Original research

Morbidity and mortality associated with prescription cannabinoid drug use in COPD

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ABSTRACT

Introduction Respiratory-related morbidity and mortality were evaluated in relation to incident prescription oral synthetic cannabinoid (nabilone, dronabinol) use among older adults with chronic obstructive pulmonary disease (COPD).

Methods This was a retrospective, population-based, data-linkage cohort study, analysing health administrative data from Ontario, Canada, from 2006 to 2016. We identified individuals aged 66 years and older with COPD, using a highly specific, validated algorithm, excluding individuals with malignancy and those receiving palliative care (n=185 876 after exclusions). An equivalent number (2106 in each group) of new cannabinoid users (defined as individuals dispensed either nabilone or dronabinol, with no dispensing for either drug in the year previous) and controls (defined as new users of a non-cannabinoid drug) were matched on 36 relevant covariates, using propensity scoring methods. Cox proportional hazard regression was used.

Results Rate of hospitalisation for COPD or pneumonia was not significantly different between new cannabinoid users and controls (HR 0.87; 95% CI 0.61–1.24). However, significantly higher rates of all-cause mortality occurred among new cannabinoid users compared with controls (HR 1.64; 95% CI 1.14–2.39). Individuals receiving higher-dose cannabinoids relative to controls were observed to experience both increased rates of hospitalisation for COPD and pneumonia (HR 2.78; 95% CI 1.17–7.09) and all-cause mortality (HR 3.31; 95% CI 1.30–9.51).

Conclusions New cannabinoid use was associated with elevated rates of adverse outcomes among older adults with COPD. Although further research is needed to confirm these observations, our findings should be considered in decisions to use cannabinoids among older adults with COPD.

Key messages

What is the key question?

► How does the new use of a prescription oral synthetic cannabinoid drug influence respiratory-related morbidity and all-cause mortality among older adults with chronic obstructive pulmonary disease (COPD)?

What is the bottom line?

► In this large, population-based cohort study, compared with non-users, propensity score-matched new cannabinoid drug users did not have significantly increased risk of hospitalisation for COPD or pneumonia, but they did have a 64% relative increase in all-cause mortality. Compared with non-users, new users of higher-dose cannabinoids had a 178% relative increase in hospitalisation for COPD or pneumonia and a 231% relative increase in all-cause mortality.

Why read on?

► Our study provides novel information on the association between new prescription oral synthetic cannabinoid use and clinically important health outcomes in older adults with COPD.

INTRODUCTION

Prescription synthetic oral cannabinoid drugs (nabilone and dronabinol) are being increasingly used among individuals with chronic obstructive pulmonary disease (COPD),[1] potentially in response to a number of issues that commonly occur in this population, including chronic musculoskeletal pain,[2] insomnia[3] and refractory dyspnoea.[4] However, there is little evidence to support using cannabinoids for these purposes among individuals with COPD.[1] With respect to refractory dyspnoea, one randomised, double-blind, placebo-controlled trial reported that sublingual cannabis reduced air hunger breathlessness sensation among individuals with COPD, but other breathlessness descriptors, breathlessness intensity by visual analogue scores, end-tidal carbon dioxide tension and minute ventilation were no different between the cannabis and placebo groups.[5] No improvements in physiological and perceptual responses during cardiopulmonary cycle exercise testing, or in spirometry, were demonstrated in another randomised, double-blind, placebo-controlled trial involving vapourised cannabis among individuals with advanced COPD.[6]

Cannabinoids may contribute to negative respiratory outcomes among individuals with COPD through several possible mechanisms: by causing sedation (which is estimated to occur in 50% of drug recipients),[7] which may then facilitate aspiration; by inducing anxiety,[8] which could then heighten dyspnoea perception and risk of a dyspnoea crisis; by provoking respiratory muscle weakness,[8] which may then contribute to respiratory depression;

through adverse immune system-related effects[9 10]; and by augmenting the activity of concomitantly used opioids[11 12] (and opioids are frequently used by individuals with COPD[13] and are known to be associated with increased risk of respiratory-related morbidity and mortality in this population).[14] Possible adverse respiratory effects of cannabinoids may occur with greater likelihood among older adults (in whom COPD is more prevalent),[15] as this group is known to less efficiently metabolise drugs.[16] Compared with smoked or vaporised cannabis, orally ingested cannabinoids are known to have greater chemical effect duration,[8] which may augment potential respiratory harms. To our knowledge, there are no published studies on prescription cannabinoid drug use and clinically meaningful health outcomes among individuals with COPD.

