Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Thursday, April 30, 2015 9:21 AM
To: Public Hearing
Subject: FW: Smoking With Style - Products do not meet child proof packaging requirements and expose very young.

From: pamela mccoll s.22(1) Personal and Confidential
Sent: Thursday, April 30, 2015 8:37 AM
To: Correspondence Group, City Clerk's Office
Subject: Smoking With Style - Products do not meet child proof packaging requirements and expose very young.

http://www.straight.com/news/694566/vancouver-police-raid-second-marijuana-dispensary-less-two-months?done=#comment-add

Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Thursday, May 14, 2015 9:41 AM
To: Public Hearing
Subject: FW: Advertising of Pot

From: PAMELA MCCOLL [s.22(1) Personal and Confidential
Sent: Thursday, May 14, 2015 9:31 AM
To: Correspondence Group, City Clerk's Office
Subject: Fwd: Advertising of Pot

No advertising on radio or t.v. , no signage on storefronts, no print advertising materials, no websites, no advertising of any kind, No false statements or unsubstantiated claims. That pretty well puts the pot stores out of business and if not then they will be pursued under the laws of Canada that protect Canadians from the promotion of narcotics under provisions of the Criminal Code of Canada.

http://www.theprovince.com/health/contravene+Criminal+Code+opponents/11053408/story.html

http://fusion.net/story/126674/these-teens-protested-against-marijuana-on-420/

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Tuesday, May 19, 2015 9:49 AM
To: Public Hearing
Subject: FW: Marijuana should be regulated by Health Canada not City due to contaminates

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Saturday, May 16, 2015 6:59 AM
To: Correspondence Group, City Clerk's Office
Cc: s.22(1) Personal and Confidential
Subject: Marijuana should be regulated by Health Canada not City due to contaminates

Dear Mayor of Vancouver:

Please read the news bulletin below. The City is not equipped to deal with regulating marijuana operations and this role should
stay with the Federal Government and Health Canada. Health Canada can not regulate the illegal operations in Vancouver and this
will leave the public at exposure of risk.

Pamela McColl

Judge: Pot believed to have pesticide can be seized

http://www.usatoday.com/story/news/nation/2015/05/15/marijuana-pesticide-use-quarantine/27367563/

May 15, 2015

DENVER — City health inspectors had the legal right to quarantine hundreds of millions of dollars worth of marijuana they believed was contaminated with pesticides, a judge ruled.

City officials quarantined plants at 11 legal marijuana grow facilities over the past several weeks over contamination concerns.

One of those growers, Organic Greens, asked a judge to block the quarantines and let it sell plants that testing showed were contaminated with several types of pesticide.

None of the pesticides have been approved for use on marijuana, which is a unique crop because it can be smoked, eaten or extracted.

The judge's decision could embolden city inspectors to take an even more aggressive stance against widespread — and apparently illegal — pesticide use by marijuana growers.

In a ruling issued late Thursday, Judge John Madden noted the Environmental Protection Agency has not approved any pesticide for use on marijuana, and that Colorado law makes it illegal for anyone to use pesticide in violation of EPA rules.

USA TODAY

Colo. tries to clamp down on pesticide use on pot

"...The issuance of an order preventing the sale of marijuana plants containing a substance that may be harmful if ingested by purchasers of the marijuana until it can be determined whether the substance is actually safe is absolutely within the scope of the Department of Environmental Health's authority," Madden ruled.

"Ultimately, the Plaintiff is seeking an injunction which would allow it to distribute marijuana in violation of federal law."

The immediate fate of the quarantined marijuana was unavailable.

City and state officials were still considering how to proceed Friday.

Organic Greens owner Andrew Boyens hired toxicologists who testified that even though the EPA hasn't specifically approved the use of Eagle 20 pesticide, it posed little risk to users.

He said the city's quarantine was hurting his business because customers couldn't get the high-quality marijuana he's known for.

Boyens said he needs to sell the 15-20 pounds of marijuana the city quarantined to stay in business.

Marijuana in Colorado wholesales for about $2,500 a pound.

"Everything we produce is safe," Boyens testified.

That position drew scoffs from city and state health experts, who said no one has done the formal studies necessary to prove that.

And they also pointedly noted that Boyens calls his company "organic" even though he admits to using pesticides on his crops.

Under federal labeling rules, marijuana can never be certified organic because it's a controlled substance.

USA TODAY

Denver halts some pot sales over bug spray worries

Colorado in 2014 legalized recreational marijuana sales under a licensing system that was intended to ensure legal pot was grown safely and cleanly.

Marijuana industry experts say the pesticide problem is a huge new stumbling block for pot growers trying to stay legal.

"We're really stuck," said Mike Elliot of the pro-legalization Marijuana Industry Group.

State regulators have repeatedly delayed rollout of a program to test all consumer marijuana for pesticide contamination, and Denver health inspectors appear to have stepped into that vacuum.

Under state law, all licensed marijuana growers are supposed to keep a log of what pesticides were applied to their plants, how much, and when.

City officials have been using those logs, in part, to decide which growers to target.

Colorado's legal marijuana marketplace is being closely watched by lawmakers around the world as they consider whether to relax their prohibitions on a widely used but otherwise entirely unregulated product.

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Wednesday, May 20, 2015 9:45 AM
To: Public Hearing
Subject: FW: Medical Marijuana Is Getting Into School Kids' Hands

From: PAMELA MCCOLL [s.22(1) Personal and Confidential
Sent: Wednesday, May 20, 2015 8:15 AM
To: Correspondence Group, City Clerk's Office
Cc: s.22(1) Personal and Confidential
Subject: Medical Marijuana Is Getting Into School Kids' Hands

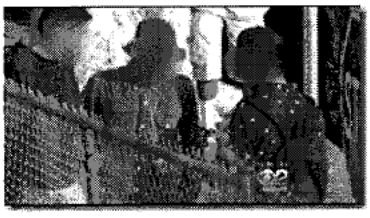
This incredible expose' by CBS2 reporter David Goldstein shows us how easy it is for children to get marijuana from dispensaries.

[Editor's note: The City Attorney's office (Los Angeles) has shut down more than 400 medical marijuana dispensaries since Prop D was enacted less than two years ago.]

Only On 2: Investigation Reveals Medical Marijuana Is Getting Into School Kids' Hands

http://losangeles.cbslocal.com/2015/02/25/only-on-2-investigation-reveals-medical-marijuana-is-getting-into-school-kids-hands/

By David Goldstein - February 25, 2015 10:45 PM



Link to video

LOS ANGELES (CBSLA.com) — In a CBS2 News exclusive, Investigative Reporter David Goldstein uncovers medical marijuana being sold to school-aged kids in broad daylight, within walking distance of local schools.

He reported the city was quick to act when he brought his disturbing findings to officials.

Goldstein recorded many instances of adults buying the marijuana and quickly turning around and re-selling it to the underage kids.

The students were shown, many times, smoking the pot minutes after leaving their schools.

The student's faces were covered because most appeared to be under 18 — the legal age for receiving doctor's approval to buy medical marijuana without a parents' consent.

So exactly how did these kids get their hands on it?

Our hidden cameras caught the students paying someone else to get it for them — like this one man who didn't want his face shown on TV.

On most afternoons, residents of the area say kids like these gather on Barton Avenue, near Western in Hollywood.

On a map, it's easy to see the area is walking distance to several schools.

With their sneakers, skateboards and backpacks, it looks like any afterschool meeting place.

Until you see what's taking place on the corner — Natural Remedies Caregivers, a marijuana dispensary.

Goldstein reports, "we saw plenty of activity."

In one instance, a group of young women is shown handing a man on a skateboard some money.

He gets on the skateboard, then walks into the store.

A few minutes later, he comes out carrying a white bag.

He passes out what looks like pill jars to the girls on the street

The jars are similar to one Goldstein found in the bushes near the dispensary.

They're used as containers for the pot.

It says right on the label, "Not for children — Keep out of reach."

But that didn't seem to stop the seller or the buyers.

The girls are shown opening up the jars and smelling their newly-purchased medical marijuana.

Goldstein and his producer also observed a customer leaving the dispensary two times in one afternoon to hand off the contents inside his white bags.

The man is shown delivering the jars to two kids on the street — then he just crumples up the bag and throws it over his head.

One teen is still holding his school notebook under his arm when he is shown tossing a jar to his friend who takes a whiff to check it out.
On another occasion, Goldstein saw two teens buying and selling what appears to be medical marijuana — exchanged openly in broad daylight.

On another day, our cameras caught a group of teens collect their money.

Their connection comes up to grab it. He goes into the dispensary and comes out with the tell-tale white bag.

He distributes the contents to his teenaged customers.

Goldstein then confronts the man.

"You just went into the dispensary and bought pot for these guys, didn't you?" he asks.

"I don't know what you're talking about," the man replies.

Goldstein tries again. "We just saw you go in there and you bought pot for these guys."

This time the man hit our camera and also made an obscene gesture.

The teens also had nothing to say.

"How old are you?" he asked several.

Goldstein then asked to speak to a manager at the dispensary.

He was told the manager "wasn't around" and that a security guard hired by the store to police the area said he didn't see anything going on.

"You are the security guard, you don't see these people coming in here and then selling to kids right around the corner?," Goldstein asks, "and you don't see anything, right?"

The guard closed the door.

Residents said they see it and complained to police and nothing was done.

"Well, it's very frustrating," said resident Dazzier Jimenez, "because you know, we have kids around the area, so they see that.

It's a bad example for our youth."

Goldstein asked City Attorney Mike Feuer why this dispensary was allowed to remain open.

His office oversees LA's Prop D marijuana law.

He said the dispensary complies with all the written requirements, as far as being a safe distance from schools and parks.

After we told him what was going on, authorities acted.

"I can report that because you provided us with that location," Feuer said, "the police conducted an investigation at the site and last evening they arrested an individual, an adult for allegedly selling medical marijuana to a minor just outside the facility."

The manager of the dispensary also emailed Goldstein.

"We are doing everything in our power to stop the illegal patient solicitations outside of the building and to also stop second-hand transactions from happening," the manager wrote.

Residents wonder why it took so long.

"Why are there now arrests when there haven't been any in the past?," said Jimenez.

"Quite frankly," says LAPD Commander Andrew Smith, "it was not a big problem location.

It was not known to us as a problem location."

Police and prosecutors told Goldstein that after seeing CBS2's undercover video, they are now cracking down.

David Goldstein, CBS2 News

[Editor's note: The City Attorney's office has shut down more than 400 medical marijuana dispensaries since Prop D was enacted less than two years ago.]

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Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 22, 2015 9:41 AM
To: Public Hearing
Subject: FW: answer to Schizophrenia question - Stevenson.
Attachments: Moore Marijuana.pdf; Zammit 2002.pdf; Stefanis 2013.pdf; Meier cannabis.pdf; Marij,Volkow 2014.pdf; Madras PNAS Commentary.pdf; Ajdacic 2007.pdf

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Thursday, May 21, 2015 9:38 PM
To: Correspondence Group, City Clerk's Office
Subject: answer to Schizophrenia question - Stevenson.

Marijuana appears to hasten the disease

Research shows that marijuana users with schizophrenia develop the illness at a younger age than nonusers. In one study, marijuana-using males with schizophrenia were first diagnosed seven years younger than nonusers.[11] However, a meta-analysis that combined the best studies showed marijuana users were first diagnosed two to three years younger than nonusers, and the difference showed up most in the heaviest users.[12]

Incidentally, alcohol abuse by itself does not cause schizophrenia to develop earlier.[13] So when people say marijuana isn't as bad as alcohol, they're not looking at this disease. For people with schizophrenia, marijuana is worse.

Can marijuana cause schizophrenia?

The most concerning research on marijuana is the evidence that it can precipitate schizophrenia in people who are genetically susceptible, pushing them over an edge they might not have crossed on their own. In 2006, Louisa Degenhardt and Wayne Hall published a review of the research. They found that teenage marijuana use is associated with higher rates of schizophrenia, and that the more often teenagers used marijuana the more likely they were to develop schizophrenia later in life.[14]

In one very large research project known as the Swedish Conscript Study, more than 50,000 people were interviewed about their marijuana use at age eighteen and then followed for the next fifteen years. Compared to people who had never used marijuana, those who had used the drug no more than ten times by age eighteen were 1.3 times more likely to develop schizophrenia as adults. Those who used marijuana fewer than fifty times were three times more likely. And those who smoked marijuana more than fifty times by age eighteen were six times as likely to develop schizophrenia.[15]

Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review

Theresa H M Moore, Stanley Zammit, Anne Lingford-Hughes, Thomas R E Barnes, Peter B Jones, Margaret Burke, Glyn Lewis

Summary

Background Whether cannabis can cause psychotic or affective symptoms that persist beyond transient intoxication is unclear. We systematically reviewed the evidence pertaining to cannabis use and occurrence of psychotic or affective mental health outcomes.

Methods We searched Medline, Embase, CINAHL, PsycINFO, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, and MEDCARIB from their inception to September, 2006, searched reference lists of studies selected for inclusion, and contacted experts. Studies were included if longitudinal and population based. 35 studies from 4804 references were included. Data extraction and quality assessment were done independently and in duplicate.

Findings There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio=1·41, 95% CI 1·20–1·65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis most frequently (2·09, 1·54–2·84). Results of analyses restricted to studies of more clinically relevant psychotic disorders were similar. Depression, suicidal thoughts, and anxiety outcomes were examined separately. Findings for these outcomes were less consistent, and fewer attempts were made to address non-causal explanations, than for psychosis. A substantial confounding effect was present for both psychotic and affective outcomes.

Interpretation The evidence is consistent with the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects, although evidence for affective outcomes is less strong. The uncertainty about whether cannabis causes psychosis is unlikely to be resolved by further longitudinal studies such as those reviewed here. However, we conclude that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.

Lancet 2007; 370: 319–28

See Editorial page 292

See Comment page 293

Academic Unit of Psychiatry (T H M Moore MSc, S Zammit PhD, A Lingford-Hughes PhD, G Lewis PhD) **and Department of Social Medicine** (M Burke MSc), **University of Bristol, Bristol, UK; Department of Psychological Medicine, Cardiff University, Cardiff, UK** (S Zammit); **Department of Psychological Medicine, Imperial College, London, UK** (T R E Barnes DSc); **and Department of Psychiatry, Cambridge University, Cambridge, UK** (P B Jones PhD)

Correspondence to:
Dr Stanley Zammit, Department of Psychological Medicine, Cardiff University, Cardiff CF14 4XN, UK
zammits@cardiff.ac.uk

Introduction

Cannabis, or marijuana, is the most commonly used illegal substance in most countries, including the UK and USA.[1–3] About 20% of young people now report use at least once per week or heavy use (use on >100 occasions).[4,5] Use has increased particularly during early adolescence, when the developing brain might be especially susceptible to environmental exposures.[6] Experimental studies[7–10] and surveys of users[11–13] provide strong evidence that cannabis intoxication can produce transient, and usually mild, psychotic and affective experiences. Of greater concern are chronic symptoms that persist beyond, or occur independently of, intoxication effects.

Whether cannabis increases the incidence of established syndromes such as schizophrenia or depression is unclear, but this question is important because these disorders lead to substantial distress for individuals and their families, and to public burden from health-care costs. Randomised controlled trials (RCTs) of cannabis for medical use[14] are unlikely to be helpful in addressing the question of causality because there are substantial differences between the pharmacokinetic profiles of such preparations and of cannabis used as a recreational drug. The typically short follow-up periods of such trials also substantially hinder interpretation of results.

Previous reviews in this field have not been very systematic, have examined broad psychosocial outcomes rather than mental illness, or have included cross-sectional data.[15–19] We have systematically reviewed longitudinal studies of cannabis use and subsequent psychotic or affective mental health outcomes, and we have assessed the strength of evidence that cannabis use and these outcomes are causally related.

Methods

Study selection and data collection

Studies were included if they were population-based longitudinal studies, or case-control studies nested within longitudinal designs. We excluded cohorts of people with mental illness or substance-use-related problems, studies of prison populations, and RCTs of cannabis for medical use.[14]

Diagnostic outcomes for psychosis included schizophrenia, schizophreniform, schizoaffective, or psychotic disorders, non-affective or affective psychoses, psychosis not otherwise specified, psychotic symptoms, delusions, hallucinations, or thought disorder. Presence of delusions, hallucinations, or thought disorder was a requirement for all psychosis outcomes. Affective, mood, or bipolar disorder, affective disorder not otherwise specified, depression, suicidal ideation or suicide attempts, anxiety, neurosis, and mania were included for affective outcomes.

We searched the following databases from their inception to Sept 5, 2006: Medline, Embase, and the Cumulative Index to Nursing and Allied Health Literature

(CINAHL) on OVID; PsycINFO on WebSPIRS; ISI Web of Knowledge and ISI Proceedings; ZETOC (a British library database of journal and conference contents); BIOSIS on EDINA; and Latin American and Caribbean Health Sciences (LILACS) and Caribbean Health Sciences Literature (MEDCARIB). We searched using the format "([psychosis or schizophrenia or synonyms] or [affective disorder or depression or synonyms]) and (cannabis or synonyms)", using text words and indexing (MeSH) terms (full details are available on GL's departmental website).

For **Glyn Lewis's departmental website** see bristol.ac.uk/Depts/Psychiatry/research/psychotic.html

The search was restricted to studies on human beings but was not limited by language or study design. We searched reference lists of included studies, and wrote to experts in the field and researchers responsible for studies to find other published and unpublished studies of relevance. We examined all titles and abstracts, and obtained full texts of potentially relevant papers. Working independently and in duplicate, we read the papers and determined whether they met inclusion criteria using eligibility record forms (available on the corresponding author's departmental website). We resolved disagreements by consensus, and extracted data independently and in duplicate.

We assessed study quality by recording how potential non-causal explanations, particularly bias and confounding factors, were accounted for in each study. We assessed information on sampling strategy, response rates, missing data, attrition, and attempts to address reverse causation, intoxication effects, and confounding factors.

Data synthesis

Where study characteristics were judged reasonably homogeneous, we grouped studies together and pooled data in a meta-analysis; otherwise, we present a narrative synthesis of data. We pooled studies using the DerSimonian and Laird random-effects model[20] and the metan command in Stata (9·0). Where studies presented data only in subgroups, these were incorporated as separate studies. We assessed heterogeneity using the I^2 statistic.[21] Presence of publication bias was investigated by use of funnel plots and Egger's Test.[22] A summary of compliance with MOOSE guidelines[23] is available on GL's departmental website.

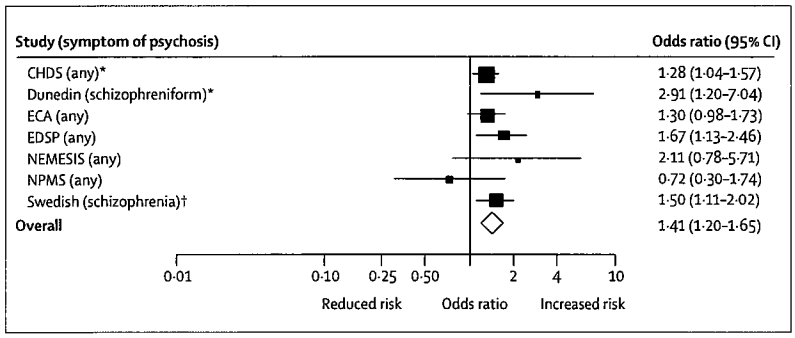

Figure 1: **Forest plot showing adjusted odds ratios and 95% CI for any psychosis outcome according to ever use of cannabis in individual studies**

Exposure was ever use of cannabis in all studies except for the NPMS, in which the measure was ever use over the past 1 year only. *Additional data were provided by investigators in these studies.[31,34] †Results were unaltered when the 4% of cases with simplex schizophrenia were omitted.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Searches of electronic bibliographic databases, expert advice, and searches of reference lists of included studies and other reviews yielded 4804 references. On the basis of their titles and abstracts, we judged that 175 (3·6%) of these references potentially contained enough detail to be relevant. 143 of these references were excluded as not relevant when we had read the whole paper. Details of the studies that were excluded at this stage, including those that we regarded as near misses, are available on GL's departmental website.

We found 11 studies of psychosis; these reports presented data from seven cohort studies. There were five adult population-based cohorts: the Epidemiological Catchment Area (ECA) study based in the USA;[24] the Early Developmental Stages of Psychopathology (EDSP) study based in Germany;[25] the Netherlands Mental Health Survey and Incidence Study (NEMESIS);[26] the National Psychiatric Morbidity Survey (NPMS) based in the UK;[27] and the 1969 Swedish Conscript Cohort.[28–30] There were also two birth cohorts, from Dunedin[31,32] and Christchurch (CHDS)[33,34] in New Zealand. For the Swedish conscripts and CHDS cohorts, data from the most recent reports[29,34] were included in each case because these had longer follow-up to cover more events, and had more comprehensive analyses to keep reverse causation and confounding effects to a minimum. Omission of individuals with schizophrenia simplex made no difference to results for schizophrenia in the study of Swedish conscripts (Zammit S, unpublished). However, results for non-schizophrenia psychoses from this cohort were not included because the diagnostic codes that were used potentially included many people without psychosis as defined in this study.

Three of the eligible studies examined psychotic disorders, which were defined as the presence of psychotic symptoms with concurrent evidence of impaired functioning (Dunedin,[31] NEMESIS,[26] and Swedish conscripts[29]), and six studies used the broader outcome of psychotic symptoms with no requirement for impaired functioning (CHDS,[34] Dunedin,[31] ECA,[24] EDSP,[25] NEMESIS,[26] and NPMS[27]).

For affective outcomes, 24 reports were identified from 15 cohort studies: two birth cohorts from New Zealand (CHDS[35–37] and Dunedin[31,32,38]); six adult population-based

cohorts, from the USA (Berkely,[39] ECA,[40,41] and NY state[42,43]), the UK (NPMS [Haynes J, University of Bristol, personal communication]), Australia (Northern Rivers Mental Health Study, NoRMHS[44]), and Colombia;[45] and seven school-based cohorts, from Australia (Victoria[46]) and the USA (AddHealth,[47,48] Baltimore,[49] Chicago,[50] LA schools,[51,52] LAT,[53] and NY schools[54,55]). Various outcomes were examined, including depression (ten studies), depressive symptoms (six studies), suicidal ideation or suicide attempts (six studies), anxiety disorders (five studies), and anxiety symptoms (one study). We identified one study that had data on mania, though there was only one event in the whole sample.[44]

Results for the seven studies included for psychosis are summarised in webtable 1 and figure 1. There was no evidence to support the presence of publication bias (Egger test, p=0·48). The unadjusted results of all studies reported evidence of an increased risk of psychosis in people who used cannabis compared with non-users. These associations were reduced, but nevertheless persisted, in six of the studies after adjustment for confounding factors.

Estimates were pooled under the assumption that measures of psychosis were on a continuum of symptoms from mild (self-report of psychotic symptoms) to severe (clinical diagnosis of schizophrenia). There was an increased risk of a psychotic outcome in individuals who ever used cannabis (adjusted odds ratio=1·41, 95% CI 1·20–1·65; heterogeneity p=0·28; I^2=19·2%).

Of the six studies that either examined a linear trend across cannabis use frequencies[25,26,29,34] or compared higher with lower frequency categories,[24,27] all reported findings that were consistent with a dose-response effect. Figure 2 shows the associations reported for people with most frequent cannabis use compared with non-users of cannabis in each study where such data were available. In the pooled analysis, there was an increased risk of a psychotic outcome in individuals who used cannabis most frequently (adjusted odds ratio=2·09, 1·54–2·84; heterogeneity p=0·11; I^2=44·1%).

We also examined the specific relation between cannabis use and risk of developing a psychotic disorder. The narrowest definition of psychotic disorder was in the Swedish conscripts study,[29] which reported an increased risk of schizophrenia in individuals who used cannabis. Studies of schizophreniform disorder from Dunedin[31] (additional data unstratified by age at first use were supplied by the researchers) and needs-based diagnosis of psychotic disorder from NEMESIS[26] also showed associations with cannabis use. Pooled data from these studies show an increased risk of psychotic disorders in individuals who had ever used cannabis (adjusted odds ratio=2·58, 1·08–6·13; heterogeneity p=0·049; I^2=66·9%).

We repeated the pooled analyses for most frequent cannabis use and for psychotic disorders but omitted the results from NEMESIS because this had the greatest effect on heterogeneity. In these sensitivity analyses, there remained an increased risk of a psychotic outcome in people who used cannabis most frequently (odds ratio=1·92, 1·50–2·47; heterogeneity p=0·26; I^2=25·0%), and also an increased risk of psychotic disorders in people who had ever used cannabis (odds ratio=1·82, 1·01–3·30; heterogeneity p=0·16; I^2=48·3%).

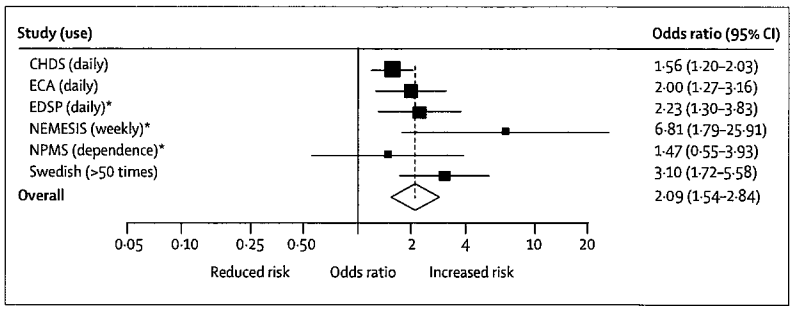

Figure 2: **Forest plot showing adjusted odds ratios and 95% CI for any psychosis outcome according to most frequent use of cannabis in individual studies**
*Results were not adjusted for other drug use.

