Adverse effects of medical cannabinoids: a systematic review

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ABSTRACT

Background: The therapeutic use of cannabis and cannabis-based medicines raises safety concerns for patients, clinicians, policy-makers, insurers, researchers and regulators. Although the efficacy of cannabinoids is being increasingly demonstrated in randomized controlled trials, most safety information comes from studies of recreational use.

Methods: We performed a systematic review of safety studies of medical cannabinoids published over the past 40 years to create an evidence base for cannabis-related adverse events and to facilitate future cannabis research initiatives. We critically evaluated the quality of published studies with a view to identifying ways to improve future studies.

Results: A total of 321 articles were eligible for evaluation. After excluding those that focused on recreational cannabis use, we included 31 studies (23 randomized controlled trials and 8 observational studies) of medical cannabis use in our analysis. In the 23 randomized controlled trials, the median duration of cannabinoid exposure was 2 weeks (range 8 hours to 12 months). A total of 4779 adverse events were reported among participants assigned to the intervention. Most (4615 [96.6%]) were not serious. Of the 164 serious adverse events, the most common was relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]) and urinary tract infection (15 events [9.1%]). The rate of nonserious adverse events was higher among participants assigned to medical cannabinoids than among controls (rate ratio [RR] 1.86, 95% confidence interval [CI] 1.57–2.21); the rates of serious adverse events did not differ significantly between these 2 groups (RR 1.04, 95% CI 0.78–1.39). Dizziness was the most commonly reported nonserious adverse event (714 events [15.5%]) among people exposed to cannabinoids.

Interpretation: Short-term use of existing medical cannabinoids appeared to increase the risk of nonserious adverse events. The risks associated with long-term use were poorly characterized in published clinical trials and observational studies. High-quality trials of long-term exposure are required to further characterize safety issues related to the use of medical cannabinoids.

Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/178/13/1669/DC1

Cannabis (*Cannabis sativa)* is widely used as a recreational drug, with an estimated worldwide annual prevalence (defined as use at least once per year) of 160 million.[1] Cannabis preparations have also been used medicinally for thousands of years. In the past 40 years the active ingredients of cannabis, Δ-9-tetrahydrocannabinol and cannabidiol, and other derivatives (termed "cannabinoids") have been identified and characterized,[2] and it is becoming clear that cannabinoids have considerable therapeutic potential.[3]

In Canada, 4 cannabinoid products are currently available for medical use, more than in any other country worldwide. These are: a herbal cannabis extract (marketed as Sativex [GW Pharmaceuticals], which contains Δ-9-tetrahydrocannabinol and cannabidiol in an oromucosal spray); dronabinol (synthetic Δ-9-tetrahydrocannabinol, marketed as Marinol [Solvay Pharmaceuticals]); nabilone (a synthetic derivative of Δ-9-tetrahydrocannabinol, marketed as Cesamet [Valeant Pharmaceuticals International]); and the herbal form of cannabis (available legally through the Medical Marijuana Access Regulations).[4,5] In Canada, dronabinol and nabilone are indicated for chemotherapy-induced nausea and vomiting, dronabinol is approved for HIV-associated anorexia, and oromucosal Δ-9-tetrahydrocannabinol–cannabidiol is conditionally approved for neuropathic pain in multiple sclerosis and cancer pain.

The efficacy of these cannabinoid medicines has been evaluated in randomized controlled trials. In addition, the use of cannabinoids as antiemetics has been systematically reviewed, and potential efficacy has been suggested.[6] There has also been considerable interest in the use of cannabinoids as adjunctive therapy for pain management, and several small randomized controlled trials have been published recently. Dronabinol and oromucosal Δ-9-tetrahydrocannabinol–cannabidiol have been proven effective for central neuropathic pain associated with multiple sclerosis.[7–11] Oromucosal Δ-9-tetrahydrocannabinol–cannabidiol reduced pain associated with rheumatoid arthritis,[12] and nabilone was effective for pain associated with fibromyalgia.[13] A recent review supported further consideration of cannabinoids for

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chronic pain but was less encouraging for their use in acute pain conditions.[3]

In addition to the use of prescription cannabinoids, the medical use of smoked herbal cannabis is substantial: an estimated 10%–20% of patients with multiple sclerosis, chronic noncancer pain, HIV/AIDS and epilepsy report smoking cannabis for therapeutic purposes. Smoked cannabis has been found to be safe[14] and effective[15] for HIV-associated disorders. As of October 2007, 2261 patients in Canada were authorized to use herbal cannabis for medical purposes under the Medical Marihuana Access Regulations.[16]

With this rising interest in therapeutic use, the safety of cannabinoids is an emerging source of concern for many physicians. The safety of therapeutic agents can be studied by a variety of methodologic approaches, including randomized controlled trials, observational studies and pharmacovigilance studies.[17,18] The adverse effects of cannabis have been summarized in several reports,[19–24] and systematic reviews have found cannabis to be a risk factor for psychosis,[25] cancer[26] and neurocognitive effects,[27] but these reports all focused on the recreational use of cannabis.