The purpose of this study was to evaluate the association between new prescription synthetic oral cannabinoid drug use and respiratory-related morbidity and mortality among older adults with COPD.

METHODS

Study design

A retrospective, population-based, data-linkage cohort study design was used, analysing health administrative data held at ICES (formerly known as Institute for Clinical Evaluative Sciences) relating to the province of Ontario, Canada (13.5 million people), for the period 1 April 2006 to 31 December 2016. Because healthcare coverage in Canada is universal, with a single public payer for all medically necessary health services, our health administrative databases contain data for the entire population of Ontario, and therefore, our analyses are population-based. ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorises ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information regarding the management, evaluation or monitoring of the healthcare system. Research projects conducted under section 45, by definition, do not require review by a research ethics board. This project was conducted under section 45 and approved by ICES' Privacy and Legal Office.

Data sources

Multiple Ontario healthcare administrative databases were linked at an individual-level using deterministic matching with unique encoded identifiers and analysed at ICES. Individuals with validated, physician-diagnosed COPD are contained in one database. COPD diagnosis was based on a highly specific algorithm of COPD health administrative codes that was previously validated against patient chart review by an expert respirology panel: three or more ambulatory claims for COPD within any 2-year period or one or more COPD hospitalisation(s) (specificity 95.4%; sensitivity 57.4%).[17] A second database, the Ontario Drug Benefit database, contains information on all publicly funded, outpatient drug dispensing to individuals aged 65 years and older, with drug claim coding error being very low (0.7%).[18] The Canadian Institute for Health Information Discharge Abstract Database contains information on all hospital admissions, including the reason for hospitalisation. The National Ambulatory Care Reporting System contains information on all emergency room (ER) visits. All patients' contact with physicians in both ambulatory and hospital settings is contained in the Ontario Health Insurance Plan database. Finally, the Office of the Registrar General–Deaths contains mortality data and information on the cause of death. Additional databases that were used and linked are described in the online supplemental file.

Study population

Ontario residents with COPD, aged 66 years and older, between 1 April 2006 and 31 October, 2016 were considered for this study. Although individuals younger than 66 years of age were excluded (because information on new drug use was not available for such persons), the majority of individuals with COPD are aged 65 years and older.[15] Individuals receiving palliative care (based on physician service codes and hospitalisation data), or having a diagnosis of cancer or HIV, on or before the index date (defined below) were intentionally excluded because these are settings where synthetic cannabinoids may be validly used (and our purpose was to evaluate more controversial off-label drug use), and because such individuals would a priori have poorer health outcomes (which might then bias results).

Exposed and control groups with index date definitions

The exposed group consisted of new users of prescription oral synthetic cannabinoid drugs (ie, nabilone or dronabinol) between 1 April 2006 and 31 October 2016. Using a previously applied approach,[14 19 20] new cannabinoid use was defined as no dispensing of any cannabinoid drug in the year prior to incident cannabinoid receipt, and if an individual met the criteria for incident use more than once during the accrual period, then only the first dispensing was considered. No drug dose or duration criteria were included in the definition of new cannabinoid use. Incident cannabinoid use was specifically considered (and prevalent drug use was not considered), as incident drug use is more relevant from a drug safety perspective and because prevalent use can be associated with 'healthy user' bias. The index date was the date that the incident synthetic cannabinoid was dispensed.

The control group was never dispensed nabilone or dronabinol between 1 April 2006 and 31 October 2016. Following a previously published approach,[14 19 20] controls entered the cohort through receipt of the most recent of any incident non-cannabinoid medication claim on or before a date chosen randomly from the accrual period. As cohort entry for the exposed group involved new use of a drug, we intentionally selected new drug exposure (but that of a non-cannabinoid drug) as the means for control cohort entry, in order to minimise bias. Incident non-cannabinoid medication use was defined as no dispensing of medication within the same class as the index non-cannabinoid medication in the year prior to control drug receipt.[14 19 20] If the most recent incident non-cannabinoid medication claim took place more than 6 months before the randomly chosen date, or if took place before the start of the accrual period, then the subject was excluded from the analysis.[14 19 20] The index date was the date the new non-cannabinoid drug was dispensed.