See Online for webtable 1

Two studies have examined differential effects of cannabis on psychosis according to age of first use of this drug. In the Dunedin study, a stronger effect of cannabis on psychotic symptoms was reported for individuals who first used cannabis before, as opposed to after, 16 years of age.[31] There was much weaker evidence for this age effect for schizophreniform disorder, although the CIs were very wide. In the Swedish conscripts study, there was no evidence that the effect of cannabis on risk of schizophrenia differed for people who first used cannabis before, as opposed to after, age 16 years.[30]

Other putative interactions were also reported. A further report on the Dunedin cohort[32] described a strong effect of cannabis on risk of schizophreniform disorder in people homozygous for the valine allele at Val158Met within the catechol-O-methyltransferase (COMT) gene (crude odds ratio=10·9, 2·2–54·1), with no apparent effect in methionine homozygotes (crude odds ratio=1·1, 0·21–5·4) and an intermediate effect in heterozygotes. This potential interaction was observed only in people who first used cannabis before age 18 years, with no evidence of interaction in those who first used it after this age.

In the EDSP study, the effect of cannabis on psychosis outcome was stronger in groups described as psychosis prone than in non-prone groups.[25] However, psychosis-prone individuals already had evidence of psychotic features at baseline, and this study was therefore not examining differences in the effects of cannabis on psychosis incidence between these groups.

We assessed the quality of the studies included for psychosis. Because reverse causation, intoxication effects, and confounding factors could have led to overestimation of the true causal association between cannabis use and psychosis, we assessed the degree to which the potential effect of these was kept to a minimum within each study (table 1).

	Attempt to limit reverse causation	Attempt to limit intoxication effects	Approximate change from crude to adjusted OR (%)*
CHDS[33,34]†	Adjusted for psychotic symptoms at previous assessment and used SEM to address direction of causation	Used SCL-90 to measure outcome. This does not allow identification of symptoms caused by drug intoxication	65% ↓
Dunedin[31]†	Adjusted for psychotic symptoms at age 11 years (cannabis measures at age 15 and 18 years)	Used DIS to measure outcome. Excluded symptoms caused solely by drug use	10% ↓
ECA[24]	Excluded people with psychotic diagnosis at baseline	Used DIS to measure outcome. Excluded symptoms caused solely by drug use	30% ↓
EDSP[25]	Adjusted for predisposition to psychosis measured at baseline	Used M-CIDI to measure outcome. Stated that no symptoms were due to acute effects of drug use	15% ↓
NEMESIS[26]	Excluded people with psychotic symptoms at baseline	Used CIDI to measure outcome. Excluded symptoms caused by drug use	50% ↓
NPMS[27]	Excluded people with psychotic symptoms at baseline	Used PSQ to measure outcome. This does not allow identification of symptoms caused by drug intoxication	80% ↓
Swedish conscripts[29,30]	Excluded people with psychotic diagnosis at baseline	Used ICD clinical diagnosis of schizophrenia as outcome, suggesting intoxication effects unlikely	60% ↓

OR=odds ratio. SEM=structural equation modelling. SCL-90=symptom checklist 90. DIS=diagnostic interview schedule. M-CIDI=Munich version of CIDI. CIDI=composite international diagnostic interview. PSQ=psychosis screening questionnaire. ICD=International classification of diseases. ↓=decrease. *Change between crude OR and that after adjustment for confounding factors was calculated as (crude OR-adjusted OR)/(crude OR-1). †Additional data, to allow estimation of change between crude and adjusted estimates, kindly provided by the researchers.

Table 1: **Information on possible alternative causes for associations reported between cannabis use and psychosis outcomes in seven cohorts**

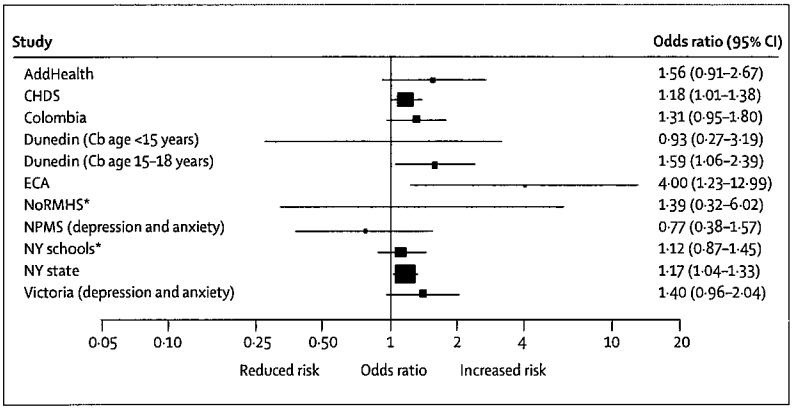

Figure 3: **Forest plot showing adjusted odds ratios and 95% CI for any depression outcome according to cannabis exposure in individual studies**

Depression outcome measures: centre for epidemiological studies (CES-D) score >22 (AddHealth); diagnostic and statistical manual of mental disorders (DSM; CHDS, Dunedin, and NY state); WHO international classification of diseases 10th revision (ICD-10; NoRMHS); DSM symptom lasting ≥2 weeks (ECA); clinical interview schedule—revised (CIS-R) score ≥12 (NPMS, Victoria); symptom checklist 90 assessment (SCL-90) upper quartile (Colombia); and SCL-90 >median score (NY schools). Subgroup data from the Dunedin study were incorporated as separate studies. Exposure to cannabis (Cb): ever use (AddHealth, Dunedin, NPMS); current use (NY schools); use less than once per week in the past 6 months (Victoria); use at least once per month (Colombia); frequency of use (a linear trend across frequency categories; CHDS, NY state); cannabis misuse disorder (ECA, NoRMHS). The point estimates of odds ratios (squares) are not visible for studies in which the variance was very high. *Unadjusted results calculated from data in tables in the original studies.[44]

Four studies[24,26,27,29] excluded participants who had experienced psychosis at baseline. In the Swedish conscripts study,[29] reverse causation was limited further by analysis restricted to patients admitted for schizophrenia at least 5 years after conscription; this analysis produced similar results to the main analysis. Three studies[25,31,34] adjusted in the analysis for psychotic symptoms at baseline. Although this approach partly addresses the problem of reverse causation, it averages the association between cannabis and psychosis incidence with that between cannabis and symptom chronicity or relapse. In CHDS,[34] structural equation modelling results suggested that cannabis use was significantly associated with subsequent increase in risk of psychotic symptoms rather than vice versa.

Intoxication effects were not specifically mentioned in reports of the ECA[24] and NEMESIS[26] studies, but the outcome assessment (also used in Dunedin[31] and EDSP[25]) instructs the interviewer to exclude psychotic symptoms that arise solely from drug use. The questionnaires used in CHDS[34] and NPMS[27] do not allow intoxication to be assessed. However, exclusion of intoxication effects in those who use cannabis every day is likely to be very difficult. In the Swedish conscripts study,[29] use of WHO International Classification of Diseases criteria suggests that misclassification of a cannabis-intoxication psychosis was unlikely; the same is probably true for the Dunedin study,[31] in which psychosis was defined by the presence of symptoms of schizophreniform disorder for longer than 1 month.

The studies listed in table 1 adjusted for about 60 different confounding factors, including other substance use, personality traits, sociodemographic markers, intellectual ability, and other mental health problems. For all studies, fully adjusted estimates were attenuated, compared with crude results, by an average of about 45% (range 10%–80%). In the CHDS, use of fixed-effects regression to adjust further for unmeasured non-varying confounding factors made little difference to results.[34] Adjustment for other substance use led to a substantial attenuation of effect in the ECA study[24] and NEMESIS,[26] whereas in the Swedish conscripts study[29] the strongest confounding factors were IQ score, urban upbringing, and other mental health disorders.

Loss to follow-up occurred for between 4%[31] and 32%[27] of the cohorts we included for psychosis. No data on attrition were available from the Swedish conscript study.[29] Sensitivity analyses from two of the studies[26,34] suggest that attrition might have had small effects on results, although reclassification of outcome in NEMESIS did not differentiate between people with different cannabis use at baseline.

Depressive outcomes were examined in 15 cohorts (webtable 2). There was no evidence to support the presence of publication bias (Egger test, ten studies; p=0·13). Of ten studies that examined a diagnosis of depression or above-threshold rating scores (figure 3),

five reported evidence of an association with cannabis use that persisted after adjustment.[31,37,40,43,46] However, in two of these,[31,46] significant associations were observed only in subgroup analyses, and in the Dunedin study[31] no baseline measures of depression were accounted for. Weak evidence for association was reported by two further studies,[45,48] and an association observed in NPMS (Haynes J, personal communication) was eliminated after adjustment. In view of the heterogeneity across these studies in relation to measures of cannabis exposure (which included ever use, frequency of use, and cannabis misuse disorder), we did not think a meta-analysis of these data would be appropriate. Using average values from these studies—of 35% having ever used cannabis and 15% having developed depression—we estimated that a sample with more than 230 events would be required for 80% power to detect an odds ratio for depression of 1·5 (a larger effect than was observed in most studies). Thus, about half the studies probably had insufficient power to observe an association of this size.

Six studies[32,38,51–54] from five cohorts examined depressive symptoms on a continuous scale. Evidence of association was observed in the Berkeley[38] and LA schools[51,52] cohorts (webtable 2). However, in the Berkeley study only crude results were presented, and the association was observed in men but not women,[39] whereas in the LA schools cohort an increased risk observed in an early part of the study[51] was not replicated in a later wave.[52]

Of the studies that examined a linear trend across cannabis use frequencies[37,41,51,52] or that compared higher with lower frequency groups[46] (Haynes J, personal communication), four reported findings that were consistent with a dose-response effect on depression outcomes (webtable 2). Figure 4 shows the associations reported for participants with most frequent cannabis use compared with non-users, with some evidence for an increased risk of depression in a pooled analysis (adjusted odds ratio=1·49, 1·15–1·94; heterogeneity p=0·192; I^2=29·6%).

Seven studies assessed suicidal ideation or suicide attempts. Four of these[10,37,47,49] reported an association between cannabis use and increased risk in adjusted analyses and one[50] showed little evidence of an association (figure 5). A reduced risk of attempts[51] but increased risk of ideation[52] were reported from the LA schools cohort (webtable 2).

Of the seven studies that specifically examined anxiety outcomes (figure 6),[35,41,42,44,45,51,52] two reported an association with cannabis use that persisted after adjustment for confounding factors.[42,45] In the ECA study of obsessive–compulsive disorder, an association was observed in a matched sample, but there was little evidence for association in the whole sample when a more valid unconditional analytical approach was used.[41]

Several studies reported putative interactions. In the NY state study,[43] there was a suggestion that risk of depression increased with earlier age of first use of cannabis. However, in the Dunedin cohort, there was no evidence for a greater risk of depression in people who first used cannabis before, as opposed to after, age 16 years.[31]

See Online for webtable 2

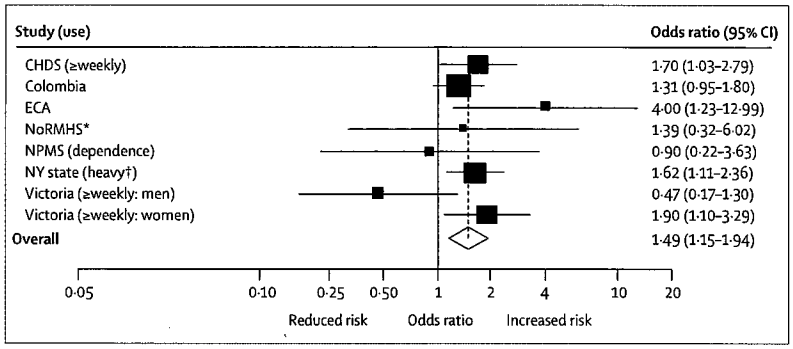

Figure 4: **Forest plot showing adjusted odds ratios and 95% CI for depression outcomes according to most frequent use of cannabis in individual studies**
Depression outcome measures: DSM diagnosis (CHDS, NY state); ICD-10 diagnosis (NoRMHS); DSM symptom lasting ≥2 weeks (ECA); CIS-R score ≥12 (NPMS, Victoria); and SCL-90 upper quartile (Colombia). Subgroup data from the Victoria study were incorporated as separate studies. *Unadjusted results calculated from data in tables in the original study.[44] †Results for the heavy use category were calculated from results for linear trend across four categories of frequency of cannabis use.

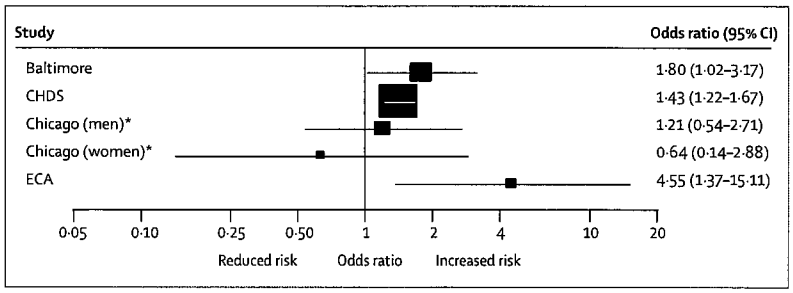

Figure 5: **Forest plot showing adjusted odds ratios and 95% CI for suicidal ideation according to cannabis exposure in individual studies**
Cannabis exposure: ever used before age 16 (Baltimore); used >40 occasions (Chicago); frequency of use (linear trend across frequency categories; CHDS); cannabis misuse disorder (ECA). *Unadjusted results; subgroup data incorporated as separate studies.

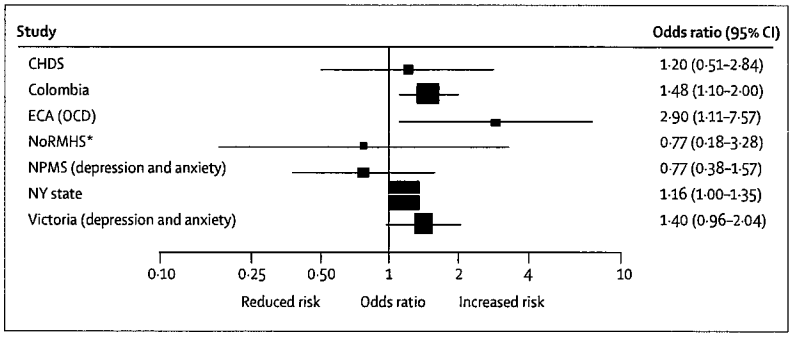

Figure 6: **Forest plot showing adjusted odds ratios and 95% CI for anxiety outcomes according to cannabis exposure in individual studies**
Anxiety outcomes: DSM diagnosis (CHDS, ECA, NY state); ICD-10 diagnosis (NoRMHS); CIS-R score ≥12 (NPMS, Victoria); SCL-90 upper quartile (Colombia). Cannabis exposure: use in past year (ECA, NPMS); use less than once per week for the past 6 months (Victoria); use at least once per month (Colombia); frequency of use (linear trend across frequency categories; CHDS, NY state); cannabis disorder (NoRMHS). OCD=obsessive-compulsive disorder. *Unadjusted results calculated from data in tables in the original study.[44]

	Attempt to limit reverse causation	Attempt to limit intoxication effects*	Approximate change from crude to adjusted OR (%)†
AddHealth[47]	Not reported. Assessed, but did not exclude or adjust, for baseline suicidal behaviour	Not reported	Only adjusted results presented
AddHealth[48]‡	Excluded people with depression at baseline (CES-D score above threshold)	Not reported. Used CES-D to measure outcome	45% ↓
Baltimore[49]	Adjusted for childhood depression at age 8 years	Not reported. Used NIMH interview to measure outcome	40% ↓ to 60% ↑
Berkeley[39]	Not reported	Not reported. Used CES-D to measure outcome	Only crude results presented
CHDS[35]	Adjusted for anxiety and depression at baseline	Not reported. Used DIS and DISC to measure outcome	50–60% ↓
CHDS[37]	Adjusted for anxiety and depression at baseline	Not reported. Used DISC and CIDI to measure outcome	25% ↓
Chicago[50]	Not reported	Not reported	Only crude results presented
Columbia[45]	Adjusted for distress (anxiety and depression) at baseline	Not reported. Used SCL-90 to measure outcome	Only adjusted results presented
Dunedin[38]	Adjusted for baseline mental disorder	Not reported. Used DIS and DISC to measure outcome	93% ↓ for all mental disorders
Dunedin[31]	Not reported. Screened, but did not exclude or adjust, for depression at baseline	Not reported. Used DIS to measure outcome	Only adjusted results presented
ECA[41]	Excluded people with history of OCD at baseline	Not reported. Used DIS to measure outcome	215% ↑
ECA[40]	Excluded people with lifetime ever DSM-III-R symptoms of depression >2 weeks	Not reported. Used DIS and symptoms present most days for >2 weeks	10% ↓
LA schools[51]	Adjusted for previous emotional distress, including depression	Not reported. Used CES-D and HSC to measure outcome	Only adjusted results presented
LA schools[52]	Not reported	Not reported. Used CES-D to measure outcome	Only adjusted results presented
LAT[33]	Not reported. Assessed, but did not exclude or adjust, for baseline depressive symptoms	Adjusting for cannabis use at outcome made no difference to results. Used CES-D and CIDI to measure outcome	Only crude results presented
NoRMHS[44]	Not reported. Did not exclude or adjust for baseline measures	Not reported. Used CIDI to measure outcome	Only crude results presented
NPMS§	Excluded people with baseline CIS-R ≥12 Adjusted for CIS-R <12	Not reported. Used CIS-R to measure outcome	80–100% ↓
NY schools[54]	Results calculated by us are with exclusion of people with baseline depressive symptoms	Not reported. Used SCL to measure outcome	Only crude results presented
NY schools[55]	Adjusted for depression score at baseline	Not reported. Used HSC to measure outcome	Only adjusted results presented
NY state[42]	Adjusted for previous depression or anxiety	Not reported. Used DISC to measure outcome	Only adjusted results presented
NY state[43]	Adjusted for previous depression	Not reported. Used CIDI to measure outcome	Only adjusted results presented
Victoria[46]	Adjusted for previous depression and anxiety	Not reported. Used CIS-R to measure outcome	Up to 40% ↓

OR=odds ratio. CES-D=centre for epidemiological studies—depression scale. DIS=diagnostic interview schedule. DISC=diagnostic interview schedule for children. CIDI=composite international diagnostic interview. SCL-90=symptom checklist 90. OCD=obsessive-compulsive disorder. DSM-III-R=diagnostic and statistical manual of mental disorders, third edition, revised. CIS-R=clinical interview schedule—revised. HSC=Hopkins symptom checklist. ↓=decrease. ↑=increase. *DIS, DISC, and CIDI potentially allow exclusion of intoxication effects, although none of the studies states explicitly that this was done. CES-D, CIS-R, HSC, and SCL do not allow attempts to exclude intoxication effects. †Change between crude OR and that after adjustment for confounding factors was calculated as (crude OR–adjusted OR)/(crude OR–1). ‡Additional data on crude and adjusted estimates were provided by the researchers. §Haynes J, personal communication.

Table 2: **Information on possible alternative causes for associations reported between cannabis use and affective outcomes in 15 cohorts**

There were single reports of interactions between cannabis use and age[37] and sex.[46] As with the results for psychosis, an interaction between cannabis use and *COMT* genotype was observed in the Dunedin cohort for depression, but not for anxiety.[32]

We assessed the quality of the studies included for affective outcomes by assessing the degree to which the potential effects of reverse causation, intoxication effects, and confounding factors were kept to a minimum within each study (table 2). Only four studies[40,41,48] (Haynes J, personal communication) excluded participants with affective symptoms at baseline. Ten reports[35,37,38,42,43,45,46,49,51,55] adjusted for the baseline measure of the outcome in the analyses but, as discussed earlier, this potentially mixes the effects of cannabis on incidence of affective outcome with those on symptom chronicity or relapse. In seven studies,[31,39,44,47,50,52,53] there was no exclusion of affected individuals or adjustment for baseline measures in the analyses. Three papers[42,43,45] from two cohorts reported that adjustment for baseline measures of the outcome had a negligible effect on results. Attempts to exclude intoxication effects were not explicitly mentioned in any of the 24 studies, although the questionnaires and interviews used for ten of these studies could have enabled raters to exclude symptoms attributed to drug intoxication.

About 50 different confounding factors were reported. Most of these were related to family and peer relationships, adverse life events, criminality, mental health problems, sociodemographic markers, and other substance use. Five studies[39,44,50,53,54] presented only unadjusted results, whereas one[55] made no mention of the confounding factors adjusted for.

For six of the eight studies in which both crude and adjusted results were presented, adjustment led to attenuation of associations with cannabis use, ranging from 10% to 100% reduction. Adjustment for a comprehensive set of confounding factors in the CHDS eliminated reasonably strong associations with depression, anxiety, and suicidal ideation,[35] although associations for depression persisted after adjustment in a longer follow-up of this cohort.[37] In one study of the Dunedin cohort,[38] adjustment for a more comprehensive set of confounding factors than in a more recent report[31] reduced the association between cannabis use and all mental disorders by 90%; however, effects specifically for affective outcomes were not presented. In the Baltimore study, both an increase in effect size for suicidal ideation and an attenuation of association with suicide attempts were observed following adjustment.[49]

Attrition from the studies included for affective outcomes ranged from 4%[31] to 70%,[51] with a median of 20%; loss to follow-up was not reported for two of the studies.[39,45] Cannabis use disorder at baseline was associated with increased attrition in NoRMHS, although weighting of the analyses to account for this made little difference to the results.[44] Attrition was associated with baseline alcohol use and disorganised thinking in the LA schools study,[52]

but was not associated with baseline substance use in the LAT study.[53] However, in the ECA study individuals with baseline depression and cannabis misuse were both more likely to be available for follow-up.[40]

Discussion

We found a consistent increase in incidence of psychosis outcomes in people who had used cannabis. There was no statistical evidence of publication bias, although this finding was based on only seven studies. The pooled analysis revealed an increase in risk of psychosis of about 40% in participants who had ever used cannabis. However, studies tended to report larger effects for more frequent use, with most studies showing a 50–200% increase in risk for participants who used most heavily. A dose-response effect was observed in all studies that examined the relation to increasing cannabis exposure. Only three studies[26,29,31] examined psychotic disorders as an outcome; the presence of functional impairment makes these studies relevant to clinical practice. The results from these studies were also consistent with an increased risk in people who used cannabis.

Studies included in the pooled analyses used different methods to measure cannabis exposure and to assess outcome. For example, use of the symptom checklist 90 assessment in the CHDS[34] might have led to inclusion of participants without psychotic symptoms as defined in this review. This heterogeneity was reflected in the large I^2 values for some of the pooled results. The features of NEMESIS[26] that caused this study to increase between-study heterogeneity to a greater extent than the other studies are not clear, but heterogeneity decreased when this study was omitted from the sensitivity analyses, even though results were largely unchanged.

Arguments for why earlier use of cannabis might have more harmful effects are intuitively compelling, but no robust evidence supports this view. The increased risk of psychosis in people using cannabis from a younger age observed in the Dunedin cohort could indicate a greater cumulative exposure to cannabis rather than a sensitive period of exposure.[31] In the Swedish conscripts study, in which cumulative use of cannabis was examined, no difference in risk according to age at first use was observed.[30] Similarly, evidence for effect modification between cannabis use and *COMT* variation on psychosis risk is very weak: this effect was observed in only a subgroup of people within the Dunedin cohort,[32] and evidence for such an interaction in an experimental setting was also observed in only a subgroup of participants.[56]

Almost all studies reported an increased risk of affective outcomes in people who used cannabis, although CIs were generally consistent with null effects. However, effect sizes were small, and many studies were probably underpowered. For example, odds ratios for depression ranged from 1·3 to 1·6 for the highest exposure categories of weekly or monthly cannabis use, with one exception (the ECA study of cannabis misuse disorder).[40]

An association seen in an observational study does not necessarily reflect a causal relation. Because most of the studies for psychosis excluded people with psychosis at baseline, the observed associations are unlikely to reflect reverse causation. However, the majority of studies for affective outcomes did not adequately address the problem of reverse causation as a possible alternative explanation for any association observed. For cannabis and psychosis, there was evidence of confounding effects, but the associations persisted in almost all studies, even after adjustment for comprehensive lists of variables, including markers of premorbid disturbances that are commonly observed in patients with schizophrenia. All of the studies that reported an association for psychosis adjusted for other drug use, although two of the studies[26,31] made no adjustment for alcohol use. Furthermore, three studies[25,26,31] for psychosis made no adjustment for other mental health disorders at baseline, and measures of disorders adjusted for in the other studies[24,25,29,34] are unlikely to have accurately captured all mental health symptoms at baseline given the scope of the assessment tools generally used.

Residual confounding by these or other factors can never be eliminated from observational studies. Adjustment for confounding factors in studies of affective outcomes seemed to be more important than in studies of psychotic outcomes, and in some studies such adjustment explained all the observed association. There was also more variation for affective outcomes than for psychosis, with increases in crude estimates reported in two studies.[41,49] Furthermore, roughly half the studies made no adjustment for alcohol or other drug use. Confounding factors seem more likely to explain the reported association between cannabis and affective outcomes than that between cannabis and psychosis.

