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SYSTEMATIC REVIEW

The Characteristics of Clinical Trials on Cannabis and Cannabinoids: A Review of Trials for Therapeutic or Drug Development Purposes

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Abstract

Introduction Patients and healthcare practitioners are increasingly interested in using cannabis and cannabinoids to address unmet clinical needs. Although we have clinical evidence on the medical use of cannabinoids, a significant portion of the data is not based on randomized clinical trials, which are considered the gold standard in clinical research. We have reviewed the registered clinical trials on cannabis and cannabinoids for therapeutic or drug development purposes to underline the past and current attempts to generate robust clinical evidence and identify existing knowledge gaps.

Methods We reviewed four clinical trial registries (International Clinical Trials Registry Program [ICTRP], ClinicalTrials.gov, European Clinical Trial Registry [EUCTR], Australian New Zealand Clinical Trial Registry [ANZCTR]) to identify clinical trials on cannabinoids (phyto- or synthetic) or cannabis-based medications between January 1, 2000, and December 31, 2021. All interventional clinical trials on cannabinoids and other compounds interacting with the endocannabinoid system, regardless of the investigated medical condition, assessed health outcomes, or choice of comparator, were included, provided they had a therapeutic or drug development purpose. Data on the primary sponsor, type of sponsor, date of registration, recruitment status, number of participants, study design, the phase of the study, country, medical conditions, investigated cannabinoids, and the route of administration were extracted. The therapeutic area and class of cannabinoids were identified based on the details of each trial.

Results We included 834 out of 2966 reviewed clinical trials. The number of registered clinical trials has constantly increased from 30 in 2013 to 103 in 2021. More than 40% of registered clinical trials in 2021 were phase II and phase III clinical trials. The mean number of trial enrollments for completed, ongoing, and terminated studies were 128, 156, and 542, respectively. Clinical research on Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), and the oral routes of administration dominate the field. Approximately two-thirds of clinical trials were conducted in five therapeutic areas (i.e., 'Chronic pain,' 'Mental, behavioral or neurodevelopmental disorders,' 'Nervous system diseases,' 'Endocrine, nutritional or metabolic diseases,' and 'Neoplasms'). Pharmaceutical companies sponsored 39% of all clinical trials. However, trial sponsorships vary noticeably in different jurisdictions, likely due to, in part, different regulatory frameworks.

Conclusion Our review highlights the diversification of clinical trials on cannabinoid-based medications in the past 21 years. This review underlines the increased interest in conducting clinical studies on new cannabinoid administration methods such as topical applications and on the investigation of emerging phyto- and synthetic cannabinoids. Moreover, more clinical trials have been designed to explore the potential therapeutic benefits of cannabinoids in areas such as mental, behavioral, or neurodevelopmental disorders and skin diseases. There is a need for granular analyses of clinical trials on more commonly studied therapeutic areas such as chronic pain, nervous system diseases, and mental and behavioral disorders to generate more actionable information and insight for all stakeholders.

1 Introduction

Cannabis has been used as a medicine for millennia; however, many countries started prohibiting cannabis use at the beginning of the twentieth century [1]. Removing cannabis from the US pharmacopeia in 1942 reinforced the idea that cannabis did not have any therapeutic value. More countries followed the US and outlawed cannabis use as a medication

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Key Points

The overwhelming majority of clinical trials have been conducted on cannabidiol (CBD) and Δ9- tetrahydrocannabinol (THC); however, there is a need for well-designed randomized controlled trials to explore the therapeutic benefits of other cannabinoids.

Commercial entities (e.g., pharmaceutical companies) have shown interest in investing in clinical research on cannabinoids. However, this interest is contingent on a robust regulatory framework.

[2]. These regulatory changes hindered the basic and clinical research on cannabis and cannabinoids. Consequently, patients and healthcare practitioners were left without essential efficacy and safety information on the medical use of cannabinoids [3].

The movement for medical cannabis legalization has strengthened since the beginning of the twenty-first century. Canada was the first G7 country to legalize the medical use of cannabis, in 2001 [4]. More Western countries (e.g., the Netherlands, Portugal, Germany, Australia, and the UK) legalized or decriminalized cannabis for medical purposes in the following years [5]. The change in the legal status of medical cannabis resulted from a shift in the public's opinion on the harm and benefit of cannabis. In a survey carried out by Ipsos in 2019, 57% of respondents believed that the use of cannabis for medical purposes was justified. In countries like the US, Chile, Canada, Australia, Poland, Germany, and the UK, more than two-thirds of people support cannabis for medical purposes [6]. A more recent survey by Gallup showed that medical cannabis legalization support has increased from 34% in 2001 to 68% in 2021 [7]. Consequently, more patients and their caregivers initiate conversations with healthcare practitioners about using cannabis as a therapeutic option.

The attitude of healthcare practitioners has also changed in recent years. Several surveys demonstrated that most healthcare practitioners supported cannabis and cannabinoids for medical purposes [8–14]. A systematic review of 40 studies between 1971 and 2019 reported that healthcare practitioners' support for the legalization of medical cannabis has increased over time [9]. This change can be the result of the increased awareness of healthcare practitioners about the pharmacokinetic and pharmacodynamic properties of cannabinoids, including the psychoactive effect of THC and the non-psychotropic properties of other cannabinoids. Systematic reviews and meta-analyses published in recent years highlighted the potential therapeutic value of cannabinoids and cannabis-based medications in managing chronic pain, spasticity in multiple sclerosis, neurodegenerative diseases, and treatment-refractory epilepsy [2, 3, 15–21]. Moreover, approval of cannabinoid-based medications boosted the medical community's confidence in the therapeutic value of cannabinoids (Table 1). However, healthcare practitioners rated their knowledge of medical cannabis and the endocannabinoid system (ECS) poor and requested more training and clinical guidelines in surveys conducted in 2019 and 2021 [11, 14].

Despite the interest and need for robust clinical evidence on the efficacy and safety of cannabinoids, there is not enough high-quality clinical evidence to answer clinicians' and patients' questions. Several systematic reviews and evidence mappings on medical cannabis highlighted the need for more controlled studies [3, 17, 18, 20, 22–25]. A systematic review in *JAMA* called for more randomized controlled trials (RCTs) in compliance with Consolidated Standards of Reporting Trials (CONSORT) reporting standards to ensure the use of appropriate tools in measuring and reporting relevant outcomes [19]. The National Academy of Science, Engineering, and Medicine report, based on the review of more than 10,000 publications on cannabinoids and cannabis-based medications, recommended more short- and long-term high-quality research by developing a set of research standards, improving surveillance capacity, and addressing research barriers such as access to standardized cannabis-based products and research funding [21].

One of the first steps in addressing these knowledge gaps is analyzing the past and current clinical trials conducted on cannabinoids and the ECS. Our research aims to analyze the data on registered clinical trials on the therapeutic effect of cannabinoids and other agents designed to assert their therapeutic effect via the ECS.

2 Methods

We identified clinical trials on cannabinoids (phyto- or synthetic) or cannabis-based medications registered between January 1, 2000, and December 31, 2021. The data from four clinical trial registries, International Clinical Trials Registry Program (ICTRP), ClinicalTrials.gov, European Clinical Trial Registry (EUCTR), and the Australian New Zealand Clinical Trial Registry (ANZCTR), were included because these databases contain the majority of registered human clinical trials.

A combination of broad (e.g., cannabinoids) and specific terms (e.g., nabiximols or cannabinol) was used for each registry to find the best balance between specificity and sensitivity of search terms (see Table 1 in the electronic supplementary material).