We report here a systematic review of the published adverse events of medical cannabinoid use. Our primary objective was to create a database of known adverse events related to the medical use of cannabis to inform physicians, policymakers and the public. In addition, we sought to critically evaluate the quality of published studies to guide future studies on the safety of medical cannabis use.

Methods

Search strategy

We conducted a comprehensive search of Ovid MEDLINE (January 1966 to week 5 of October 2007), PsycINFO (January 1967 to week 5 of October 2007) and EMBASE (January 1980 to week 42 of 2007), using the following key words: "bhang," "charas," "cannabis," "cannabinoids," "dagga," "ganja," "hashish," "hemp," "marijuana," "marihuana" and "tetrahydrocannabinol or THC." We included studies that specified "human," "safety," "case report," "case–control," "cohort," "cross-sectional," "crossover," "randomized controlled trial," "longitudinal" or "epidemiological" in the title or key words. The detailed search strategy is presented in Appendix 1 (available at www.cmaj.ca/cgi/content/full/178/13/1669 /DC2). We identified additional studies from the reference lists of selected articles and review articles.

Study selection

Two reviewers (T.W. and M.W.) independently reviewed the titles and abstracts for relevance according to the following criteria. We included randomized controlled trials evaluating the safety and efficacy of cannabis if adverse events were quantified. We included observational studies in which cannabis represented the main exposure, provided the outcome of interest was adverse events. We included case reports if they described adverse events in people exposed to cannabis.

We excluded studies that focused on adverse effects of cannabis occurring in combination with other agents,

those that involved synthetic cannabinoids (e.g., nabilone, levonantradol), those that studied treatment of cannabis dependence or cannabis cessation, and those that focused on the effects of cannabis on school achievement, marriage, criminal behaviour (e.g., homicide, violent crimes) or hormone levels. We also excluded studies of mechanisms of action, studies of pharmacodynamic or pharmacokinetic effects and studies with other basic experimental designs. Finally, we excluded studies published in languages other than English, French, Spanish or German. The 2 primary reviewers resolved disagreements regarding study selection through discussion. We obtained the full text of papers identified on the basis of titles and abstracts and applied additional criteria for final selection of the studies for review and meta-analysis.

Finally, we classified the selected articles by reason for cannabis use (medical or recreational) and by study design. For this review, we evaluated only studies focusing on the safety of cannabinoids used for medical purposes.

Assessment of study quality

Two raters (T.W. and one other person) independently assessed study quality. We used the scale proposed by Jadad and associates[28] to assess the methodologic quality of randomized controlled trials and the Downs and Black checklist[29] to assess the quality of observational studies involving a control group. The raters resolved disagreements regarding quality assessment through discussion.

Data extraction

We identified serious adverse events and nonserious adverse events according to the definitions recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (referred to hereafter as the International Conference on Harmonisation).[30] Under these guidelines, a "serious adverse event" is defined as any untoward medical occurrence that requires admission to hospital or prolongation of an existing admission, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life-threatening or that results in death. A "nonserious adverse event" is defined as any untoward medical occurrence in a patient or participant; the event need not have a causal relation to the treatment. We used the guidelines of the International Conference on Harmonisation to define the expectedness of an adverse event, whereby an "unexpected" adverse event is one for which "the nature or severity ... is not consistent with the applicable product information."[30] We coded all identified adverse events using the *Medical Dictionary for Regulatory Activities* headings "system organ classes" and "preferred terms."[31] One of us (T.W.) performed the data extraction and *Medical Dictionary for Regulatory Activities* coding, and a second medically qualified reviewer (M.W.) verified the data extraction and coding.

Data analysis

We used *Medical Dictionary for Regulatory Activities* coding[31] and information about study design to categorize seri-

ous and nonserious adverse events. For descriptive purposes, we estimated the incidence rates of serious and nonserious adverse events in randomized controlled trials by dividing the number of events by the corresponding cumulative person-years. To generate a cumulative estimate of person-years, we combined the person-years for all participants exposed to cannabis. We applied the same logic to estimate total person-years exposed to the control. For participants in crossover trials, the person-years of exposure could be applied more than once to the cumulative estimate of person-years. When the duration of exposure for a participant who withdrew from a randomized controlled trial was unclear, we estimated the person-year contribution of that person as half of the complete follow-up time per person in the trial.

