A national survey of marijuana use among us adults with medical conditions, 2016–2017. *JAMA Netw. Open* 2019, 2, e1911936. [CrossRef]

12. Ellis, J.D.; Resko, S.M.; Szeczy, K.; Smith, R.; Early, T.J. Characteristics associated with attitudes toward marijuana legalization in Michigan. *J. Psychoact. Drugs* 2019, 51, 1–8. [CrossRef]

13. Briscoe, J.; Casarett, D. Medical marijuana use in older adults. *J. Am. Geriatr. Soc.* 2018, 66, 859–863. [CrossRef] [PubMed]

14. Lloyd, S.L.; Striley, C.W. Marijuana use among adults 50 years or older in the 21st century. *Gerontol. Geriatr. Med.* 2018, 4. [CrossRef]

15. Guy, W. Clinical global impression (CGI). Available online: https://www.psywellness.com.sg/docs/CGL.pdf (accessed on 20 January 2020).

16. Sativex(R). Delta-9-Tetrahydrocannabinol and Cannabidiol; GW Pharma: Cambridge, UK, 2005.

17. Hall, W.; Renstrom, M.; Poznyak, V. (Eds.) *The Health and Social Effects of Nonmedical Cannabis Use*: World Health Organization: Geneva, Switzerland, 2016.

18. Hall, W.; Weier, M. Assessing the public health impacts of legalizing recreational cannabis use in the USA. *Clin. Pharm.* 2015, 97, 607–615. [CrossRef] [PubMed]

19. Resko, S.; Ellis, J.; Early, T.J.; Szeczy, K.A.; Rodriguez, B.; Agius, E. Understanding public attitudes toward cannabis legalization: Qualitative findings from a statewide survey. *Subst. Use Misuse* 2019, 54, 1247–1259. [CrossRef]

20. Volkow, N.D.; Baler, R.D.; Compton, W.M.; Weiss, S.R. Adverse health effects of marijuana use. *N. Engl. J. Med.* 2014, 370, 2219–2227. [CrossRef]

21. Whiting, P.F.; Wolff, R.F.; Deshpande, S.; Di Nisio, M.; Duffy, S.; Hernandez, A.V.; Keurentjes, J.C.; Lang, S.; Misso, K.; Ryder, S.; et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 2015, 313, 2456–2473. [CrossRef]

22. ElSohly, M.A.; Radwan, M.M.; Gul, W.; Chandra, S.; Galal, A. Phytochemistry of cannabis sativa L. *Prog. Chem. Org. Nat. Prod.* 2017, 103, 1–36. [CrossRef]

23. Elsoby, M.A.; Slade, D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. *Life Sci.* 2005, 78, 539–548. [CrossRef]

24. Jiang, R.; Yamaori, S.; Takeda, S.; Yamamoto, I.; Watanabe, K. Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. *Life Sci.* 2011, 89, 165–170. [CrossRef]

25. Brown, J.D.; Winterstein, A.G. Potential adverse drug events and drug-drug interactions with medical and consumer cannabidiol (CBD) use. *J. Clin. Med.* 2019, 8, 989. [CrossRef]

26. Bergamaschi, M.M.; Queiroz, R.H.; Zuardi, A.W.; Crippa, J.A. Safety and side effects of cannabidiol, a cannabinoid constituent. *Curr. Drug. Saf.* 2011, 6, 237–249. [CrossRef] [PubMed]

27. Ifland, K.; Grotenhermen, F. An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. *Cannabis Cannabinoid Res.* 2017, 2, 139–154. [CrossRef] [PubMed]