Most studies of psychosis made some attempt to reduce the chance that the outcome examined was due directly to effect of intoxication with cannabis, although this can be a difficult judgment in people who use cannabis frequently. Misdiagnosis as cannabis intoxication was unlikely in the Swedish conscripts study,[29] in which the outcome was admission to hospital with schizophrenia, or in the Dunedin cohort,[31] in which the outcome was presence of schizophreniform symptoms for longer than 1 month. The possibilities of intoxication and withdrawal effects were not considered in any of the studies of affective outcomes, although both of these can result from cannabis consumption.[7,57]

We would expect both confounding factors and intoxication to lead to an increase in the observed association. However, underestimation of effects could also have occurred. Measurement of cannabis use is especially difficult because there is almost certainly large variation in biologically available cannabinoid concentrations, resulting from different sources of cannabis and from different intake practices; self-reported frequency of use is also prone to error. Such misclassification, if ran-

	Review type	Methods	Studies included in review	Meta-analysis
Semple et al[19]	Systematic review of cannabis use and psychosis	Search strategy specified databases, search terms used, and dates of search Stated criteria for inclusion of studies Did not assess study quality Did not provide statement of compliance with MOOSE guidelines	Cross-sectional and longitudinal studies of high-risk groups	Included cross-sectional and longitudinal data Results from this meta-analysis are not consistent with our results; however, use of unadjusted estimates in this meta-analysis, and combining effects for ever-use of cannabis with those for dependence, makes it difficult to compare directly with our findings
Macleod et al[18]	Systematic review of cannabis and other illicit drugs and psychological and social harm	Search strategy specified databases, search terms used, and dates Stated criteria for inclusion of studies Assessed study quality Did not provide statement of compliance with MOOSE guidelines	Longitudinal studies Examined several broad psychosocial outcomes, one of which was psychological problems	None
Arseneault et al[15]	Narrative review of cannabis and psychosis	Search strategy specified databases searched, but not search terms used or dates of search Stated criteria for inclusion of studies Did not describe methods used to assess study quality	Cross-sectional and longitudinal, although results were reported separately	Meta-analysis was of longitudinal studies only. Included duplication of Swedish conscript data and one stratum of subgroup data for the Dunedin study. Combination of effects for ever-use of cannabis with those for dependence makes it difficult to compare with our findings
Henquet et al[17]	Narrative review of cannabis and psychosis	Did not describe search strategy Did not state criteria for inclusion of studies Did not describe methods used to assess study quality	Cross-sectional and longitudinal	Included cross-sectional and longitudinal data Combination of effects for ever-use of cannabis with those for dependence makes it difficult to compare with our findings

Table 3: **Summary of previously published systematic reviews or narrative reviews with meta-analyses**

dom, would usually make detection of an association more difficult. However, differential misclassification could lead to overestimates of association. For example, stimulant use is more common in people who use cannabis than in those who do not, so under-reporting of stimulant use might differentially affect the results from cannabis users.

Attrition in cohort studies is more likely in people who use drugs and in those who develop mental health problems than in other participants,[58,59] and this would also lead to underestimates of association. Evidence for such a pattern of attrition was present in NoRMHS[44] and the LA schools study.[52] In the ECA study,[40] participants with baseline depression were more likely to remain in the study, although pattern of loss in relation to incident depression is unknown. The extent to which such bias would affect the results is unclear, although modelling for attrition in CHDS,[34] NEMESIS,[26] and NoRMHS[44] suggests that bias caused by attrition had little effect on the overall findings.

Recent estimates of the proportion of adolescents and young adults in the UK who have ever used cannabis are around 40%.[2] If having ever used cannabis increases risk of a psychotic outcome by 1·4 times (as suggested from the pooled analysis), we can estimate that about 14% (95% CI 7–19) of psychotic outcomes in young adults currently in the UK would not occur if cannabis were not consumed. However, such estimates rely heavily on the assumption that the association between cannabis use and psychosis is causal, and that the pooled relative risk is an accurate estimate of this causal effect.

Projected trends for schizophrenia incidence have not paralleled trends in cannabis use over time, and this apparent mismatch has been used as an argument against causal effects.[60] However, other projections suggest that time lags and a lack of reliable incidence data might mean that changes in schizophrenia incidence are not yet fully apparent.[61]

Even seemingly robust findings from observational studies have sometimes not been confirmed by RCTs.[62] However, in some situations RCTs are not feasible, and reliance must be placed on interpretation of results from the best available evidence from observational studies.[63] The neurobiological sequelae of cannabis use, including modulated activity of dopaminergic, GABAergic, and glutamatergic neurons,[64–66] are consistent with abnormalities described in people with psychotic disorders.[67] Furthermore, evidence that cannabis can produce transient psychotic and mood-altering symptoms in experimental studies[7–10] lends support to a causal explanation for the associations between cannabis use and more chronic psychotic and affective disorders.

We are not aware of any other systematic reviews that focus on the relation between cannabis and affective outcomes. A previous systematic review of cannabis use and psychosis included cross-sectional studies and did not address study quality.[19] Another systematic review examined broader psychosocial outcomes,[18] but the lack of focus specifically on psychotic or affective disorders meant that the explanations for associations could not be examined in detail. Previous meta-analyses from both systematic[19] and narrative[15,17] reviews (table 3) have included cross-sectional data[17,19] or used unadjusted results,[19] and combined effects for ever-use of cannabis with those for dependence.[15,17,19] As might be expected, all report larger effects than observed in this study, although direct comparison of these effects with our findings is difficult.

There are potential problems with meta-analyses of observational data.[68] However, we applied robust methods to identify as many publications as we could, and attempted to interpret the findings as appropriately as possible by including a thorough critique of individual

studies, and by doing a comprehensive assessment of alternative explanations for associations reported.

Even if the methods of future longitudinal studies are more robust, these studies are likely to encounter similar limitations to those discussed here. However, improvement in the measurement of cannabis exposure and elimination of intoxication effects might reduce some of the uncertainty. Animal models of long-term effects of cannabis on neuropsychological domains relevant to psychotic or affective states could also improve knowledge.[69] Further study is needed to establish whether cannabis is more harmful in younger age groups, and whether risk is modified by genetic or other factors. The question of whether cannabis causes psychotic or affective disorders is perhaps the wrong one to be asking, because it will be difficult to answer with any degree of certainty. What is more pertinent is whether the evidence that is now available can justify policy implications, such as public education campaigns to alert people to the possible risks associated with cannabis.

In conclusion, we have described a consistent association between cannabis use and psychotic symptoms, including disabling psychotic disorders. The possibility that this association results from confounding factors or bias cannot be ruled out, and these uncertainties are unlikely to be resolved in the near future. Despite the inevitable uncertainty, policymakers need to provide the public with advice about this widely used drug. We believe that there is now enough evidence to inform people that using cannabis could increase their risk of developing a psychotic illness later in life. The evidence that cannabis use leads to affective outcomes is less strong than for psychosis but is still of concern. Although individual lifetime risk of chronic psychotic disorders such as schizophrenia, even in people who use cannabis regularly, is likely to be low (less than 3%), cannabis use can be expected to have a substantial effect on psychotic disorders at a population level because exposure to this drug is so common.

Contributors

GL secured funding for the study. MB, SZ, GL, and THMM participated in designing of search strategies and undertook searches. THMM, SZ, AL-H, TREB, PBJ, and GL participated in screening of search results and retrieved papers. THMM, SZ, and GL extracted data and appraised quality of papers. THMM and SZ analysed data. THMM, SZ, AL-H, TREB, PBJ, and GL interpreted data. THMM coordinated the review and managed data. THMM and SZ co-wrote the review. AL-H, TREB, PBJ, MB, and GL edited and refined the review. All authors saw and approved the final version of the report.

Conflict of interest statement

PBJ and TREB were both invited experts on the Advisory Council on the Misuse of Drugs Cannabis Review in 2005. SZ, PBJ, TJ, GL, and AL-H have received honoraria for lectures and talks or consultancy fees (for work unrelated to cannabis) from pharmaceutical companies. AL-H has received an honorarium from Sanofi-Aventis for attending a meeting about cannabinoid antagonists, and has received consultancy fees from Bristol Myers Squibb and unrestricted research monies from Merck. TREB has received consultancy fees from Servier, Johnson & Johnson, and Bristol-Myers Squibb regarding antipsychotic medication. THMM and MB have no conflicts of interest.

Acknowledgments

We thank Helen Davies for assistance with the retrieval of papers, and the authors of the papers we considered for inclusion and the experts we contacted for assistance with the search for suitable papers—Louisa Degenhardt, Wayne Hall, Jonathan Haynes, Robert Ferdinand, John Macleod, Robert Pandina, Robin Murray, Jean Paul Selten, Jim van Os, Helene Verdoux, and Mark Weiser. We also thank Louise Arseneault, David Fergusson, and David Pevalin for providing us with data from additional analyses for our review. This work was funded by the Department of Health, UK. SZ is funded through a Clinician Scientist Award funded by the National Assembly for Wales.

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Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study

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Abstract

Objectives An association between use of cannabis in adolescence and subsequent risk of schizophrenia was previously reported in a follow up of Swedish conscripts. Arguments were raised that this association may be due to use of drugs other than cannabis and that personality traits may have confounded results. We performed a further analysis of this cohort to address these uncertainties while extending the follow up period to identify additional cases.

Design Historical cohort study.

Setting 1969-70 survey of Swedish conscripts (>97% of the country's male population aged 18-20).

Participants 50 087 subjects: data were available on self reported use of cannabis and other drugs, and on several social and psychological characteristics.

Main outcome measures Admissions to hospital for ICD-8/9 schizophrenia and other psychoses, as determined by record linkage.

Results Cannabis was associated with an increased risk of developing schizophrenia in a dose dependent fashion both for subjects who had ever used cannabis (adjusted odds ratio for linear trend of increasing frequency 1.2, 95% confidence interval 1.1 to 1.4, $P<0.001$), and for subjects who had used only cannabis and no other drugs (adjusted odds ratio for linear trend 1.3, 1.1 to 1.5, $P<0.015$). The adjusted odds ratio for using cannabis >50 times was 6.7 (2.1 to 21.7) in the cannabis only group. Similar results were obtained when analysis was restricted to subjects developing schizophrenia after five years after conscription, to exclude prodromal cases.

Conclusions Cannabis use is associated with an increased risk of developing schizophrenia, consistent with a causal relation. This association is not explained by use of other psychoactive drugs or personality traits relating to social integration.

Introduction

The relation between cannabis use and subsequent onset of psychosis is complex.[1-3] Although it is clear that high doses of cannabis may lead to a short lived toxic psychosis, it is unclear whether cannabis increases the risk of psychotic illness persisting after abstinence from the drug. An association between self reported use of cannabis in adolescence and subsequent risk of schizophrenia was reported from a cohort study of Swedish conscripts,[4] which supports the view that cannabis might act as an independent risk factor for schizophrenia. Several uncertainties have, however, been raised regarding the interpretation of this result.

Firstly, the apparent effect of cannabis may be caused by other drugs (such as amphetamines) that are more likely to have been misused among cannabis users than among non-users.[5,6] Secondly, premorbid personality traits may have predisposed individuals both to developing schizophrenia and to using cannabis. Traits relating to social behaviour are likely to be particularly important in this respect. Thirdly, use of cannabis may have been secondary to the presence of schizophrenia, as a form of "self medication" for symptoms, despite failure to identify the disorder at the time of conscription.[7] Review of case histories of a small subsample from this cohort shows that the association was not due to use of other drugs and that use of cannabis preceded any mental illness,[8] but the causal pathways are difficult to disentangle and merit further study.

We are not aware of any other cohort studies that have investigated the association between drug use and subsequent risk of schizophrenia, and case-control studies are susceptible to recall bias. In this study we perform a further analysis of the Swedish conscript cohort to address some of the above concerns.[4] The follow up period is now 27 years (15 years in the original study) and covers almost the whole period of risk for schizophrenia.[9] Our improved understanding of risk factors for schizophrenia has also enabled us better to adjust for factors such as personality traits that potentially confound this relation.[10-13]

Methods

Subjects

The cohort consisted of 50 087 Swedish men conscripted for compulsory military training in 1969-1970. More than 98% (49 321) were 18-20 years of age. Only 2-3% of the male population were excused conscription because of severe mental or physical handicap. The conscription procedure included intelligence tests and non-anonymous self reported ques-

Editorial by Rey and Tennant
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bmj.com 2002;325:1199

tionnaires on family, social background, behaviour during adolescence, and substance use—including first drug used, drug most commonly used, frequency of use, and direct questions regarding use of a list of specified drugs. Details of the procedure and results of studies of its validity have been reported previously.[14]

All subjects underwent a structured interview conducted by a psychologist, and those reporting any psychiatric symptoms were interviewed by a psychiatrist and given a diagnosis according to ICD-8 (international classification of diseases, 8th revision) where applicable.[15] Thirty four cases of psychosis diagnosed at conscription were excluded from the study. Permission to use the anonymised database was granted by the Karolinska Institute research ethics committee and the Swedish data inspection board.

Follow up

The Swedish national hospital discharge register recorded about 70% of all psychiatric admissions in 1970, rising to 83% in 1973. Coverage was 97% in 1974-83, 95% in 1984-6, and has been virtually complete since 1987. The linkage reported here was from 1970 to 1996. The incomplete registration during some periods is unlikely to have affected the results. Misclassification of outcomes is likely to be low, given that over 90% of people with schizophrenia are admitted to hospital at some point during their illness.[16]

Patients were given clinical diagnoses according to the Nordic version of ICD-8 (ICD-9 from 1987). Outcomes investigated were schizophrenia (codes 295.00-295.99) and other psychoses (including affective and paranoid psychoses, codes 296.00-298.99). It is unlikely that cases diagnosed as schizophrenia in this cohort were either toxic psychoses induced by cannabis (or amphetamine) or acute, transient drug induced psychoses, given the restrictive tradition in Sweden regarding the diagnosis of schizophrenia.[17] Satisfactory validity of schizophrenia diagnoses in a small sample from this cohort has been observed,[8] and ICD-8 diagnoses from the register have shown high specificity with criteria for schizophrenia as defined in DSM-III (*Diagnostic and Statistical Manual of Mental Disorders*, third edition).[18]

Analysis

We used logistic regression to calculate odds ratios and 95% confidence intervals for developing schizophrenia in subjects who used cannabis compared with subjects with no history of drug use, both before and after adjustment for potential confounders. Odds ratios may be interpreted as rate ratios because schizophrenia is a rare outcome.[19] Although a few subjects died during follow up, analysis by using Cox regression made no difference to the results obtained by using logistic regression, which we therefore retained as the method of choice.

Previous research has found that psychiatric diagnosis at conscription, IQ score, personality variables concerned with interpersonal relationships, place of upbringing, paternal age, and cigarette smoking are all associated with schizophrenia.[10-13 20 21] We included these variables as potential confounders in the regression model. Disturbed behaviour in childhood, history of alcohol misuse, family history of psychiatric illness, financial situation of the family, and father's occupation were also considered to be potential confounders and included in the analysis. The variable relating to poor social integration as an aspect of personality was a summed score of questions regarding number of close friends, history of relationships with girlfriends, and individual sensitivity. We selected these questions after a factor analysis of over 40 questions relating to childhood and adolescent behaviour from one of the questionnaires. Only 3% of the sample had missing data for any of the questions.

Subjects were stratified into those receiving a diagnosis within five years of conscription (0-5 years) and those receiving a diagnosis after this time (>5 years) to investigate possible effects of a prodrome at the time of conscription.

Results

Out of the 50 053 subjects, 362 (0.71%, 95% confidence interval 0.65% to 0.80%) received a diagnosis of schizophrenia by 1996. Data on drug use, derived from all sources of information, were missing on 16 (4.4%) of subjects developing schizophrenia and on 1522 (3.1%) of non-cases ($P < 0.2$).

Of 11 variables initially included as potential confounders, only five had any effect on the adjusted results. Table 1 shows a summary of these in relation to cannabis use. Adjusting for poor social integration made minimal difference to results but is also included in table 1. For the purposes of table 1 only, we treated IQ score, poor social integration, and disturbed behaviour as dichotomous variables, using the 10th percentile as a cut-off point for coding.

Ever used cannabis

Altogether 5391 subjects (10.8% of the cohort) had ever used cannabis, and 73 of these (1.4%) developed schizophrenia. In 69 subjects who started using drugs before 1969, 19 (31%; 95% confidence interval 20% to 44%) of those developing schizophrenia had stopped using drugs before conscription, as opposed to 2810 (64%; 62% to 65%) of the 4418 who did not develop schizophrenia ($P < 0.001$).

Table 1 Summary of confounders in relation to subjects' history of drug use at conscription. Values are numbers (percentages) of cohort sample

Subjects by type of drug use	Diagnosis of psychiatric illness on conscription*	Disturbed behaviour	Low IQ score	Brought up in city	Cigarette smoking	Poor social integration
Cannabis (n=5391)	1408 (27)	1582 (31)	297 (6)	2262 (43)	4582 (86)	130 (2.5)
Cannabis only (n=1648)	235 (15)	271 (17)	65 (4)	653 (40)	1331 (81)	34 (2.1)
Any drug (n=11 783)	2325 (20)	2557 (23)	1007 (9)	3358 (31)	8835 (80)	246 (2.3)
No drug (n=36 753)	2827 (8)	1681 (5)	3510 (10)	6759 (19)	19 229 (52)	841 (2.4)

Owing to missing data for each of the confounders, the precentages presented may not tally precisely with the numbers of subjects reported
*Except psychosis or learning disability.

The crude and adjusted odds ratios with 95% confidence intervals for developing schizophrenia given a history of ever using cannabis are presented in tables 2, 3, and 4. The crude odds ratio for developing schizophrenia any time after conscription was 2.2 (1.7 to 2.8) and this association persisted, although reduced, after adjustment (adjusted odds ratio 1.5, 1.1 to 2.0).

We found a dose dependent relation between frequency of cannabis use and risk of schizophrenia, with an adjusted odds ratio for linear trend across the categories of frequency of cannabis use used in this study of 1.2 (1.1 to 1.4, $P<0.001$). The adjusted odds ratio for subjects with a history of heaviest use of cannabis (>50 occasions) was 3.1 (1.7 to 5.5).

The association between cannabis use and schizophrenia was greater in subjects admitted in the first five years after conscription (adjusted odds ratio 2.1, 1.2 to 3.7) compared with those admitted after five years (1.2, 0.8 to 1.8). Frequency of cannabis use was associated with schizophrenia in both the early onset group (adjusted odds ratio for linear trend 1.3, 1.1 to 1.6, $P<0.001$) and the later onset group (1.2, 1.1 to 1.3, $P<0.02$).

Cannabis only

Altogether 1648 subjects (3.3% of cohort, 3.1% to 3.5%) had used only cannabis, and 18 of these (1.1%, 0.6 to 1.7%) developed schizophrenia. Those who used only cannabis had an increased risk of schizophrenia compared with those who reported no drug use. The odds ratio before adjustment (1.9, 1.2 to 3.0) and afterwards (1.9, 1.1 to 3.1) was similar (table 5). We found a dose dependent relation for frequency of use, with an adjusted odds ratio for linear trend of 1.3 (1.0 to 1.5, $P<0.02$).

Stimulant use

We found an association between schizophrenia and stimulant use in the crude analysis (crude odds ratio 3.8, 2.7 to 5.4), but this became non-significant after adjustment for confounders (adjusted odds ratio 1.5, 0.9 to 2.4). Adjusting for frequency of cannabis use further reduced the association between stimulant use and risk of schizophrenia (adjusted odds ratio 1.1, 0.6 to 2.1). The association observed between schizophrenia and frequency of cannabis use was unchanged after adjustment for stimulant use.

Other psychoses

A total of 446 subjects were admitted with other psychoses. Subjects who had ever used cannabis had an increased risk of developing a psychosis other than schizophrenia (crude odds ratio 1.4, 1.1 to 1.9), but this effect was reduced after adjustment (adjusted odds ratio 1.1, 0.8 to 1.5). A similar pattern was observed for the association with cannabis frequency, with a linear trend odds ratio of 1.1 (1.0 to 1.2, $P<0.02$) before adjustment and of 1.0 (0.9 to 1.1, $P<0.85$) after adjustment.

For all the analyses, diagnosis on conscription, IQ score, and place of upbringing contributed most to confounding. Adjusting for the other potential confounders made virtually no difference to the final adjusted results.

Table 2 Crude and adjusted odds ratios with 95% confidence intervals for developing schizophrenia any time after conscription in subjects who have ever used cannabis

Drug use	No of subjects	No (%) of subjects developing schizophrenia	Odds ratio (95% CI)	
			Crude	Adjusted*
Cannabis ever†	5391	73 (1.4)	2.2 (1.7 to 2.8)	1.5 (1.1 to 2.0)
Frequency of use of cannabis (ever):				
None	36 429	215 (0.6)	1.0†	1.0†
Once	608	2 (0.3)	0.6 (0.1 to 2.2)	0.6 (0.1 to 2.3)
2-4 times	1380	8 (0.6)	1.0 (0.5 to 2.0)	0.9 (0.4 to 1.9)
5-10 times	806	9 (1.1)	1.9 (1.0 to 3.7)	1.4 (0.7 to 2.8)
11-50 times	689	13 (1.9)	3.2 (1.8 to 5.7)	2.2 (1.2 to 4.0)
>50 times	731	28 (3.8)	6.7 (4.5 to 10.0)	3.1 (1.7 to 5.5)
Linear trend for frequency of use	—	—	1.4 (1.3 to 1.5)	1.2 (1.1 to 1.4)

*Adjusted for diagnosis at conscription to IQ score to poor social integration to disturbed behaviour to cigarette smoking to and place of upbringing.
†No drug use as baseline comparison.

Table 3 Crude and adjusted odds ratios with 95% confidence intervals (95% CI) for developing schizophrenia in years 0-5 after conscription in subjects who have ever used cannabis

Drug use	No of subjects	No (%) of subjects developing schizophrenia	Odds ratio (95% CI)	
			Crude	Adjusted*
Cannabis ever†	5320	33 (0.6)	2.2 (1.7 to 2.8)	2.1 (1.2 to 3.7)
Frequency of use of cannabis (ever):				
None	36 429	47 (0.1)	1.0†	1.0†
Once	608	0	—	—
2-4 times	1380	2 (0.1)	1.1 (0.3 to 4.6)	1.0 (0.2 to 4.4)
5-10 times	806	4 (0.5)	3.9 (1.4 to 10.7)	2.6 (0.8 to 7.9)
11-50 times	689	4 (0.6)	4.5 (1.6 to 12.6)	2.8 (0.9 to 8.8)
>50 times	731	13 (1.8)	14.0 (7.5 to 26.0)	4.7 (1.8 to 12.4)
Linear trend for frequency of use		—	1.6 (1.4 to 1.8)	1.3 (1.1 to 1.6)

*Adjusted for diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing.
†No drug use as baseline comparison.

Table 4 Crude and adjusted odds ratios with 95% confidence intervals (95% CI) for developing schizophrenia in years 5+ after conscription in subjects having ever used cannabis

Drug use	No of subjects	No (%) of subjects developing schizophrenia	Odds ratio (95% CI)	
			Crude	Adjusted*
Cannabis ever†	5287	40 (0.8)	1.6 (1.1 to 2.2)	1.2 (0.8 to 1.8)
Frequency of use of cannabis (ever):				
None	36 382	168 (0.5)	1.0†	1.0†
Once	608	2 (0.3)	0.7 (0.2 to 2.9)	0.8 (0.2 to 3.2)
2-4 times	1378	6 (0.4)	0.9 (0.4 to 2.1)	0.9 (0.4 to 2.0)
5-10 times	802	5 (0.6)	1.4 (0.6 to 3.3)	1.0 (0.4 to 2.5)
11-50 times	685	9 (1.3)	2.9 (1.5 to 5.6)	2.1 (1.0 to 4.5)
>50 times	718	15 (2.1)	4.6 (2.7 to 7.8)	2.5 (1.2 to 5.1)
Linear trend for frequency of use	—	—	1.3 (1.2 to 1.4)	1.2 (1.0 to 1.3)

*Adjusted for diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing.
†No drug use as baseline comparison.

Discussion

Self reported use of cannabis in early adulthood was associated with an increased risk of developing schizophrenia. Risk increased in a dose dependent manner with increasing frequency of cannabis use, and this relation remained when analysis was restricted to subjects who had used only cannabis and no other drugs before conscription. The largest risk was seen in subjects reporting use of cannabis on more than 50 occasions. We found no association between cannabis and other psychotic illnesses, which implies that cannabis has a rather specific association with an increased risk of schizophrenia.

Table 5 Adjusted odds ratios with 95% confidence intervals for developing schizophrenia any time after conscription for subjects taking cannabis only

Drug use	No of subjects	No (%) of subjects developing schizophrenia	Odds ratio (95% CI)	
			Crude	Adjusted*
Cannabis ever†	1635	18 (1.1)	1.9 (1.2 to 3.0)	1.9 (1.1 to 3.1)
Frequency of use of cannabis (ever):				
None	36 429	215 (0.6)	1.0†	1.0†
Once	245	0	—	—
2-4 times	499	5 (1.0)	1.7 (0.7 to 4.2)	1.9 (0.8 to 4.8)
5-10 times	255	3 (1.2)	2.0 (0.6 to 6.3)	1.7 (0.5 to 5.7)
11-50 times	176	1 (0.6)	1.0 (0.1 to 6.9)	0.8 (0.1 to 6.0)
>50 times	70	4 (5.7)	10.2 (3.7 to 28.3)	6.7 (2.1 to 21.7)
Linear trend for frequency of use	—	—	1.3 (1.1 to 1.6)	1.3 (1.0 to 1.5)

*Adjusted for diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing.
†No drug use as baseline comparison.