We conducted a random-effects meta-analysis to assess the occurrence of adverse events, serious and nonserious, among participants assigned to cannabis exposure or control. We derived rate ratios (RRs) and variances for each trial and added a correction value of 0.5 to each count in the case of zero events. We computed point estimates with corresponding 95% confidence intervals (CIs) for pooled RRs.[32] We assessed all pooled estimates for heterogeneity, using the heterogeneity χ^2 test and the I^2 statistic (the percentage of variation across studies that is due to heterogeneity[33]). We prospectively studied adverse events according to the type of cannabis preparation (oromucosal Δ-9-tetrahydrocannabinol–cannabidiol, oral Δ-9-tetrahydrocannabinol, oral Δ-9-tetrahydrocannabinol–cannabidiol) and performed predefined subgroup analyses (for duration of exposure [> 2 weeks, ≤ 2 weeks], study design [parallel, crossover] and study population [people with and without cancer]) within each medical cannabis preparation. For nonserious adverse events, we also estimated pooled RRs and corresponding 95% CIs for each system organ class.

Results

We identified a total of 1720 articles with the initial search strategy (Figure 1). We excluded 1443 articles that did not satisfy the inclusion and exclusion criteria, including 28 randomized controlled trials that did not report quantifiable adverse event data. One trial was presented in 2 separate publications: one with safety data reported up to 15th week[10] and the other with safety data collected from the 16th to the 52nd week;[11] we counted these 2 articles as a single trial. We excluded 11 case reports and 2 observational epidemiological studies because of the language of publication.

We identified an additional 57 studies (49 case reports and 8 observational studies) by examining the reference lists of review articles. We also included one in-press randomized controlled trial (which has now been published).[7]

We therefore identified a total of 321 studies regarding safety issues of cannabis published between January 1966 to October 2007. Of these, 290 (90.3%), consisting of 92 observational studies and 198 case reports, focused on recreational use; for the purposes of this study, we did not consider these

studies further. We analyzed data from the remaining 31 studies (9.7%), 23 randomized controlled trials and 8 observational studies, in which the safety of medical cannabinoid use could be evaluated.

For the 23 randomized controlled trials of medical cannabinoid use,[7–12,34–51] summarized in Table 1, the median Jadad score was 4/5 (range 2 to 5, where higher score indicates better quality). Four of the trials did not provide information on the number of participants withdrawn or the reasons for withdrawal.[34–37] Seventeen (74%) of the 23 trials had a sample size less than 100, and 11 (48%) of them had fewer than 50 participants. The median duration of cannabinoid exposure was 2 weeks (range 8 hours to 12 months). The total number of participants exposed to cannabinoid therapy was 1932, yielding 445 person-years of cannabinoid exposure. Among the 1209 people assigned to control groups (either placebo or standard care), there were 239 person-years of exposure; of these, 1121 people (accounting for 236 person-years) received placebo. (The total number of participants in the treatment and control groups is
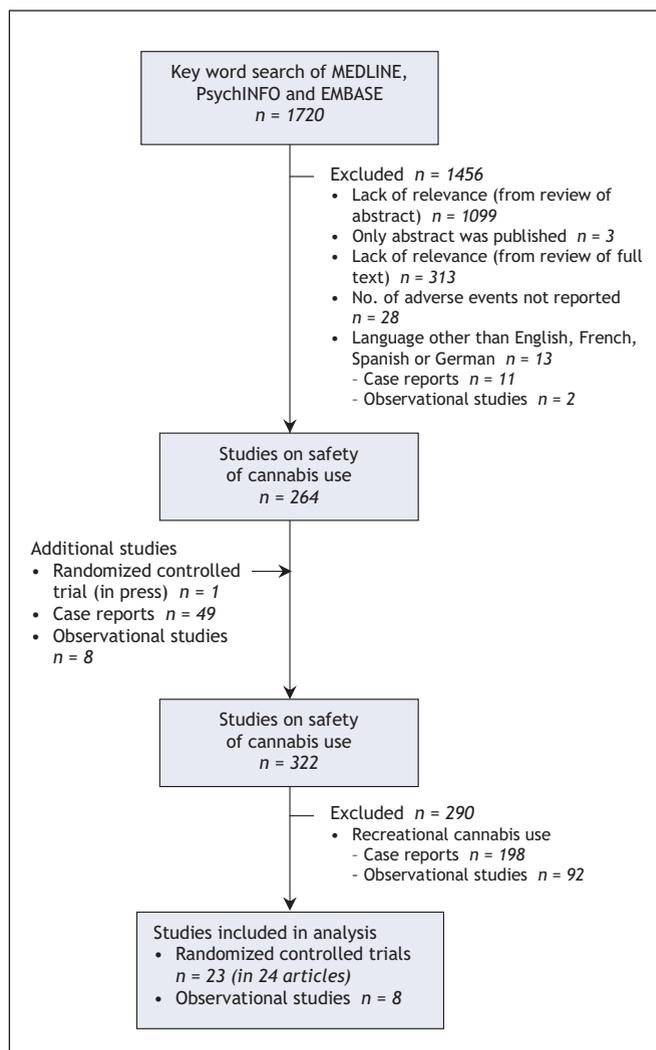
Figure 1: Retrieval and selection of studies of safety of cannabinoid preparations.