Table 1 List of medically approved cannabinoid-based products [22]

Name	Trade name	Active ingredient	Approved indication(s)	Approved by
Dronabinol	Marinol®	Synthetic THC	CINV, anorexia and weight loss in HIV patients	FDA, EMA
Nabilone	Cesamet™	Synthetic THC	CINV	FDA, EMA
Nabiximols	Sativex®	THC and CBD	Spasticity in MS patients	EMA, Health Canada
Cannabidiol	Epidiolex®	CBD	Seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in pediatric patients	FDA, EMA

CBD cannabidiol, *CINV* chemotherapy-induced nausea and vomiting, *EMA* European Medicine Agency, *FDA* Food and Drug Administration, *HIV* human immunodeficiency virus, *MS* multiple sclerosis, *THC* Δ9-tetrahydrocannabinol

Clinical trials were included if they investigated a compound that interacted with the ECS or impacted the metabolism of cannabinoids or endogenous cannabinoids for therapeutic or drug development purposes. These included synthetic analogs of cannabinoids, ligands for a cannabinoid receptor, enzyme inhibitors, or plant-based cannabinoids. All clinical trials, regardless of the investigated medical condition, assessed health outcomes, or choice of comparator, were included in the review. Clinical trials designed to measure the effectiveness of cognitive-behavioral therapy methods, devices, or mobile applications or trials that assessed the abuse potential of cannabinoids were excluded.

The identified trials were exported into Microsoft Excel 365, and duplicates were removed using trial identification numbers. Then two researchers reviewed the trials' data independently to remove duplicates that might not have similar ID numbers due to registration in two different registries or dual registration of a single study (Table 2 in the electronic supplementary material).

We extracted the data on the primary sponsor, type of sponsor, date of registration, recruitment status, number of participants, study type (i.e., interventional or observational), study design, the phase of the study, country, medical condition, investigated cannabinoids, and the route of administration. The therapeutic area and class of cannabinoids were identified based on the details of each trial.

We used the actual number of participants in clinical trials (if the data were available). We used the estimated enrollment if the actual number was not available.

Multicenter clinical trials were assigned to the country of the main sponsor or principal investigator because otherwise the number of clinical trials could be inflated. Therefore, we assigned each clinical trial to the country of the primary sponsor for multicenter trials if the country of the main sponsor was among the locations where patients had been recruited. If there was no patient recruitment in the main sponsor country, we considered the country of the principal investigator or main responsible organization as the country of the clinical trial.

In the absence of an agreed-upon classification for therapeutic areas, we decided to use the International Classification of Diseases 11th Revision (ICD-11) developed by the World Health Organization (WHO), because it is the 'global standard for diagnostic health information' [26]. This classification has been designed to address the needs of clinicians and researchers, and the codes are regularly updated based on emerging medical conditions or new definitions of existing conditions. We used the top level of each category to create a therapeutic classification with two exceptions: (1) lower-level ICD-11 codes (i.e., MG30 for chronic pain and MG31 for acute pain) were used for trials on pain for a more precise analysis, instead of classifying under the 'Symptoms, signs or clinical findings, not elsewhere classified'; (2) 'cancer-related' symptoms (excluding cancer-related pain, categorized under chronic pain) were grouped in the 'Neoplasms' category because no codes represented 'cancer-related' symptoms. To avoid confusion, we reported the number of trials investigating cancer and 'cancer-related symptoms' separately.

The trials that were not designed to assess a specific medical condition and, for that reason, could not be assigned to a specific therapeutic area were categorized as 'multiple therapeutic areas'

Cannabinoids were categorized according to the objectives of trials and their impact on patients' outcomes. All investigated cannabinoids were recorded if more than one cannabinoid was investigated in a trial. Trials investigating a high ratio (defined as 20:1 or higher) of Δ9-tetrahydrocannabinol (THC) to cannabidiol (CBD) or vice versa were categorized by the dominant cannabinoid. Trials that investigated the 1:1 ratio of THC and CBD were

categorized as 'THC:CBD,' while other ratios were categorized as 'THC/CBD.'

Trials sponsors were grouped using the ANZCTR classification of clinical trial sponsors [27]. Two more categories, 'Government/academia partnership' and 'Industry/academia partnership,' were added to reflect the partnership among sponsors of clinical trials.

3 Results

The search identified 2966 clinical trials from four clinical trial registries, of which 834 were included in our review after excluding 762 duplicates and 1369 studies that did not meet the inclusion criteria (228 observational studies, one expanded access study, 1140 interventional studies that did not investigate cannabinoids or did not assess cannabinoids for therapeutic or drug development purposes) (Fig. 1). We also excluded one study (NCT03944447) that met the inclusion criteria, because the estimated number of participants was 200,000, which was more than the total number of participants in all clinical trials on all registries combined.

The median and mean numbers of participants for all clinical trials were 52 and 147, respectively. The mean trial enrollments for completed, ongoing, and terminated studies were 128, 156, and 542, respectively.

The review of the characteristics of clinical trials on cannabis and cannabinoids shows that most clinical trials were randomized, phase II, and registered on ClinicalTrials.gov, with a sample size of less than 49 participants (Table 2). The US, the UK, Australia, Canada, and Israel contributed to 609 clinical trials (73.0%), and the US had the highest contribution with 306 trials (36.7%) (Table 3).

The annual number and size of clinical trials on cannabinoids have changed in the last 21 years (Fig. 2). The mean number of participants in clinical trials in 2021 was 88 compared to 1338 in 2005, which shows a 93.4% decline. The number of registered phase I, II, and III clinical trials between 2005 and 2008 were nine, 43, and 82, respectively, while 66 phase I, 128 phase II, and only 53 phase III clinical trials were registered between 2018 and 2021 (Fig. 3). The mean number of participants in phase III trials has dropped from 2358 in 2005 to 187 in 2021, indicating a 92.1% reduction. The mean number of participants in phase II trials has declined from 206 in 2005 to 75 in 2021, a 63.6% decrease. In contrast, the mean number of phase I trials has increased from 23 in 2005 to 45 in 2021, showing a 101.2% growth, and the mean number of participants in phase IV trials has grown from 24 in 2005 to 65 in 2021, indicating a 169.2% increase.

Approximately two-thirds of clinical trials (569) were conducted in five therapeutic areas. 'Chronic pain' with 158 (18.9%), 'Mental, behavioral or neurodevelopmental disorders' with 152 (18.2%), 'Nervous system diseases' with 140 (16.8%), 'Endocrine, nutritional or metabolic diseases' with 71 (8.5%), and 'Neoplasms' with 48 (5.8%) were the most investigated therapeutic areas. The therapeutic area in 96 clinical trials (11.5%) were not specified (Fig. 4). Out of 48 trials under the category of 'Neoplasms,' 35 (72.9%) assessed 'cancer-related' symptoms such as chemotherapy-induced nausea, vomiting, cancer-related cachexia, and anorexia.

Approximately two thirds of all clinical trials, 566 (67.9%), were conducted on three classes of cannabinoids: 295 (35.4%) with Cannabinoid (CB) allosteric modulators (i.e., CBD), 199 (23.9%) with partial CB_1/CB_2 agonists (i.e., THC and its synthetic analogs), and 72 (8.6%) with selective CB_1 antagonist/inverse agonists (i.e., rimonabant). Multiple cannabinoids were studied in 201 trials (24.1%).

The top five most studied cannabinoids were CBD with 289 trials (34.7%), THC:CBD with 113 (13.5%), dronabinol with 91 (10.9%), THC with 75 (9.0%), and rimonabant with 72 (8.6%). Although the vast majority of clinical trials, 351 (83.8%), have been conducted on these cannabinoids in the past 5 years, there has been an increasing interest in novel ECS modulators such as palmitoylethanolamide (PEA), lenabasum, and cannabidivarin, with seven, six, and three registered trials, respectively (Fig. 5).