The association between use of cannabis and schizophrenia was stronger in subjects who were first admitted within five years of conscription. One explanation is that subjects with a prodrome of schizophrenia at conscription may have increased their cannabis use, perhaps as a means of self medication.[2] But all subjects were screened at conscription, and we adjusted for other psychiatric problems recorded at that time. The relation with cannabis use was also observed in the later onset group, admitted more than five years after conscription. It seems more likely that the reduced association in the group with later onset is due to misclassification, as the number of people who discontinued cannabis use accumulated over time.[22]

Although adjustment for confounders substantially reduced the odds ratios, adjusting for poor social integration had only minimal effects. A similar effect was observed in the original study by Andreasson et al, who adjusted for the number of friends that the subjects reported having.[4] We used a more comprehensive measure of social integration as it is likely that on its own this question was not a strong measure of sociable personality traits. Personality traits are difficult to measure accurately, however, and residual confounding remains a possibility. The association between cannabis and schizophrenia persisted even after adjusting for use of alcohol, cigarettes, and other drugs, all of which are likely to be indicative of risk taking behaviour. This implies that a shared risk factor (be it biological, genetic, or through personality traits) for developing schizophrenia and for using psychoactive substances does not adequately explain the association observed.

We are limited in that we have only data regarding use of cannabis before conscription. But if the pattern of increased initiation and reduced cessation of drug use seen in the schizophrenia group persisted after the time of conscription, this would result in us underestimating the effect size of cannabis. Fewer subjects in this cohort claimed to have used cannabis and other illicit drugs compared with similar cohorts that used anonymous questionnaires.[23] The effect of under-reporting would again result in an underestimate of the true effect size. Non-response was similar for subjects developing schizophrenia and non-cases, although, as a further check, we repeated the analyses, having recoded non-responders as either users or non-users of cannabis. This made no difference when recoding was non-differential between cases and non-cases, but it increased the odds ratios substantially when recoding was differential.

What is already known about this topic

Use of cannabis has been associated with an increased risk of developing schizophrenia

Alternative explanations for this association include confounding by personality or by use of other drugs such as amphetamines, and use of cannabis as a form of self medication secondary to the disorder

What this study adds

Self reported cannabis use is associated with an increased risk of subsequently developing schizophrenia, consistent with a causal relation

This association is not explained by sociability personality traits, or by use of amphetamines or other drugs

Self medication with cannabis is an unlikely explanation for the association observed

It is possible that use of stimulants could explain the results if stimulants were able to induce a chronic psychotic illness, identical to schizophrenia. But we did not find an independent association between use of stimulants and schizophrenia, although power was reduced compared with other analyses. Although studies from the United States have found that initiation of amphetamine use peaks by age 18-20,[22] it is possible that initiation of stimulants after conscription was more likely in subjects who had previously used only cannabis. But the absence of an independent association with use of stimulants in our data implies that cannabis is potentially the more important agent.

These findings are in keeping with accumulating evidence that cannabis has detrimental effects on mental health in some people.[3] Molecular studies have shown that Δ^9-tetrahydrocannabinol, the active component of cannabis, increases release of dopamine in the mesolimbic pathway.[24] Given the suggested relation between increased mesolimbic dopamine and positive symptoms of schizophrenia,[25] such observations provide support for the hypothesis that cannabis may act as a risk factor for this disorder.

Use of cannabis use has increased substantially over the past few decades in the United Kingdom, and 50% of the population now report having used cannabis at least once.[26] If cannabis increases the risk of schizophrenia by 30%, as implied by these results, then 13% of cases of schizophrenia could be prevented if cannabis use was eliminated from the population, assuming that a causal relation between cannabis use and schizophrenia really exists. The overall weight of evidence is that occasional use of cannabis has few harmful effects overall,[2] and the drug is less likely to be used regularly and cause dependence than nicotine. Nevertheless, these results indicate a potentially serious risk to the mental health of people who use cannabis, particularly in the presence of other risk factors for schizophrenia. Such risks need to be considered in the current move to liberalise and possi-

bly legalise the use of cannabis in the United Kingdom and other countries.

We thank Hollie Thomas and Diane McCracken for their help and advice, and Jonas Sadigh for his help with data management.

Contributors: SZ contributed to the conception of the study, data analysis, and drafting of the manuscript. PA contributed to the conception and design of the study, and drafting of the manuscript. SA contributed to the conception and design of the study, and drafting of the manuscript. IL contributed to the design of the study and drafting of the manuscript. GL contributed to the conception of the study, data analysis, and drafting of the manuscript. SZ is the guarantor.

Funding: This research is funded from a clinical training fellowship grant, awarded to SZ by the Medical Research Council, UK (grant no. G84/5689).

Competing interests: None declared.

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(Accepted 12 September 2002)

Schizophrenia Bulletin vol. 39 no. 2 pp. 251–254, 2013
doi:10.1093/schbul/sbs188
Advance Access publication January 11, 2013

Age at Initiation of Cannabis Use Predicts Age at Onset of Psychosis: The 7- to 8-Year Trend

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We investigated the existence of a temporal association between age at initiation of cannabis use and age at onset of psychotic illness in 997 participants from the 2010 Survey of High Impact Psychosis (SHIP) in Australia. We tested for group differences in age at onset of psychotic illness and in the duration of premorbid exposure to cannabis (DPEC). Analyses were repeated in subgroups of participants with a schizophrenia-spectrum disorder (SSD), a diagnosis of lifetime cannabis dependence (LCD), and a comorbid SSD/ LCD diagnosis. The association between age at initiation of cannabis use and age at onset of psychotic illness was linear and significant, $F(11, 984) = 13.77$, $P < .001$, even after adjusting for confounders. The effect of age at initiation of cannabis use on DPEC was not significant (mean duration of 7.8 years), and this effect was similar in participants with a SSD, LCD, and comorbid SSD/ LCD diagnosis although a shift toward shorter premorbid exposure to cannabis was noted in the SSD/LCD subgroup (mean duration of 7.19 years for SSD/LCD). A temporal direct relationship between age at initiation of cannabis use and age at onset of psychotic illness was detected with a premorbid exposure to cannabis trend of 7–8 years, modifiable by higher severity of premorbid cannabis use and a diagnosis of SSD. Cannabis may exert a cumulative toxic effect on individuals on the pathway to developing psychosis, the manifestation of which is delayed for approximately 7–8 years, regardless of age at which cannabis use was initiated.

Key words: cannabis/psychosis/schizophrenia/age at onset/causality/DIP/SHIP

Introduction

There is ongoing debate regarding the association between cannabis use and age at onset of psychosis (AOP). A recent meta-analysis by Large et al. (2011)[1] reported an earlier mean AOP in samples with cannabis use and made a strong argument for causality, although increased use of cannabis by those approaching the onset of psychosis, ie, "self-medication" was considered a reasonable interpretation of the association. If cannabis use brings forward the AOP, then one may anticipate that a temporal relationship between age at initiation of cannabis use (AIC) and AOP might be observed after adjustment for confounder effects. However, few studies have specifically addressed this question within sufficiently large samples of participants with psychosis.

Several small studies have demonstrated that AIC is significantly associated with AOP.[2–5] In 123 consecutive referrals with first-episode psychosis to an early intervention service, Barnett et al. (2007)[2] reported that AIC, cocaine, ecstasy, and amphetamine use was significantly associated with age at first-psychotic symptoms. In a sample of 99 participants with a first-psychotic episode, Leeson et al. (2012)[3] reported a linear relationship between AIC and age at onset of psychotic symptoms. The average duration of premorbid exposure to cannabis (DPEC) was reported as 6 years and 33 days. In a sample of 57 participants with a nonaffective psychotic disorder who gave a history of heavy cannabis use, Galvez-Buccollini et al. (2012)[4] also reported a significant association between AIC and AOP after adjusting for cofounding variables; the DPEC was reported as 7 ± 4.3 years. In a sample of 80 young participants with early onset schizophrenia-spectrum disorders (mean AOP was 16.6 years), Estrada et al. (2011)[5] reported that AIC correlated significantly with AOP. Taken together, these small studies suggest a temporal relationship between AIC and AOP in nonaffective psychotic disorders.

Our goal was to further investigate the association between AIC, AOP, and DPEC in a large Australian sample of participants with psychotic disorders.

Methods

Participants

Information on participants was obtained from the 2010 Survey of High Impact Psychosis (SHIP), which recruited people with psychosis from across 7 sites in 5 states of Australia in 2010. The survey used a 2-phase representative sampling design covering an estimated resident population aged 18–64 years of 1.5 million people, or approximately 10% of the Australian population in that age range.[6,7] Of the 7955 people in contact with mental health services who screened positive for psychosis, 1825 were randomly selected and engaged in the interview and assessment process, and all participants provided written informed consent. For full details of the methodology, see Morgan et al. (2012).[6]

Measures of Diagnoses and Substance Use

Participants were assessed using the Diagnostic Interview for Psychosis (DIP), a standardized semistructured interview for psychosis.[8] National training workshops were conducted for all interviewers, in addition to onsite training, with weekly intersite teleconferences throughout the survey. Interrater reliability was assessed in the course of the field interviews and the level of agreement achieved among interviewers was good (averaged pairwise agreement of 0.94 for ICD-10 diagnoses). Diagnostic classification of cases was made using the OPCRIT diagnostic computer algorithm[9] to score the DIP responses; this aticle uses diagnoses based on ICD-10 criteria. The DIP also enables the interviewer to assess family history for schizophrenia and other psychiatric disorders. In addition, the DIP includes items on current and past substance use for alcohol, tobacco, cannabis, amphetamines, lysergic acid diethylamide (LSD), cocaine, ecstasy, and heroin, yielding age of first use, frequency of use in the 12 months prior to psychiatric symptoms first appearing, frequency of substance use in the 12 months prior to interview, and a lifetime diagnosis of substance dependence. For the purposes of this study, 997 participants who reported use of cannabis prior to onset of psychosis (daily/almost daily use, use 1–2 days/week, use 2–4 times/month, or use less frequently than once per month) were considered for further analysis.

Definition of AOP

AOP was determined after interviewing the participant and reviewing the hospital file if consent was given. AOP was recorded to the nearest year and defined as the earliest age at which medical advice was sought for psychiatric reasons, or age at which any psychiatric symptom diagnostic of psychotic or major affective illnesses began to cause subjective distress or impair functioning. If there were no clear symptoms described, then age at first hospital admission was recorded.

Results

Univariate General Linear Models (GLM) framework was used to test for group differences in AOP among patients clustered in AIC groups and for possible sex differences. AIC were clustered into 9 groups (ranging from ≤12 to 21+). The effect of AIC on AOP was significant, $F(8,978) = 25.37$, $P < .001$, adjusted $R^2 = 0.19$ (see figure 1a), whereas the effect of sex was not, $F(1,977) = 2.02$, $P = .16$. The effect of AIC on AOP remained significant after family history of schizophrenia or other psychiatric disorders was used as covariate, $F(11, 984) = 13.77$, $P < .001$, $R^2 = 0.20$. Age at interview, SSD, and lifetime cannabis dependence (LCD) were not considered as covariates because they shared large proportion of variance with both dependent and independent variables.[10] However, a potential confounding influence of SSD and LCD was indirectly examined by analyzing separately these subsets of the entire SHIP sample. Using the Curve Estimation procedure (to examine which regression model best fit to the data), we tested 3 models (linear, cubic, and quadratic) and found that a linear model of association provided a better fit to the data, $F(1,994) = 224.32$, $P < .001$.

Based on the observed linear association between AIC and AOP, univariate GLM was also used to test for group differences in DPEC. Furthermore, we examined potential trends in our data. For the entire sample the effect of AIC on DPEC was not significant, $F(8,988) = 1.28$, $P = .25$, adjusted $R^2 = 0.002$, for trend $F(8,988) = 0.944$, $P = .33$. Mean DPEC for the entire SHIP sample was 7.85 ($SD = 6.2$) years (figure 1b).

In order to further ascertain whether greater presumed *severity* of premorbid use of cannabis, *diagnosis* of schizophrenia-spectrum disorder (SSD), or a *combination* may alter mean DPEC and DPEC among AIC groups, we repeated these analyses for 3 overlapping subsets. In patients who had a LCD, the effect of AIC on DPEC was just significant, $F(8,781) = 1.99$, $P = .044$, adjusted $R^2 = 0.01$, but there was no significant trend observed, $F(8,781) = 2.60$, $P = .11$; the mean DPEC was 7.51 ($SD = 5.6$) years (figure 1c). In patients who had an ICD-10 SSD (schizophrenia, schizoaffective disorder, and delusional disorder), the effect of AIC on DPEC was not significant, $F(8,725) = 1.18$, $P = .31$, adjusted $R^2 = 0.002$, and no significant trend was observed, $F(8,725) = 0.75$, $P = .39$; mean DPEC was 7.50 (SD=5.9) years (figure 1d). Finally, in patients who had SSD and comorbid LCD, the effect of AIC on DPEC was just significant, $F(8, 581) = 2.01$, $P = .043$, $R^2 < 0.014$, but there was no significant trend observed, $F(8, 581) = 2.01$, $P = .15$; the mean DPEC was 7.19 ($SD = 5.4$) years.

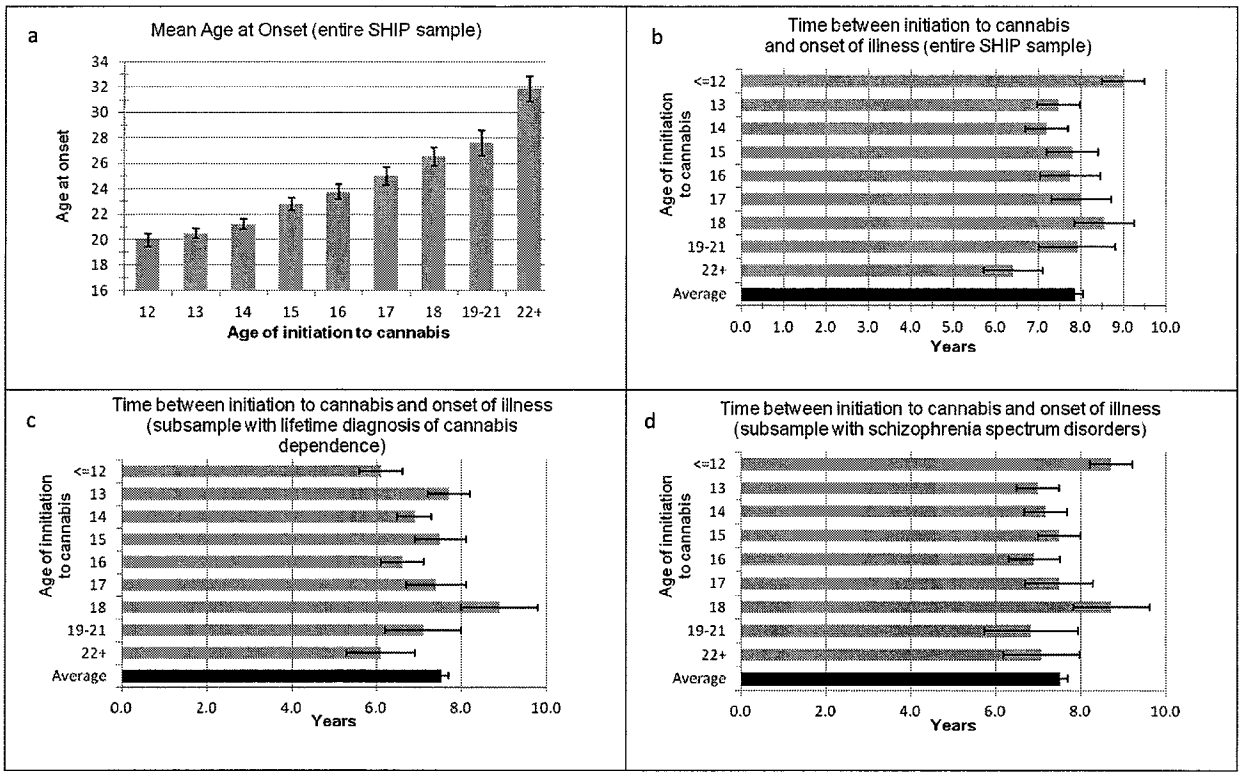

Fig. 1. Figure showing mean (with standard errors) age at onset of psychosis according to age at initiation of cannabis use and time gap between initiation to cannabis and onset of psychosis.

Discussion

These findings, derived retrospectively from a large population of representatively ascertained participants with psychosis in Australia,[6,7] extend previous reports on the association between cannabis and onset of psychosis by demonstrating that AIC is directly and linearly associated with AOP and that an average delay of 7–8 years (mean 7.85, $SD = 6.2$) is observed from the first exposure to cannabis to the onset of psychotic disorders.

Our study can be seen as complementary to previous work in the general population that has established a temporal association between early cannabis use and risk for psychotic disorders[11,12] and with McGrath et al. (2010)[13] who demonstrated in a prospective birth cohort that significant risk for nonaffective psychosis increases after 6 years of exposure to cannabis. We also confirm previously reported linear association between AIC and AOP and offer validation to previous work reporting similar mean DPEC (approximately 6–8 years).[2–4] Notwithstanding some of the inherent limitations to our study imposed by acquiring retrospective information from the DIP (ie, possible recall bias, lack of data on the premorbid pattern of use of other illicit substances until the year prior to onset of psychosis) and the limitation of excluding from analysis illicit substances other than cannabis that may further modulate AOP, this is the largest study examining the effects of AIC use in psychotic disorders.

Much research has focused on adolescence as a particularly vulnerable period of brain maturation for those exposed to cannabis. This neurodevelopmental "window of vulnerability" is supported by findings that demonstrate that early cannabis exposure is a risk factor for psychosis-related outcomes in young adults.[11,13–16] Despite the fact that we also demonstrate a linear trend between early AIC and AOP, our findings do not support a neurodevelopmental "window of vulnerability" hypothesis because those participants who first used cannabis at 12 years of age, for instance, had on average a similar temporal trajectory to illness to those who were first exposed to cannabis at 19 years of age. As noted by Moore et al. (2007),[17] arguments for why earlier use of cannabis might have more harmful effects are intuitively compelling, but no robust evidence supports this view. The increased risk of psychosis in people using cannabis from a younger age observed in the Dunedin cohort[11] could indicate, for instance, a greater cumulative exposure to cannabis rather than a sensitive period of exposure.

We can only speculate on the reasons behind the apparent 7–8-year consistent trend of cannabis exposure in people who develop psychosis. It could be argued that both AIC and AOP tend to cluster independently of each other in particular periods in the life-span (AIC in adolescence, AOP in early adulthood); therefore, collinearity resulting in a relatively constant DPEC might be expected even if no causal link between cannabis and

psychosis existed. However, this is unlikely to explain why mean DPEC is relatively constant across a wide range of AIC groups extending from 12 to over 21 years of age. Furthermore, if the observed temporal association between AIC and AOP was entirely unrelated to causal effects of cannabis exposure on psychosis onset, we would not observe a shift toward a shorter mean DPEC (7.19 years) in participants with SSD and comorbid LCD.

Our findings would be consistent with the notion that cannabis exposure exerts a cumulative toxic effect, particularly in people on the pathway to developing SSD, the manifestation of which is delayed for approximately 7–8 years, regardless of the AIC. While the mechanisms by which cannabis may exert such delayed effects are unclear, several authors have suggested a mechanism involving sensitization of the mesolimbic dopaminergic system, triggered by repeated stimulation with cannabis, to which susceptible individuals may be especially vulnerable,[14,18,19] possibly due to a heightened, genetically determined sensitivity to the psychotomimetic effects of cannabis.[20]

Funding

Australian Government Department of Health and Ageing.

Acknowledgments

This publication is based on data collected in the framework of the 2010 Australian National Survey of High Impact Psychosis. The members of the Survey of High Impact Psychosis Study Group are: V. Morgan (National Project Director), A. Jablensky (Chief Scientific Advisor), A. Waterreus (National Project Coordinator), R. Bush, V. Carr, D. Castle, M. Cohen, C. Galletly, C. Harvey, B. Hocking, A. Mackinnon, P. McGorry, J. McGrath, A. Neil, S. Saw, H. Stain. Ethics approvals for the study were obtained from relevant institutional human research ethics committees. The study was funded by the Australian Government Department of Health and Ageing. This report acknowledges, with thanks, the hundreds of mental health professionals who participated in the preparation and conduct of the survey and the many Australians with psychotic disorders who gave their time and whose responses form the basis of this publication. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Persistent cannabis users show neuropsychological decline from childhood to midlife

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Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved July 30, 2012 (received for review April 23, 2012)

Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

marijuana | longitudinal | cognition

Cannabis, the most widely used illicit drug in the world, is increasingly being recognized for both its toxic and its therapeutic properties (1). Research on the harmful and beneficial effects of cannabis use is important because it can inform decisions regarding the medicinal use and legalization of cannabis, and the results of these decisions will have major public-health consequences. As debate surrounding these issues continues in the United States and abroad, new findings concerning the harmful effects of cannabis on neuropsychological functioning are emerging.

Accumulating evidence suggests that long-term, heavy cannabis use may cause enduring neuropsychological impairment—impairment that persists beyond the period of acute intoxication (2). Studies of long-term, heavy cannabis users fairly consistently show that these individuals perform worse on neuropsychological tests (2–5), and some (6–8) but not all (9) studies suggest that impairment may remain even after extended periods of abstinence. The magnitude and persistence of impairment may depend on factors such as the quantity, frequency, duration, and age-of-onset of cannabis use (2), as more severe and enduring impairment is evident among individuals with more frequent and prolonged heavy use and a younger age-of-onset (3, 6, 8, 10–16).

The extant evidence base draws on case–control studies of recruited cannabis users and comparison subjects. These studies screen participants for potential confounding factors, such as alcohol and drug dependence, and compare them on neuropsychological test performance after a period of abstinence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, precannabis-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is reliance on retrospectively reported quantity, frequency, duration, and age-of-onset of cannabis use, often inquired about years after initiation of heavy use.

A prospective, longitudinal investigation of the association between cannabis use and neuropsychological impairment could redress these limitations and strengthen the existing evidence base by assessing neuropsychological functioning in a sample of youngsters before the onset of cannabis use, obtaining prospective data on cannabis use as the sample is followed over a number of years, and readministering neuropsychological tests after some members of the sample have developed a pattern of long-term cannabis use. To our knowledge, only one prospective, longitudinal study of the effects of cannabis on neuropsychological functioning has been conducted (21), and, in this study, the sample was small and the average duration of regular cannabis use was only 2 y.

In the present study, we investigated the association between persistent cannabis use—prospectively assessed over 20 y—and neuropsychological functioning in a birth cohort of 1,037 individuals. Study members underwent neuropsychological testing in 1985 and 1986 before the onset of cannabis use and again in 2010–2012, after some had developed a persistent pattern of cannabis use. We tested six hypotheses. First, we tested the "cognitive decline" hypothesis that persistent cannabis users evidence greater decline in test performance from childhood to adulthood than nonusers. By examining within-person change in neuropsychological functioning, any effect of premorbid deficits on later (postcannabis-initiation) test performance was nullified. Second, we tested the "specificity" hypothesis to address whether impairment is confined to specific neuropsychological domains or whether it is more global. To test this hypothesis, we administered multiple tests for each of five specific domains, as different tests may be differentially sensitive to cannabis-associated neuropsychological impairment. In conducting our analyses, we tested alternative explanations for the association between per-

Author contributions: M.H.M., A.C., and T.E.M. designed research; M.H.M., A.C., A.A., H.H., R.H., R.S.E.K., K.M., A.W., R.P., and T.E.M. performed research; M.H.M., A.C., R.H., and T.E.M. analyzed data; and M.H.M., A.C., and T.E.M. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

See Commentary on page 15970.

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See Author Summary on page 15980 (volume 109, number 40).

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1206820109/-/DCSupplemental.

sistent cannabis use and neuropsychological functioning by ruling out potential confounding effects of (*i*) acute or residual cannabis intoxication, (*ii*) tobacco dependence, (*iii*) hard-drug dependence (e.g., heroin, cocaine, amphetamines), (*iv*) alcohol dependence, and (*v*) schizophrenia. Third, we tested the "education" hypothesis that persistent cannabis users experience neuropsychological decline simply because they have eschewed academics and other opportunities for learning. Recent evidence suggests that staying in school can boost one's intelligence quotient (IQ) (22), and cannabis users tend to receive less schooling than nonusers (23). Therefore, we tested whether the association between persistent cannabis use and neuropsychological decline remained after controlling for years of education. Fourth, we queried third-party informants to test the "everyday cognition" hypothesis that cannabis-induced neuropsychological impairment translates into functional problems in daily life. Fifth, we tested the "developmental vulnerability" hypothesis that individuals who begin cannabis use as adolescents are particularly vulnerable to the effects of persistent cannabis use on neuropsychological functioning, as evidence suggests that cannabis has especially toxic effects on the developing brain (24–31). Sixth, we tested the "recovery" hypothesis that former persistent users who quit or reduce their cannabis use may be able to restore their neuropsychological health.

Results

Do Study Members with More Persistent Cannabis Use Show Greater IQ Decline? Table 1 (far right column) shows effect sizes for within-person IQ change from childhood to adulthood as a function of persistent cannabis dependence. In this analysis, each study member served as his or her own control; given that the groups were not equivalent on childhood IQ, we accounted for premorbid IQ differences by looking at IQ change from childhood to age 38 y. Study members with more persistent cannabis dependence showed greater IQ decline. For example, study members who never used cannabis experienced a slight increase in IQ, whereas those who diagnosed with cannabis dependence at one, two, or three or more study waves experienced IQ declines of −0.11, −0.17, and −0.38 SD units, respectively. An IQ decline of −0.38 SD units corresponds to a loss of ~6 IQ points, from 99.68 to 93.93. Results of analyses for persistent cannabis dependence and persistent regular cannabis use were similar (Table 1).

Table 2 expands the analysis by showing results for the subtests of different cognitive abilities that constitute the IQ. Persistent cannabis dependence was associated with greater decline on the majority of the subtests.

