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ORIGINAL ARTICLE

Adverse events following cannabis for medical use in Tuscany: An analysis of the Italian Phytovigilance database

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Aims: Despite a significant increase in using cannabis for medical purposes, current evidence on its safety in real-world clinical practice is still poorly characterised. By a case-by-case analysis of spontaneous reports of suspected adverse events (AEs) collected in Tuscany within the Italian Phytovigilance database, the aim of the present study was to describe AEs occurred in patients exposed to medical cannabis.

Methods: We evaluated all reports of cannabis-related suspected AEs collected within the Phytovigilance database up to December 2018. Information regarding cannabis therapy, patient's demographic and clinical characteristics, concomitant medications, AE description according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, AE seriousness and AE outcome, were collected. The causality assessment was performed following World Health Organisation–Uppsala Monitoring Centre criteria.

Results: Fifty-three cannabis-related AE reports were analysed. The majority of patients were females (77.3%), with a mean age of 61.9 years. Thirty-nine (73.6%) cases were defined as nonserious and the majority of them (86.9%) showed a complete resolution or improvement. Forty-six (86.8%) cases were judged as probably related to cannabis consumption. The most frequently reported system organ class was psychiatric and nervous system disorders, and a potential drug–drug interaction was present in 16 cases.

Conclusion: Cannabis was generally well tolerated and the majority of AEs were mild and transient. Our analysis highlighted important safety issues for clinical practice, in particular the need for an accurate prescription monitoring during the titration phase, particularly in the presence of concomitant medications.

KEYWORDS

adverse drug reactions, clinical pharmacology, drug safety, general practice, medical cannabis

Giada Crescioli and Niccolò Lombardi are co-first authors.

1 | INTRODUCTION

Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main active substances in *Cannabis sativa*, and have several pharmacological targets that include both cannabinoid (CB) receptors (CB1 and CB2), the calcitonin gene-related peptide orphan receptor, the ligand-gated ion channels of human 5-HT_{3A} receptors, and other additional ionic channels and enzymes.[1,2] The action of THC and CBD on these targets is responsible for their therapeutic properties, ranging from pain relief to antiemetic, antiepileptic and anticraving effects.[3]

Recent evidence shows the positive effects of medical cannabis use both as first-line treatment and as adjuvant therapy in several clinical conditions, identifying cannabis as a valid therapeutic option. In a study published by Bellnier and colleagues, the use of cannabis has led patients with chronic pain to discontinue their opioids, or to reduce opioids doses by approximately 75%.[4] In patients affected by Dravet syndrome, CBD administration have reduced monthly drop seizure frequency from baseline by 43.9%, with the occurrence of mild or moderate adverse events (AEs).[5] In a systematic review and meta-analysis performed to evaluate the efficacy and safety of cannabinoids in different clinical settings, 79 trials for a total of 6462 participants have been included. Compared with placebo, a higher number of patients treated with cannabinoids have shown: (i) nausea and vomiting complete response; (ii) greater reduction in numerical rating scale pain assessment; (iii) greater reduction in the Ashworth spasticity scale. The study has highlighted an increased risk of short-term AEs with cannabinoids, including those classified as serious.[6] Another study by Nugent and colleagues[7] reviewed the benefits of cannabis preparations for treating chronic pain in adults and the harms of cannabis use in chronic pain and general adult populations. Authors performed a systematic review of 27 chronic pain trials, 11 systematic reviews and 32 primary studies, concluding that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain. They also highlighted that cannabis is associated with an increased risk for adverse mental health effects.

In studies evaluating the safety of medical cannabis over all indications, it has been found to be safe and well tolerated,[8] and its AEs have been considered less severe than those of other prescribed drugs.[9] Nevertheless, different suspected AEs have been reported following cannabis consumption, and despite the significant increase in use, the current evidence on safety of medical cannabis in real-world clinical practice are is poorly characterised.

Italy legally recognised medical use of cannabis since 2006, when the Ministry of Health authorised cannabis import from the Netherlands. In 2016, Italian production of cannabis was authorised and the Military Pharmaceutical Chemical Works (Florence) started growing and processing cannabis in a controlled and standardised setting, according to Good Manufacturing Practice. Medical cannabis can be prescribed as magistral preparations, such as oil extracts, decoction filter bags, and bags for inhalation through an authorised device. Medical use of cannabis is authorised in Italy and reimbursed within the National Health System for selected medical conditions (as reported in the Official Gazette no. 279 from 30 November 2015): (i) analgesia in diseases involving spasticity associated with pain (multiple sclerosis, spinal cord injury) resistant to conventional therapies; (ii) analgesia in chronic pain (with particular reference to neurogenic pain) in which treatment with nonsteroidal anti-inflammatory drugs or with cortisone or opioid drugs has proved to be ineffective; (iii) anti-motion sickness and antiemetic effect in nausea and vomiting, caused by chemotherapy, radiotherapy, human immunodeficiency virus therapies, which cannot be obtained with traditional treatments; (iv) appetite stimulating effect in cachexia, anorexia, loss of appetite in cancer patients or patients with AIDS and in anorexia nervosa, which cannot be obtained with standard treatments; (v) hypotensive effect in glaucoma resistant to conventional therapies; (vi) reduction of involuntary body and facial movements in Tourette syndrome, which cannot be achieved with standard treatments.[10-12]

What is already known about this subject

- Cannabis is a therapeutic option in multiple clinical conditions, including chronic pain, AIDS, cancer, glaucoma, Tourette syndrome and multiple sclerosis. Despite a significant increase in medical cannabis use, its safety in clinical practice is poorly characterised.