greater than the sum of sample sizes in Table 1 because participants in the crossover trials contributed to both group totals.)

With the exception of one trial involving 12 healthy cannabis-naive volunteers,[48] all trials involved patients with medical conditions, such as cancer or multiple sclerosis, and use of cannabis was intended to address symptoms such as nausea and vomiting induced by chemotherapy or pain (see Table 1). Oral Δ-9-tetrahydrocannabinol or Δ-9-tetrahydrocannabinol–cannabidiol (15 trials) and oromucosal Δ-9-tetrahydrocannabinol–cannabidiol (8 trials) were the cannabinoid preparations studied. No randomized controlled trials of medical cannabis administered by smoking were included in the review, since adverse events were not quantified in any such studies.

Adverse events

Through our review, we identified 164 serious adverse events among people assigned to cannabinoid therapy and 60 among controls. There was no evidence of a higher incidence of serious adverse events following medical cannabis use compared with control (rate ratio [RR] 1.04, 95% CI 0.78–

1.39). The serious adverse events are categorized in Table 2. Respiratory (16.5%), gastrointestinal (16.5%) and nervous system disorders (15.2%) were the most frequently reported categories of serious adverse events among those assigned to cannabinoids, whereas nervous system disorders (30.0%) were the most frequently reported among controls. Relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]) and urinary tract infection (15 events [9.1%]) were the most commonly reported serious adverse events among people assigned to receive cannabinoids. The majority of serious adverse events (163 among cannabinoid users and 58 among controls) were reported in 2 trials, which contributed 88.8% of person-years of cannabinoid exposure and 84.1% of exposure to control.[10,11,44]

Fifteen deaths (3.4 per 100 person-years) were reported among cannabinoid users (3 because of pneumonia, 1 because of cervix carcinoma, 1 because of convulsion, 10 not specified), and 3 deaths (1.3 per 100 person-years) were reported among controls (1 pneumonia, 1 myocardial ischemia, 1 not specified). The difference in death rate between these 2 groups was not statistically significant (RR 2.66, 95% CI 0.77–9.28). The mortality RR was mainly influenced by one

Table 1: Randomized controlled trials of medical cannabinoid preparations, published between 1966 and late 2007 and reporting detailed adverse event data, by mode of administration (part 1)

Mode of administration; study design	Reference	Condition characterizing study population	Sample size	Age, mean (range), yr	Sex, % male	Duration of exposure	Most frequently reported adverse event: n/N (%)*
Oromucosal spray (Δ-9-tetrahydrocannabinol–cannabidiol)							
Parallel randomized controlled trial	Blake et al.[12]	Rheumatoid arthritis	58	62.8	21	5 wk	Nervous system disorders: 13/23 (57)
	Collin et al.[38]	Multiple sclerosis	189	49.1	40	6 wk	Nervous system disorders: 68/169 (40.2)
	Nurmikko et al.[7]	Neuropathic pain	125	53	41	5 wk	Gastrointestinal disorders: 40/101 (39.6)
	Rog et al.[8]	Multiple sclerosis	66	49 (27-72)	21	4 wk	Nervous system disorders: 22/56 (39)
	Wade et al.[39]	Multiple sclerosis	160	51 (27-74)	38	6 wk	Nervous system disorders: 45/112 (40.2)
Crossover randomized controlled trial	Berman et al.[40]	Brachial plexus avulsion	48	39 (23-63)	96	2 wk	Nervous system disorders: 48/62 (77)
	Tomida et al.[37]	Glaucoma	6	55	100	18 h	Gastrointestinal disorders: 5/18 (28)
	Wade et al.[41]	Neuropathic pain	21	48	50	2 wk	Nervous system disorders: 11/36 (31)
Oral (Δ-9-tetrahydrocannabinol or Δ-9-tetrahydrocannabinol–cannabidiol)							
Parallel randomized controlled trial	Buggy et al.[42]	Postoperative pain	40	44.8	0	24 h	Nervous system disorders: 34/82 (41)
	Frytak et al.[43]	Chemotherapy-induced nausea	116	61	60	4 d	Nervous system disorders: 56/78 (72)
	Strasser et al.[44]	Cancer-related anorexia-cachexia syndrome	243	61	54	6 wk	Gastrointestinal disorders: 70/187 (37.4)
	Timpone et al.[45]	HIV wasting syndrome	50	40	88	12 wk	Nervous system disorders: 3/11 (27)