IQ decline was most pronounced among the most persistent cannabis-dependence group (i.e., the 3+ group; $n = 38$), but the effect of persistent cannabis dependence on IQ decline was not solely attributable to this group. For example, the association between persistent cannabis dependence and full-scale IQ decline was still apparent after excluding the study members with 3+ cannabis-dependence diagnoses from the analysis ($t = -2.94$, $P = 0.0034$). Table S1 shows parallel results for persistent regular cannabis use and persistent cannabis dependence.

Is Impairment Specific to Certain Neuropsychological Domains or Is It Global? Table 3 shows the effects of persistent cannabis dependence on five different areas of mental function assessed at age 38 y. Effects represent mean neuropsychological test performance at age 38 y, adjusted for childhood IQ. Across different areas of mental function, study members with more persistent cannabis dependence generally showed greater neuropsychological impairment. Inspection of the means suggests that the greatest impairments were for the domains of executive functioning and processing speed. To test whether impairment was relatively greater for certain domains, we compared cannabis-associated neuropsychological impairment across the four Wechsler Adult Intelligence Scale-IV (WAIS-IV) indexes (i.e., working memory index, processing speed index, perceptual reasoning index, and verbal comprehension index), which share psychometric properties (i.e., reliability) important for such a test. Using a model-fitting approach, we fitted (*i*) a model allowing the association between persistent cannabis dependence and age-38 neuropsychological impairment, adjusted for childhood IQ and sex, to vary across the four WAIS-IV indexes and (*ii*) a model equating this association across the four WAIS-IV indexes. Results showed that associations between persistent cannabis dependence and all four WAIS-IV indexes could be equated without a resultant deterioration in model fit ($\Delta\chi^2 = 2.13$, df = 3, $P = 0.55$), which suggests that impairment was not statistically significantly different across neuropsychological domains.

Is Impairment Attributable to Persistent Cannabis Use or Are There Alternative Explanations? We ruled out six alternative explanations for the observed effects of persistent cannabis use on neuropsychological functioning, namely that these effects could be explained by (*i*) past 24-h cannabis use, (*ii*) past-week cannabis use, (*iii*) persistent tobacco dependence, (*iv*) persistent hard-drug dependence, (*v*) persistent alcohol dependence, and (*vi*) schizophrenia. We recalculated the mean change in full-

Table 1. IQ before and after cannabis use

	N	% male	Age 7–13 full-scale IQ	Age 38 full-scale IQ	Δ IQ effect size*
Persistence of cannabis dependence					
Never used, never diagnosed	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never diagnosed	479	49.48	102.32 (13.34)	101.25 (14.70)	−0.07
1 diagnosis	80	70.00	96.40 (14.31)	94.78 (14.54)	−0.11
2 diagnoses	35	62.86	102.14 (17.08)	99.67 (16.11)	−0.17
3+ diagnoses	38	81.58	99.68 (13.53)	93.93 (13.32)	−0.38
Persistence of regular cannabis use					
Never used	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never regularly	508	50.59	102.27 (13.59)	101.24 (14.81)	−0.07
Used regularly at 1 wave	47	72.34	101.42 (14.41)	98.45 (14.89)	−0.20
Used regularly at 2 waves	36	63.89	95.28 (10.74)	93.26 (11.44)	−0.13
Used regularly at 3+ waves	41	78.05	96.00 (16.06)	90.77 (13.88)	−0.35

Means (SDs) are presented for child and adult full-scale IQ as a function of the number of study waves between ages 18 y and 38 y for which study members met criteria for cannabis dependence or reported using cannabis on a regular basis (at least 4 d/wk). The last column shows that study members with more persistent cannabis use showed greater IQ decline from childhood to adulthood.
*This coefficient indicates change in IQ from childhood to adulthood, with negative values indicating decreases in IQ. These change scores are in SD units, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large changes, respectively.

Table 2. IQ subtest changes

IQ test/subtest	Never used, never diagnosed, $n = 242$	Used, never diagnosed, $n = 479$	1 diagnosis, $n = 80$	2 diagnoses, $n = 35$	3+ diagnoses, $n = 38$	Linear trend t test*	P
Full-scale IQ	0.05	−0.07	−0.11	−0.17	−0.38	−4.45	<0.0001
Verbal IQ	0.02	−0.05	−0.13	−0.19	−0.31	−4.15	<0.0001
Information subtest	0.05	−0.08	0.02	−0.25	−0.15	−2.40	0.0168
Similarities subtest	0.03	−0.05	−0.03	−0.19	−0.44	−2.78	0.0056
Vocabulary subtest	0.07	−0.05	−0.16	−0.16	−0.45	−3.67	0.0003
Arithmetic subtest	−0.05	−0.07	−0.05	0.00	0.06	−0.73	0.47
Performance IQ	0.08	−0.08	−0.09	−0.08	−0.42	−2.84	0.0046
Digit symbol coding subtest	0.15	−0.09	−0.17	−0.23	−0.62	−5.60	<0.0001
Block design subtest	−0.03	−0.07	−0.01	−0.11	0.02	−0.55	0.58
Picture completion subtest	−0.01	−0.08	0.08	0.05	0.15	1.18	0.24

Mean change in IQ subtest scores from childhood to adulthood is presented in SD units as a function of the number of study waves between ages 18 y and 38 y for which a study member met criteria for cannabis dependence. These change scores can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large effects, respectively. Persistent cannabis dependence was associated with IQ decline for the majority of IQ subtests administered in both childhood and adulthood, i.e., when each study member served as his or her own control.
*To test for a dose–response effect, we conducted an ordinary least-squares regression, estimating the linear trend controlling for sex.

scale IQ as a function of persistent cannabis dependence, excluding each of the aforementioned groups. We elected to show results just for full-scale IQ for this analysis as well as all subsequent analyses because full-scale IQ captures overall intellectual functioning. Fig. 1 shows that excluding each of these groups of study members did not alter the initial finding; effect

Table 3. Five areas of mental function

Age 38 y neuropsychological tests	Never used, never diagnosed, $n = 242$	Used, never diagnosed, $n = 479$	1 diagnosis, $n = 80$	2 diagnoses, $n = 35$	3+ diagnoses, $n = 38$	Linear trend t test*	P
Tests of executive functions							
WAIS-IV Working Memory Index	0.01	0.03	−0.16	−0.03	−0.16	−2.16	0.0311
Wechsler Memory Scale Months of the Year Backward	0.24	0.01	−0.38	−0.23	−0.63	−5.24	<0.0001
Trail-Making Test B Time†	−0.04	−0.03	0.16	0.08	0.19	1.15	0.25
CANTAB Rapid Visual Information Processing A Prime (Vigilance)	0.05	0.01	−0.02	−0.04	−0.45	−2.58	0.0100
CANTAB Rapid Visual Information Processing Total False Alarms†	−0.02	0.01	0.06	0.04	−0.14	−0.05	0.96
Tests of memory							
Rey Auditory Verbal Learning Total Recall	0.11	0.06	−0.26	−0.22	−0.48	−2.65	0.0081
Rey Auditory Verbal Learning Delayed Recall	0.14	0.02	−0.22	−0.28	−0.31	−2.11	0.0348
Wechsler Memory Scale Verbal Paired Associates Total Recall	0.07	0.06	−0.21	−0.21	−0.12	−1.48	0.14
Wechsler Memory Scale Verbal Paired Associates Delayed Recall	0.07	0.06	−0.19	−0.15	−0.14	−1.07	0.29
CANTAB Visual Paired Associates Learning First Trial Memory Score	0.09	0.01	−0.06	−0.36	−0.10	−2.22	0.0270
CANTAB Visual Paired Associates Learning Total Errors†	−0.07	−0.03	0.17	0.33	−0.06	1.41	0.16
Tests of processing speed							
WAIS-IV Processing Speed Index	0.14	0.03	−0.21	−0.05	−0.61	−3.64	0.0003
CANTAB Rapid Visual Information Processing Mean Latency†	−0.13	0.04	0.06	−0.20	0.25	1.92	0.06
CANTAB Reaction Time 5-Choice Reaction Time†	0.19	−0.11	−0.13	−0.01	0.18	−0.38	0.71
Tests of perceptual reasoning							
WAIS-IV Perceptual Reasoning Index	0.08	−0.02	0.07	−0.18	−0.12	−2.33	0.0202
Tests of verbal comprehension							
WAIS-IV Verbal Comprehension Index	0.10	−0.01	−0.03	0.02	−0.23	−3.04	0.0025

Neuropsychological test scores at age 38 y are shown as a function of the number of study waves between ages 18 y and 38 y for which study members met criteria for cannabis dependence. Scores are standardized means adjusted for baseline (childhood) full-scale IQ assessed before the onset of cannabis use. These means can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large effects, respectively. Persistent cannabis dependence was associated with impairment in each of the five areas of mental function. CANTAB, Cambridge Neuropsychological Test Automated Battery; WAIS-IV, Wechsler Adult Intelligence Scale-IV.
*To test for a dose–response effect, we conducted an ordinary least-squares regression, estimating the linear trend controlling for childhood full-scale IQ and sex.
†Higher score indicates worse performance.

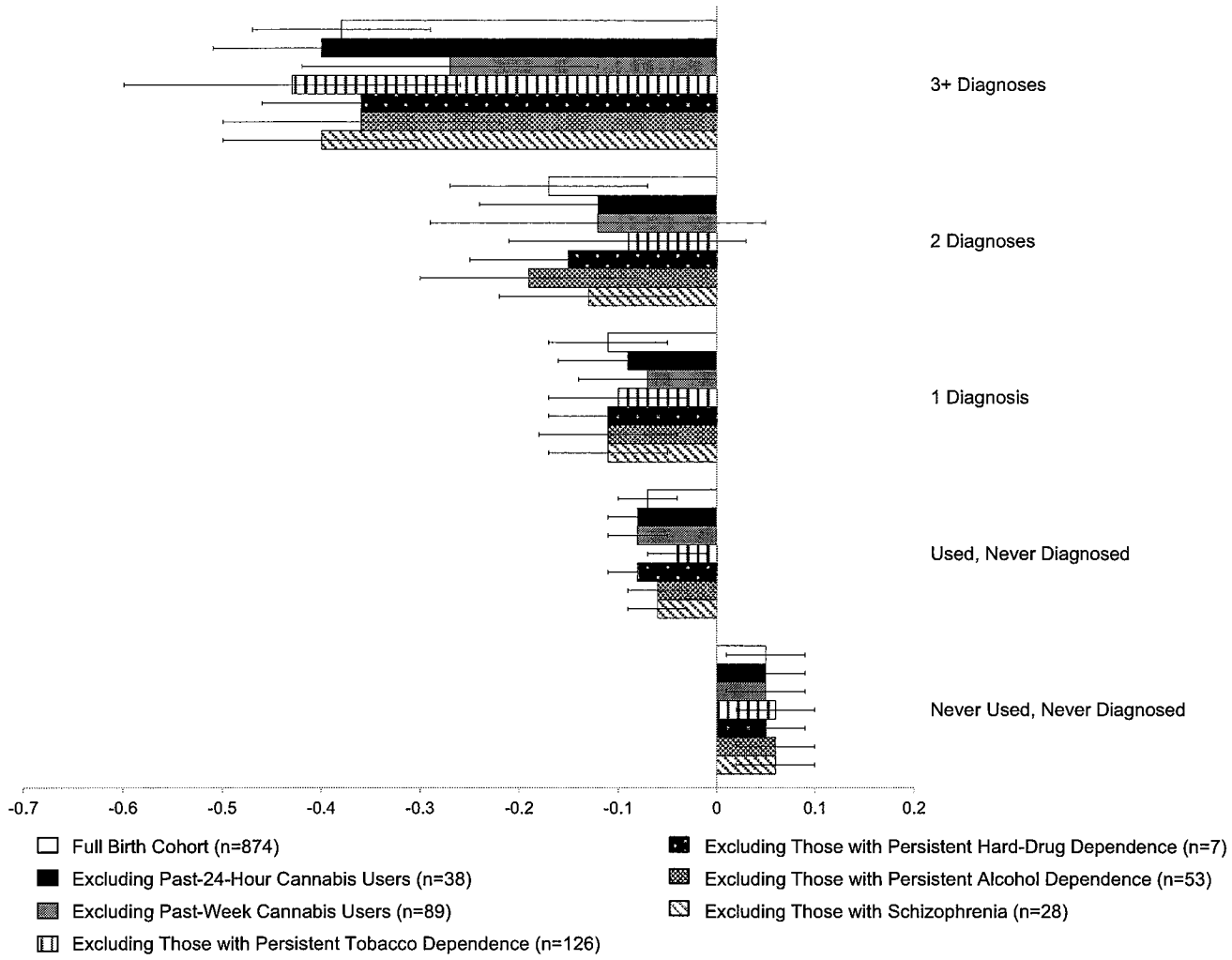

Fig. 1. Ruling out alternative explanations. Shown is change in full-scale IQ (in SD units) from childhood to adulthood as a function of the number of study waves between ages 18 y and 38 y for which a study member met criteria for cannabis dependence. Change scores are presented for the full birth cohort and the cohort excluding (*i*) past 24-h cannabis users, (*ii*) past-week cannabis users, (*iii*) those with persistent tobacco dependence, (*iv*) those with persistent hard-drug dependence, (*v*) those with persistent alcohol dependence, and (*vi*) those with lifetime schizophrenia. Persistent tobacco, hard-drug, and alcohol dependence were each defined as dependence at three or more study waves. IQ decline could not be explained by other factors. Error bars = SEs.

sizes, representing within-person IQ change as a function of persistent cannabis dependence, remained virtually the same and remained statistically significant (see Table S2 for IQ subtests). Furthermore, a multivariate regression of the effect of persistent cannabis dependence on full-scale IQ decline, controlling for past 24-h cannabis use, persistent substance dependence (the number of study waves for which study members diagnosed with tobacco, hard-drug, or alcohol dependence), and schizophrenia remained statistically significant ($t = -2.20$, $P = 0.0282$).

Is Impairment Apparent Even After Controlling for Years of Education? The linear effect of persistent cannabis dependence on change in full-scale IQ was significant before controlling for years of education ($t = -4.45$, $P < 0.0001$; Table 2, top row) and remained

Table 4. IQ decline after holding education constant

Sample	Never used, never diagnosed	Used, never diagnosed	1 diagnosis	2 diagnoses	3+ diagnoses	Linear trend *t* test*	*P*
Full sample	0.05 (n = 242)	−0.07 (n = 479)	−0.11 (n = 80)	−0.17 (n = 35)	−0.38 (n = 38)	−4.45	<0.0001
High-school education or less	−0.03 (n = 59)	−0.14 (n = 130)	−0.16 (n = 43)	−0.25 (n = 20)	−0.48 (n = 26)	−3.36	0.0009

Mean change in full-scale IQ from childhood to adulthood is presented in SD units as a function of the number of study waves between ages 18 y and 38 y for which a study member met criteria for cannabis dependence. These change scores can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large effects, respectively. Change scores are presented for the full sample and for the sample of study members with a high-school education or less. Persistent cannabis dependence was associated with IQ decline in the full sample and the sample of study members with a high-school education or less.

*To test for a dose–response effect, we conducted an ordinary least-squares regression, estimating the linear trend controlling for sex.

significant after controlling for years of education ($t = -3.41$, $P = 0.0007$). Moreover, although fewer persistent cannabis users pursued education after high school ($\chi^2 = 63.94$, $P < 0.0001$), among the subset with a high-school education or less, persistent cannabis users experienced greater IQ decline (Table 4).

Does Cannabis-Associated Neuropsychological Impairment Translate into Functional Problems in Daily Life? Informant reports of study members' neuropsychological functioning were also obtained at age 38 y. Study members nominated people "who knew them well." These informants were mailed questionnaires and asked to complete a checklist, including whether the study members had problems with their attention and memory over the past year. Table 5 shows mean informant-reported cognitive problems, adjusted for childhood IQ, as a function of persistent cannabis dependence. Informants reported observing significantly more attention and memory problems among those with more persistent cannabis dependence.

Are Adolescent Cannabis Users Particularly Vulnerable? Adolescent-onset users, who diagnosed with cannabis dependence before age 18 y, tended to become more persistent users, but Fig. 2 shows that, after equating adolescent- and adult-onset cannabis users on total number of cannabis-dependence diagnoses, adolescent-onset users showed greater IQ decline than adult-onset cannabis users. In fact, adult-onset cannabis users did not appear to experience IQ decline as a function of persistent cannabis use. Because it might be difficult to develop cannabis dependence before age 18 y, we also defined adolescent-onset cannabis use in terms of weekly use before age 18 y [the correspondence between cannabis dependence before age 18 y and weekly use before age 18 y was not perfect ($\kappa = 0.64$)]. Results of this analysis (Fig. S1) were similar.

What Is the Effect of Cessation of Cannabis Use? Given that adolescent-onset cannabis users exhibited marked IQ decline and given speculation that this could represent a toxic effect of cannabis on the developing brain, we examined the cessation effect separately within adolescent-onset and adult-onset cannabis users. Fig. 3 shows that, among adolescent-onset persistent cannabis users, within-person IQ decline was apparent regardless of whether cannabis was used infrequently (median use = 14 d) or frequently (median use = 365 d) in the year before testing. In contrast, within-person IQ decline was not apparent among adult-onset persistent cannabis users who used cannabis infrequently (median use = 6 d) or frequently (median use = 365 d) in the year before testing. Thus, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset former persistent cannabis users.

Discussion

Persistent cannabis use over 20 y was associated with neuropsychological decline, and greater decline was evident for more persistent users. This effect was concentrated among adolescent-onset cannabis users, a finding consistent with results of several studies showing executive functioning or verbal IQ deficits among adolescent-onset but not adult-onset chronic cannabis users (8, 10, 14, 15), as well as studies showing impairment of learning, memory, and executive functions in samples of adolescent cannabis users (11–13, 32).

The present study advances knowledge in five ways. First, by investigating the association between persistent cannabis use and neuropsychological functioning prospectively, we ruled out premorbid neuropsychological deficit as an explanation of the link between persistent cannabis use and neuropsychological impairment occurring after persistent use. Second, we showed that the impairment was global and detectable across five domains of neuropsychological functioning. Third, we showed that cannabis-associated neuropsychological decline did not occur solely because cannabis users completed fewer years of education. Fourth, we showed that impairment was apparent to third-party informants and that persistent cannabis use interfered with everyday cognitive functioning. Fifth, we showed that, among adolescent-onset former persistent cannabis users, impairment was still evident after cessation of use for 1 y or more. Collectively, these findings are consistent with speculation that cannabis use in adolescence, when the brain is undergoing critical development, may have neurotoxic effects.

The study's results must be interpreted in the context of its limitations. First, although we were able to rule out a set of plausible alternative explanations for the association between persistent cannabis use and neuropsychological functioning, such as premorbid neuropsychological deficit and hard-drug and alcohol dependence among persistent cannabis users, our data cannot definitively attest to whether this association is causal. For example, there may be some unknown "third" variable that could account for the findings. The data also cannot reveal the mechanism underlying the association between persistent cannabis dependence and neuropsychological decline. One hypothesis is that cannabis use in adolescence causes brain changes that result in neuropsychological impairment. Several lines of evidence support this possibility (24–31, 33, 34). First, puberty is a period of critical brain development, characterized by neuronal maturation and rearrangement processes (e.g., myelination, synaptic pruning, dendritic plasticity) and the maturation of neurotransmitter systems (e.g., the endogenous cannabinoid system), making the pubertal brain vulnerable to toxic insult (33). Second, cannabis administration in animals is associated with structural and functional brain differences, particularly in hippocampal regions, with structural differences dependent on age and duration of exposure to cannabinoids (33). Third, studies of human adolescents have shown structural and functional brain differences associated with cannabis use (26, 29, 35). Alternatively, persistent cannabis users may experience greater neuropsychological decline relative to nonusers because they receive less education. Our results suggest that cannabis-associ-

Table 5. Cognitive problems outside the laboratory

Age 38 y informant reports	Never used, never diagnosed, $n = 228$	Used, never diagnosed, $n = 457$	1 diagnosis, $n = 71$	2 diagnoses, $n = 31$	3+ diagnoses, $n = 35$	Linear trend t test*	P
Informant-reported attention problems†	−0.21	−0.07	0.31	0.64	0.96	7.74	<0.0001
Informant-reported memory problems†	−0.27	−0.03	0.38	0.78	0.75	7.65	<0.0001

Shown are informant reports of cognitive problems at age 38 y as a function of the number of study waves between ages 18 y and 38 y for which study members met criteria for cannabis dependence. Scores are standardized means adjusted for baseline (childhood) full-scale IQ assessed before the onset of cannabis use. These means can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large effects, respectively. Cognitive problems among persistent cannabis users were apparent to the "naked-eye."

*To test for a dose–response effect, we conducted an ordinary least-squares regression, estimating the linear trend controlling for childhood full-scale IQ and sex.

†Higher score indicates worse everday problems.

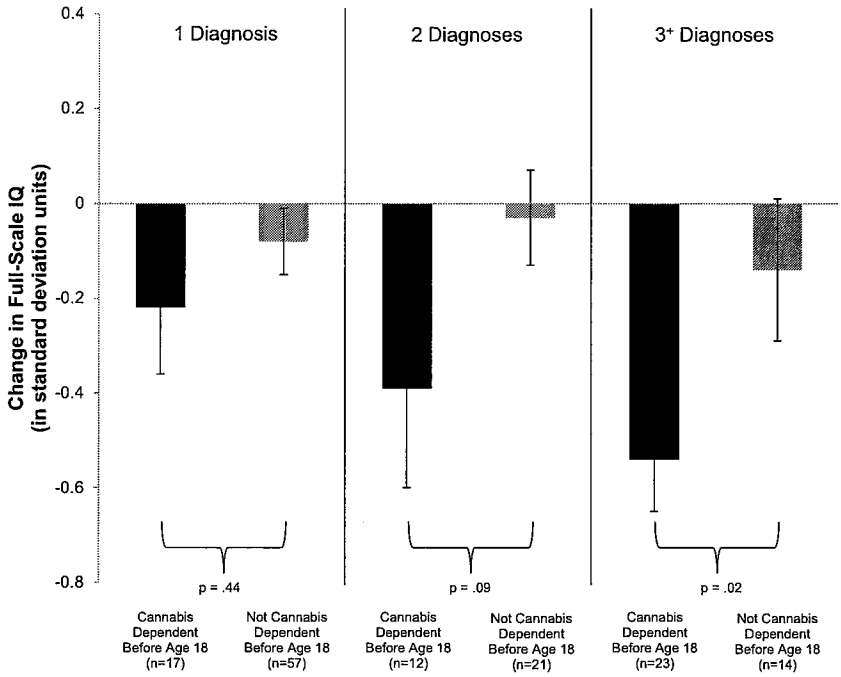

Fig. 2. Adolescent vulnerability. Shown is change in full-scale IQ (in SD units) from childhood to adulthood among study members with 1, 2, or 3+ diagnoses of cannabis dependence as a function of age of onset of cannabis dependence. Individuals with adolescent-onset cannabis dependence (black bars) experienced greater IQ decline than individuals with adult-onset cannabis dependence (gray bars). IQ decline of approximately −0.55 SD units among individuals with adolescent-onset cannabis dependence in the 3+ group represents a decline of 8 IQ points. Error bars = SEs.

ated neuropsychological decline does not occur solely for this reason, because the association between persistent cannabis use and neuropsychological decline was still apparent after controlling for years of education. Notably, the aforementioned processes are not mutually exclusive and may, in fact, be interrelated. For example, the toxic effects of cannabis on the brain may result in impaired neuropsychological functioning, poor academic performance, and subsequent school dropout, which then results in further neuropsychological decline. In this case, our statistical control for education in the analysis of the association between persistent cannabis use and neuropsychological decline is likely an overcontrol (36).

A second limitation is that we obtained information on past-year cannabis dependence and self-reported frequency of cannabis use with no external validation of use (e.g., biological assays). Validation of cannabis use through laboratory measures could have helped detect cannabis users who did not report use. Underreporting of cannabis use due to concerns about admitting to using an illegal substance is unlikely, however, because study members, interviewed repeatedly over 38 y about a number of illegal activities, have learned to trust the Dunedin Study's confidentiality guarantee. Moreover, any such misclassification would have mitigated against differences. Third, additional research is needed to define the parameters of use sufficient to produce neuropsychological impairment, such as the quantity, frequency, and age-of-onset of use. Our findings suggest that regular cannabis use before age 18 y predicts impairment, but others have found effects only for younger ages (10, 15). Given that the brain undergoes dynamic changes from the onset of puberty through early adulthood (37, 38), this developmental period should be the focus of future research on the age(s) at which harm occurs. Fourth, additional research is needed to determine whether cannabis-related neuropsychological impairment is reversible. Our finding of neuropsychological difficulties among adolescent-onset former persistent cannabis users who quit or reduced their use for 1 y or more suggests that neuropsychological functioning is not fully restored in this time. Fifth, these findings are limited to a cohort of individuals born in Dunedin, New Zealand in the 1970s. Notably, the prevalence of cannabis dependence is somewhat higher among New Zealanders than Americans (39), but the potency of cannabis obtained from police seizures in New Zealand is similar to that of cannabis in the United States (40, 41).

Increasing efforts should be directed toward delaying the onset of cannabis use by young people, particularly given the recent trend of younger ages of cannabis-use initiation in the United States and evidence that fewer adolescents believe that cannabis use is associated with serious health risk (42). In the present study, the most persistent adolescent-onset cannabis users evidenced an average 8-point IQ decline from childhood to adulthood. Quitting, however, may have beneficial effects, preventing additional impairment for adolescent-onset users. Prevention and policy efforts should focus on delivering to the public the message that cannabis use during adolescence can have harmful effects on neuropsychological functioning, delaying the onset of cannabis use at least until adulthood, and encouraging cessation of cannabis use particularly for those who began using cannabis in adolescence.