Outcomes

Hospitalisation for COPD or pneumonia was considered the primary outcome, as it is a clinically significant COPD-related event. Secondary outcomes included: outpatient respiratory exacerbations (defined similarly to previous[14 19 20] as oral corticosteroid or respiratory antibiotic receipt within ±7 days of an outpatient physician visit for COPD or pneumonia, with the corticosteroid or antibiotic prescription having a supply of 5–21 days); ER visits for COPD or pneumonia that did not directly result in a hospitalisation; COPD or pneumonia-related

mortality; and all-cause mortality. COPD and pneumonia diagnoses were based on relevant International Classification of Diseases (ICD) codes (eg, in ICD-10: J41, J42 J43, J44 for COPD; J09-18, J20-22, J40 for pneumonia). All outcomes were examined within a 60-day period following the index date, as our purpose was to examine for acute drug-related effects and because the median duration of incident cannabinoid dispensing among older adults with COPD was previously found to be 30 days.[1]

Propensity score matching

Propensity score matching was used to match exposed and control individuals on demographic and health characteristics that have been previously found to influence incident cannabinoid drug exposure.[1] A 1:1 matching ratio was used as this approach has been previously demonstrated to be optimal.[21] Following published recommendations,[22] we matched individuals on the logit of the propensity score using a width calliper equal to 0.2 of the SD of the logit of the propensity score. A propensity score for a new cannabinoid drug receipt was developed using logistic regression modelling incorporating 36 variables, including multiple markers of COPD severity (most importantly, COPD exacerbation frequency),[23] comorbidities, healthcare system utilisation, other relevant prescription medication receipt and demographics. A full list of variables included in the propensity score model can be found in the online supplemental material and an abridged list is contained in table 1. Exposed and control individuals were matched on the index date on the propensity score, as well as on the variable COPD exacerbation frequency in the year prior to the index date (in order to facilitate a planned sensitivity analysis by that variable, which will be described further down).

Statistical analysis

Descriptive statistics with standardised differences for the exposed and control groups on all covariates were calculated, before and after propensity score matching, in order to assess the adequacy of the matching process.[24] For all non-mortality outcomes, HRs with 95% CIs were calculated using cause-specific modelling that accounted for the competing risk of death. For COPD or pneumonia-related mortality, cause-specific hazard modelling was used that accounted for the competing risk of death due to other causes. For all-cause mortality, we used a Cox proportional model to regress the hazard of death on exposure status. All regression models used a robust variance estimator.[25]

Sensitivity analyses

We performed several sensitivity analyses. First, we evaluated our outcomes stratifying by COPD exacerbation history in the year prior to the index date, defined as a three-level, mutually exclusive variable: no exacerbation versus one or more outpatient exacerbation (with no exacerbation requiring presentation to the hospital) versus one or more exacerbation requiring presentation to hospital. The purpose of this sensitivity analysis was to evaluate our outcomes among individuals with differing COPD severity, in order to minimise possible healthy user bias by examining outcomes among individuals experiencing exacerbations requiring hospital admission, and possible confounding by indication by examining outcomes among individuals not experiencing exacerbations. Second, we evaluated our outcomes by differing levels of daily cannabinoid drug dose use, in order to look for possible dose–adverse response relationships. In order to undertake a dosing analysis with ease, we included only nabilone users in this specific analysis, as nabilone accounts for >98% of all the cannabinoid use among older Ontarians with COPD.[1] We considered two drug dose levels: ≤1.5 mg/day (lower dose) and >1.5 mg/day (higher dose). A 1.5 mg/day threshold was chosen to delineate lower and higher doses, as this was previously found to be the mean daily cannabinoid dose used by older adults with COPD.[1] Third, we evaluated our outcomes among incident cannabinoid drug users, but with the control group limited to incident opioid drug users, in order to compare the adversity profile between the two drugs, because both are prescribed for similar indications and because opioids have been previously demonstrated to be associated with adverse respiratory outcomes among older adults with COPD.[14] We excluded concomitant opioid users from the exposed group and concomitant cannabinoid users from the control group, to avoid group contamination. The propensity score was re-estimated for each specific sensitivity analysis.