randomized controlled trial studying the effects of Δ-9-tetrahydrocannabinol on cancer-related anorexia–cachexia syndrome (RR 2.61, 95% CI 0.33–20.37).[44]

In the 23 randomized controlled trials, there were 4615 nonserious adverse events among people assigned to cannabinoid therapy (incidence rate 10.37 events/person-year) and 1641 events among controls (incidence rate 6.87 events/person-year). Nervous system disorders was the most frequently reported category for both groups (accounting for 36.7% of events among people assigned to cannabinoids and 31.3% of events among controls) (Table 3). Dizziness was the most commonly reported nonserious adverse event among cannabinoid-exposed participants; details of other nonserious adverse events are shown in Appendix 2 (available at www.cmaj.ca/cgi/content/full/178/13/1669/DC2).

The incidence rate of nonserious adverse events was significantly higher among subjects assigned to cannabinoid therapy than among controls (RR 1.86, 95% CI 1.57–2.21) (Figure 2).[7–12,34–51] We found a high degree of variance among the studies (heterogeneity $\chi^2 = 187.42$, $p < 0.001$; $I^2 = 86.7\%$). Subgroup analysis by type of cannabinoid prepara-

tion reduced the heterogeneity (Appendix 3; available at www.cmaj.ca/cgi/content/full/178/13/1669/DC2). The average rate of nonserious adverse events was significantly higher among people receiving oromucosal Δ-9-tetrahydrocannabinol–cannabidiol (RR 1.88, 95% CI 1.48–2.39) or oral Δ-9-tetrahydrocannabinol (RR 2.18, 95% CI 1.59–2.99) than among controls; there was no difference between the oral Δ-9-tetrahydrocannabinol–cannabidiol and control groups (RR 1.31, 95% CI 0.88–1.96). One study had a different duration of exposure for the intervention (oral Δ-9-tetrahydrocannabinol–cannabidiol, 2 weeks) and placebo (1 week) groups, and the incidence rate was significantly lower in the intervention group.[51] Exclusion of this study increased the pooled RR for oral Δ-9-tetrahydrocannabinol–cannabidiol from 1.31 (95% CI 0.88–1.96) to 1.54 (95% CI 1.14–2.08). Further subgroup analysis by study design and study population did not significantly alter the pooled RR for nonserious adverse events for each medical cannabinoid preparation (Appendix 3; available at www.cmaj.ca/cgi/content/full/178/13/1669/DC2).

In the 8 observational studies that focused on safety issues related to medical cannabinoid preparations,[52–59] a total

Table 1: Randomized controlled trials of medical cannabinoid preparations, published between 1966 and late 2007 and reporting detailed adverse event data, by mode of administration (part 2)

Mode of administration; study design	Reference	Condition characterizing study population	Sample size	Age, mean (range), yr	Sex, % male	Duration of exposure	Most frequently reported adverse event: n/N (%)*
	Zajicek et al.[10]†	Multiple sclerosis	630	50 (18-64)	34	15 wk	Nervous system disorders: 710/1849 (38.4)
	Zajicek et al.[11]†	Multiple sclerosis	611	50 (18-64)	34	37 wk	Nervous system disorders: 124/655 (18.9)
Crossover randomized controlled trial	Carroll et al.[46]	Idiopathic Parkinson disease	19	67 (51-78)	63	4 wk	Nervous system disorders: 17/38 (45)
	Killestein et al.[47]	Multiple sclerosis	16	46	NR	4 wk	Nervous system disorders: 23/39 (59)
	Naef et al.[48]	Healthy, cannabis-naïve volunteers	12	Female: 25 Male: 27	50	8 h	Psychiatric disorders: 60/123 (48.8)
	Neidhart et al.[34]	Chemotherapy-induced vomiting	73	43	58	2 d	Nervous system disorders: 60/106 (56.6)
	Noyes et al.[35]	Pain associated with cancer	10	51	20	3 d	Nervous system disorders: 112/218 (51.4)
	Noyes et al.[49]	Pain associated with cancer	36	51	28	1 d	Nervous system disorders: 173/430 (40.2)
	Orr et al.[36]	Chemotherapy-induced nausea	79	46 (22-71)	35	1 d	Psychiatric disorders: 49/76 (64)
	Petro et al.[50]	Multiple sclerosis	9	NR	NR	1 d	Psychiatric disorders: 1/1 (100)
	Svendsen et al.[9]	Multiple sclerosis	24	50 (23-55)	42	3 wk	Nervous system disorders: 53/100 (53)
	Vaney et al.[51]	Multiple sclerosis	57	54.9	49	2 wk	Psychiatric disorders: 21/45 (47)