Although oral administration was the most studied delivery method, with 576 trials (69.1%), there has been more interest in other delivery methods in recent years. Since 2017, 48 clinical trials have been registered to assess topical, sublingual, and transdermal delivery methods, constituting 85.7% of all trials on these routes of administration (Fig. 6).

Commercial entities have sponsored 325 trials (39.0%). In comparison, universities and hospitals have sponsored 248 (29.7%) of all clinical trials (Fig. 7). Commercial entities sponsored 50 (58.1%) of all registered clinical trials on cannabinoids in Australia. In comparison, they have only sponsored 77 (25.2%) of 306 registered clinical trials in the US. Universities and government partnerships played a more substantial role in the US by sponsoring 118 trials (38.6%) (Table 4).

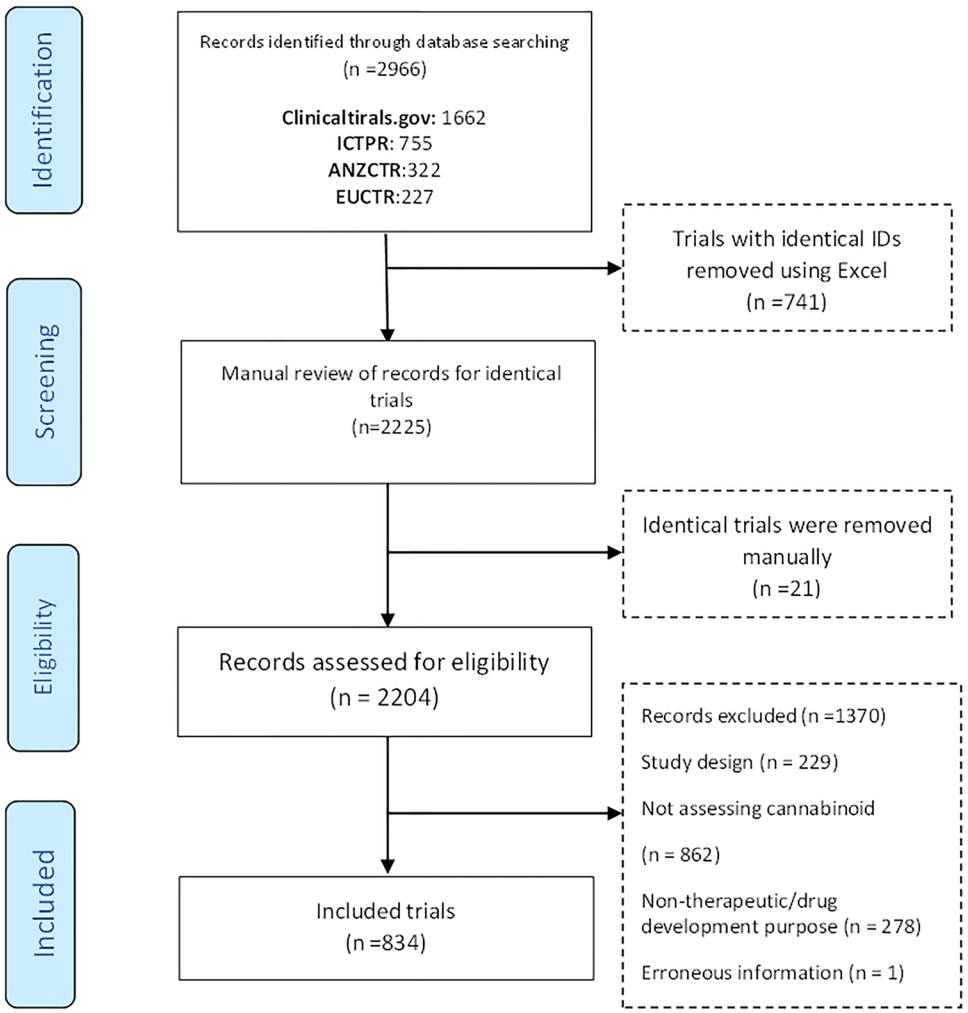

Fig. 1 Flow chart for study selection. *ANZCTR* Australian New Zealand Clinical Trial Registry, *EUCTR* European Clinical Trial Registry, *ICTRP* International Clinical Trials Registry Program

4 Discussion

Our review highlights the interest of a wide range of stakeholders, including commercial entities, academic institutions, and governments, to conduct clinical trials on less investigated cannabinoids, novel delivery methods, and expanded therapeutic areas in recent years. The first notable sign of increased interest in clinical research in cannabinoids dates back to 2005, when Sanofi-Aventis developed and sponsored several clinical trials to generate clinical evidence to receive the market authorization of rimonabant as a centrally acting weight loss agent [28]. These trials contributed to the increase in the number of participants in phase III clinical trials in 'Endocrine, nutritional or metabolic diseases' (i.e., obesity and dyslipidemia) between 2005 and 2008. Due to adverse psychiatric side effects, particularly depression, rimonabant was withdrawn from the market in 2008, and consequently, there was a significant decline in the number of registered clinical trials [29]. The suspension of rimonabant registration resulted in the termination of further investments in clinical trials on cannabinoids [30]. The total number of registered clinical trials increased again from 2013; however, this time, the diversity of the registered clinical trials was improved compared to the past.

More studies have been registered on new therapeutic areas, minor cannabinoids, and more diverse delivery methods since 2015. Our review highlighted an increased interest in assessing new therapeutic areas such as diseases of the musculoskeletal system, developmental anomalies, and skin diseases since 2015 (Fig. 4). This increase can be attributed to a reduction of the main barriers (i.e., regulatory status,

Table 2 Characteristics of included cannabis and cannabinoids clinical trials based on the targeted therapeutic areas