RESULTS

Description of the cohort

There were 185 876 older adults with COPD identified, 2106 (1.1%) of whom newly received a cannabinoid drug (figure 1). Before propensity score matching, a greater proportion of exposed than controls consisted of women and the mean age was lower among exposed vs controls (table 1 and online supplemental material). There were no meaningful differences between exposed and controls in terms of proportion with low income, long-term care home residence and rural residence. Baseline health characteristics among exposed and control before propensity score matching are shown in table 1 and the online supplemental material. All exposed individuals were matched to a control individual, and new matched users and controls were well balanced on baseline characteristics, with standardised differences being below 10% for all variables (table 1 and online supplemental material).

Overall cohort analysis

There were no significant associations observed between new cannabinoid use and hospitalisation for COPD or pneumonia, outpatient respiratory exacerbation, ER visit for COPD or pneumonia, and COPD or pneumonia-related mortality (table 2). However, compared with non-users, new cannabinoid users had significantly increased rates of all-cause mortality (HR 1.64; 95% CI 1.14–2.39; p=0.01, number of events among new users vs non-users: 72/2106 vs 51/2106).

Sensitivity analyses

By COPD exacerbation frequency

In the subgroup of individuals who experienced no exacerbation in the year prior to the index, new users had significantly higher rates of all-cause mortality than non-users (HR 3.60; 95% CI 1.81–7.68; p=0.001, number of events among new users vs non-users: 31/1260 vs 12/1176) (table 3). No other associations were statistically significant in any of the subgroups.

By cannabinoid dose

Among higher-dose cannabinoid users, significantly greater rates of hospitalisation for COPD or pneumonia were observed relative to non-users (HR 2.78; 95% CI 1.17–7.09; p value=0.06, number of events among new users versus non-users: 18/546 vs 10/547) (table 4). No significant association was observed between the use of lower dose cannabinoids and hospitalisation

Table 1 Cohort baseline characteristics, before and after propensity score matching (abridged set of covariates*)

	Prior to propensity score matching			After propensity score matching		
Baseline characteristics	**New users (N=2106)**	**Non-users (N=1 83 770)**	**Standardised difference†**	**New users (N=2106)**	**Non-users (N=2106)**	**Standardised difference†**
Women (%)	60.4	51.5	0.18	60.4	61.0	0.01
Age (years), mean+SD, IQR	75.4±7.1, 69–80	77.9±8.1, 71–84	0.34	75.4±7.1, 69–80	75.3±7.7, 69–81	0.01
Low income as per ODB (%)	22.2	24.6	0.06	22.2	22.4	0.00
Long-term care residence (%)	10.6	13.6	0.09	10.6	11.4	0.02
Rural residence (%)	17.0	16.4	0.02	17.0	18.1	0.03
COPD duration (%)						
<2 years	21.5	31.7	0.23	21.5	21.1	0.01
2–5 years	19.7	19.1	0.01	19.7	19.5	0.01
>5 years	58.8	49.2	0.20	58.8	59.4	0.01
COPD exacerbation history past year (%)						
0 exacerbations	59.8	58.2	0.03	59.8	59.8	0.00
≥1 outpatient exacerbation	16.3	17.1	0.02	16.3	16.3	0.00
≥1 exacerbation associated with hospital presentation	23.9	24.7	0.02	23.9	23.9	0.00
COPD exacerbation past 30 days (%)	7.0	11.5	0.15	7.0	6.2	0.03
Respiratory medication use past 6 months (%)						
Long-acting beta-agonist inhaler	41.0	37.4	0.07	41.0	41.2	0.00
Long-acting anticholinergic inhaler	38.8	37.7	0.02	38.8	38.1	0.01
Inhaled corticosteroid	12.1	13.8	0.05	12.1	11.7	0.01
Oral corticosteroid	23.0	16.1	0.17	23.0	24.0	0.02
Theophylline	2.1	2.0	0.01	2.1	1.6%	0.04
Respiratory antibiotic	53.1	48.3	0.10	53.1	54.7	0.03
Spirometry receipt past year (%)	24.7	24.5	0.00	24.7	24.5	0.00
Total number outpatient visits past year, mean+SD	20.6±13.8	15.3±11.4	0.42	20.6±13.8	20.0±15.1	0.04
Total number hospitalisations past year, mean+SD	1.3±1.7	1.0±1.4	0.18	1.3±1.7	1.3±2.0	0.01
Any ICU admission past year, mean+SD	10.2	8.6	0.05	10.2	9.9	0.01
Any surgery past year, mean+SD	10.4	8.0	0.08	10.4	10.1	0.01
Non-COPD lung disease‡ (%)	38.3	36.2	0.04	38.3	39.0	0.02
Myocardial infarction (%)	11.2	11.6	0.01	11.2	11.0	0.00
Congestive heart failure (%)	29.9	34.3	0.09	29.9	29.9	0.00
Diabetes (%)	36.5	36.1	0.01	36.5	36.8	0.00
Stroke and other cerebrovascular disease‡ (%)	12.2	11.2	0.03	12.2	12.2	0.00
Musculoskeletal or connective tissue disease‡ (%)	91.7	75.0	0.46	91.7	92.0	0.01
Osteoporosis‡ (%)	13.7	10.0	0.11	13.7	12.0	0.05
Psychotic psychiatric disease‡ (%)	11.0	6.9	0.14	11.0	11.7	0.02
Non-psychotic psychiatric disease‡ (%)	60.5	41.8	0.38	60.5	60.2	0.01
Sleep disorder‡ (%)	51.9	47.1	0.10	51.9	51.2	0.01
Dementia‡ (%)	20.1	21.5	0.03	20.1	19.1	0.03
Smoking cessation medication§ receipt past year (%)	7.2	3.0	0.19	7.2	6.8	0.01
Benzodiazepine receipt past 3 months	38.0	21.1	0.38	38.0	36.8	0.03
Opioid receipt past 3 months	64.4	22.2	0.94	64.4	65.7	0.03