Note: NR = not reported.
*Grouped by system order classes of the *Medical Dictionary for Regulatory Activites*.[31] Data presented as number and percentage of all nonserious adverse events in the most common category.
†These 2 reports refer to the same study, with follow-up data for different periods. The total duration of the study was 52 weeks, with the first article reporting events up to the 15th week and the second article reporting events from the 16th to the 52nd week.

of 39 serious adverse events and 3553 nonserious adverse events were reported (Table 4; and Appendix 4, available at www.cmaj.ca/cgi/content/full/178/13/1669/DC2). None of these studies had a control group. Nervous system disorders were the most frequently reported category for both serious adverse events (9 [23.1%]) and nonserious adverse events (1412 [39.7%]). Psychiatric disorders were the second frequently reported category (4 serious adverse events [10.3%] and 1265 nonserious adverse events [35.6%]). The adverse events reported in observational studies are summarized in Appendix 2 (available at www.cmaj.ca/cgi/content/full/178/13/1669/DC2).

Table 2: Serious adverse events (fatal and nonfatal) reported in randomized controlled trials of medical cannabinoid preparations

Serious adverse event	Cannabinoid exposure n = 164		Control n = 60	
	No. (%)	Rate*	No. (%)	Rate*
Respiratory, thoracic and mediastinal disorders	27 (16.5)	0.06	7 (11.7)	0.03
Dyspnea	13		3	
Pneumonia	11 (3 deaths)		3 (1 death)	
Pleural effusion	2		0	
Lower respiratory tract infection	1		0	
Pulmonary embolism	0		1	
Gastrointestinal disorders	27 (16.5)	0.06	4 (6.7)	0.02
Vomiting	16		1	
Diarrhea	6		0	
Gastroenteritis	2		0	
Abdominal pain	1		0	
Constipation	1		3	
Duodenal ulcer	1		0	
Nervous system disorders	25 (15.2)	0.06	18 (30.0)	0.08
Relapse of multiple sclerosis	21		11	
Convulsion	2 (1 death)		4	
Dizziness	1		0	
Multiple sclerosis	1		1	
Cerebrovascular disorder	0		2	
General disorders and administration-site conditions	21 (12.8)	0.05	8 (13.3)	0.03
Death	10		1	
Pain	6		4	
Pyrexia	5		2	
Chest pain	0		1	
Renal and urinary disorders	16 (9.8)	0.04	8 (13.3)	0.03
Urinary tract infection	15		8	
Hematuria	1		0	
Neoplasm, benign and malignant	14 (8.5)	0.03	2 (3.3)	0.01
Neoplasm progression	13		2	
Cervix carcinoma	1 (1 death)		0	
Psychiatric disorders†	11 (6.7)	0.02	1 (1.7)	< 0.01
Other	23 (14.0)	0.05	12 (20.0) (1 death‡)	0.05
Total	164	0.37	60	0.25

*Incidence rate = events/person-years. The number of person-years was 445 for cannabinoid exposure and 239 for control.
†For both cannabinoid exposure and control, all events in this category were classified as "altered mood."
‡Due to myocardial ischemia.

Interpretation

In our review, we identified 8371 adverse events related to medical cannabinoid use, 4779 of which were reported in 23 randomized controlled trials and 3592 in 8 observational studies. Most of the events were not serious. None of the reported adverse events was unexpected, according to the International Conference on Harmonisation criteria.[30]

Although the randomized controlled trial is a powerful study design, several aspects of the quality of reporting of adverse events in published trials limited our results. First, not all published cannabinoid trials provided safety information; we excluded 28 randomized controlled trials, including 2 trials that examined cannabis smoked by patients with HIV infection,[14,15] because they did not quantify adverse events or they reported events for only one intervention group. The Jadad score does not adequately reflect the quality of safety reporting in randomized controlled trials, which meant that rating by the Jadad scale indicated good methodologic quality for these studies, despite their poor reporting of safety. Second, most of the trials selected did not provide both the absolute number of adverse events and the number of participants reporting at least 1 event, as recommended by the Consolidated Standards of Reporting Trials (CONSORT) statement.[60] This meant that we could focus only on the inci-

dence of adverse events, rather than being able to analyze both the incidence rates of events and the risks for participants who had reported at least 1 event. Third, because of the lack of data on frequency of adverse events for each patient, we had to assume that the occurrence of adverse events was independent, which would not be a valid assumption if a patient had experienced more than 1 event (a likely scenario for nonserious adverse events). This assumption would result in generation of artificially narrow CIs around the RR estimates, which might have affected the results of significance testing.