What this study adds

- This study shows that medical cannabis is generally well tolerated and the majority of observed AEs are mild and transient. Important safety issues for clinical practice include the need for accurate prescription and monitoring during the titration phase, particularly in presence of concomitant medications.

Spontaneous reports of suspected AEs to natural health products (including galenic preparations containing herbals) are collected in Italy within the Italian Phytovigilance system coordinated by the National Institute of Health.[13]

In this context, the aim of the present study was to describe the safety profile of cannabis for medical use, with a case-by-case analysis of spontaneous reports of suspected AEs collected in Tuscany (Italy) within the Italian Phytovigilance database.

2 | METHODS

We considered and evaluated all spontaneous reports of cannabis-related suspected AEs collected within the Italian Phytovigilance database (coordinated by the Italian National Institute of Health) since 2006 (date of cannabis for medical use approval) until December 2018. All reports associated with registered products or magistral preparations containing cannabis were extracted from the database. From the reporting form (available online at: http://www.epicentro.

iss.it/fitosorveglianza/pdf/scheda_fito.pdf), we collected all information on: (i) patient's demographical (i.e. age, sex etc.) and clinical status; (ii) AE, codified using the Medical Dictionary for Regulatory Activities (MedDRA) classification, and described using the preferred terms (PT) and system organ class (SOC) most frequently reported[14,15]; (iii) AE degree of seriousness, classified according to the World Health Organisation criteria as fatal, life-threatening, or requiring hospitalisation of the patient, or causing serious/permanent disability, or causing congenital abnormalities, or other clinically relevant conditions (https://apps.who.int/iris/bitstream/handle/10665/67378/WHO_EDM_QSM_2002.2.pdf;jsessionid=EF4F54EFF6FBD634E21D2C075ADCA3C0?sequence=1; 29661234); (iv) AE outcome; (v) ongoing cannabis therapy (i.e. product type, indication, dosage, length of exposure, and administration route); (vi) concomitant medications.

The causality assessment (categorised as certain, probable/likely, possible, unlikely or unclassifiable) was performed using the World Health Organisation–Uppsala Monitoring Centre system for standardised case causality assessment (https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf).

Moreover, a multidisciplinary group of experts in pharmacology, phytotherapy, clinical toxicology, pharmacovigilance and phytovigilance fields performed a case-by-case clinical evaluation by, with the aim of identifying potential factors (i.e. presence of drug–drug interaction, DDI), which may have contributed to the AEs collected.

Drug targets reported in the present manuscript conform to the IUPHAR/BPS Guide to PHARMACOLOGY nomenclature classification.[16]

Data a presented as number and percentages or, for continuous variables, as mean and standard deviation (SD).

3 | RESULTS

During the study period (2006–2018), a total of 103 suspected AE reports concerning medical cannabis use in Italy have been collected in the Italian Phytovigilance database, of which 61 (59%) were reported by Tuscany healthcare professionals. We have excluded 8 reports due to lacking information which did not allow us to perform their clinical evaluation.

Table 1 and Table 2 show general patients' characteristics and a case-by-case clinical description of the 53 evaluated reports, respectively. The majority of patients were female (*n* = 41, 77.3%), with a mean age of 61.9 (±SD, 15.9) years. Out of all reports evaluated, 39 (73.6%) were defined as nonserious and only in 2 cases AE seriousness was not specified. Most AE reports (*n* = 45, 84.9%) showed *complete resolution* or *improvement* as AE outcome. Only 2 cases were still unresolved at the time of AE reporting. Neuropathic pain and chronic or nonspecified pain were the most reported indication for medical cannabis use, amounting to 23 (43.4%) and 21 (39.6%) cases, respectively. Indication for fibromyalgia and multiple sclerosis were reported in 5 and 2 cases, respectively. Only 1 patient took his medication by inhalation, while all other patients used cannabis orally, at a mean dose of 138.5 (±SD, 139.0) mg per day. Length of exposure before AE onset largely vary among cases, ranging from 1 day to 37 months (mean 149.3 ± 242.4 days). Thirty-eight cases (71.7%) reported the presence of concomitant medications, mainly represented by pregabalin, gabapentin and other pain medication, such as paracetamol/codeine or oxycodone/naloxone fixed association.

Regarding the causality assessment, 46 (86.8%) and 5 (9.4%) cases were judged as probably or possibly related to cannabis consumption, respectively. Only 1 case was defined as certainly associated to cannabis administration, while for 1 case, information has not

TABLE 1 General patients' characteristics

Cases characteristics	No. of cases *n* = 53 (%)
Patient age, y	
19–64	25 (47.2)
65–79	24 (45.3)
≥80	4 (7.5)
Mean ± standard deviation, y	61.9 ± 15.9
Sex	
Female	41 (77.3)
Male	12 (22.7)
Cannabis administration route	
Oral	52 (98.1)
Inhalation	1 (1.9)
Mean dose ± standard deviation, mg	138.5 ± 139.0
No. of concomitant medications	
None	15 (28.3)
1	13 (24.5)
≥2	25 (47.2)
Potential drug–drug interaction	
No	37 (69.8)
Yes	16 (30.2)
Seriousness	
Nonserious	39 (73.6)
Serious	12 (22.6)
Not reported	2 (3.8)
Outcome	
Complete resolution	36 (67.9)
Improvement	9 (17.0)
Still unresolved	2 (3.8)
Not reported	6 (11.3)
Causality assessment	
Certain	1 (1.9)
Probable	46 (86.8)
Possible	5 (9.4)
Not classifiable	1 (1.9)