Continued

Table 1 Continued

Baseline characteristics	Prior to propensity score matching			After propensity score matching		
	New users (N=2106)	Non-users (N=1 83 770)	Standardised difference†	New users (N=2106)	Non-users (N=2106)	Standardised difference†
Serotonergic antidepressant receipt past 3 months	35.8	19.7	0.37	35.8	34.1	0.04
Loop diuretic receipt past 3 months	35.9	36.7	0.02	35.9	36.4	0.01
Cohort entry during influenza season¶ (%)	32.3	38.3	0.13	32.3	31.6	0.02

*A full list of the variables included in the propensity score model can be found in the online supplemental material.
†Standardised differences of >0.10 are thought to indicate potentially meaningful differences.
‡Presence of comorbidities was based on 3-year look-back from the index date.
§Includes bupropion and varenicline.
¶Defined as 1 November to 31 March.
COPD, chronic obstructive pulmonary disease; ER, emergency room; ICU, intensive care unit; ODB, Ontario Drug Benefit.

for COPD or pneumonia. A dose–response relationship was also observed among new cannabinoid users and all-cause mortality (lower dose: HR 1.74; 95% CI 1.11–2.75; p value=0.02, number of events among new users vs non-users: 53/1545 vs 34/1545; higher dose: HR 3.31; 95% CI 1.30–9.51; p value=0.04, number of events among new users vs non-users: 19/547 vs 8/548). No other associations were statistically significant.

New cannabinoid users versus new opioid users

None of our outcomes were significantly different between new cannabinoid users versus new opioid users (table 5).

DISCUSSION

Our large, population-based, data-linkage study involving 185 876 older adults with COPD is, to our knowledge, the first to report on the association between incident prescription oral synthetic cannabinoid use and clinically important health outcomes in this population. New cannabinoid use in this population was not associated with increased rates of hospitalisation for COPD or pneumonia, nor with increased rates of outpatient respiratory exacerbation, ER visits for COPD or pneumonia or COPD or pneumonia-related mortality. However, we observed the novel finding that all-cause mortality was elevated among new cannabinoid users relative to controls, and particularly among those receiving higher cannabinoid doses.