	Chronic pain	Mental, behavioral or neurodevelopmental disorders	Diseases of the nervous system	Multiple therapeutic areas[a]	Endocrine, nutritional or metabolic diseases	Neoplasms	Diseases of the digestive system	Diseases of the skin	Developmental anomalies	Acute pain	Other	Total
Registry												
ClinicalTrials.gov	118 (74.7)	116 (76.3)	96 (68.6)	75 (78.1)	40 (56.3)	24 (50.0)	22 (88.0)	12 (57.1)	14 (70.0)	13 (81.3)	63 (72.4)	593 (71.1)
EUCTR	20 (12.7)	10 (6.6)	29 (20.7)	8 (8.3)	30 (42.3)	8 (16.7)	2 (8.0)	2 (9.5)	3 (15.0)	2 (12.5)	11 (12.6)	125 (15.0)
ANZCTR	13 (8.2)	14 (9.2)	7 (5.0)	12 (12.5)	0 (0)	10 (20.8)	1 (4.0)	6 (28.6)	3 (15.0)	0 (0)	11 (12.6)	77 (9.2)
ICTRP	7 (4.4)	12 (7.9)	8 (5.7)	1 (1.0)	1 (1.4)	6 (12.5)	0 (0)	1 (4.8)	0 (0)	1 (6.2)	2 (2.3)	39 (4.7)
Randomization												
Yes	131 (82.9)	135 (88.8)	110 (78.6)	89 (92.7)	70 (98.6)	36 (75.0)	23 (92.0)	19 (90.5)	12 (60.0)	16 (100)	70 (80.5)	711 (85.3)
No	11 (7.0)	11 (7.2)	8 (5.7)	4 (4.2)	1 (1.4)	7 (14.6)	1 (4.0)	1 (4.8)	3 (15.0)	0 (0)	7 (8.0)	54 (6.5)
Not applicable	16 (10.1)	6 (3.9)	22 (15.7)	3 (3.1)	0 (0.0)	5 (10.4)	1 (4.0)	1 (4.8)	5 (25.0)	0 (0)	10 (11.5)	69 (8.3)
Number of participants												
≥ 1000	0 (0.0)	1 (0.7)	0 (0.0)	0 (0)	11 (15.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (3.4)	15 (1.8)
500–999	4 (2.5)	6 (3.9)	4 (2.9)	0 (0)	19 (26.8)	2 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	36 (4.3)
100–499	51 (32.3)	35 (23.0)	38 (27.1)	10 (10.4)	23 (32.4)	13 (27.1)	5 (20.0)	6 (28.6)	9 (45.0)	8 (50.0)	18 (20.7)	216 (25.9)
50–99	28 (17.7)	36 (23.7)	26 (18.6)	13 (13.5)	10 (14.1)	10 (20.8)	8 (32.0)	2 (9.5)	0 (0)	4 (25.0)	16 (18.4)	153 (18.3)
< 49	75 (47.5)	74 (48.7)	72 (51.4)	73 (76.0)	8 (11.3)	23 (47.9)	12 (48.0)	13 (61.9)	11 (55.0)	4 (25.0)	49 (56.3)	414 (49.6)
Phase												
Early phase I	7 (4.4)	5 (3.3)	3 (2.1)	6 (6.2)	0 (0)	0 (0)	0 (0)	1 (4.8)	0 (0)	1 (6.3)	3 (3.4)	26 (3.2)
Phase I	21 (13.3)	16 (10.5)	9 (6.4)	66 (68.8)	1 (1.4)	9 (18.8)	0 (0)	6 (28.6)	0 (0)	1 (6.3)	9 (10.3)	138 (16.6)
Phase I–II	13 (8.2)	15 (9.9)	7 (5.0)	0 (0)	1 (1.4)	8 (16.7)	5 (20.0)	1 (4.8)	2 (1.0)	0 (0)	10 (11.5)	62 (7.5)
Phase II	49 (31.0)	73 (48.0)	52 (37.1)	7 (7.3)	10 (14.1)	18 (37.5)	11 (44.0)	7 (33.3)	7 (35.0)	4 (25.0)	38 (43.7)	276 (33.2)
Phase II–III	5 (3.2)	10 (6.6)	5 (3.6)	0 0	3 (4.2)	2 (4.2)	1 (4.0)	2 (9.5)	3 (15.0)	2 (12.5)	8 (9.2)	41 (4.9)
Phase III	37 (23.4)	15 (9.9)	52 (37.1)	1 (1.0)	46 (64.8)	7 (14.6)	2 (8.0)	1 (4.8)	8 (40.0)	3 (18.8)	9 (10.3)	181 (21.8)
Phase IV	13 (8.2)	5 (3.3)	9 (6.4)	6 (6.3)	10 (14.1)	2 (4.2)	2 (8.0)	1 (4.8)	0 (0)	3 (18.8)	4 (4.6)	55 (6.6)
Not applicable	12 (7.6)	12 (7.9)	3 (2.1)	10 (10.4)	0 (0)	2 (4.2)	4 (16.0)	2 (9.5)	0 (0)	2 (12.5)	6 (6.9)	53 (6.4)
Information not available	1 (0.6)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.2)
Grand total	**158** (100)	**152** (100)	**140** (100)	**96** (100)	**71** (100)	**48** (100)	**25** (100)	**21** (100)	**20** (100)	**16** (100)	**87** (100)	**834** (100)

Data are presented as *n* (%)

ANZCTR Australian New Zealand Clinical Trial Registry, *EUCTR* European Clinical Trial Registry, *ICTRP* International Clinical Trials Registry Program

[a]The trials that were not designed to assess a specific medical condition and, for that reason, could not be assigned to a specific therapeutic area were categorized as 'multiple therapeutic areas'

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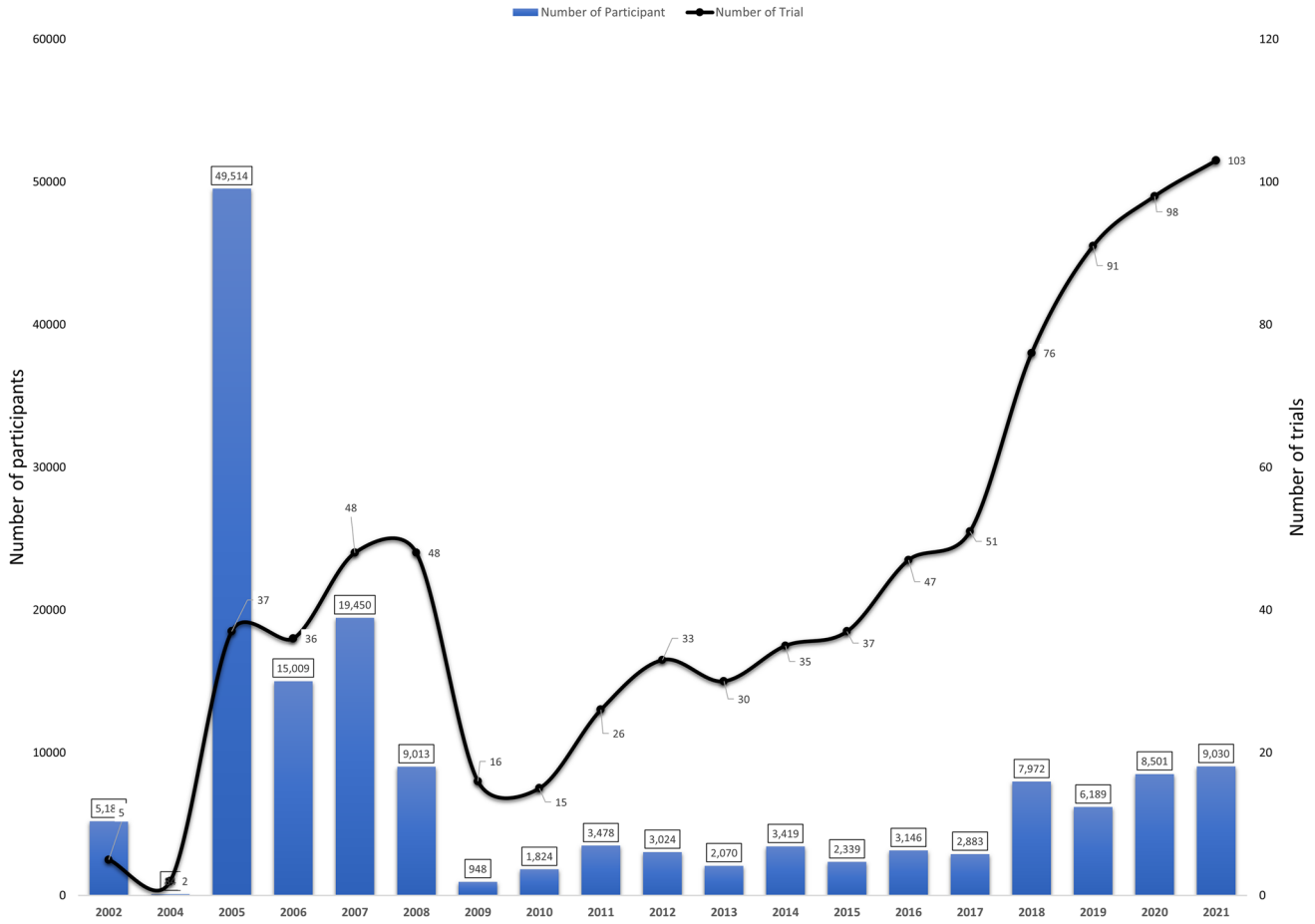


Fig. 2 Trends of registered cannabis and cannabinoids clinical trials and the total number of participants (2000–2021). No eligible studies were found in years 2000, 2001, and 2003