28. GW Research Ltd. Drug Approval Package: Epidiolex (Cannabidiol). Available online: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm (accessed on 9 June 2019).
29. Brown, J.D. Potential adverse drug events with tetrahydrocannabinol (THC) due to drug-drug interactions. *J. Clin. Med.* 2020, 9, 919. [CrossRef] [PubMed]
30. Corsonello, A.; Pedone, C.; Incalzi, R.A. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. *Curr. Med. Chem.* 2010, 17, 571–584. [CrossRef]
31. Trifiro, G.; Spina, E. Age-related changes in pharmacodynamics: Focus on drugs acting on central nervous and cardiovascular systems. *Curr. Drug Metab.* 2011, 12, 611–620. [CrossRef]
32. Dowling, G.J.; Weiss, S.R.; Condon, T.P. Drugs of abuse and the aging brain. *Neuropsychopharmacology* 2008, 33, 209–218. [CrossRef]
33. Qato, D.M.; Alexander, G.C.; Conti, R.M.; Johnson, M.; Schumm, P.; Lindau, S.T. Use of prescription and over-the-counter medications and dietary supplements among older adults in the united states. *JAMA* 2008, 300, 2867–2878. [CrossRef]
34. Schneider, K.L.; Kastenmüller, K.; Weckbecker, K.; Bleckwenn, M.; Bohme, M.; Stingl, J.C. Potential drug-drug interactions in a cohort of elderly, polymedicated primary care patients on antithrombotic treatment. *Drugs Aging* 2018, 35, 559–568. [CrossRef]
35. Tulner, L.R.; Frankort, S.V.; Gijsen, G.J.; van Campen, J.P.; Koks, C.H.; Beijnen, J.H. Drug-drug interactions in a geriatric outpatient cohort: Prevalence and relevance. *Drugs Aging* 2008, 25, 343–355. [CrossRef]
36. Nobili, A.; Pasina, L.; Tettamanti, M.; Lucca, U.; Riva, E.; Marziona, I.; Monesi, L.; Cucchiani, R.; Bortolotti, A.; Fortino, I.; et al. Potentially severe drug interactions in elderly outpatients: Results of an observational study of an administrative prescription database. *J. Clin. Pharm.* 2009, 34, 377–386. [CrossRef]
37. Johnell, K.; Klarin, I. The relationship between number of drugs and potential drug-drug interactions in the elderly: A study of over 600,000 elderly patients from the Swedish prescribed drug register. *Drug Saf.* 2007, 30, 911–918. [CrossRef] [PubMed]
38. Brown, J.D.; Hutchison, L.C.; Li, C.; Painter, J.T.; Martin, B.C. Predictive validity of the beers and screening tool of older persons’ potentially inappropriate prescriptions (STOPP) criteria to detect adverse drug events, hospitalizations, and emergency department visits in the United States. *J. Am. Geriatr. Soc.* 2016, 64, 22–30. [CrossRef] [PubMed]
39. American geriatrics society 2019 updated AGS beers criteria(R) for potentially inappropriate medication use in older adults. *J. Am. Geriatr. Soc.* 2019, 67, 674–694. [CrossRef]
40. O’Mahony, D.; O’Sullivan, D.; Byrne, S.; O’Connor, M.N.; Ryan, C.; Gallagher, P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. *Age Ageing* 2015, 44, 213–218. [CrossRef] [PubMed]
41. Rudolph, J.L.; Salow, M.J.; Angelini, M.C.; McGlinchey, R.E. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch. Intern. Med.* 2008, 168, 508–513. [CrossRef]
42. Budnitz, D.S.; Pollock, D.A.; Weidenbach, K.N.; Mendelsohn, A.B.; Schroeder, T.J.; Annest, J.L. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* 2006, 296, 1858–1866. [CrossRef]
43. Budnitz, D.S.; Shehab, N.; Kegler, S.R.; Richards, C.L. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann. Intern. Med.* 2007, 147, 755–765. [CrossRef]
44. Gurwitz, J.H.; Field, T.S.; Harrold, L.R.; Rothschild, J.; Debelis, K.; Seger, A.C.; Cadoret, C.; Fish, L.S.; Garber, L.; Kelleher, M.; et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003, 289, 1107–1116. [CrossRef]
45. Budnitz, D.S.; Lovegrove, M.C.; Shehab, N.; Richards, C.L. Emergency hospitalizations for adverse drug events in older Americans. *N. Engl. J. Med.* 2011, 365, 2002–2012. [CrossRef]
46. Brown, J.D.; Painter, J.; Li, C.; Hutchison, L.C.; Martin, B. Adverse drug events in the elderly occurring in emergency, inpatient, and outpatient departments in an administrative claims database. *Value Health* 2014, 17, A155. [CrossRef]
47. Hanlon, J.T.; Schmader, K.E.; Koronkowski, M.J.; Weinberger, M.; Landsman, P.B.; Samsa, G.P.; Lewis, I.K. Adverse drug events in high risk older outpatients. *J. Am. Geriatr. Soc.* 1997, 45, 945–948. [CrossRef] [PubMed]
48. Poudel, D.R.; Acharya, P.; Ghimire, S.; Dhital, R.; Bharati, R. Burden of hospitalizations related to adverse drug events in the USA: A retrospective analysis from large inpatient database. *Pharm. Drug Saf.* 2017, 26, 635–641. [CrossRef] [PubMed]
49. Riaz, M.; Brown, J.D. Association of adverse drug events with hospitalization outcomes and costs in older adults in the USA using the nationwide readmissions database. *Pharm. Med.* 2019, 33, 1–9. [CrossRef] [PubMed]

50. Winterstein, A.G.; Sauer, B.C.; Hepler, C.D.; Poole, C. Preventable drug-related hospital admissions. *Ann. Pharm.* 2002, 36, 1238–1248. [CrossRef] [PubMed]

51. Von Laue, N.C.; Schwappach, D.L.; Koeck, C.M. The epidemiology of preventable adverse drug events: A review of the literature. *Wien. Klin. Wochenschr.* 2003, 115, 407–415. [CrossRef] [PubMed]

52. Thomsen, L.A.; Winterstein, A.G.; Sondergaard, B.; Haugbolle, L.S.; Melander, A. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. *Ann. Pharm.* 2007, 41, 1411–1426. [CrossRef]

53. Kanjanarat, P.; Winterstein, A.G.; Johns, T.E.; Hatton, R.C.; Gonzalez-Rothi, R.; Segal, R. Nature of preventable adverse drug events in hospitals: A literature review. *Am. J. Health Syst. Pharm.* 2003, 60, 1750–1759. [CrossRef]

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