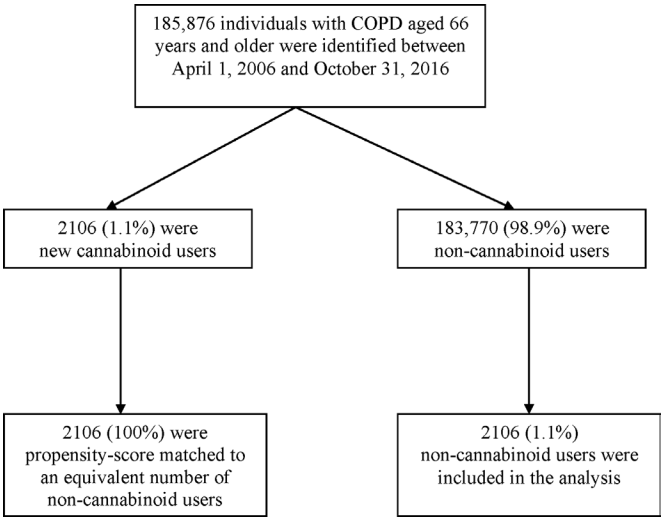

Figure 1 Flow diagram outlining exposed and control group identification. COPD, chronic obstructive pulmonary disease.

In the overall cohort analysis, only one outcome (ie, all-cause mortality) was found to occur with significantly increased rates among new cannabinoid users. It is possible that the small numbers of individuals experiencing our respiratory-related morbidity outcomes contributed to findings of non-significance. However, the dose of cannabinoid an individual receives also appears to be an important factor influencing the relationship between the drug and health outcomes, as those individuals receiving higher cannabinoid doses (defined in this study as >1.5 mg/day of nabilone) experienced increased rates of hospitalisation for COPD or pneumonia, but those receiving lower doses did not. The fact that COPD or pneumonia-related mortality was not observed to occur with significantly greater rates among cannabinoid users with COPD may suggest that the

Table 2 HRs with CIs for outcomes in the propensity score-matched sample

Outcomes	Cannabinoid use status	Events, N (%)	HR (95% CI), p value
Outpatient respiratory exacerbations	New cannabinoid users	143 (6.8)	1.12 (0.88–1.43), 0.36
	Non-cannabinoid users	127 (6.0)	Referent
ER visit for COPD or pneumonia	New cannabinoid users	45 (2.1)	1.37 (0.87–2.19), 0.16
	Non-cannabinoid users	33 (1.6)	Referent
Hospitalisation for COPD or pneumonia	New cannabinoid users	63 (3.0)	0.87 (0.61–1.24), 0.43
	Non-cannabinoid users	72 (3.4)	Referent
COPD or pneumonia-related mortality	New cannabinoid users	8 (0.4)	*
	Non-cannabinoid users	≤5†	Referent
All-cause mortality	New cannabinoid users	72 (3.4)	**1.64 (1.14–2.39), 0.01**
	Non-cannabinoid users	51 (2.4)	Referent

Results in bold font are statistically significant.
*Unable to produce reliable estimate because of small sample sizes.
†Data have been suppressed, according to ICES guidelines, because of small sample size.
COPD, chronic obstructive pulmonary disease; ER, emergency room; ICES, Institute for Clinical Evaluative Sciences.

Table 3 HRs with CIs for outcomes* in the propensity score-matched sample, stratified by COPD exacerbation history

COPD exacerbation history	Cannabinoid use status	Outpatient respiratory exacerbation: Events, N (%)	Outpatient respiratory exacerbation: HR (95% CI), p value	ER visit for COPD or pneumonia: Events, N (%)	ER visit for COPD or pneumonia: HR (95% CI), p value	Hospitalisation for COPD or pneumonia: Events, N (%)	Hospitalisation for COPD or pneumonia: HR (95% CI), p value	All-cause mortality: Events, N (%)	All-cause mortality: HR (95% CI), p value
0 exacerbations in the year prior to index	New users	45 (3.6)	1.09 (0.69–1.71), 0.72	16 (1.3)	2.05 (0.83–5.59), 0.11	19 (1.5)	2.10 (0.97–4.86), 0.09	31 (2.5)	**3.60 (1.81–7.68), 0.001**
	Non-users	37 (3.2)	Referent	7 (0.6)	Referent	10 (0.9)	Referent	12 (1.0)	Referent
≥1 outpatient respiratory exacerbation in the year prior to index	New users	41 (12.0)	0.86 (0.56–1.31), 0.50	≤5†	‡	7 (2.0)	‡	10 (2.9)	2.12 (0.49–9.91), 0.55
	Non-users	53 (12.8)	Referent	8 (1.9)	Referent	7 (1.7)	Referent	6 (1.5)	Referent
≥1 exacerbation requiring presentation to hospital in the year prior to index	New users	57 (11.3)	0.95 (0.65–1.41), 0.81	26 (5.2)	0.71 (0.41–1.22), 0.22	37 (7.4)	1.16 (0.71–1.90), 0.57	31 (6.2)	1.63 (0.91–2.96), 0.12
	Non-users	59 (11.3)	Referent	34 (6.5)	Referent	33 (6.3)	Referent	24 (4.6)	Referent