Methods

Participants. Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of the health and behavior of a complete birth cohort of consecutive births between April 1, 1972, and March 31, 1973, in Dunedin, New Zealand. The cohort of 1,037 children (91% of eligible births; 52% boys) was constituted at age 3 y. Cohort families represent the full range of socioeconomic status in the general population of New Zealand's South Island and are primarily of white European ancestry. Follow-up assessments were conducted with informed consent at 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and most recently at 38 y of age, when 96% of the 1,004 living study members underwent assessment in

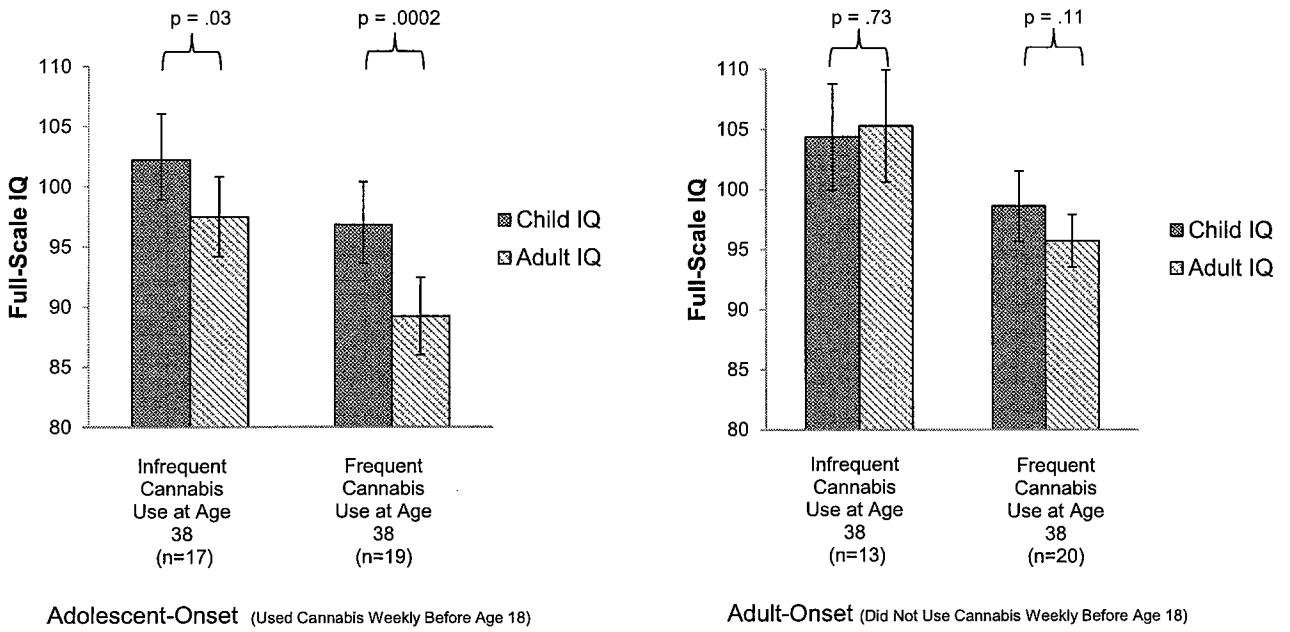

Fig. 3. Postcessation IQ among former persistent cannabis users. This figure is restricted to persistent cannabis users, defined as study members with two or more diagnoses of cannabis dependence. Shown is full-scale IQ in childhood and adulthood. IQ is plotted as a function of (*i*) age of onset of at least weekly cannabis use and (*ii*) the frequency of cannabis use at age 38 y. Infrequent use was defined as weekly or less frequent use in the year preceding testing at age 38 y. Median use among infrequent and frequent adolescent-onset cannabis users was 14 (range: 0–52) and 365 (range: 100–365) d, respectively. Median use among infrequent and frequent adult-onset cannabis users was 6 (range: 0–52) and 365 (range: 100–365) d, respectively. IQ decline was apparent even after cessation of cannabis use for adolescent-onset former persistent cannabis users. Error bars = SEs.

2010–2012. The Otago Ethics Committee approved each wave of the study. Study members gave informed consent before participating.

Because individuals with missing data at one wave tend to return to the study at some later wave(s), the attrition in the Dunedin Study has not been cumulative, and reasons for missing assessments seem to be idiosyncratic rather than systematic. There was no evidence of differential attrition for cannabis-dependent individuals. For example, the 4% of study members who did not participate at age 38 y were no more likely to have been cannabis dependent at age 18 y than study members who did participate ($F = 2.22$, $P = 0.14$).

Measures. ***Cannabis use.*** Past-year cannabis dependence was assessed with the Diagnostic Interview Schedule (43, 44) at ages 18, 21, 26, 32, and 38 y following criteria for the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (45, 46). Cohort members having missing data from three or more of the five study waves (ages 18, 21, 26, 32, and 38 y) were excluded when we defined our cannabis-exposure variables: 97% of living cohort members were studied, composed of 83% of living study members with no missing data points, 11% with one missing data point, and 3% with two missing data points. Our main exposure, persistence of cannabis dependence, was defined as the total number of study waves out of five at which a study member met criteria for cannabis dependence. Study members were grouped according to their number of dependence diagnoses: (*i*) those who never used cannabis at any study wave and thus could not have become dependent, (*ii*) those who used cannabis at least once at one or more study waves but never diagnosed, (*iii*) those who diagnosed at one wave, (*iv*) those who diagnosed at two waves, and (*v*) those who diagnosed at three or more waves.

Because there were some study members who used cannabis on a regular basis but never met full criteria for a diagnosis of cannabis dependence, we repeated analyses using persistent regular cannabis use as the exposure. At each of the five study waves between ages 18–38 y, study members self-reported the total number of days (0–365) they used cannabis over the preceding year. Persistence of regular cannabis use was defined as the total number of study waves out of five at which a study member reported using cannabis 4 d/wk or more (the majority of days in a week). Study members were grouped as those who (*i*) never used cannabis, (*ii*) used but never regularly, (*iii*) used regularly at one wave, (*iv*) used regularly at two waves, and (*v*) used regularly at three or more waves. Correspondence between cannabis dependence and regular cannabis-use groups was high but not perfect (weighted $\kappa = 0.77$).

The Dunedin Study uses past-year reporting to maximize validity and reliability of recall. A potential consequence is that individuals could have experienced dependence only during a gap between the Study's five 12-mo assessment windows and gone uncounted. Our "net" of 1-y assessments at ages 18, 21, 26, 32, and 38 y captured all but four of the cohort members who reported receiving treatment for a drug-use problem between assessment windows. Three of the four were hard-drug and alcohol dependent, and the remaining person sought counseling for cannabis use only as part of a child custody dispute. As these four cohort members reported cannabis use but not dependence, they were classified as "used but never diagnosed."

Neuropsychological functioning. Intelligence was assessed in childhood at ages 7, 9, 11, and 13 y, before the onset of cannabis use (only seven study members reported trying cannabis by age 13 y), and again in adulthood at age 38 y. We report comparison of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (47) and the WAIS-IV (48), both with $M = 100$ and SD = 15. At age 38 y, additional neuropsychological tests were administered, including the Wechsler Memory Scale-III (WMS-III) (49), the Trail-Making Test (50), the Cambridge Neuropsychological Test Automated Battery (CANTAB) (51), and the Rey Auditory Verbal Learning Test (52). Because the sample is a representative birth cohort, it formed its own norms. Table S3 provides further details about each test. Each study member attended the research unit for an 8-h day of assessments. All testing occurred in the morning in two 50-min counterbalanced sessions.

Informant reports of study members' neuropsychological functioning were also obtained at age 38 y. Study members nominated people who knew them well. These informants were mailed questionnaires and asked to complete a checklist, including whether the study members had problems with their attention and memory over the past year. The informant-reported attention problems scale consisted of four items: "is easily distracted, gets sidetracked easily," "can't concentrate, mind wanders," "tunes out instead of focusing," and "has difficulty organizing tasks that have many steps" (internal consistency reliability = 0.79). The informant-reported memory problems scale consisted of three items: "has problems with memory," "misplaces wallet, keys, eyeglasses, paperwork," and "forgets to do errands, return calls, pay bills" (internal consistency reliability = 0.64).

Control variables. Past 24-h cannabis use and past-week cannabis use were assessed at age 38 y on the day of neuropsychological testing. Persistent DSM (45, 46) tobacco, hard-drug, and alcohol dependence were assessed over the same 20-y period during which cannabis dependence was assessed, and the number of study waves during which study members diagnosed was counted and used as covariates. For Fig. 1, persistent dependence was defined as having been diagnosed at three or more study waves. Research diagnoses of lifetime schizophrenia (53) are also reported.

Statistical Analysis. First, for the IQ test and subtests (47, 48) administered in both childhood and adulthood, change scores were created by subtracting the precannabis childhood IQ averaged across ages 7, 9, 11 and 13 y (or, for the seven members who reported trying cannabis by age 13 y, ages 7, 9, and 11 y) from postcannabis adulthood IQ. Negative scores indicate IQ decline. Ordinary least-squares linear regression was used to test whether persistent cannabis use (entered as a five-level independent variable, with each study member receiving a score ranging from 1 to 5) predicted amount of IQ change. Second, for the neuropsychological tests administered only in adulthood, ordinary least-squares linear regression, including full-scale childhood IQ as a covariate, was used to test whether persistent cannabis use predicted neuropsychological test performance in adulthood (i.e., residualized change scores).

Tables 2–5 present the t tests associated with the regression coefficient testing the linear effect of persistent cannabis use on change in neuropsychological functioning, under the hypothesis that more persistent cannabis use predicts greater decline in neuropsychological functioning. Change scores are presented in SD units as a function of persistence of cannabis use. These scores can be interpreted as effect sizes, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large change, respectively (54). Sex was included as a covariate in all statistical tests.

ACKNOWLEDGMENTS. We thank the Dunedin Study members, their families, the Dunedin Multidisciplinary Health and Development Research Unit staff, and study founder Phil Silva. The Dunedin Multidisciplinary Health and Development Research Unit is supported by the New Zealand Health Research Council. This research received support from UK Medical Research Council Grants G0100527 and MR/K00381X/1, US National Institute on Aging Grant AG032282, US National Institute of Mental Health Grant MH077874, and US National Institute on Drug Abuse Grant P30 DA023026. Additional support was provided by the Jacobs Foundation.

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REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Adverse Health Effects of Marijuana Use

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N Engl J Med 2014;370:2219-27.
DOI: 10.1056/NEJMra1402309

In light of the rapidly shifting landscape regarding the legalization of marijuana for medical and recreational purposes, patients may be more likely to ask physicians about its potential adverse and beneficial effects on health. The popular notion seems to be that marijuana is a harmless pleasure, access to which should not be regulated or considered illegal. Currently, marijuana is the most commonly used "illicit" drug in the United States, with about 12% of people 12 years of age or older reporting use in the past year and particularly high rates of use among young people.[1] The most common route of administration is inhalation. The greenish-gray shredded leaves and flowers of the *Cannabis sativa* plant are smoked (along with stems and seeds) in cigarettes, cigars, pipes, water pipes, or "blunts" (marijuana rolled in the tobacco-leaf wrapper from a cigar). Hashish is a related product created from the resin of marijuana flowers and is usually smoked (by itself or in a mixture with tobacco) but can be ingested orally. Marijuana can also be used to brew tea, and its oil-based extract can be mixed into food products.

The regular use of marijuana during adolescence is of particular concern, since use by this age group is associated with an increased likelihood of deleterious consequences[2] (Table 1). Although multiple studies have reported detrimental effects, others have not, and the question of whether marijuana is harmful remains the subject of heated debate. Here we review the current state of the science related to the adverse health effects of the recreational use of marijuana, focusing on those areas for which the evidence is strongest.

ADVERSE EFFECTS

RISK OF ADDICTION

Despite some contentious discussions regarding the addictiveness of marijuana, the evidence clearly indicates that long-term marijuana use can lead to addiction. Indeed, approximately 9% of those who experiment with marijuana will become addicted[3] (according to the criteria for dependence in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV]). The number goes up to about 1 in 6 among those who start using marijuana as teenagers and to 25 to 50% among those who smoke marijuana daily.[4] According to the 2012 National Survey on Drug Use and Health, an estimated 2.7 million people 12 years of age and older met the DSM-IV criteria for dependence on marijuana, and 5.1 million people met the criteria for dependence on any illicit drug[1] (8.6 million met the criteria for dependence on alcohol[1]). There is also recognition of a bona fide cannabis withdrawal syndrome[5] (with symptoms that include irritability, sleeping difficulties, dysphoria, craving, and anxiety), which makes cessation difficult and contributes to relapse. Marijuana use by adolescents is particularly troublesome. Adolescents' increased vulnerability to adverse long-term outcomes from marijuana use is probably related

Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Effects of short-term use
Impaired short-term memory, making it difficult to learn and to retain information
Impaired motor coordination, interfering with driving skills and increasing the risk of injuries
Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases
In high doses, paranoia and psychosis
Effects of long-term or heavy use
Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*
Altered brain development*
Poor educational outcome, with increased likelihood of dropping out of school*
Cognitive impairment, with lower IQ among those who were frequent users during adolescence*
Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*
Symptoms of chronic bronchitis
Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders

* The effect is strongly associated with initial marijuana use early in adolescence.

to the fact that the brain, including the endocannabinoid system, undergoes active development during adolescence.[6] Indeed, early and regular marijuana use predicts an increased risk of marijuana addiction, which in turn predicts an increased risk of the use of other illicit drugs.[7] As compared with persons who begin to use marijuana in adulthood, those who begin in adolescence are approximately 2 to 4 times as likely to have symptoms of cannabis dependence within 2 years after first use.[8]

EFFECT ON BRAIN DEVELOPMENT

The brain remains in a state of active, experience-guided development from the prenatal period through childhood and adolescence until the age of approximately 21 years.[9] During these developmental periods, it is intrinsically more vulnerable than a mature brain to the adverse long-term effects of environmental insults, such as exposure to tetrahydrocannabinol, or THC, the primary active ingredient in marijuana. This view has received considerable support from studies in animals, which have shown, for example, that prenatal or adolescent exposure to THC can recalibrate the sensitivity of the reward system to other drugs[10] and that prenatal exposure interferes with cytoskeletal dynamics, which are critical for the establishment of axonal connections between neurons.[11]

As compared with unexposed controls, adults who smoked marijuana regularly during adolescence have impaired neural connectivity (fewer fibers) in specific brain regions. These include the precuneus, a key node that is involved in functions that require a high degree of integration (e.g., alertness and self-conscious awareness), and the fimbria, an area of the hippocampus that is important in learning and memory.[12] Reduced functional connectivity has also been reported in the prefrontal networks responsible for executive function (including inhibitory control) and the subcortical networks, which process habits and routines.[13] In addition, imaging studies in persons who use cannabis have revealed decreased activity in prefrontal regions and reduced volumes in the hippocampus.[14] Thus, certain brain regions may be more vulnerable than others to the long-term effects of marijuana. One study showed that selective down-regulation of cannabinoid-1 (CB1) receptors in several cortical brain regions in long-term marijuana smokers was correlated with years of cannabis smoking and was reversible after 4 weeks of abstinence.[15] Changes in CB1 receptors were not seen in subcortical regions.

The negative effect of marijuana use on the functional connectivity of the brain is particularly prominent if use starts in adolescence or young adulthood,[12] which may help to explain the finding of an association between frequent use of marijuana from adolescence into adulthood and significant declines in IQ.[16] The impairments in brain connectivity associated with exposure to marijuana in adolescence are consistent with preclinical findings indicating that the cannabinoid system plays a prominent role in synapse formation during brain development.[17]

POSSIBLE ROLE AS GATEWAY DRUG

Epidemiologic and preclinical data suggest that the use of marijuana in adolescence could influence multiple addictive behaviors in adulthood. In rodents exposed to cannabinoids during adolescence, there is decreased reactivity of the dopamine neurons that modulate the brain's reward regions.[18] The exposure of rodents to

cannabis in utero alters the developmental regulation of the mesolimbic dopamine system of affected offspring.[19] If reduced dopamine reactivity in the brain's reward regions does follow early exposure to marijuana, this effect could help to explain the increased susceptibility to drug abuse and addiction to several drugs later in life, which has been reported in most epidemiologic studies.[20] This theory is also consistent with animal models showing that THC can prime the brain for enhanced responses to other drugs.[21] Although these findings support the idea that marijuana is a gateway drug, other drugs, such as alcohol and nicotine, can also be categorized as gateway drugs, since they also prime the brain for a heightened response to other drugs.[22] However, an alternative explanation is that people who are more susceptible to drug-taking behavior are simply more likely to start with marijuana because of its accessibility and that their subsequent social interactions with other drug users would increase the probability that they would try other drugs.

RELATION TO MENTAL ILLNESS

Regular marijuana use is associated with an increased risk of anxiety and depression,[23] but causality has not been established. Marijuana is also linked with psychoses (including those associated with schizophrenia), especially among people with a preexisting genetic vulnerability,[24] and exacerbates the course of illness in patients with schizophrenia. Heavier marijuana use, greater drug potency, and exposure at a younger age can all negatively affect the disease trajectory (e.g., by advancing the time of a first psychotic episode by 2 to 6 years).[25]

However, it is inherently difficult to establish causality in these types of studies because factors other than marijuana use may be directly associated with the risk of mental illness. In addition, other factors could predispose a person to both marijuana use and mental illness. This makes it difficult to confidently attribute the increased risk of mental illness to marijuana use.

EFFECT ON SCHOOL PERFORMANCE AND LIFETIME ACHIEVEMENT

In the 2013 Monitoring the Future survey of high-school students,[26] 6.5% of students in grade 12 reported daily or near-daily marijuana use, and this figure probably represents an underestimate of use, since young people who have dropped out of school may have particularly high rates of frequent marijuana use.[27] Since marijuana use impairs critical cognitive functions, both during acute intoxication and for days after use,[28] many students could be functioning at a cognitive level that is below their natural capability for considerable periods of time. Although acute effects may subside after THC is cleared from the brain, it nonetheless poses serious risks to health that can be expected to accumulate with long-term or heavy use. The evidence suggests that such use results in measurable and long-lasting cognitive impairments,[16] particularly among those who started to use marijuana in early adolescence. Moreover, failure to learn at school, even for short or sporadic periods (a secondary effect of acute intoxication), will interfere with the subsequent capacity to achieve increasingly challenging educational goals, a finding that may also explain the association between regular marijuana use and poor grades.[29]

The relationship between cannabis use by young people and psychosocial harm is likely to be multifaceted, which may explain the inconsistencies among studies. For example, some studies suggest that long-term deficits may be reversible and remain subtle rather than disabling once a person abstains from use.[30] Other studies show that long-term, heavy use of marijuana results in impairments in memory and attention that persist and worsen with increasing years of regular use[31] and with the initiation of use during adolescence.[32] As noted above, early marijuana use is associated with impaired school performance and an increased risk of dropping out of school,[27,29] although reports of shared environmental factors that influence the risks of using cannabis at a young age and dropping out of school[33] suggest that the relationship may be more complex. Heavy marijuana use has been linked to lower income, greater need for socioeconomic assistance, unemployment, criminal behavior, and lower satisfaction with life.[2,34]

RISK OF MOTOR-VEHICLE ACCIDENTS

Both immediate exposure and long-term exposure to marijuana impair driving ability; marijuana is the illicit drug most frequently reported in connection with impaired driving and accidents, including fatal accidents.[35] There is a relationship between the blood THC concentration

and performance in controlled driving-simulation studies,[36] which are a good predictor of real-world driving ability. Recent marijuana smoking and blood THC levels of 2 to 5 ng per milliliter are associated with substantial driving impairment.[37] According to a meta-analysis, the overall risk of involvement in an accident increases by a factor of about 2 when a person drives soon after using marijuana.[37] In an accident culpability analysis, persons testing positive for THC (typical minimum level of detection, 1 ng per milliliter), and particularly those with higher blood levels, were 3 to 7 times as likely to be responsible for a motor-vehicle accident as persons who had not used drugs or alcohol before driving.[38] In comparison, the overall risk of a vehicular accident increases by a factor of almost 5 for drivers with a blood alcohol level above 0.08%, the legal limit in most countries, and increases by a factor of 27 for persons younger than 21 years of age.[39] Not surprisingly, the risk associated with the use of alcohol in combination with marijuana appears to be greater than that associated with the use of either drug alone.[37]

RISK OF CANCER AND OTHER EFFECTS ON HEALTH

The effects of long-term marijuana smoking on the risk of lung cancer are unclear. For example, the use of marijuana for the equivalent of 30 or more joint-years (with 1 joint-year of marijuana use equal to 1 cigarette [joint] of marijuana smoked per day for 1 year) was associated with an increased incidence of lung cancer and several cancers of the upper aerodigestive tract; however, the association disappeared after adjustment for potential confounders such as cigarette smoking.[40] Although the possibility of a positive association between marijuana smoking and cancer cannot be ruled out,[41] the evidence suggests that the risk is lower with marijuana than with tobacco.[40] However, the smoking of cigarettes that contain both marijuana and tobacco products is a potential confounding factor with a prevalence that varies dramatically among countries.

Marijuana smoking is also associated with inflammation of the large airways, increased airway resistance, and lung hyperinflation, associations that are consistent with the fact that regular marijuana smokers are more likely to report symptoms of chronic bronchitis than are nonsmokers[42]; however, the long-term effect of low levels of marijuana exposure does not appear to be significant.[43] The immunologic competence of the respiratory system in marijuana smokers may also be compromised, as indicated by increased rates of respiratory infections and pneumonia.[44] Marijuana use has also been associated with vascular conditions that increase the risks of myocardial infarction, stroke, and transient ischemic attacks during marijuana intoxication.[45] The actual mechanisms underlying the effects of marijuana on the cardiovascular and cerebrovascular systems are complex and not fully understood. However, the direct effects of cannabinoids on various target receptors (i.e., CB1 receptors in arterial blood vessels) and the indirect effects on vasoactive compounds[46] may help explain the detrimental effects of marijuana on vascular resistance and coronary microcirculation.[47]

LIMITATIONS OF THE EVIDENCE AND GAPS IN KNOWLEDGE

Most of the long-term effects of marijuana use that are summarized here have been observed among heavy or long-term users, but multiple (often hidden) confounding factors detract from our ability to establish causality (including the frequent use of marijuana in combination with other drugs). These factors also complicate our ability to assess the true effect of intrauterine exposure to marijuana. Indeed, despite the use of marijuana by pregnant women,[48] and animal models suggesting that cannabis exposure during pregnancy may alter the normal processes and trajectories of brain development,[49] our understanding of the long-term effects of prenatal exposure to marijuana in humans is very poor.

The THC content, or potency, of marijuana, as detected in confiscated samples, has been steadily increasing from about 3% in the 1980s to 12% in 2012[50] (Fig. 1A). This increase in THC content raises concerns that the consequences of marijuana use may be worse now than in the past and may account for the significant increases in emergency department visits by persons reporting marijuana use[51] (Fig. 1B) and the increases in fatal motor-vehicle accidents.[35] This increase in THC potency over time also raises questions about the current relevance of the findings in older studies on the effects of marijuana use, especially studies that assessed long-term outcomes.

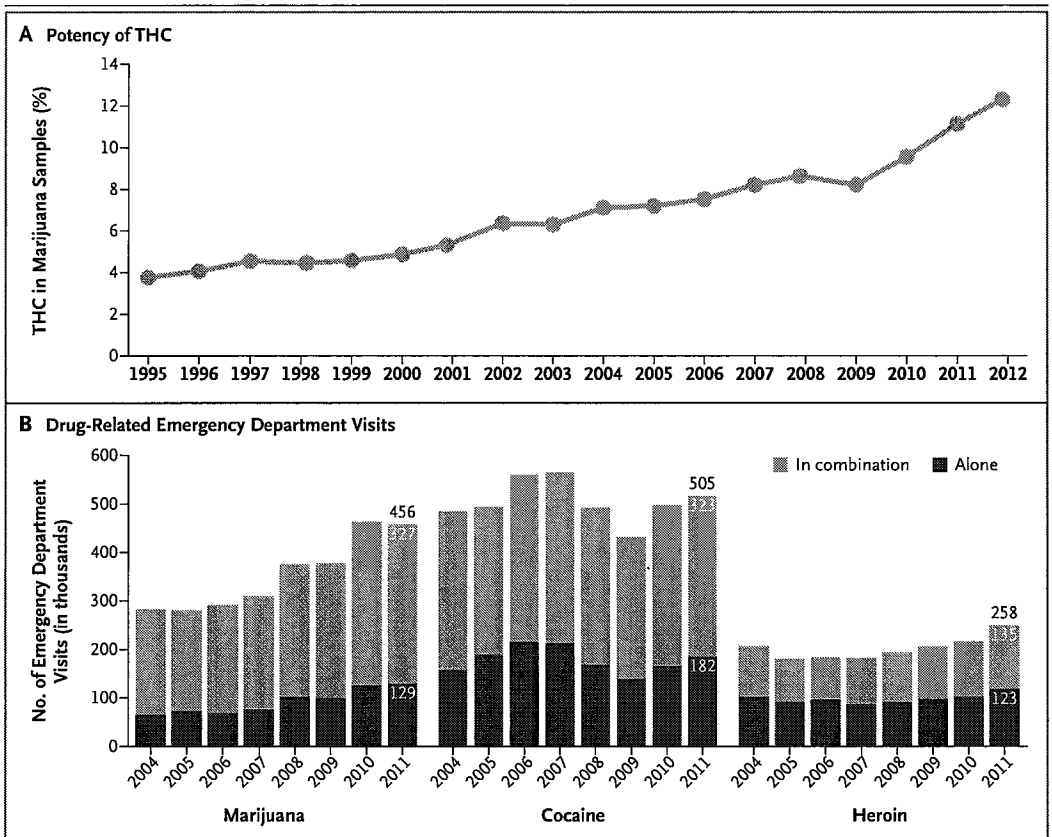

Figure 1. Increases over Time in the Potency of Tetrahydrocannabinol (THC) in Marijuana and the Number of Emergency Department Visits Involving Marijuana, Cocaine, or Heroin.