We found 3592 adverse events reported in 8 observational studies. However, those studies were limited by lack of control groups and lack of adjustment for potential confounders, such as use of tobacco, alcohol or other recreational drugs and drug–cannabis interactions.

In our analysis, we did not include data from studies examining the synthetic cannabinoid nabilone, because this agent has different pharmacokinetic and pharmacodynamic properties, and its safety profile may differ from that of Δ-9-tetrahydrocannabinol. Although nabilone is currently being used for medical purposes, we caution that our safety data cannot be extended to this drug, and the safety of nabilone must be studied separately. In addition, we excluded the 2 published randomized controlled trials of

Table 3: Frequency of nonserious adverse events reported in randomized controlled trials of medical cannabinoid preparations

System organ class*	No. (%) of nonserious adverse events		Pooled rate ratio (95% CI)
	Cannabinoid exposure n = 4615	Control n = 1641	
Nervous system disorders	1695 (36.7)	513 (31.3)	1.87 (1.53-2.30)
Gastrointestinal disorders	758 (16.4)	246 (15.0)	1.52 (1.19-1.93)
General disorders and administration-site conditions	651 (14.1)	294 (17.9)	1.15 (1.00-1.32)
Psychiatric disorders	512 (11.1)	122 (7.4)	2.73 (1.69-4.41)
Musculoskeletal, connective tissue and bone disorders	331 (7.2)	174 (10.6)	1.01 (0.84-1.21)
Renal and urinary disorders	236 (5.1)	134 (8.2)	0.91 (0.77-1.07)
Infections and infestations	134 (2.9)	70 (4.3)	0.96 (0.73-1.26)
Eye disorders	106 (2.3)	16 (1.0)	1.97 (1.23-3.17)
Injury, poisoning and procedural complications	37 (0.8)	11 (0.7)	1.25 (0.73-2.14)
Metabolism and nutrition disorders	37 (0.8)	4 (0.2)	1.47 (0.75-2.86)
Respiratory, thoracic and mediastinal disorders	36 (0.8)	7 (0.4)	1.42 (0.77-2.62)
Skin and subcutaneous tissue disorders	30 (0.7)	27 (1.6)	0.60 (0.38-0.94)
Blood and lymphatic system disorders	26 (0.6)	8 (0.5)	0.90 (0.50-1.60)
Cardiac disorders	22 (0.5)	12 (0.7)	1.12 (0.63-2.00)
Vascular disorders	3 (0.1)	2 (0.1)	0.69 (0.32-1.51)
Investigations	1 (< 0.1)	1 (0.1)	0.68 (0.31-1.53)