Results in bold font are statistically significant
*Results for the outcome COPD or pneumonia-related mortality are not shown because of small sample sizes.
†Data has been suppressed, according to ICES guidelines, because of small sample size.
‡Unable to produce reliable estimate because of small sample sizes.
COPD, chronic obstructive pulmonary disease; ER, emergency room; ICES, Institute for Clinical Evaluative Sciences.

increased all-cause mortality finding was not being driven by adverse respiratory-related drug effects, as we hypothesised, and instead was possibly a result of unresolved confounding. Even though rates of COPD or pneumonia-related mortality were not significantly greater among new versus non-cannabinoid users, lung disease was the most frequent cause of death among new cannabinoid users (21%) (followed by ischaemic heart disease (19%)). The credibility of a true link between cannabinoids and all-cause mortality is strengthened by the consistent finding of a positive association across multiple sensitivity analyses: a drug dose–mortality relationship was demonstrated and increased all-cause mortality was observed among non-exacerbators, which is a healthier subgroup of people, less likely to be under the influence of confounding by indication. Although one may have anticipated that heightened mortality in association with cannabinoid use would have extended to the sicker individuals in our cohort experiencing respiratory exacerbations necessitating hospital presentation, selective drug prescribing by physicians in this subgroup (out of concern for minimising drug side-effects in more vulnerable people) may explain why this was in fact not observed to be the case.

We have previously reported,[14] as have others,[26–28] that opioid drugs (which have similar prescribing indications as cannabinoids) are associated with increased respiratory-related morbidity and mortality among individuals with COPD. Although some have argued that cannabis products may have a superior safety profile relative to opioids,[29] our study results do not support this perspective insofar as the older adult COPD population is concerned, as new cannabinoid use was not found to be associated with significantly lower rates of respiratory-related morbidity and mortality compared with new opioid use. In fact, point estimates for ER visits for COPD or pneumonia, hospitalisations for COPD or pneumonia, and all-cause mortality were higher among new cannabinoid users than new opioid users. The small numbers of individuals experiencing events in this sensitivity analysis may have influenced our findings of non-significance.

Several limitations need to be acknowledged. Causation cannot be firmly concluded as an explanation for any positive associations found in this observational study. Unmeasured confounding may account for positive findings, as a result of unmeasured differences between our exposed and control

Table 4 HRs with CIs for outcomes* in the propensity score-matched sample, distinguishing by Nabilone daily dose level

Nabilone daily dose level	Cannabinoid use status	Outpatient respiratory exacerbation: Events, N (%)	Outpatient respiratory exacerbation: HR (95% CI), p value	ER visit for COPD or pneumonia: Events, N (%)	ER visit for COPD or pneumonia: HR (95% CI), p value	Hospitalisation for COPD or pneumonia: Events, N (%)	Hospitalisation for COPD or pneumonia: HR (95% CI), p value	All-cause mortality: Events, N (%)	All-cause mortality: HR (95% CI), p value
Lower dose (≤1.5 mg/day)	New users	110 (7.1)	1.21 (0.91–1.61), 0.18	31 (2.1%)	1.44 (0.81–2.59), 0.22	45 (2.9)	1.33 (0.83–2.15), 0.26	53 (3.4)	**1.74 (1.11–2.75), 0.02**
	Non-users	92 (6.0)	Referent	23 (1.5%)	Referent	33 (2.1)	Referent	34 (2.2)	Referent
Higher dose (>1.5 mg/day)	New users	32 (5.9)	1.16 (0.68–2.00), 0.60	13 (2.4)	†	18 (3.3)	**2.78 (1.17–7.09), 0.06**	19 (3.5)	**3.31 (1.30–9.51), 0.04**
	Non-users	31 (5.7)	Referent	9 (1.7)	Referent	10 (1.8)	Referent	8 (1.5)	Referent

Results in bold font are statistically significant
*Results for the outcome COPD or pneumonia-related mortality are not shown because of small sample sizes.
†Unable to produce reliable estimate because of small sample size.
COPD, chronic obstructive pulmonary disease; ER, emergency room.