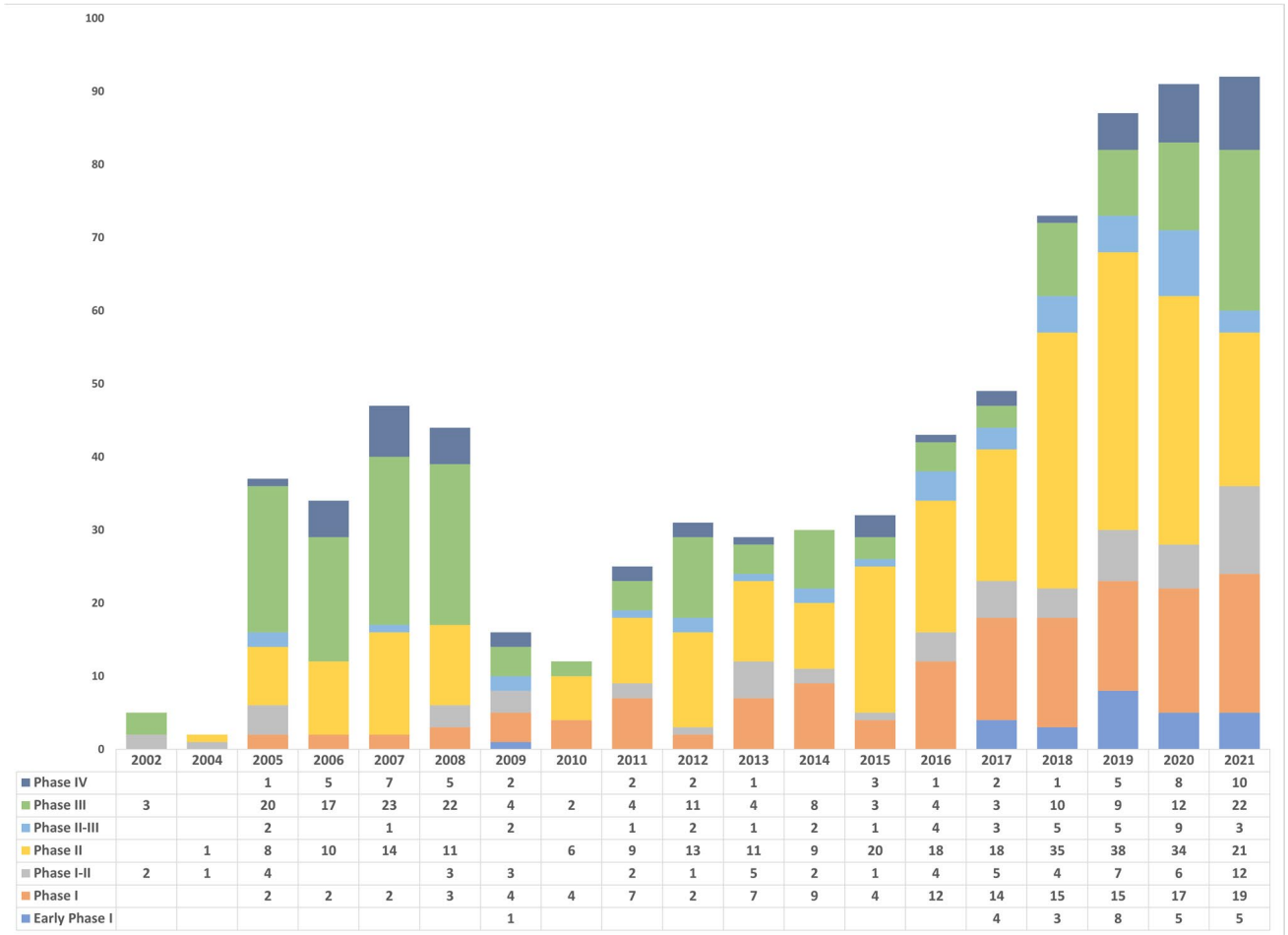
research funding and cannabinoid supply). More countries (and states in the US) have developed regulatory frameworks for using medical cannabis and conducting research. Research funding has increased since 2015 [31], and the supply of cannabinoids has improved [21, 31]. For instance, National Institutes of Health (NIH) research expenditures on all four categories of cannabinoid, CBD, endocannabinoid, and therapeutic cannabinoids increased between 2015 and 2019. The total NIH research investment on cannabinoids was US$339 million in 2019 compared to US$141 million in 2015 [31]. All these factors enabled researchers to design trials for new therapeutic areas such as skin diseases and developmental anomalies.

THC and CBD are the main cannabinoids produced by the cannabis plant and are considered major cannabinoids. In contrast, other cannabinoids with a lower concentration in the cannabis plant are known as minor cannabinoids [32]. Minor cannabinoids are not psychoactive [33], which can substantially improve their safety profile. Most

Table 3 Top 15 countries with the most registered cannabis and cannabinoids clinical trials

Countries	Clinical trials
United States	306 (36.7)
United Kingdom	113 (13.5)
Australia	86 (10.3)
Canada	62 (7.4)
Israel	42 (5.0)
France	40 (4.8)
Germany	30 (3.6)
Netherlands	28 (3.4)
Italy	19 (2.3)
Austria	17 (2.0)
Denmark	16 (1.9)
Spain	13 (1.6)
Switzerland	8 (1.0)
Brazil	7 (0.8)
Iran	6 (0.7)

Data are presented as *n* (%)