TABLE 2 Case-by-case clinical description of all evaluated reports

Case	Age (y)	M/F	Adverse events (PT)	Seriousness	Outcome	Product	Indication	Dosage	Exposure length	Administration route	Concomitant drugs	Causality assessment
1	62	M	Anxiety Panic attack Acute psychosis	Serious	Complete resolution	Bedrocan	Neuropathic pain	50 mg	110 days	Inhaled	Alprazolam	Probable
2	72	F	Dysphoria Visual hallucinations Drowsiness Accidental overdose	Serious	Complete resolution	Bedrocan	Neuropathic pain	800 mg	70 days	Oral	Pregabalin Irbesartan Salbutamol Fluticasone	Probable
3	46	F	Altered mental status Mental confusion Lipothymia Vomiting	Serious	Complete resolution	Bedrocan	Neuropathic pain	150 mg daily	125 days	Oral	Fentanyl	Probable
4	71	F	Mental confusion	Serious	Complete resolution	Cannabis inflorescences	Neuropathic pain	10 mg daily	1 day	Oral	Tapentadole	Probable
5	22	F	Lack of efficacy Drowsiness	Nonserious	Complete resolution	Cannabis inflorescences	Facial neuralgia	150 mg daily	4 months	Oral	--	Probable
6	80	F	Drowsiness Balance disorder	Nonserious	Complete resolution	Bedrocan	Chronic pain	200 mg daily	130 days	Oral	Paracetamol/codeine association Metformin Esomeprazole	Probable
7	75	F	Epistaxis	Nonserious	Improvement	Cannabis inflorescences	NR	NR	3 months	NR	Acetylsalicylic acid Paracetamol/oxycodone association Omeprazole Pregabalin	Possible
8	45	M	Difficulty speaking Dizziness	Nonserious	NR	Bedrocan	Neuropathic pain, neuralgia	400 mg daily	2 days	Oral	--	Probable
9	69	F	Mental confusion Dizziness	Nonserious	Complete resolution	Bedrocan	Neuropathic pain	100 mg	20 days	Oral	Codeine Pregabalin Anxiolytics (not specified)	Probable
10	61	F	Mental confusion Xerophthalmia Xerostomia	Nonserious	Complete resolution	Bedrocan	Chronic pain	50 mg	3 weeks	Oral	--	Probable

(Continues)

TABLE 2 (Continued)

Case	Age (y)	M/F	Adverse events (PT)	Seriousness	Outcome	Product	Indication	Dosage	Exposure length	Administration route	Concomitant drugs	Causality assessment
11	78	F	Dizziness Fall Amnesia	Nonserious	Complete resolution	Bedrocan	Neuropathic pain	50 mg	5 days	Oral	--	Probable
12	50	F	Headache Nausea	Nonserious	Complete resolution	Bedrocan	Neuropathic pain	25 mg	4 days	Oral	--	Probable
13	50	M	Major depression Suicidal ideation	Serious	Complete resolution	Bedrocan	Neuropathic pain, headache	300 mg	7 months	Oral	Valproic acid	Probable
14	66	M	Bradyarrhythmia Lipothymia Balance disorder	Serious	Complete resolution	Bedrocan	Chronic neuropathic pain	150 mg	1 day	Oral	Tramadol Ibuprofen	Probable
15	80	F	Drowsiness	Nonserious	Complete resolution	Bedrocan	Chronic pain	50 mg	20 days	Oral	--	Probable
16	72	F	Supraventricular tachycardia Aphasia Agnosia	Nonserious	Complete resolution	Bedrocan	Neuropathic pain	50 mg daily	4 months	Oral	Acetylsalicylic acid Losazide	Probable
17	78	F	Mental confusion	Nonserious	Complete resolution	FM2	Chronic pain	30 mg	NR	Oral	Pregabalin Oxycodone/naloxone association	Not
			classifiable	18	64	F	Drowsiness			Nonserious	NR	Bedrocan
			Chronic pain	150 mg daily	30 months	Oral	Colchicine Paracetamol/acetylsalicylic acid/caffeine association Etoricoxib		Probable	19	79	F
			Mental confusion	Nonserious	Complete resolution	Bediol	Chronic pain	60 mg daily	20 days	Oral	--	Probable
20	77	F	Nausea Lack of appetite	Nonserious	NR	Bedrocan	Chronic pain	100 mg daily	49 days	Oral	Nimesulide Pregabalin	Possible
21	55	F	Drowsiness Mental confusion Biliary vomiting	Nonserious	Improvement	Cannabis inflorescences	Neuropathic pain (autoimmune neuropathy)	NR	15 days	NR	Insulin Pantoprazole Duloxetine Pregabalin Escitalopram Alprazolam Oxycodone	Probable

(Continues)

TABLE 2 (Continued)