Table 5 HRs with CIs for outcomes* in the propensity score-matched sample, with new opioid users serving as controls

Outcomes	Cannabinoid/opioid use status	Events, N (%)	HR (95% CI), p value
Outpatient respiratory exacerbation	New cannabinoid users	42 (6.0)	0.88 (0.57–1.35), 0.58
	New opioid users	49 (7.0)	Referent
ER visit for COPD or pneumonia	New cannabinoid users	18 (2.6)	1.46 (0.66–3.31), 0.36
	New opioid users	13 (1.9)	Referent
Hospitalisation for COPD or pneumonia	New cannabinoid users	20 (2.9)	1.24 (0.61–2.55), 0.57
	New opioid users	17 (2.4)	Referent
All-cause mortality	New cannabinoid users	22 (3.2)	1.30 (0.68–2.53), 0.48
	New opioid users	20 (2.9)	Referent

*Results for the outcome of COPD or pneumonia-related mortality are not shown because of small sample sizes.
COPD, chronic obstructive pulmonary disease; ER, emergency room

groups (eg, symptoms, tobacco or cannabis smoking, occupational exposures and lung function). Such clinical data were not available in our health administrative databases to incorporate in our propensity score model. Nevertheless, we purposefully used several methodological approaches to help minimise confounding: we intentionally excluded individuals with pre-existing malignancy and those receiving palliative care from the analysis, as such persons would have a greater a priori likelihood of poor health outcomes; we propensity score matched exposed and control individuals on a long and broad list of variables, including multiple markers of COPD severity (most importantly, COPD exacerbation frequency)[23]; control group entry was based on incident medication receipt (but of a non-cannabinoid drug) in order to try minimise potential differences in acute health status change and health-seeking behaviour between exposed and control individuals; and we evaluated our outcomes among individuals with differing COPD severity in order to see if any positive findings would hold in the healthiest subgroup of people, who would be least likely to be influenced by confounding by indication. We acknowledge that we may not have excluded all individuals receiving palliative care prior to the index date using our health administrative databases and that residual inclusion of such persons may have contributed to our finding of increased all-cause mortality associated with cannabinoid use. However, possible residual inclusion of individuals receiving palliative care in our study would less likely explain the finding of increased rates of hospitalisation for COPD or pneumonia among higher-dose cannabinoid users. The fact that we also excluded from our analysis individuals with any cancer diagnosis in the 5 years prior to the index minimises the chances of residual inclusion of individuals receiving palliative care. Our health administrative databases do not contain information on the reason for drug receipt, so sensitivity analyses by indication for drug receipt could not be easily undertaken. Our sensitivity analyses are generally based on small sample sizes, and therefore, these results need to be interpreted with some caution. Finally, our findings may not be generalisable to all individuals with COPD, as our study included only those aged 66 years and older, and our COPD identification algorithm, while highly specific, had modest sensitivity.[17]

Implications of findings for clinical practice

Cannabinoid drugs are not contraindicated for use among older adults with COPD, based on our findings. There can be legitimate reasons for using cannabinoids in this population, such as to help treat chemotherapy-related nausea and vomiting, and possibly for end-of-life care. Our findings inform that there is a significantly increased risk of adverse events occurring in association with new use cannabinoid drug use among older adults with COPD and that this information should be discussed with patients and incorporated in prescribing decision-making and management plans. Our results highlight the potential importance of using lower drug dosing to help minimise the occurrence of cannabinoid-related adverse events. Our study also informs that cannabinoids may not be a safer alternative to opioids in the older adult COPD population.

In conclusion, among older adults with COPD, new cannabinoid drug use was associated with significantly increased rates of hospitalisation for COPD or pneumonia among those receiving higher doses, and increased rates of all-cause mortality, regardless of cannabinoid dose. Cannabinoids may not be any safer to use among older adults with COPD than opioids, which are also associated with a heightened risk of respiratory-related morbidity and mortality.[14 26–28] While further research is needed to confirm the safety profile of cannabinoid drugs among older adults with COPD, our findings should be taken into consideration in prescribing decision making in this population.

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