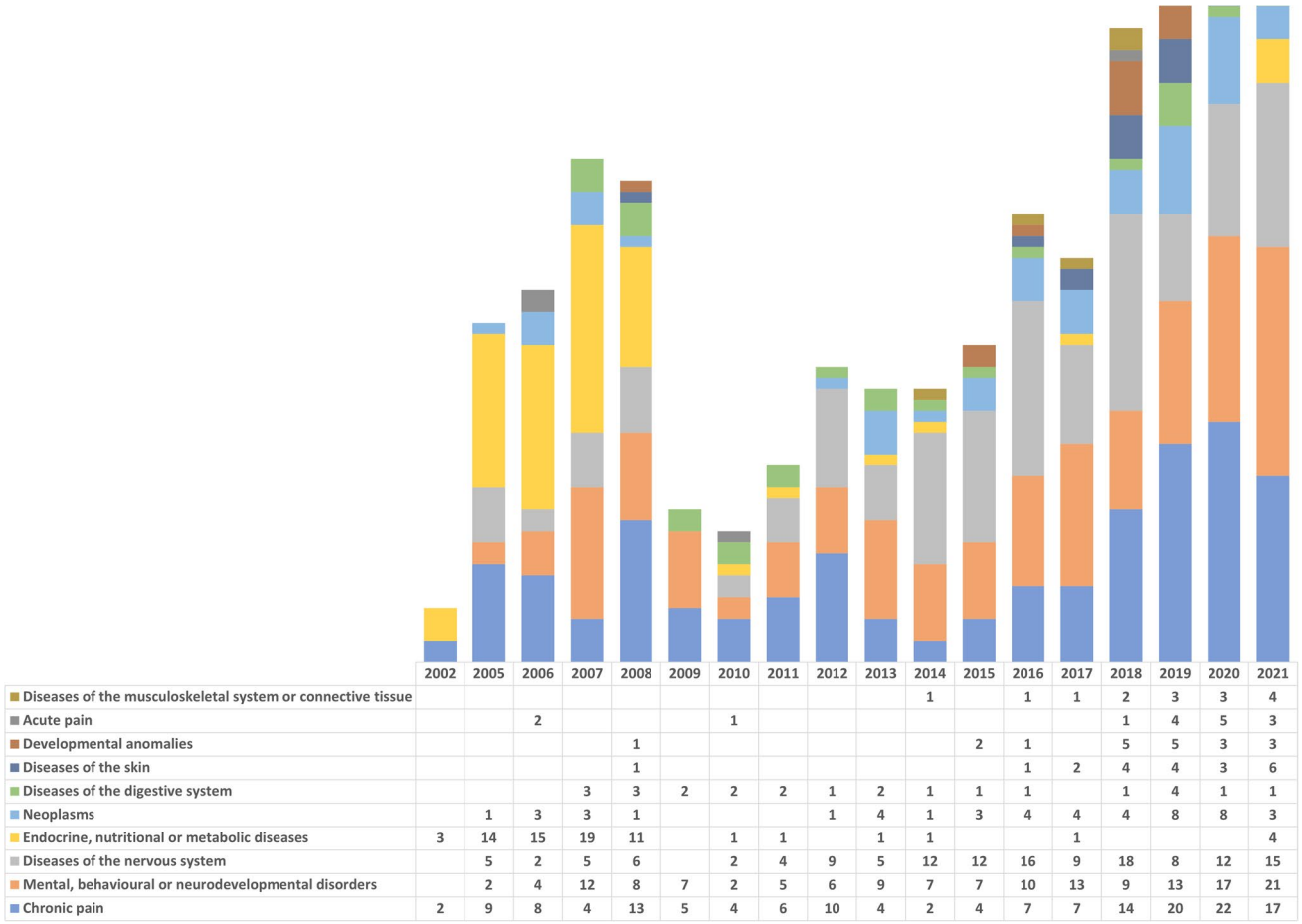


	2002	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Phase IV			1	5	7	5	2		2	2	1		3	1	2	1	5	8	10
Phase III	3		20	17	23	22	4	2	4	11	4	8	3	4	3	10	9	12	22
Phase II-III			2		1		2		1	2	1	2	1	4	3	5	5	9	3
Phase II		1	8	10	14	11		6	9	13	11	9	20	18	18	35	38	34	21
Phase I-II	2	1	4			3	3		2	1	5	2	1	4	5	4	7	6	12
Phase I			2	2	2	3	4	4	7	2	7	9	4	12	14	15	15	17	19
Early Phase I							1								4	3	8	5	5

Fig. 3 Number of cannabis and cannabinoids clinical trials by the phase of studies (2000–2021)

reported adverse events of cannabis-based medications are because of the psychoactive nature of THC [15], and the use of nonpsychoactive cannabinoids can address the primary safety concern of cannabis-based medications and expand their clinical applications. The opioid crisis has also contributed to the recent increased interest in clinical research on cannabinoids. In the US alone, 50,000 people die every year from opioid overdose, and prescription opioids are a factor in one-third of all opioid overdose deaths [34]. Twenty-five percent of all patients who received opioids for their non-cancer pain for longer than 12 months showed signs of opioid dependence [35]. There is substantial evidence about the analgesic effect of cannabinoids [21], which makes them a potential candidate for a substitution or an adjuvant treatment to opioids in managing chronic pain. There is a strong incentive for researchers to conduct more clinical studies on minor cannabinoids [36].

The registration of more clinical trials to investigate non-oral formulations can signify the transition of cannabis-based medications toward mainstream medicine. One of the barriers to the acceptance of cannabis-based medications in daily practice by clinicians has been the lack of clinical evidence [21] due to the lack of clinical research. The lack of products designed to meet the requirement of clinical studies and regulatory authorities (such as predictable delivery of active ingredients) was one of the hurdles in conducting clinical studies [31]. Availability of a wide range of formulations and delivery methods is a big step to overcoming one of the barriers to conducting clinical research on different therapeutic areas and acceptance of investigated products by clinicians. While there are various cannabis-based formulations available, there is still a gap between cannabis-based and conventional medications. For instance, there are not enough clinical trials



	2002	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Diseases of the musculoskeletal system or connective tissue											1		1	1	2	3	3	4
Acute pain			2				1								1	4	5	3
Developmental anomalies					1							2	1		5	5	3	3
Diseases of the skin					1								1	2	4	4	3	6
Diseases of the digestive system				3	3	2	2	2	1	2	1	1	1		1	4	1	1
Neoplasms		1	3	3	1				1	4	1	3	4	4	4	8	8	3
Endocrine, nutritional or metabolic diseases	3	14	15	19	11		1	1		1	1			1				4
Diseases of the nervous system		5	2	5	6		2	4	9	5	12	12	16	9	18	8	12	15
Mental, behavioural or neurodevelopmental disorders		2	4	12	8	7	2	5	6	9	7	7	10	13	9	13	17	21
Chronic pain	2	9	8	4	13	5	4	6	10	4	2	4	7	7	14	20	22	17

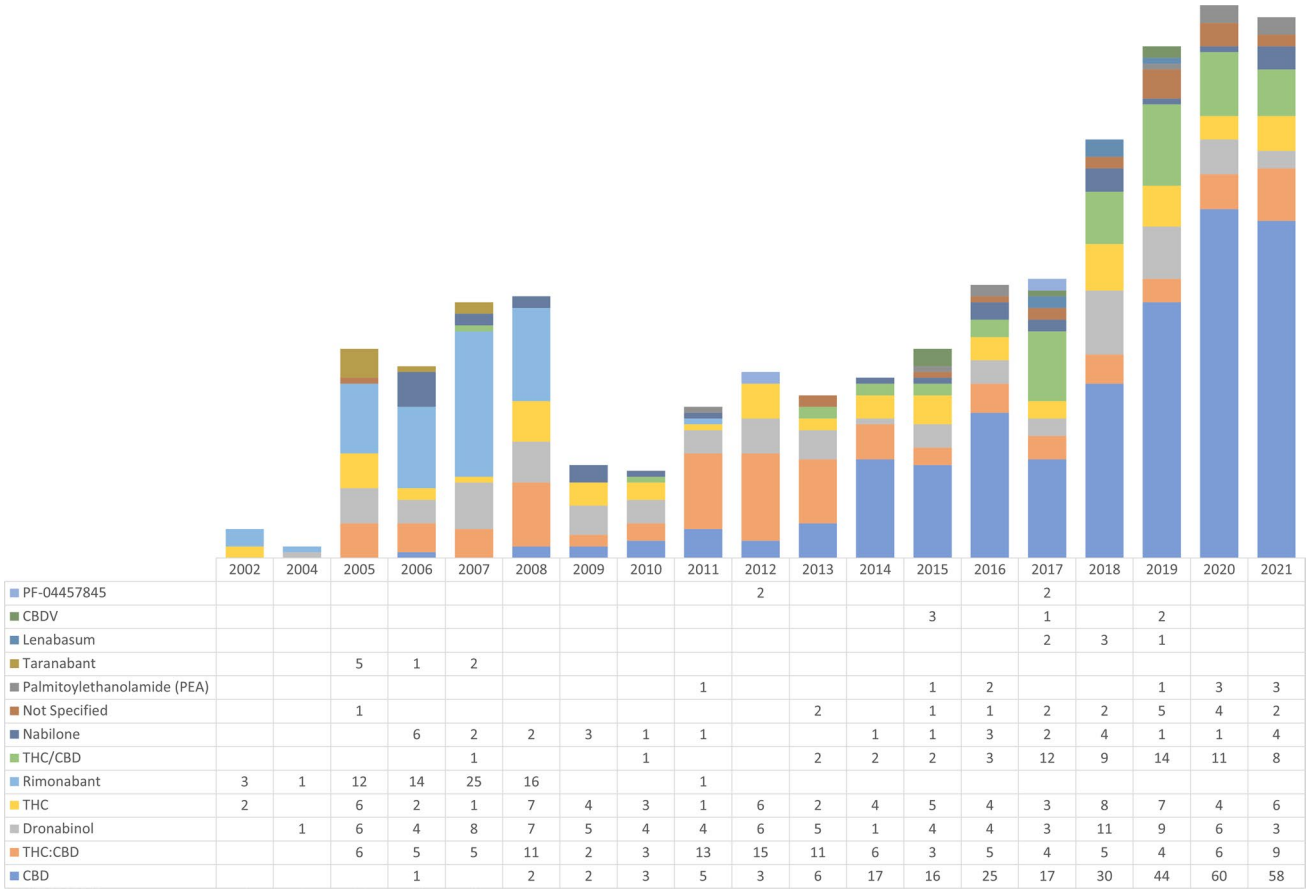
Fig. 4 Top 10 most investigated therapeutic areas for cannabis and cannabinoids (2000–2021)

on cannabis-based medications investigating injectable forms, while an analysis of Food and Drug Administration (FDA)-approved medications highlighted that 22.5% of all approved products are injections [37].