Panel A shows the increasing potency of marijuana (i.e., the percentage of THC) in samples seized by the Drug Enforcement Administration (DEA) between 1995 and 2012.[50] Panel B provides estimates of the number of emergency department visits involving the use of selected illicit drugs (marijuana, cocaine, and heroin) either singly or in combination with other drugs between 2004 and 2011.[51] Among these three drugs, only marijuana, used either in combination with other drugs or alone, was associated with significant increases in the number of visits during this period (a 62% increase when used in combination with other drugs and a 100% increase when used alone, $P<0.05$ for the two comparisons).

There is also a need to improve our understanding of how to harness the potential medical benefits of the marijuana plant without exposing people who are sick to its intrinsic risks. The authoritative report by the Institute of Medicine, *Marijuana and Medicine*,[52] acknowledges the potential benefits of smoking marijuana in stimulating appetite, particularly in patients with the acquired immunodeficiency syndrome (AIDS) and the related wasting syndrome, and in combating chemotherapy-induced nausea and vomiting, severe pain, and some forms of spasticity. The report also indicates that there is some evidence for the benefit of using marijuana to decrease intraocular pressure in the treatment of glaucoma. Nonetheless, the report stresses the importance of focusing research efforts on the therapeutic potential of synthetic or pharmaceutically pure cannabinoids.[52] Some physicians continue to prescribe marijuana for medicinal purposes despite limited evidence of a benefit (see box). This practice raises particular concerns with regard to long-term use by vulnerable populations. For example, there is some evidence to suggest that in patients with symptoms of human immunodeficiency virus (HIV) infection or AIDS, marijuana use may actually exacerbate HIV-associated cognitive deficits.[75] Simi-

Clinical Conditions with Symptoms That May Be Relieved by Treatment with Marijuana or Other Cannabinoids.*

Glaucoma

Early evidence of the benefits of marijuana in patients with glaucoma (a disease associated with increased pressure in the eye) may be consistent with its ability to effect a transient decrease in intraocular pressure,[53,54] but other, standard treatments are currently more effective. THC, cannabinol, and nabilone (a synthetic cannabinoid similar to THC), but not cannabidiol, were shown to lower intraocular pressure in rabbits.[55,56] More research is needed to establish whether molecules that modulate the endocannabinoid system may not only reduce intraocular pressure but also provide a neuroprotective benefit in patients with glaucoma.[57]

Nausea

Treatment of the nausea and vomiting associated with chemotherapy was one of the first medical uses of THC and other cannabinoids.[58] THC is an effective antiemetic agent in patients undergoing chemotherapy,[59] but patients often state that marijuana is more effective in suppressing nausea. Other, unidentified compounds in marijuana may enhance the effect of THC (as appears to be the case with THC and cannabidiol, which operate through different antiemetic mechanisms).[60] Paradoxically, increased vomiting (hyperemesis) has been reported with repeated marijuana use.

AIDS-associated anorexia and wasting syndrome

Reports have indicated that smoked or ingested cannabis improves appetite and leads to weight gain and improved mood and quality of life among patients with AIDS.[61] However, there is no long-term or rigorous evidence of a sustained effect of cannabis on AIDS-related morbidity and mortality, with an acceptable safety profile, that would justify its incorporation into current clinical practice for patients who are receiving effective antiretroviral therapy.[62] Data from the few studies that have explored the potential therapeutic value of cannabinoids for this patient population are inconclusive.[62]

Chronic pain

Marijuana has been used to relieve pain for centuries. Studies have shown that cannabinoids acting through central CB1 receptors, and possibly peripheral CB1 and CB2 receptors,[63] play important roles in modeling nociceptive responses in various models of pain. These findings are consistent with reports that marijuana may be effective in ameliorating neuropathic pain,[64,65] even at very low levels of THC (1.29%).[66] Both marijuana and dronabinol, a pharmaceutical formulation of THC, decrease pain, but dronabinol may lead to longer-lasting reductions in pain sensitivity and lower ratings of rewarding effects.[67]

Inflammation

Cannabinoids (e.g., THC and cannabidiol) have substantial antiinflammatory effects because of their ability to induce apoptosis, inhibit cell proliferation, and suppress cytokine production.[68] Cannabidiol has attracted particular interest as an antiinflammatory agent because of its lack of psychoactive effects.[58] Animal models have shown that cannabidiol is a promising candidate for the treatment of rheumatoid arthritis[58] and for inflammatory diseases of the gastrointestinal tract (e.g., ulcerative colitis and Crohn's disease).[69]

Multiple sclerosis

Nabiximols (Sativex, GW Pharmaceuticals), an oromucosal spray that delivers a mix of THC and cannabidiol, appears to be an effective treatment for neuropathic pain, disturbed sleep, and spasticity in patients with multiple sclerosis. Sativex is available in the United Kingdom, Canada, and several other countries[70,71] and is currently being reviewed in phase 3 trials in the United States in order to gain approval from the Food and Drug Administration.

Epilepsy

In a recent small survey of parents who use marijuana with a high cannabidiol content to treat epileptic seizures in their children,[72] 11% (2 families out of the 19 that met the inclusion criteria) reported complete freedom from seizures, 42% (8 families) reported a reduction of more than 80% in seizure frequency, and 32% (6 families) reported a reduction of 25 to 60% in seizure frequency. Although such reports are promising, insufficient safety and efficacy data are available on the use of cannabis botanicals for the treatment of epilepsy.[73] However, there is increasing evidence of the role of cannabidiol as an antiepileptic agent in animal models.[74]

* AIDS denotes acquired immunodeficiency syndrome, CB1 cannabinoid-1 receptor, and CB2 cannabinoid-2 receptor, HIV human immunodeficiency virus, and THC tetrahydrocannabinol.

larly, more research is needed to understand the potential effects of marijuana use on age-related cognitive decline in general and on memory impairment in particular.

Research is needed on the ways in which government policies on marijuana affect public health outcomes. Our understanding of the effects of policy on market forces is quite limited (e.g., the allure of new tax-revenue streams from the legal sale of marijuana, pricing wars, youth-targeted advertising, and the emergence of cannabis-based medicines approved by the Food and Drug Administration), as is our understanding of the interrelated variables of perceptions about

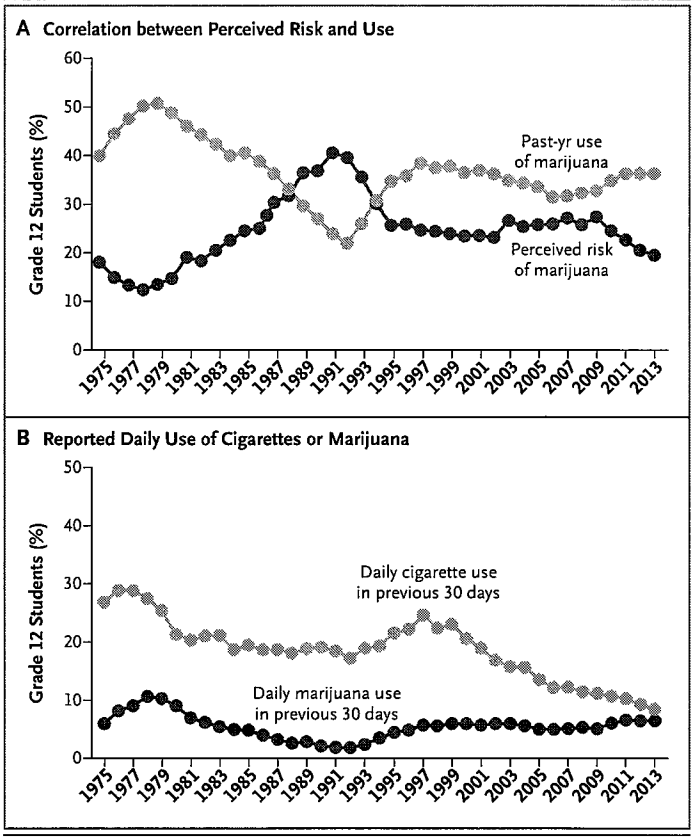

Figure 2. Use of Marijuana in Relation to Perceived Risk and Daily Use of Tobacco Cigarettes or Marijuana among U.S. Students in Grade 12, 1975–2013.

Panel A shows the inverse correlation between the perception of the risk associated with marijuana use and actual use. Perceived risk corresponds to the percentage of teenagers who reported that the use of marijuana is dangerous. Panel B shows the percentage of students who reported daily use of tobacco cigarettes or marijuana in the previous 30 days. Data for both graphs are from Johnston et al.[26]

use, types of use, and outcomes. Historically, there has been an inverse correlation between marijuana use and the perception of its risks among adolescents (Fig. 2A). Assuming that this inverse relationship is causal, would greater permissiveness in culture and social policy lead to an increase in the number of young people who are exposed to cannabis on a regular basis? Among students in grade 12, the reported prevalence of regular marijuana smoking has been steadily increasing in recent years and may soon intersect the trend line for regular tobacco smoking (Fig. 2B). We also need information about the effects of second-hand exposure to cannabis smoke and cannabinoids. Second-hand exposure is an important public health issue in the context of tobacco smoking, but we do not have a clear understanding of the effects of second-hand exposure to marijuana smoking.[76] Studies in states (e.g., Colorado, California, and Washington) and countries (e.g., Uruguay, Portugal, and the Netherlands) where social and legal policies are shifting may provide important data for shaping future policies.

CONCLUSIONS

Marijuana use has been associated with substantial adverse effects, some of which have been determined with a high level of confidence (Table 2). Marijuana, like other drugs of abuse, can result in addiction. During intoxication, marijuana can interfere with cognitive function (e.g., memory and perception of time) and motor function (e.g., coordination), and these effects can have detrimental consequences (e.g., motor-vehicle accidents). Repeated marijuana use during adolescence may result in long-lasting changes in brain function that can jeopardize educational, professional, and social achievements. However, the effects of a drug (legal or illegal) on individual health are determined not only by its pharmacologic properties but also by its availability and social acceptability. In this respect, legal drugs

Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low

* The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.

(alcohol and tobacco) offer a sobering perspective, accounting for the greatest burden of disease associated with drugs[77] not because they are more dangerous than illegal drugs but because their legal status allows for more widespread exposure. As policy shifts toward legalization of marijuana, it is reasonable and probably prudent to hypothesize that its use will increase and that, by extension, so will the number of persons for whom there will be negative health consequences.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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COMMENTARY

Dopamine challenge reveals neuroadaptive changes in marijuana abusers

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The current watershed in legal status and rising use of marijuana can be traced to a California ballot initiative (Prop. 215, its legal successor SB420), that enabled widespread access to smokeable or edible forms of marijuana for self-reported medical conditions. Circumventing the Food and Drug Administration (FDA) drug approval process, the movement in California was replicated by ballot or legislative initiatives in 23 states and the District of Columbia, and culminated in the legalization of marijuana in 2012 by Washington state and Colorado. The shifting status of marijuana reflects a change in public perception and belief that marijuana is harmless. Marijuana use in the population over age 12 is escalating; 60% of 12th graders do not perceive marijuana as harmful, and daily or nearly daily use has risen dramatically in this cohort (1, 2). Paradoxically, public perception of marijuana as a safe drug is rising simultaneously with accumulating evidence that frequent marijuana use is associated with adverse consequences, especially among youth (3). In PNAS, Volkow et al. register compelling new observations that marijuana abusers manifest adaptive behavioral, physiological, and biological responses, which conceivably contribute to marijuana addiction and compromised function (4). In response to a dopamine challenge (methylphenidate) and compared with non-using controls, marijuana abusers self-reported blunted reward (less "high") and heightened negative responses (anxiety and restlessness), which were associated with attenuated dopamine responses in brain and cardiovascular responses.

Dopamine, Reward, the Adapted Brain

The role of the neurotransmitter dopamine in drug reward and addiction is the key to understanding the rationale for interrogating dopamine function in long-term marijuana abusers. The dopamine hypothesis of addiction was formulated by preclinical observations showing that opiates, cocaine, amphetamine, nicotine, alcohol, and (delta-9)-tetrahydrocannabinol (THC, the psychoactive constituent of marijuana), raise extracellular dopamine levels in the dopamine-rich nucleus accumbens, a brain region associated with reward (5, 6). Repeated drug-induced dopamine surges were subsequently shown to engender neuroadaptive changes in brain regions implicated in drug salience, drug reward, motivation, memory, and executive function (7–9). In humans dependent on alcohol, cocaine, methamphetamine, nicotine, or heroin, adaptation of dopamine signaling is manifest by reduced D2 dopamine receptor availability and blunted dopamine release in cocaine, heroin, and alcohol abusers challenged with a psychostimulant (10–14). Interrogation of whether marijuana abusers manifest parallel adaptive changes in dopamine signaling has yielded inconsistent results (15).

By integrating behavioral and brain-imaging measures following a dopamine challenge (methylphenidate) in marijuana abusers, Volkow et al. (4) add a new dimension to clarifying the impact of long-term marijuana use on brain dopamine response. Methylphenidate, a surrogate for dopamine, elevates extracellular levels of dopamine (and norepinephrine) by blocking the dopamine transporter (DAT) in dopamine-expressing neurons. As the DAT sequesters dopamine in dopamine-releasing neurons, the blockade raises extracellular dopamine levels in dopamine-rich brain regions. The rapid rise in dopamine triggers self-reports of a "high." Marijuana abusers self-reported blunted measures of "high," drug effects, increased anxiety, and restlessness. The magnitude and peak behavioral effects of methylphenidate were more robust in controls than marijuana abusers. Cardiovascular responses (diastolic blood pressure, pulse rate) were also attenuated in the abusers. Significantly, the younger marijuana use was initiated, the higher the scores for negative emotionality. These findings reinforce the accumulating evidence that earlier age of initiation of marijuana abuse is associated with worse outcomes (3, 16). Collectively this phase of the study suggests that brain dopaminergic, possibly noradrenergic systems, are significantly modified in long-term, heavy marijuana abusers. These changes conceivably contribute to reduced rewarding effects, emotionality and motivation, increased propensity for addiction, with early initiators being more vulnerable.

D2/D3 dopamine receptors are critical mediators of the initial responses to drugs of abuse. PET imaging of brain revealed a more complex pattern of change in dopamine signaling than previously reported for other specific drugs of abuse. D2/D3 dopamine receptor availability, measured with the D2/D3 receptor antagonist [11C]raclopride, was not reduced in marijuana abusers, in contrast to reduced dopamine receptor availability observed in subjects with other specific substance use disorders (11–14). This conclusion remains tentative, as the age of the marijuana-abusing cohort was considerably younger than drug-abusing subjects previously interrogated for D2 dopamine receptor availability.

[11C]Raclopride can also serve as an indirect measure of dopamine production, release, and extracellular levels (17). Reduced [11C]raclopride binding-site availability is detectable following administration of a psychostimulant (e.g., methylphenidate or amphetamine), which elevates the extracellular dopamine by blocking transport or promoting its release from neurons. The dopamine surge competes with [11C]raclopride for binding to the D2/D3 receptor, with [11C]raclopride displacement proportional to extracellular dopamine. In marijuana abusers, diminished dopamine responses were observed in the ventral striatum compared with controls, and were inversely correlated with addiction severity and craving. The attenuated responses to methylphenidate are consistent with decreased brain reactivity to dopamine stimulation in marijuana abusers, which conceivably contributes to the increase in stress responses, irritability,

Author contributions: B.K.M. wrote the paper.

The author declares no conflict of interest.

See companion article 10.1073/pnas.1411228111.

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and addictive behaviors. Thus, marijuana joins the roster of other abusable drugs in promoting blunted dopaminergic responses in a brain region implicated in drug reward, but deviates from other drugs in that it apparently does not promote a decline in D2/D3 receptor availability.

The study yielded several unanticipated discoveries. Marijuana abusers displayed enhanced dopamine release in the substantia nigra/subthalamic nucleus, which correlated with marijuana and tobacco craving, as well as addiction severity. Because this brain region has relatively high densities of the D3 receptor, this preliminary finding reinforces the need to expand PET imaging to multiple, discrete brain regions, with higher-resolution cameras, and to enlist other probes capable of selective monitoring of each of five dopamine receptor subtypes. Another surprising observation was the decrease in distribution volume in the cerebellum by methylphenidate in controls, but not in marijuana abusers, another manifestation of a blunted response. This brain region characteristically is used as a reference region to normalize for nonspecific binding ("baseline") of PET imaging probes if comparing group differences, possibly resulting in overestimates of the methylphenidate response in other brain regions of marijuana abusers. This finding, which may reflect vascular changes engendered by marijuana, highlights the necessity of heightened scrutiny of the cerebellum as a "neutral" baseline region for dopamine receptor monitoring in group comparisons.

Collectively, abnormal behavioral responses to a methylphenidate challenge implicate dopamine signaling adaptation in marijuana abusers. Even though a decrease in striatal D2 receptor density does not account for the responses, other components of the synapse (e.g., DAT, dopamine synthetic capacity, the dopamine signaling cascade, events downstream of dopamine receptors) conceivably contribute to manifestations of blunted subjective responses.

Future Multidisciplinary Research

The current research (4), providing strong evidence that marijuana abuse is associated with blunted dopamine responses and reward, is a major contribution to a growing body of evidence that heavy marijuana use is associated with brain changes that could be detrimental to normal brain function. Numerous other brain-imaging studies have been conducted in heavy adult marijuana users (e.g., ref. 18), with reported changes in brain morphology and density, deformation of specific structures, altered connectome (e.g., hippocampus), and function. The current research, which integrates behavioral and physiological changes within the context of a specific neurochemical substrate, dopamine, provides important leads for integrating with other changes gleaned from MRI technologies. Intriguingly, evidence that dopamine receptor signaling can affect expression of genes encoding axonal guidance molecules that are critical for brain development and neuroadaptation (19) may provide a link between drug-induced receptor activity and gross and discrete altered morphology and circuitry characteristic of the drug-adapted brain.

There remains a compelling need for prospective, integrated longitudinal research in this field, especially in adolescent marijuana users, as the impact of marijuana on the developing brain is more robust with early age of initiation (3, 16). Imaging studies are predominantly snapshots in time, relying on self-reports of marijuana use, dose, and frequency, with subjects of varying ages, group sizes, differing imaging techniques, and other variables that confound meta-analyses or integration of data from different sites to expand study power. A critical longitudinal study showing a significant IQ decline in early marijuana users is a prime example of the direction in which the field should be going, but with coordinated brain-imaging approaches (20).

Preclinical studies can circumvent the limitations of some clinical metrics, and establish causality for specific changes that are not feasible to measure in humans. Yet the divergence of the human brain anatomically and functionally limits unfettered extrapolation from animals to humans. Large-scale, multicenter prospective longitudinal human research starting before initiation of drug use and extending for three decades of life is needed to further pursue causal relationships of marijuana and adverse consequences reported in numerous shorter-term studies. Research design could include: (*i*) brain imaging to document occurrence of, resolution, or persistence of structural, circuitry, vascular, and associated and neuropsychological decrements; (*ii*) neurocognitive function; (*iii*) behavioral, emotional assessment; (*iv*) neural, cognitive, epigenetic, proteomic, and affective markers; and (*v*) preclinical, relevant parallel studies.

In view of the growing public health concerns of escalating high-dose, high-frequency marijuana use, early age of initiation and daily use, high prevalence of marijuana addiction, rising treatment needs, the void of effective treatment, high rates of relapse, association with psychosis and IQ reduction, a rising tide of emergency room episodes, and vehicular deaths, constitute compelling reasons to expand marijuana research and to clarify its underlying biology and treatment targets/strategies. Longitudinal studies that begin before initiation of use, and that integrate brain imaging with behavioral, cognitive, and other parameters, will facilitate shaping of public perception and public policy with more informed scientific evidence.

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Schizophrenia Research 95 (2007) 9–18
SCHIZOPHRENIA RESEARCH
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Changing incidence of psychotic disorders among the young in Zurich

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Received 3 April 2006; received in revised form 8 June 2007; accepted 10 June 2007
Available online 16 July 2007

Abstract

There is controversy over whether the incidence rates of schizophrenia and psychotic disorders have changed in recent decades. To detect deviations from trends in incidence, we analysed admission data of patients with an ICD-8/9/10 diagnosis of psychotic disorders in the Canton Zurich / Switzerland, for the period 1977–2005. The data was derived from the central psychiatric register of the Canton Zurich. Ex-post forecasting with ARIMA (Autoregressive Integrated Moving Average) models was used to assess departures from existing trends. In addition, age-period-cohort analysis was applied to determine hidden birth cohort effects. First admission rates of patients with psychotic disorders were constant in men and showed a downward trend in women. However, the rates in the youngest age groups showed a strong increase in the second half of the 1990's. The trend reversal among the youngest age groups coincides with the increased use of cannabis among young Swiss in the 1990's.

Keywords: Psychotic disorders; Schizophrenia; Incidence; Time series; Cannabis; Switzerland

1. Introduction

There is a growing body of evidence indicating that incidence rates of schizophrenia vary more than one would expect from an "egalitarian disorder" (McGrath, 2005). For example, there is considerable evidence of variations in incidence according to gender, urban or rural upbringing, and ethnicity (van Os, 2004). In recent decades, evidence of a rate decrease (Brewin et al., 1997; Der et al., 1990; Eagles et al., 1988; Eagles and Whalley, 1985; Suvisaari et al., 1999; Takei et al., 1996; Waddington and Youssef, 1994; Woogh, 2001), has been reported from studies of incidence or first admission rates, the latter being a proxy for incidence rates (Geddes et al., 1993; Jones et al., 1997). A few studies have reported constant incidence rates or first admission rates (Harrison et al., 1991; Oldehinkel and Giel, 1995; Osby et al., 2001), and others have reported increasing rates (Boydell et al., 2003; Preti and Miotto, 2000; Tsuchiya and Munk-Jorgensen, 2002).

We set out to examine the sex and age-specific trends of first admission rates of people with psychotic disorders in the Canton Zurich/Switzerland from 1977–2005, to detect incidence trends as well as departures from trends. To determine the latter, two different approaches were

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doi:10.1016/j.schres.2007.06.001

used: ex-post forecasting within ARIMA modelling, and age-period-cohort analysis.

2. Materials and methods

First admission data for schizophrenia and other psychoses was obtained from the Psychiatric Case Register in Zurich. All mental health services in the Canton Zurich provide detailed information about diagnostic, treatment-related and socio-demographic characteristics of all patients to the central psychiatric register. The data is collected by means of a basic documentation system, which assesses information via standard forms completed both at admission, and at discharge (Lauber et al., 2005).

The register contains basic information on all psychiatric inpatients in the Canton Zurich since 1974. The place of residence has been recorded since 1977. The catchment area, the Canton of Zurich, is a mixed urban-rural area with a population of 1.2 million, which comprises about one sixth of the total Swiss population.

Discharge diagnoses were used. The discharge protocol allowed up to 4 diagnoses until 1997, and up to 9 diagnoses from 1998 onwards. The diagnoses were based on ICD-8 from 1974–1978, on ICD-9 from 1979–1991, and on ICD-10 since 1992. Two different definitions of schizophrenia/psychotic disorder were applied in this analysis: firstly, a narrow variant restricted to codes F20 (ICD-10) and 295 (ICD-8 and ICD-9) and, secondly, a broader variant covering all F2 codes (ICD-10) and the codes 295, 297, 298, 299 (ICD-8 and ICD-9). The introduction of ICD-10 caused a shift in the reporting of narrowly defined schizophrenia, which was compensated by other F2-categories. Therefore, to avoid biasing effects of changing definitions over time, our analyses were based on the broad definition of schizophrenia and other psychotic disorders.

Between 1977 and 2005, a total of over 180,000 admissions were registered. The narrow schizophrenia diagnosis was applied to 38,000 admissions, and the broader psychotic disorder diagnosis to more than 52,000 admissions. Slightly more than 10% of the records related to people not living in the Canton Zurich, and were therefore excluded.

The denominator (i.e. the population of Canton Zurich) was interpolated from the census data (1970, 1980, 1990, 2000).