Case	Age (y)	M/F	Adverse events (PT)	Seriousness	Outcome	Product	Indication	Dosage	Exposure length	Administration route	Concomitant drugs	Causality assessment
22	50	F	Asthma Diarrhoea Gastritis	Nonserious	Complete resolution	Bedrocan	Chronic pain	90 mg	NR	Oral	--	Probable
23	57	F	Mental confusion Balance disorder	Nonserious	Complete resolution	Bedrocan	Pain (nonresponsive to conventional therapies)	90 mg daily	NR	Oral	--	Probable
24	71	F	Smell alteration	NR	Still unresolved	Bedrocan	Chronic neuropathic pain	120 mg	NR	Oral	Acetylsalicylic acid	Probable
25	53	M	Tachycardia Pain Lack of efficacy Dulling	Nonserious	Complete resolution	Bediol oil (magistral preparation)	Chronic pain	175 mg	200 days	Oral	--	Probable
26	69	F	Memory loss Balance disorder	Nonserious	NR	FM2 oil (magistral preparation)	Chronic pain	400 mg	132 days	Oral	--	Probable
27	69	F	Bronchospasm	Nonserious	Complete resolution	FM2 oil (magistral preparation)	Chronic pain (nonresponsive to conventional therapies)	200 mg	36 days	Oral	--	Probable
28	72	F	Dulling Swoon Hypoxia Frequent hospitalisation	Serious	NR	FM2 oil (magistral preparation)	NR	300 mg	1 month	Oral	Pregabalin Fentanyl Amitriptiline	Probable
29	22	F	Lack of efficacy Drowsiness	Nonserious	Complete resolution	Bedrocan	Headache and facial neuralgia	150 mg	15 months	Oral	Etoricoxib Colchicine Paracetamol/acetylsalicylic acid/caffeine association	Probable
30	80	F	Balance disorder Dulling Drowsiness	Nonserious	Complete resolution	Bediol oil (magistral preparation)	Chronic pain	200 mg	100 days	Oral	Metformin Esomeprazole Paracetamol/codeine association	Probable
31	72	M	Drowsiness	Nonserious	Complete resolution	Bedrocan	Chronic pain	120 mg daily	1 month	Oral	Levothyroxine Apixaban Lacidipine Flecainide	Probable

(Continues)

TABLE 2 (Continued)

Case	Age (y)	M/F	Adverse events (PT)	Seriousness	Outcome	Product	Indication	Dosage	Exposure length	Administration route	Concomitant drugs	Causality assessment
32	55	F	Major depression Psychotic crisis	Nonserious	Complete resolution	Bediol oil 1 g/10 mL (magistral preparation)	Fibromyalgia and chronic pain, headache	150 mg daily	37 months	Oral	Pregabalin Duloxetina *Smilax aspera*	Probable
33	68	F	Body altered perception Catastrophic thoughts Tachyarrhythmia Hypertension	Nonserious	Complete resolution	Bedrocan oil 10% (magistral preparation)	Fibromyalgia and mixed pain with vertebral canal stenosis	100 mg daily	2 months	Oral	Oxycodone Pregabalin	Probable
34	74	F	Leg swelling Leg itching	Nonserious	Improvement	FM2	Chronic pain	50 mg	6 days	Oral	Pregabalin	Probable
35	83	M	Myasthenic crisis General muscle weakness and related eye disorder	Nonserious	Complete resolution	Bedrocan oil 10% (magistral preparation)	Neuropathic pain and myelopathy	100 mg	49 days	Oral	Not specified drugs for myasthenia treatment	Possible
36	77	F	Increased appetite Weight gain	Nonserious	Improvement	Bedrocan	Chronic pain	30 mg	18 months	Oral	Pregabalin	Probable
37	31	F	Tachycardia	Nonserious	Improvement	Bedrocan	Chronic pain	30 mg	18 months	Oral	Duloxetine Gabapentin	Probable
38	26	F	Drowsiness Dizziness Balance disorder	Nonserious	Improvement	Pedanios oil (magistral preparation)	Fibromyalgia and neuropathic pain	100 mg	6 days	Oral	Pregabalin Cyclobenzaprine	Probable
39	79	F	Anxious depressive syndrome	Nonserious	Complete resolution	Bedrocan	Chronic pain	60 mg daily	2 months	Oral	Enalapril Methylprednisolone	Probable
40	44	F	Tachyarrhythmia Dizziness Dysphoria	Serious	Complete resolution	Bedrocan oil 10% (magistral preparation)	Fibromyalgia and neuropathic pain	150 mg daily	111 days	Oral	Magnesium Pregabalin Duloxetine	Probable
41	47	F	Dysphoria Hallucinations Panic attack	Nonserious	Complete resolution	Bedrocan oil 10% (magistral preparation)	Fibromyalgia and neuropathic pain	100 mg	43 days	Oral	Pregabalin Duloxetine	Probable
42	64	F	Palpitation Nausea	NR	Complete resolution	Magistral preparation 15% THC	Trigeminal neuralgia	80 gtt/die	1 day	Oral	Insulin	Probable

(Continues)

TABLE 2 (Continued)