Note: CI = confidence interval.
*Classified according to *Medical Dictionary for Regulatory Activities*.[31]
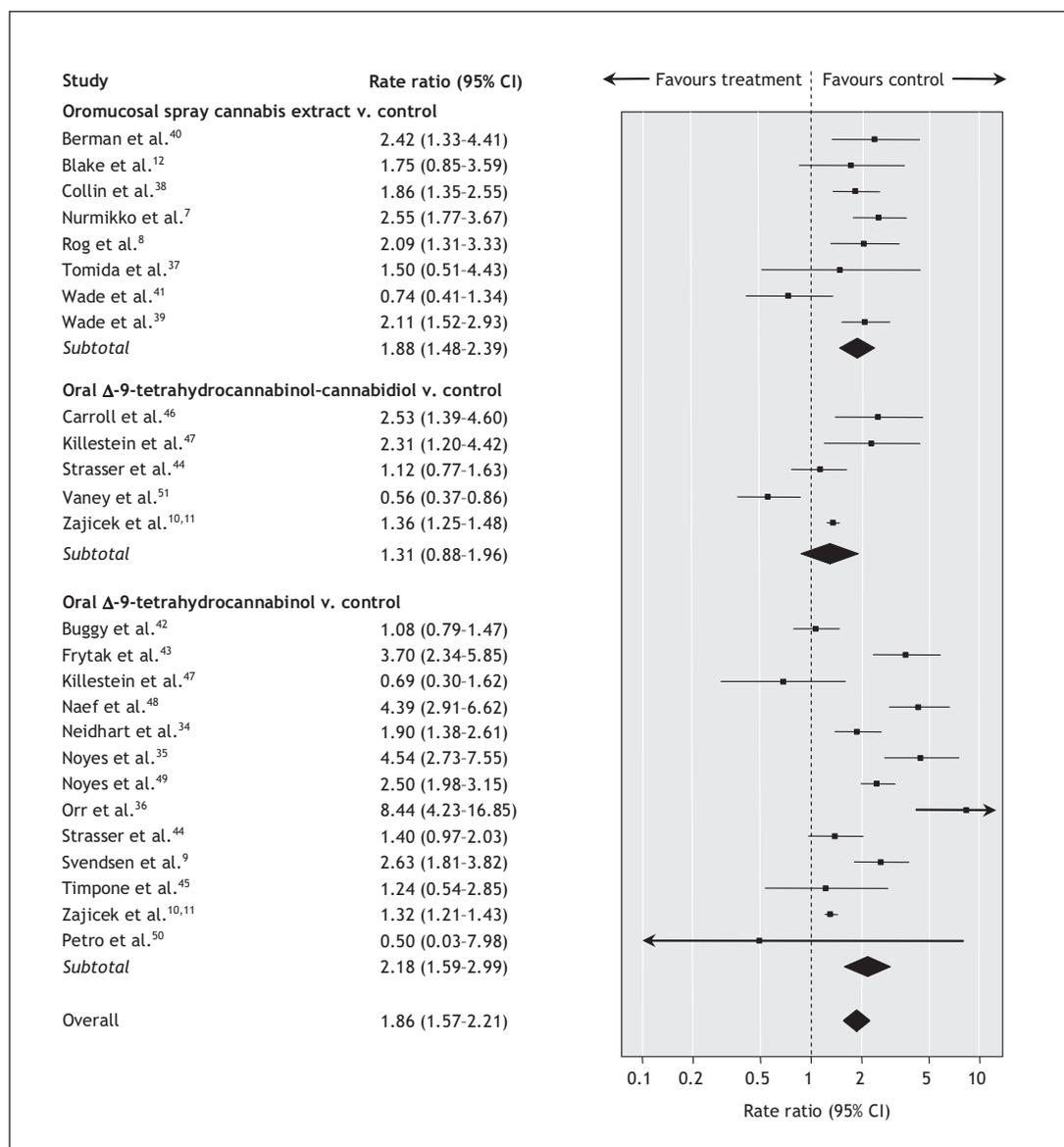
Figure 2: Incidence rates and rate ratios (random-effects model) for nonserious adverse events among participants assigned to medical cannabinoid therapy or control in 23 randomized controlled trials. Dotted vertical line represents no difference between the intervention and the control. CI = confidence interval.

smoked cannabis because of a lack of quantifiable adverse event data.[14,15] Given the extent of legal use of medical cannabis and the potential risks associated with administration by smoking, good-quality safety and efficacy data on smoked cannabis are urgently needed. We also caution against assuming that the adverse effects of recreational cannabis use can be expected to occur with medical cannabinoid use. The amounts used, the existence of comorbidities and the methods of drug delivery are different in the 2 populations, which should therefore be evaluated separately.

We found that the rate of nonserious adverse events was 1.86 times higher among medical cannabinoid users than among controls. However, we did not find a higher incidence rate of serious adverse events associated with medical

cannabinoid use. The fact that 99% of the serious adverse events from randomized controlled trials were reported in only 2 trials suggests that more studies with long-term exposure are required to further characterize safety issues. Such studies are crucial to detect rare adverse events and to address specific concerns regarding the development of tolerance and the development of cognitive and behavioural effects of medical cannabinoid use. The findings of our systematic review may stimulate future high-quality controlled observational studies and clinical trials to explore the safety of medical cannabinoid use. We believe that systematic collection of data related to adverse events associated with cannabis use should continue, and the results should be made publicly available, to assist in clinical, regulatory and political decision-making.

Table 4: Frequency of nonserious adverse events reported in observational studies of medical cannabinoid preparations

System organ class*	No. (%) of nonserious adverse events n = 3553
Nervous system disorders	1412 (39.8)
Psychiatric disorders	1265 (35.6)
Gastrointestinal disorders	558 (15.7)
Vascular disorders	141 (4.0)
Cardiac disorders	107 (3.0)
General disorders and administration-site conditions	42 (1.2)
Investigations	13 (0.4)
Injury, poisoning and procedural complications	7 (0.2)
Eye disorders	6 (0.2)
Respiratory, thoracic and mediastinal disorders	2 (0.1)

*Classified according to *Medical Dictionary for Regulatory Activities*.[31]

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