The diversification of clinical trials may also indicate the initial steps in introducing a more diverse range of cannabis-based medications. Understanding the ECS, its complex signaling mechanisms, and its interaction with non-cannabinoid receptors is crucial with regard to designing efficient pharmacological interventions [38]. Studying different aspects of cannabinoids, such as advanced medication delivery methods and their impact on other medications and conditions, can generate the required evidence for introducing a successful drug candidate. Otherwise, we may have another failed experience like rimonabant if we rush to launch a cannabis-based medication before realizing the relationship between the ECS, cannabinoids, and other organs.

The different patterns of sponsoring clinical trials among countries can be attributed to the various regulatory frameworks. Cannabis is currently considered a drug with no accepted medical use at the federal level in the US [39]. This classification has resulted in supply and funding barriers for clinical research on medical cannabis [21, 31] and discouraged the commercial sector from investing in clinical research. On the contrary, Australia's transparent national regulatory framework for access to medical cannabis and cannabis-based medications [40] has encouraged commercial entities to invest in clinical research.

This is the first comprehensive analysis of clinical trials of cannabis, cannabinoids, and their analogs to the best of our knowledge. Goyal and his colleagues published a similar analysis but with limited scope to investigate clinical trials in



	2002	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
PF-04457845										2					2				
CBDV													3		1		2		
Lenabasum															2	3	1		
Taranabant			5	1	2														
Palmitoylethanolamide (PEA)									1				1	2			1	3	3
Not Specified			1								2		1	1	2	2	5	4	2
Nabilone				6	2	2	3	1	1			1	1	3	2	4	1	1	4
THC/CBD					1			1			2	2	2	3	12	9	14	11	8
Rimonabant	3	1	12	14	25	16			1										
THC	2		6	2	1	7	4	3	1	6	2	4	5	4	3	8	7	4	6
Dronabinol		1	6	4	8	7	5	4	4	6	5	1	4	4	3	11	9	6	3
THC:CBD			6	5	5	11	2	3	13	15	11	6	3	5	4	5	4	6	9
CBD				1		2	2	3	5	3	6	17	16	25	17	30	44	60	58

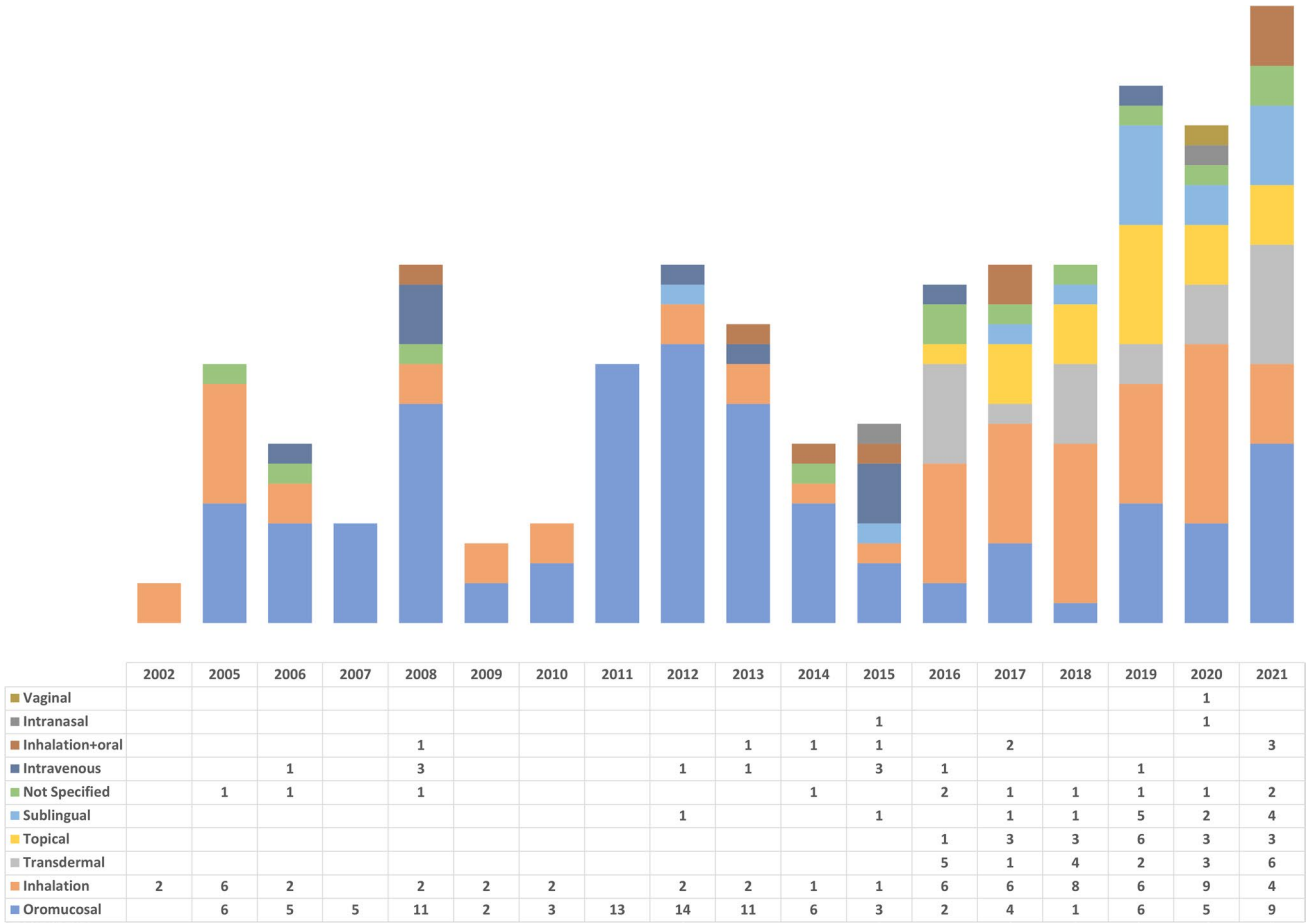
Fig. 5 Cannabinoids with more than three registered clinical trials (2000–2021). THC:CBD indicates the products with a 1:1 ratio of THC and CBD, while other investigated ratios of THC and CBD are present as THC/CBD. *CBD* cannabidiol, *CBDV* cannabidivarin, *THC* Δ9-tetrahydrocannabinol

oncology with cannabinoids or CBD [41]. Two other papers analyzed the clinical trials designed to assess the therapeutic effects of cannabinoids [2, 42]. Ben Amar analyzed the published clinical trials on cannabinoids until July 2005 [2]. Also, Kowal et al. conducted a similar analysis on trials published between 2005 and 2009 [42]. However, these papers only focused on the clinical trials with published results, excluding all studies without published results, withdrawn, suspended, or ongoing clinical trials. All clinical studies (with and without published results) are summarized in our work, demonstrating the changes in the types and phases of clinical trials over the last 21 years. The analysis of current and past clinical trials may signal future clinical studies and highlight the necessary trials to address unmet needs.