Case	Age (y)	M/F	Adverse events (PT)	Seriousness	Outcome	Product	Indication	Dosage	Exposure length	Administration route	Concomitant drugs	Causality assessment
43	77	M	Mental confusion	Nonserious	Complete resolution	Cannabis inflorescences	Neuropathic pain	50 mg	NR	Oral	--	Probable
44	52	F	Supraventricular tachycardia	Serious	Complete resolution	Bedrocan	Neuropathic pain	150 mg daily	107 weeks	Oral	Venlafaxine	Probable
45	63	F	Abdominal pain Gastroesophageal reflux	Serious	Improvement	Bedrocan	Neuropathic pain	175 mg daily	11 days	Oral	Lansoprazole	Probable
46	66	M	Bradycardia	Nonserious	NR	Bedrocan oil (magistral preparation)	Neuropathic pain	450 mg daily	5 months	Oral	--	Probable
47	44	M	Anxiety Lipothymia Hyperhidrosis Blurred vision	Nonserious	Improvement	Cannabis inflorescences	Pain	NR	1 day	NR	Ramipril Oxycodone/naloxone association Paracetamol/codeine association	Probable
48	45	M	Mental confusion Pharmacological interaction Memory impairment Tachycardia Lipothymia Shaking Urinary retention	Serious	Improvement	Cannabis inflorescences	Neuropathic pain	NR	6 months	NR	Gabapentin	Probable
49	74	F	Lack of efficacy	Nonserious	Complete resolution	FM2	Multiple sclerosis	60 mg	1 month	Oral	Paracetamol/codeine association Warfarin	Probable
50	44	F	Lack of efficacy Lower limb spasticity	Serious	Complete resolution	Bediol	Multiple sclerosis	60 mg	2 months	Oral	Vitamin D	Probable
51	51	F	Dizziness	Nonserious	Still unresolved	Nor specified cannabis	Chronic pain	100 mg	1 month	Oral	Gabapentin	Probable
52	78	M	Mental confusion	Nonserious	Complete resolution	Cannabis inflorescences	Neuropathic pain, neuralgia	50 mg	When needed	Oral	--	Probable

(Continues)

TABLE 2 (Continued)

Case	Age (y)	M/F	Adverse events (PT)	Seriousness	Outcome	Product	Indication	Dosage	Exposure length	Administration route	Concomitant drugs	Causality assessment
53	71	F	Hallucinations Nausea	Nonserious	Complete resolution	Bediol	Chronic pain	100 mg daily	9 months	Oral	Acetylsalicylic acid Ranitidine Cyclosporine Metoprolol Prednisolone Potassium kanrenoate	Possible

been sufficient to assess a causality relationship, thus, it has been defined as *not classifiable*.

Overall, 53 AE reports referred to a total of 118 AEs, whose distribution is reported according to SOC classification (Figure 1). Following MedDRA hierarchy, the 5 most frequently reported SOC are: *psychiatric disorders* (26.3%, *n* = 31 out of 118 AEs), followed by *nervous system disorders* (22.0%, *n* = 26), *ear and labyrinth disorders* (10.2%, *n* = 12), *gastrointestinal disorders* (10.2%, *n* = 12), *general disorders and administration site condition* (8.5%, *n* = 10) and *cardiac disorders* (8.5%, n = 10). Consequently, within each SOC the most frequently reported PT were (see also Table 2): mental confusion, dysphoria, and anxiety (among *psychiatric disorders*); drowsiness and lipothymia (among *nervous system disorders*); dizziness and balance disorders (among *ear and labyrinth disorders*); nausea and vomiting (among *gastrointestinal disorders*); lack of efficacy and dulling (among *general disorders and administration site condition*); tachycardia and tachyarrhythmia, and bradycardia (among *cardiac disorders*).

4 | DISCUSSION

Since 2006 (date of cannabis for medical use approval) until December 2018, the Italian National Institute of Health collected within its Phytovigilance database a total of 103 AE reports following cannabis for medical use administration, mainly coming from Tuscany (61 reports).[17] The high number of AE reports collected in this Italian region could be related to the well-established use of medical cannabis[18] and to the clinicians' knowledge of AE reporting procedures.[19] To the best of our knowledge this is the first case series study describing all medical cannabis-related AEs observed in the general population (all age groups).

Our study showed that cannabis treatment was not associated with a high number of AEs, the majority of which were nonserious and resolved completely without sequelae. Moreover, our results were in line with those published in the study by Whiting and colleagues,[6] who found a statistically significant association between cannabis use and the occurrence of dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, diarrhoea, drowsiness, disorientation, confusion, loss of balance and hallucination. Moreover, in their systematic review, a statistically significant association was highlighted for the following SOCs: gastrointestinal, psychiatric and nervous system disorders, general disorders and administration site conditions, ear and labyrinth disorders, and renal and urinary disorders.[6] Following, the description of our case-by-case clinical evaluation and the biological explanation of observed AEs, reported according to the SOCs most frequently reported (Table 2).

4.1 | Psychiatric and nervous system disorders

Among people who use cannabis for recreational purposes, desired psychotropic THC-related acute effects of mild euphoria, relaxation and general pleasant feelings are well characterised. By contrast,

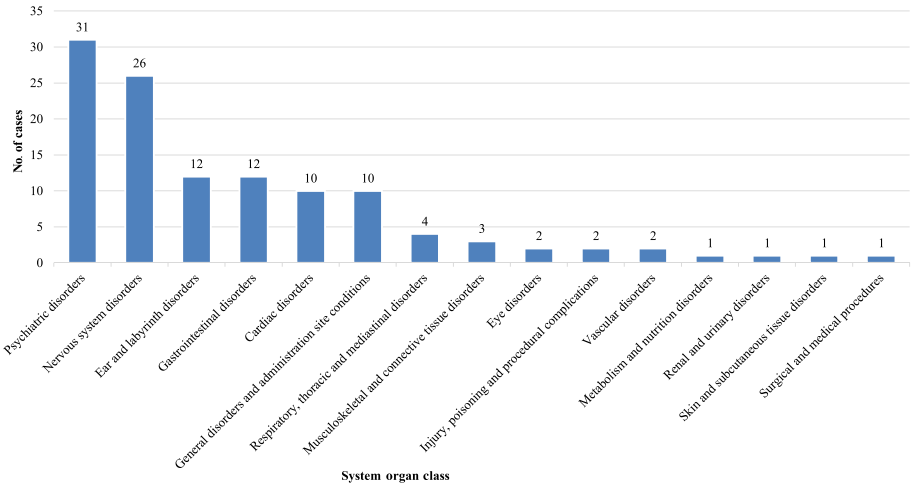

FIGURE 1 Distribution of medical cannabis-related adverse events according to system organ classes

recreational use of cannabis, especially in naïve individuals, can cause motor coordination and executive function impairment, anxiety, panic attacks and psychotic episodes. Despite AEs of therapeutic cannabis resemble to those experienced during the recreational use, there are major differences both in terms of spectrum and intensity of these effects.[20]

In our sample, psychiatric disorders include several AEs (reported as PT), such as: mental confusion; depression and suicidal ideation; anxiety; acute psychosis; body altered perception; and panic attacks. In only 2 cases did patients report episodes of hallucinations. These transient psychotic-like experiences are described in the literature[21] and, differently to psychotic disorders, they resolve within a few hours and rarely cause distress. A study published in 2004 and performed on healthy volunteers underlines the occurrence of both positive (i.e. hallucinations, delusions, racing thoughts etc.) and negative symptoms (i.e. apathy, lack of emotion, poor or nonexistent social functioning etc.), similar to those experienced by schizophrenic patients. Nevertheless, no serious AEs has occurred during this study.[21] Moreover, neurological or psychiatric AEs seems to increase with higher THC concentrations, suggesting a potential relationship between cannabis dosages and AEs seriousness,[22] as in our case of accidental overdose (case 2).

A systematic review has collected data from 11 studies on psychosis highlighting an increased risk of psychotic outcome in individuals who never used cannabis, and an increased risk of psychotic outcome and depression in those who frequently used cannabis. Four of the included studies reported an association between cannabis use and increased risk of suicidal ideation, while the other 7 studies emphasised an association with anxiety outcomes.[23] Another systematic review of randomised controlled trials of medical cannabinoids confirmed a significant higher rate in patients exposed to cannabis both for nervous system and psychiatric disorders.[24]

The hypothesis of the association between the use of cannabinoids and the development of psychosis is still debated. Epidemiological studies have consistently demonstrated that cannabis use is associated with an increased risk of schizophrenia-like psychoses. This risk varies according to the dose and duration of use, on top of age use and genetic factors, including partially shared genetic predisposition with schizophrenia.[25]

Considering patients' average age in our sample, it is important to note that cannabis-induced nervous system disorders are not specific to older adults, even if, during clinical trials, sedation-like symptoms such as drowsiness, tiredness and somnolence are more reported in older subjects exposed to cannabis than in controls.[26] Clinicians should always take these kind of AEs into account, particularly to better manage patients' adherence to cannabis prescriptions. This aspect is also important because it has been found that experiencing a cannabis-related AE (i.e. dizziness, fatigue, mild anxiety and feeling "weird") is more common among nonadhering patients than among adhering ones.[27] Thus, improving patients' education on cannabis treatments, could improve their therapy compliance, and reduce nonadherence affects, in particular psychiatric and nervous system AEs.

4.2 | Ear and labyrinth disorders

Among chronic users of cannabis, a decrease in maximum amplitude on torsion swing and an increase in incidence of nystagmus in supine positions have been observed since the 1970s.[28] Following studies, based on immunohistochemistry, demonstrate that CB1 and CB2 receptors are localised in the central nervous system and cover areas involved in movement control (i.e. basal ganglia, cerebral cortex, and cerebellum). Endocannabinoids are also involved in setting the baseline activity of the spinal locomotor circuitry, where CB1 activation or antagonism results in an increase and decrease of locomotor frequency, respectively.[29] Moreover, it has been demonstrated that CB1 receptors exist in significant densities in the vestibular nucleus complex and are likely to contribute to the neurochemical control of vestibular reflexes.[30] Given that CB1 receptors have apparently an exclusive presynaptic localisation, in the vestibular nucleus complex

they could be situated on presynaptic glutamatergic axon terminals where they would reduce glutamate release during vestibular stimulation.[31] In this frame, the activation of these receptors could explain the occurrence of loss of balance and labyrinth disorders as cannabis-related AEs.[30]

In chronic users of cannabis, the cerebellum presents neuroanatomical alterations that impair its ability to execute postural adjustments, resulting in trembling.[32,33] Results from a study published in 2017 suggest that cannabis users show subtle changes in gait, primarily in open-chain components of walking gait, but not in balance.[34]

The main clinical concern refers to cannabis use in older patients, as those in our sample, who are notably susceptible to AEs due to physiological changes, comorbidities, concurrent medication use and cognitive impairment.[35] Even if this assumption has not been already confirmed, sedation-like neurological AEs of cannabis may expose the elderly to an increased risk of falls. In this frame, a recent study examines the effect of THC on balance and gait in old demented adults using cannabinoids. THC administration in elderly significantly increases sway during standing and stride length and trunk sway during walking.[36] Another systematic review and meta-analysis included 7 randomised controlled trials that reported data about hearing AEs after cannabis use. The combined risk for all hearing-related AEs has been significantly higher among cannabis users compared to placebo-exposed patients, with tinnitus, loud noise, ringing in the ears, and vertigo as the most commonly reported AEs.[37]

4.3 | Gastrointestinal disorders

In our sample, gastrointestinal disorders include several AEs (reported as PT), such as: nausea, vomiting, and gastritis. A systematic review and meta-analysis published by Aviram and colleagues[37] has collected evidence on gastrointestinal AEs in patients treated with cannabis-based medicines for chronic and postoperative pain management. From 20 randomised controlled trials, the combined risk ratio for all gastrointestinal AEs was significantly higher in patients exposed to cannabinoids than in controls, especially in those who used oromucosal and oral cannabis preparations.[37] Furthermore, cannabis-related nausea and vomiting appear to be THC-dose-dependent AEs: at low doses, THC is characterised by antiemetic properties, but at high doses, is proemetic.[38]