The lack of accurate data on clinical trial characteristics is the most significant limitation of our analysis. Sponsors and investigators are responsible for updating clinical trial data, and the trial registries do not verify the information [43–45]. The unsupervised supply of information into registries may result in data inaccuracy. The inconsistent governing requirements for clinical trial registration were another limitation in our analysis. Many jurisdictions do not require registration of phase I clinical trials [46, 47], which may result in underreporting phase I clinical trials in registries and, consequently, our review. We also searched four central trial registries; however, there might be clinical studies that were not captured in those registries.

5 Conclusion

Our review highlights the increase in the number and variety of clinical trials on cannabinoids. The number of registered clinical trials has increased constantly since 2013. Phase I and II clinical trials represented a higher share of total registered clinical trials after 2013, contrasting with



	2002	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Vaginal																	1	
Intranasal												1					1	
Inhalation+oral					1					1	1	1		2				3
Intravenous			1		3				1	1		3	1			1		
Not Specified		1	1		1						1		2	1	1	1	1	2
Sublingual									1			1		1	1	5	2	4
Topical													1	3	3	6	3	3
Transdermal													5	1	4	2	3	6
Inhalation	2	6	2		2	2	2		2	2	1	1	6	6	8	6	9	4
Oromucosal		6	5	5	11	2	3	13	14	11	6	3	2	4	1	6	5	9

Fig. 6 Trends of the investigated routes of administration in cannabis and cannabinoids clinical trials (2000–2021)

clinical trials registered between 2005 and 2008. Moreover, more interventional clinical trials have been designed to investigate various formulations and novel cannabinoids in recent years. This review also highlighted the interest and commitment of the private sector in clinical research on cannabinoids and cannabis-based medications. Our review also underscores the disparity of clinical research among different therapeutic areas. Further research is

Table 4 The comparison of clinical trial sponsorship in four countries with most registered clinical trials for cannabis and cannabinoids

Type of sponsor	Australia	Canada	The United Kingdom	The United States	Total
Commercial sector/industry	50 (58.1)	13 (21.0)	93 (82.3)	77 (25.2)	233 (41.1)
University	15 (17.4)	7 (11.3)	8 (7.1)	68 (22.2)	98 (17.3)
Government/academia partnership	1 (1.2)	2 (3.2)	1 (0.9)	50 (16.3)	55 (9.5)
Other collaborative groups	2 (2.3)	11 (17.7)	2 (1.8)	38 (12.4)	53 (9.3)
Hospital	5 (5.8)	8 (12.9)	4 (3.5)	22 (7.2)	39 (6.9)
Industry/academia partnership	2 (2.3)	15 (24.2)	1 (0.9)	16 (5.2)	34 (6.0)
Charities/societies/foundations	2 (2.3)	6 (9.7)	1 (0.9)	23 (7.5)	32 (5.6)
Government body	3 (3.5)	0 (0.0)	3 (2.7)	9 (2.9)	15 (2.6)
Individual	2 (2.3)	0 (0.0)	0 (0.0)	3 (1.0)	5 (0.9)
Other	4 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)
Total	86 (100.0)	62 (100.0)	113 (100.0)	306 (100.0)	567 (100.0)

Data are presented as *n* (%)

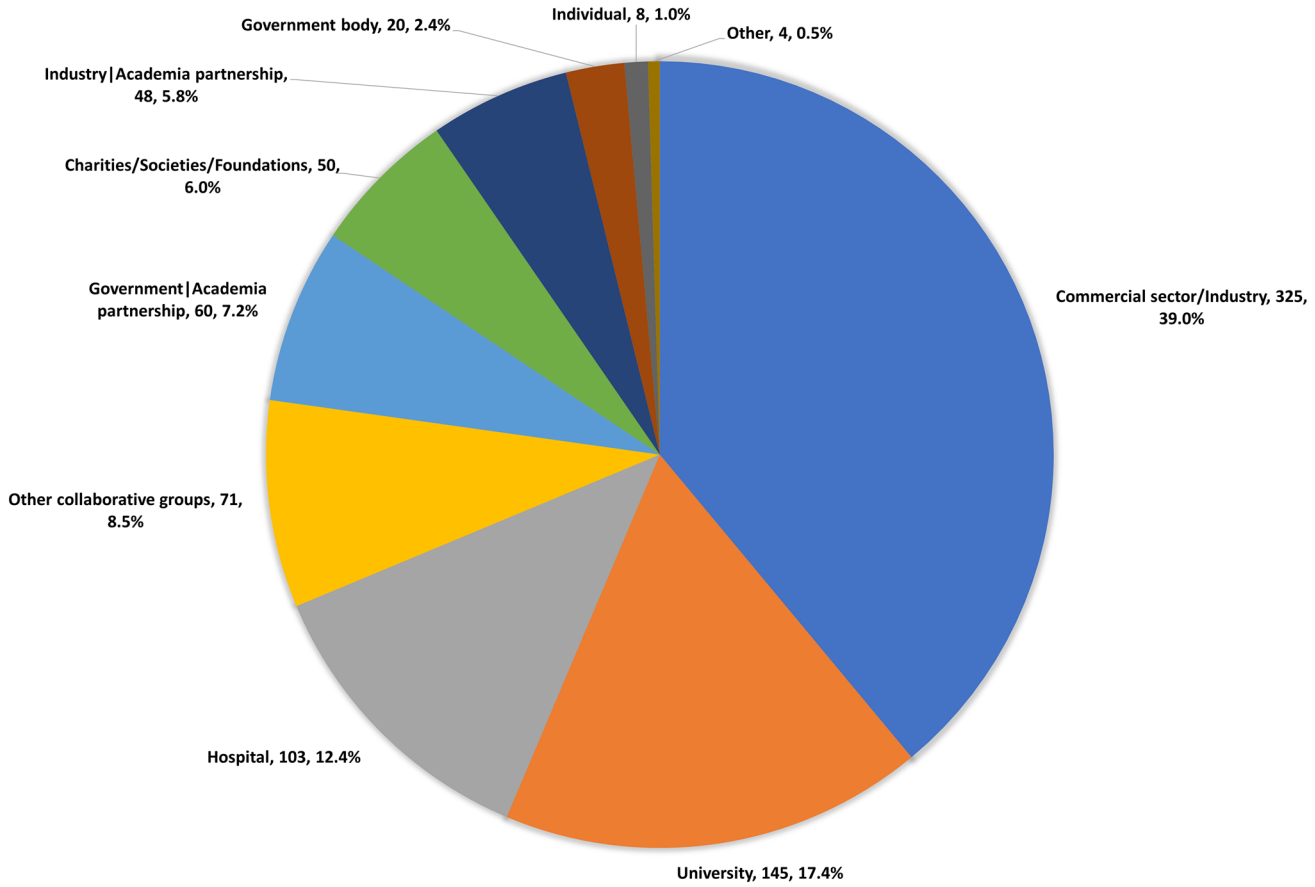


Fig. 7 Distribution of types of sponsors of cannabis and cannabinoids clinical trials (2000–2021)

required to understand the reasons behind this discrepancy. There is also a need for a more granular analysis of clinical trials on more commonly studied therapeutic areas such as chronic pain, nervous system diseases, and mental and behavioral disorders to generate more actionable information and insight for all stakeholders.

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Declarations

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Conflict of Interest FM and KT declare that this study was conducted without any commercial or financial relationships that could be considered a potential conflict of interest.

Authors' Contributions FM: Conceptualization, methodology, investigation, data curation, writing—original draft, review and editing, visualization. KT: Conceptualization, methodology, investigation, data curation, writing—review and editing, visualization. All authors approved the final version of this manuscript to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Access Statement Data supporting this study are openly available from the website of respective clinical trial registries: https://clinicaltrials.gov/, https://www.clinicaltrialsregister.eu/, https://www.anzctr.org.au/Default.aspx, https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal.

Ethical Approval There is no human subject or identifiable personal information in this article, and informed consent is not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

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