Despite antiemetic effects of cannabis are well described, as in animal models cannabinoids show both an antiemetic/emetic response,[39] a paradoxical syndrome of hyperemesis resultant from cannabinoids exposure has been already defined also in humans. This syndrome is labelled cannabinoid hyperemesis syndrome (CHS), and consists of nausea, vomiting and abdominal pain particularly associated with chronic use.[40] A recent retrospective observational study shows that, among cannabis users, gastrointestinal symptoms, including CHS, are the most common cause of cannabis-related emergency departments visits.[41] Two main hypothesis involving THC try to explain this phenomenon. The first suggests that THC directly activates cannabinoid receptors in the enteric nervous system, reducing gastric motility, and promoting a proemetic state. A second explanation of this phenomenon has taken into account (i) the impairing in thermoregulation and (ii) the alteration of the hypothalamic–pituitary–adrenal axis caused by cannabinoids, which reduces body temperature and prolactin, gonadotropin, and growth hormone release, and increases corticotrophin secretion.[42] Impaired body temperature and hypothalamic–pituitary–adrenal axis alterations have been also associated with the development of CHS, which is characterised by 3 phases: prodromal, hyperemetic and recovery phase. Patients usually access emergency departments during the hyperemetic phase, presenting profuse vomiting.[43] Even if mild, nausea and vomiting could have a deep impact on patients' morbidity and quality of life, and an economic burden for hospitals and healthcare systems. Therefore, clinicians should consider cannabis as a cause of cyclic nausea and vomiting, especially in chronic cannabis users and in patients treated with oral cannabis preparations, particularly in oncological patients.

4.4 | General disorders and administration site condition

In our sample, among *general disorders and administration site condition*, *lack of efficacy* is the most frequently reported PT. Such event can derive from (i) the prescription of an inadequate dosage of prescribed/administered cannabis, (ii) presence of interactions that can reduce the effectiveness of the preparation, (iii) incorrect intake, or (iv) personal sensitivity.

In 2015 the Italian Ministry of Health has recommended clinicians to start a therapy based on cannabis with the minimum dose needed and, if necessary, to increase the dosage gradually.[44] Moreover, clinicians have to declare in their prescription which type of cannabis should be used for the preparation, according to the proper level of THC and CBD, and the total dose of cannabis should be adapted according to patient's clinical characteristics (i.e. age, sex, weight, comorbidity and presence of concomitant medications). Due to the need for a titration phase and to the accumulation in adipose tissue, until the circulating active fraction of THC and CBD raises, first administrations may result ineffective.[45] Of note, standard dosages for cannabis are currently not available from guidelines. Evidences provided by clinical trials allowed to establish the maximum daily doses recommended in clinical practice that ranges, from an initial dose of 25 mg to around 130 mg of cannabis with 19% of THC, both for chronic pain and multiple sclerosis, respectively.[46]

In our sample we encountered a total of 5 cases of *lack of efficacy*, and its onset differed among them. In particular, 3 patients (cases 5, 25 and 29) are affected by chronic neuropathic pain and 2 women (cases 49 and 50) are affected by multiple sclerosis. All of them have been treated with oral preparation of cannabis within the recommended therapeutic dose range. Moreover, in cases 29 and 49, patients were treated with cannabis concomitantly with other drugs, in particular analgesics (paracetamol/acetylsalicylic acid/caffeine and paracetamol/codeine fixed associations), etoricoxib,

colchicine and warfarin. Since patients with multiple sclerosis (cases 49 and 50) have been treated with very low doses of cannabis (60 mg daily) for a short period (1 and 2 months, respectively), we hypothesise that their titration phase was still ongoing when the AE *lack of efficacy* was reported. Considering that the length of medical cannabis treatment was very heterogeneous among these patients, and given the lack of information about individual factors, such as comorbidities, concomitant treatment, and genetic factors, we were not able to evaluate the possible relationship between length of medical cannabis exposure and the event *lack of efficacy*. Further investigations, with a larger sample of patients, could be performed to better clarify this issue. Moreover, to date no interaction between cannabinoids and etoricoxib and colchicine has been clearly identified. However, given that THC and CBD are both substrates and modulators of cytochrome (CYP) P450,[47] DDIs could not be excluded, particularly with drugs at low therapeutic index as warfarin.[48]

4.5 | Cardiac disorders

In our sample, we also observed some cardiovascular (CV) AEs, in particular (reported as PT): bradyarrhythmia (case 14) and bradycardia (case 46), tachycardia and tachyarrhythmia (cases 25, 33, 37, 40, and 48), supraventricular tachycardia (cases 16 and 44), and palpitations (case 42).

Regarding CV AEs related to medical cannabis (e.g. atrial fibrillation, acute coronary syndromes, ventricular tachycardia, and even sudden death), available evidence appears to be insufficient to draw a definitive conclusion on the effects of cannabis on these kind of manifestations and its possible mechanism.[49] It is well known that CB2 receptors are located in cardiac myocyte and in the smooth muscles of blood vessels. Nevertheless, the exact mechanism of the various vascular effect of cannabis is not yet clear.[50] Furthermore, in the study published by Whiting and colleagues, the authors did not find any statistically significant association between cannabis use and the occurrence of CV AEs.[6]

4.6 | Drug-drug interactions

In the majority of cases reported in our sample, patients are administered with at least another concomitant prescribed medication over their cannabis prescription. Although DDIs are a major concern for physicians, few studies have examined the effects of DDIs involving cannabis preparations. Most available evidence derives only from preclinical studies and currently the extent of cannabis-related DDIs in real-world practice remains poorly investigated.

As mentioned above, oral cannabinoids are metabolised by the enzyme family of CYP450, and THC and CBD are inhibitors of CYP2C9, CYP3A4, and CYP2C19, while smoked cannabis is demonstrated to induce CYP1A1 and CYP1A2.[51] Moreover, CBD inhibits P-glycoprotein mediated transports in a dose-dependent manner.[52] Established cannabis-related DDIs involve THC and psychotropic agents,[51] CBD and anticancer agents,[53] CBD and gabapentin,[54] and cannabinoids and warfarin.[48] In general, clinicians should always take into account that medical cannabis could bidirectionally interact with concomitant administered agents by affecting membrane transporters and/or metabolising enzymes.[47]

In our sample, among patients treated with at least another prescribed medication over cannabis, only in 1 case (case 48) did the physician specifically report *pharmacological interaction* as PT. However, from our case-by-case analysis, we have identified other 16 cases in which the presence of DDI could be involved in the AE. Alteration of the mental status, dysphoria, dizziness, drowsiness and balance disorders are reported concomitantly to the use of opioids, such as fentanyl (cases 3 and 28), tapentadol (case 4), codeine (alone or in association, cases 6, 9, 30 and 47), oxycodone and naloxone (cases 17, 21, 33 and 47), and concomitantly to the use of pregabalin (cases 2, 9, 17, 21, 28, 33, 38 and 40) and gabapentin (case 48). One patient (case 21) has shown as concomitant medications alprazolam, escitalopram, oxycodone and pregabalin, together with duloxetine, insulin and pantoprazole. Furthermore, we observed a patient concomitantly exposed to cannabis and cyclosporine (case 53), after a renal transplant, who experienced hallucinations and nausea. This case is particularly relevant due to the fact that the concomitant exposure to cannabis and cyclosporine could be related to a transplant failure.[55]

These results allow us to make some considerations. Considering that the AEs reported in all these cases are common to cannabis and opioid derivatives, benzodiazepines and antiepileptic agents, and that are listed as adverse drug reactions in the summary of products characteristics for all the concomitant medications registered, we believe that all reported AEs may be due to a synergistic interaction between cannabis and other agents. Moreover, in a clinically complex condition such those represented by some of our cases and considering the excellent analgesic properties of cannabis,[4] it should be advisable to gradually reduce the administration of opioids, up to interrupt it when possible, in order to reduce the potential inappropriate prescription. Finally, according to pharmacovigilance and phytovigilance guidelines,[56,57] the quite low number of DDIs identified and reported in our sample, probably highlights the need to increase physicians' awareness about this clinically relevant event as cannabis-related cause of AEs.

5 | STRENGTHS AND LIMITATIONS

This study has some limitations and strengths. First, our analysis is based on AE reports that are affected by limits that include inaccurate and incomplete information, mainly related to lack of clinical data. Given that, the absence of information that was not listed in AE reports and that might have influenced the clinical evaluation of each report (i.e. the lack of information on previous and/or current patient medical conditions which could affect the clinical evaluation of each case) could not always be excluded. Moreover, data concerning medical cannabis prescriptions in Tuscany among the study period were not available.

Despite these limitations, this is the first study describing all medical cannabis-related AEs observed in the general population. Furthermore, considering that medical cannabis-related AEs reporting is mandatory for clinicians, we can affirm that our case series includes the totality of patients who experienced a cannabis-related AE in Tuscany within the study period.

6 | CONCLUSIONS

Our case-by-case assessment of AEs following medical cannabis treatment underlined several potential safety issues of great importance for clinical practice.

Cannabis was well tolerated and the majority of AEs were mild and transient. Nevertheless, prescribing cannabis, clinicians should be aware that, especially during the titration phase, cannabis could result ineffective and that the occurrence of psychiatric and gastrointestinal AEs, mainly paradoxical nausea and vomiting, may increase as cannabis dosages increase too fast and if cannabis is administered orally. Moreover, clinicians should be aware of the possible occurrence of cannabis-related AEs in older or complex patients, exposed to concomitant synergic medications, for whom phenomena can occur not only of interaction, but also of inappropriate prescribing. Our results have also highlighted that cannabis was used as adjunct treatment in a relevant proportion of cases, particularly in pain management, thus justifying the importance of monitoring prescriptions.

The risks associated with long-term use of medical cannabis are still poorly characterised in published clinical trials and observational studies. A good vigilance of cannabis-related AEs may improve our knowledge of cannabis safety profile, filling the gaps of clinical studies. Moreover, these results could ameliorate current clinical practice and lead to correct use of cannabis exploiting its full potential.

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CONTRIBUTORS

Study design was contributed by GC, NL, VM, and AV, with assistance from the rest of the authors. Data acquisition was performed by FMI, RDC, MDL, EG and FF. Data interpretation was performed by GC, NL, VM, and AV, with assistance from the other authors. The manuscript was written primarily by GC and NL, with assistance from the other authors, and revised by AB, AM, and AV. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Italian National Institute of Health (Istituto Superiore di Sanità, ISS). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the Italian National Institute of Health (Istituto Superiore di Sanità, ISS).

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