2.1. Identification of patients at first admission

The admission records lacked for the most part a unique identification number for each patient. Thus, several filtering and matching steps had to be applied in identifying the first admissions of F2-patients. They included the following criteria (Fig. 1):

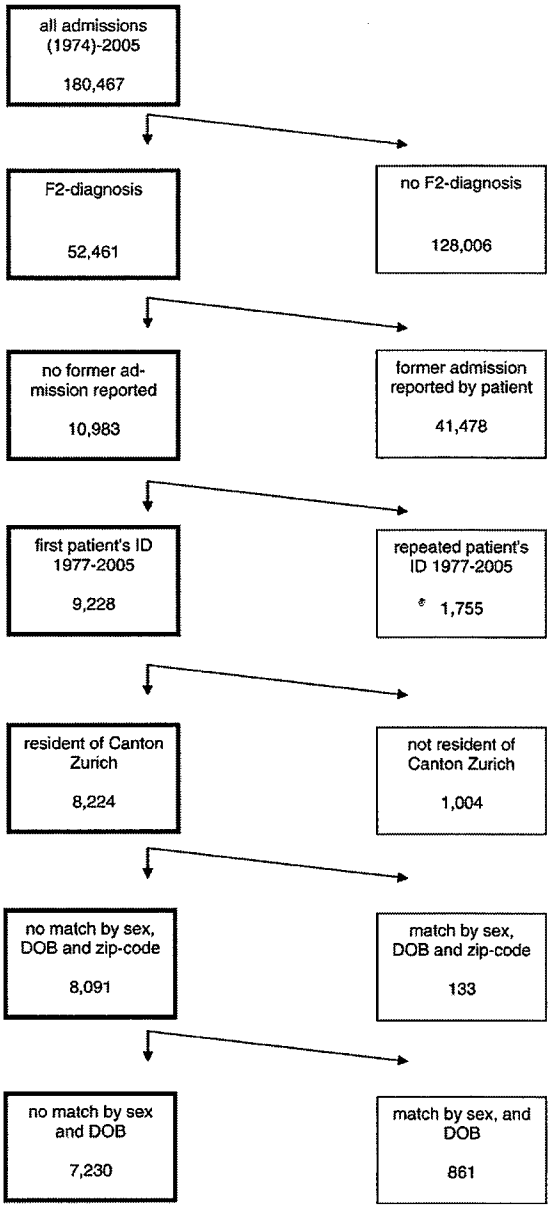

Fig. 1. Selection of first admissions with F2 diagnoses from the central psychiatric register of the Canton Zurich, Switzerland.

- mention of F2-diagnosis on the discharge protocol
- exclusion of previous psychiatric admissions in the admission protocol (self-reported); it was not possible to differentiate between previous F2 admissions and admissions due to other diagnoses; therefore, the

F2 first admissions were underestimated to some extent

- exclusion of second (and later) occurrence of an identification code after matching by sex and date of birth; the identification codes were specific for each hospital, however, they turned out not to be unique which meant that additional matching by sex and date of birth was necessary
- inclusion of residents of the Canton Zurich; this step was introduced rather late because of pragmatic reasons (programming)
- exclusion of records with identical information regarding sex, date of birth and the zip code; this step ruled out those patients who were treated in several hospitals, but failed to deliver any appropriate information about prior hospitalization
- exclusion of records with identical information only about sex and date of birth; this step was more restrictive than the previous one.

In this way, we identified 3972 first admissions which received a narrow schizophrenia diagnosis, and 7230 first admissions with a broader psychotic disorder diagnosis. In addition, we found 328 (837) duplicate entries with regard to sex and date of birth, which is more than one might expect. Therefore we calculated the incidence figures without using duplicate entries. Only the first record of a sex and birth date match was kept. This measure contributed to a certain amount of underestimation of first admission rates.

2.2. ARIMA modelling

To ascertain departures from trends, the time series were modelled by means of ARIMA, also known as the Box–Jenkins approach (Box and Jenkins, 1970; Gottman, 1981). Rates in 1977–1995, that is, the period before the presumed increase of first admission rates, served to build preliminary models. The rates were calculated semi-annually to provide a greater number of observations. ARIMA models rely on estimation of autoregressive (AR) and moving average (MA) processes inherent in the time series, eventually preceded by data transformation operations and differencing (de-trending). These models were used to ex-post forecast values from 1996 onwards when the increase of the first admission rates in the young began. The rest of the time series from 1996 onwards served to confirm the validity of the previously stated model. Deviations from the forecasted values (and their 95% confidence intervals) indicate that specific fluctuations or trend reversals emerge, which do not conform to the former time series patterns.

2.3. Age-period-cohort (APC) analysis

The main aim of APC analysis is to describe historical change by disentangling direct, immediate effects as against delayed birth cohort effects on any outcome variables such as incidence or mortality of a disease. APC analysis is usually based on repeatedly (for example, annually) collected age-stratified data pooled in so-called cohort tables (Fienberg and Mason, 1985). It differentiates simultaneously between the effects of age (age effects), the effects of historical change (period effects), and the generational succession (cohort effects). The main obstacle is that there is a redundancy between linear age, period and cohort effects. Any two of the dimensions age, period and cohort determines the third. Thus, additional restrictions or conventions are required (Holford, 1985, 1991). In this study, we used a simple approach to deal with the identification problem in APC analysis. Analogous to the drift-approach (Clayton and Schifflers, 1987a,b), age effects act as a mandatory component in all models, and, furthermore, as the target for subsequent constraints. Since age effects were shown to largely determine the data structure in preliminary one-factor and two-factor analyses (Table 1), the full APC models were calculated after restricting age estimates according to the results in the preliminary AC models. In the analyses reported below, we confined the restrictions to the first age estimate only, that is, by adopting the respective parameter from the AC model.

APC analyses were calculated within the framework of log-linear analysis, i.e., logit models, based on a cohort table with 5-year intervals for age (15–19, 20–24,..., 50–54) and period (1977–81, 1982–86 etc.; the last period relies only on data for the four years (2002–5)). The goodness of fit or, rather, the lack of fit, was assessed

Table 1
APC analyses of first admission data of patients with psychotic disorders in the Canton Zurich, Switzerland, from 1977–2005; 5-year period and age intervals (age range 15–49), by sex

	Males			Females		
Effects	*df*[a]	Deviance	*p*-value	*df*[a]	Deviance	*p*-value
1. Intercept	41	947.8	.000	41	244.2	.000
2. Age	35	93.5	.000	35	132.5	.000
3. Period	36	917.9	.000	36	160.0	.000
4. Cohort	30	618.7	.000	30	173.4	.000
5. Age period	30	63.1	.000	30	45.4	.036
6. Age cohort	24	59.8	.000	24	20.5	.669
7. Period cohort	25	342.1	.000	25	122.2	.000
8. Age period cohort[b]	20	38.6	.008	20	18.0	.588

[a] *df*: degrees of freedom.
[b] Model with 1 restricted parameter (set on the first age estimate).

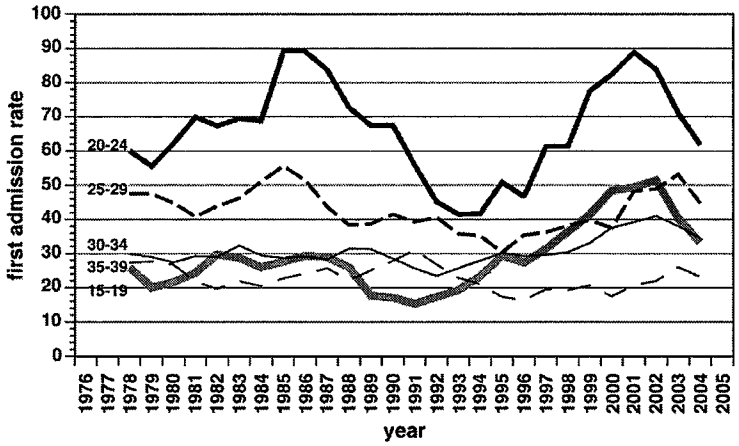

Fig. 2. Age-specific first admission rates for schizophrenia and other psychotic disorders in the Canton Zurich, Switzerland, 1977–2005; men, 3-year moving averages, ages 15–19, 20–24, 25–29, 30–34 and 35–39.

by the deviance or likelihood-ratio. The deviance of all one-or two-effect models was assessed routinely.

The values depicted in the figures represent estimates after exponentiation. All computations were performed using SAS (SAS Institute Inc., 1996).

3. Results

Between 1977 and 2005, there were 8091 first admissions who received a diagnosis of schizophrenia or other psychoses at discharge: 3767 (46.5%) men and 4324 women (53.5%). After excluding duplicate entries with regard to sex and the date of birth, there remained 7230 first admissions, i.e., 3331 men and 3899 women.

The overall first admission rates in men were on a similar level round the year 1980 and after 2000 (~20 per 100,000), whereas the rates of women decreased from ~30 to ~20 per 100,000. The age-specific first admission rates (rates available on request) for men showed a steep increase in young adulthood resulting in a peak in the age group 20–24. In women, the peak in the rates occurred in the age-groups 25–29 and 30–34, and was lower than in males. However, the decrease thereafter was distinctly more gradual than in males. The age shapes were similar over the whole period.

The longitudinal perspective shows a slightly decreasing trend in first admission rates in most male age groups, and a decrease in all female age groups until

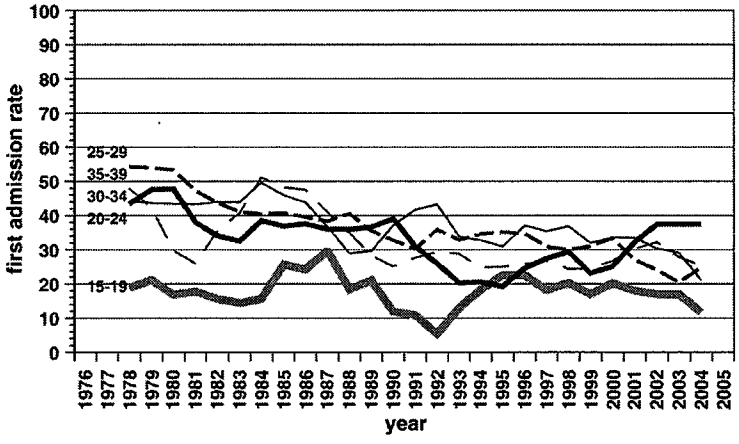

Fig. 3. Age-specific first admission rates for schizophrenia and other psychotic disorders in the Canton Zurich, Switzerland, 1977–2005; women, 3-year moving averages, ages 15–19, 20–24, 25–29, 30–34 and 35–39.

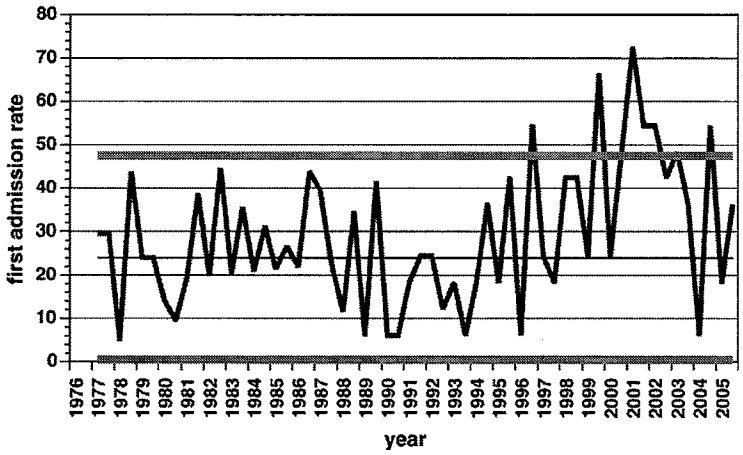

Fig. 4. Ex-post forecasting of semi-annual first admission rates for schizophrenia and other psychotic disorders of 15–19-year old men in the Canton Zurich, Switzerland; rates (dark bold line), predicted/forecasted values (dark thin line) and 95% confidence intervals (grey lines); ARIMA modelling was based on 1977–1995 values.

the 1990s. In the 1990s the trend changed for the youngest male age group (15–19 years) and, with some time delay, also in the 20–24 year olds (Fig. 2). No similar change of trend is obvious in the youngest female age groups (Fig. 3). No trend reversal is apparent in older age groups. Over the entire time series, the young male age groups seem to be most prone to fluctuating patterns, and also show an interim peak in the early 1980s.

The ARIMA analyses support this interpretation. Ex-post forecasting of the rates after 1995 showed that the values of the youngest male age groups (15–19 and 20–24 year old) temporarily left the 95%-confidence intervals (Figs. 4 and 5). This is despite the fact that the confidence intervals are broad since relatively few observations were used in the model building. In all other sex-age subgroups, the departures from trend were less impressive or not existent (data available on request).

Table 1 shows the improvement of the model fit in APC-analysis while introducing the A-, P- and C-effects. It is obvious from the deviance values that the full APC model fitted the males data clearly more satisfactorilythan any two effects model. In females, the

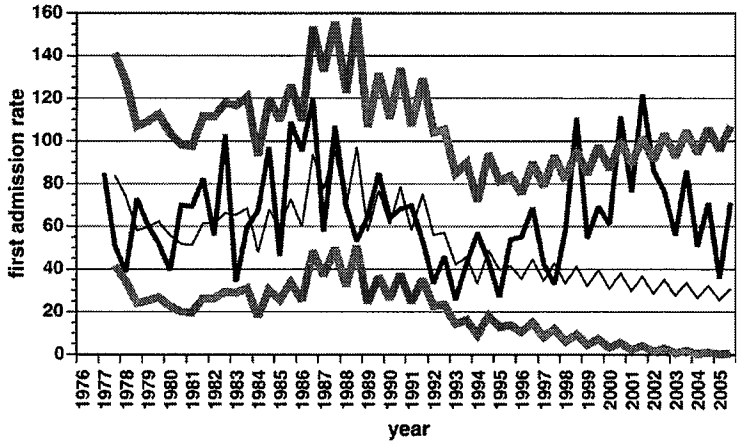

Fig. 5. Ex-post forecasting of semi-annual first admission rates for schizophrenia and other psychotic disorders of 20–24-year old men in the Canton Zurich, Switzerland; rates (dark bold line), predicted/forecasted values (dark thin line) and 95% confidence intervals; ARIMA modelling was based on 1977–1995 values.

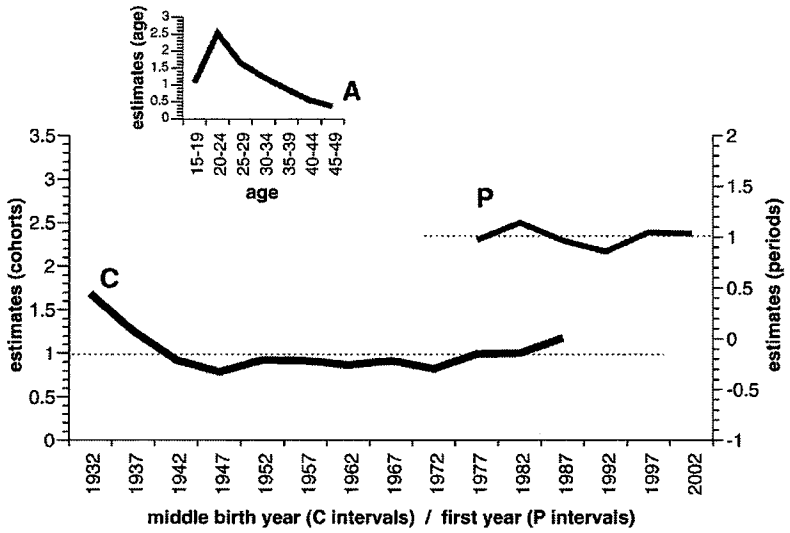

Fig. 6. Age-period-cohort analysis of male first admissions for schizophrenia and other psychotic disorders in the Canton Zurich, Switzerland, 1977–2005; logit analysis of 5 * 5-standard cohort tables, first age estimate being fixed.

full APC model provided only minimal improvement with respect to the AC model. The estimates derived from the APC analyses are depicted in Figs. 6 and 7. The A-section shows the shape of the age-estimates, the P-section shows the period estimates and the C-section the cohort estimates. APC analysis of first admissions of male patients with schizophrenia and other psychoses (Fig. 6) indicates that the increase of the rates during the 1980s is related to period effects, whereas the recent increase of the rates in the young is partitioned into period and cohort effects. The period estimates suggest a temporary increase whereas the cohort estimates suggest a more lasting phenomenon. Since the latter rely mainly on the most recent birth cohorts with few observations, they also could be interpreted as short-term age-period interactions. In females, the birth cohorts estimates show

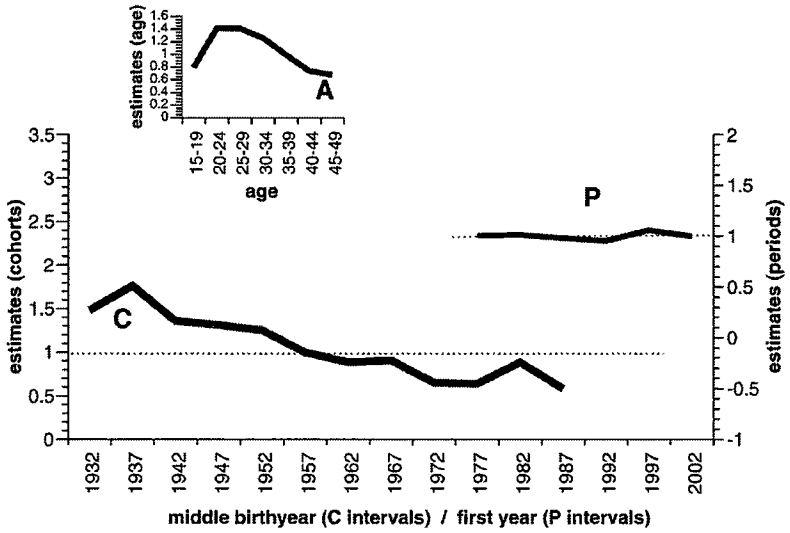

Fig. 7. Age-period-cohort analysis of female first admissions for schizophrenia and other psychotic disorders in the Canton Zurich, Switzerland, 1977–2005; logit analysis of 5 * 5-standard cohort tables, first age estimate being fixed.

only a slight disturbance among the most recent cohorts (Fig. 7).

4. Discussion

Since the 1980s, possible changes in incidence rates of schizophrenia have been discussed extensively. While some researchers argued that there is a real decrease (Brewin et al., 1997; Eagles and Whalley, 1985; Geddes et al., 1993), others have suggested artificial effects (Allardyce et al., 2000; Boydell et al., 2003; Kendell et al., 1993; Munk-Jorgensen and Mortensen, 1992; Osby et al., 2001). An alternative perspective has come recently from Danish data: after a decrease of schizophrenia incidence rates up to the 1980s (Munk-Jorgensen and Mortensen, 1992), the trend reversed and the rates then began to rise (Tsuchiya and Munk-Jorgensen, 2002). An increase in schizophrenia incidence rates since the 1960s was also demonstrated in Camberwell (south-east London), particularly among the young age groups (Boydell et al., 2003).

The present data shows that the initial stationary, or possibly decreasing, trend in the Canton Zurich/Switzerland has selectively changed among adolescents and young adults during recent years. Males seem to be more affected than females. The deviation from the previous pattern was demonstrated by two different methodical approaches, i.e., ex-post forecasting with ARIMA models, and age-period-cohort (APC) analysis.

The figures are based on first admissions of patients with schizophrenia and other psychotic disorders to psychiatric inpatient services in a catchment area with 1.1 million residents between 1977 and 2005. Since schizophrenia is a disease in which patients are usually admitted to hospital (Geddes et al., 1993; Jones et al., 1997), first admission figures are only a proxy of the real incidence. In contrast to most other studies dealing with the change of schizophrenia incidence rates, the Zurich register offers both a large data base, and a relatively long observation period. We compared different inclusion criteria to account for the possibility that all of the duplicate entries with regard to sex and the date of birth were re-admissions instead of first admissions. The results did not alter substantially. As in other studies (Oldehinkel and Giel, 1995), the decrease of the rates was not so marked when a broader definition of psychotic disorders was used, thus suggesting some change occurring between diagnostic criteria over the recent decades. The use of the broader definition was necessary because the diagnostic practice in narrowly defined schizophrenia obviously changed with the introduction of the ICD-10 coding in 1992.

The limitations of this study are those of the register data. The figures are based on first admissions of psychotic disorders in inpatient services and do not exactly mirror the time of disease onset. Moreover, the information on previous admissions derived from the admission protocol turned out to be lacking or inappropriate in some instances. Thus, we introduced an additional control by excluding cases after matching by combined sex/birth date/ZIP code data. Presumably, the matching was less successful at the beginning of the examined period, that is in the 1970s and the early 1980s, than later.

The register data does not include information about the lifetime use of legal and illicit drugs. Moreover, the limitations stem from effects, which might interfere with time series of incidence data: change of classification systems (ICD-8, -9 and -10), change of diagnostic habits (mainly schizophrenia vs. other diagnoses of psychotic disorders), changes in health service organisation, delays in the use of inpatient services, early intervention programmes, and, finally, use of outpatient and alternative services. However, it is not plausible that such effects would bias the incidence rates of schizophrenia and other psychoses in an age and sex-specific manner. Moreover, the increasing importance of outpatient services would suggest a decrease rather than an increase of rates. To exclude artificial effects in register-based incidence rates is more problematic with regard to long-term change, than to short-term fluctuations.

Provided that the limitations mentioned above do not basically change any conclusions reached, the Zurich figures have shed a new light on the incidence of psychotic disorders. In Zurich, as elsewhere, incidence rates of schizophrenia and other psychoses have declined over recent decades. As elsewhere, the decrease seems to have affected women rather than men (Geddes et al., 1993; Jones et al., 1997; Kendell et al., 1993; Waddington and Youssef, 1994). Specifically, in Zurich there has been a trend-reversal in incidence rates in young men. The rates for young men in former years have also exhibited remarkable fluctuations — such as the peak in the 1980s.

There are not many plausible explanations for such deviating incidence patterns in the young (Maki et al., 2005). It is unlikely that such short-term fluctuations in incidence could be related to risk factors related to pregnancy and delivery, such as famine experienced by the mother during pregnancy, prenatal infections or obstetric complications. Such risk factors appertain to birth cohort effects and determine slow change phenomena. Among the known risk factors, drug use is the only one which might generate fast changing incidences of psychotic disorders on the population level (McCormick and Goff, 1991).

In fact, during the 1990s the patterns of drug use have markedly changed among young people in Western

Europe. Two trends have been obvious. On the one hand, cannabis has become more popular and broadly available, and on the other, a new party and dancing scene has emerged which extensively used ecstasy (MDMA) and to a lesser extent other synthetic amphetamines and hallucinogens (von Sydow et al., 2002). According to information from the Zurich police (personal communication from Dr. Bovens of the Scientific Department), the latter drugs as well as phencyclidine (PCP) have remained clearly a peripheral phenomenon in the region of Zurich. Cannabis and ecstasy (or any interactions of these two substances with other ones) appear to be the most promising candidates to explain the trend change in incidence of first admissions in psychotic disorders.

In recent years, cannabis use has been the focus of much attention in the research on etiology of psychotic disorders. The ability of cannabis in inducing an acute psychosis has been known for a long time. Since the end of the 1980s there has been speculation about an association between cannabis and psychotic disorders, which goes beyond transient effects (Macleod et al., 2004). Evidence for cannabis as a risk factor has come from several longitudinal studies (Arseneault et al., 2002; Boydell et al., 2006; Fergusson et al., 2005, 2003; Henquet et al., 2005a; van Os et al., 2002), the most impressive being the Swedish conscript cohort study (Zammit and Lewis, 2004), which assessed admissions for schizophrenia in about 50,000 former military conscripts using data-linkage methods. They found a dose-response relationship between former cannabis use and later onset of schizophrenia. The odds ratios increased from 1.2 (ever used cannabis before conscription) to greater than 6 in persons with frequent cannabis use before conscription. In meta-analyses, the odds ratio for schizophrenia related outcome in cannabis users was shown to be slightly above 2 after adjustment for potential confounders (Arseneault et al., 2004; Henquet et al., 2005b).

Despite growing evidence for an association between cannabis use and the onset of schizophrenia, there is still some scepticism about the link between the two (Degenhardt et al., 2003; Hall et al., 2004). A major issue is whether cannabis use is a potential cause of psychotic disorders or rather triggers the onset in vulnerable persons (Caspi et al., 2005). The second source for scepticism has emerged from the fact that no upward trends in incidence rates of psychotic disorders have been shown in a population as a whole despite the increasing use of cannabis products (Arseneault et al., 2004; Macleod et al., 2006; Rey and Tennant, 2002). The Zurich figures appear to provide the missing link.

The evidence for an association between cannabis use, and the changing first admission trends in Zurich, includes the following:

- *the increasing first admission rates of patients with schizophrenia / psychotic disorders in the second half of the 1990's:* cannabis availability (hemp shops) and consumption distinctly increased in the 1990's; Swiss data from the Health Behaviour in School-Aged Children (HBSC) survey shows that lifetime prevalence of cannabis use in 15–16 year old teenagers rose from 15% (boys) / 5% (girls) in 1990 to 41% / 30% in 1998 and to 50% / 39% in 2002 (Delgrande Jordan et al., 2004; Kuntsche, 2004)
- *the increase tended to hit the youngest age groups:* epidemiological data on the use of illicit drugs have indicated that the popularity and frequency of cannabis use in the 1990's has changed most distinctly in adolescents and young adults (De Preux et al., 2004; Drewe et al., 2004);
- *the trend reversal started first in the teen years and, after some delay, in the twenties:* this is in line with the finding reported above that cannabis use precipitates the onset of schizophrenia and psychotic disorders
- *the trend reversal was stronger in men than in women:* while the lifetime prevalence rates of cannabis use in men and in women differ only slightly, men were shown to consume distinctly more frequently (see above: dose-response relationship); for example, in the 2002 SMASH survey 13% of 16–20 year old boys (4% of girls) indicated daily use of cannabis (De Preux et al., 2004; Narring et al., 2004)

The ecstasy hypothesis in psychosis research has yielded ambiguous evidence. Although there are case reports suggesting that persistent psychosis may occur after an intake of ecstasy (Van Kampen and Katz, 2001), the evidence from epidemiological studies is lacking. Psychopathological symptoms seem to be associated mainly with regular cannabis use in recreational ecstasy users (Daumann et al., 2004).

It seems possible that interactions between cannabis and other amphetaminic or hallucinogenic drugs increase the risk of psychotic disorders. A detailed assessment of substance use patterns might provide further information on this issue in future investigations.

To sum up, the change in incidence of psychotic disorders depends on environmental influences, which may exhibit systematic short-term fluctuations. Such changes were demonstrated in this analysis of the Zurich data, for the period 1977–2005, using two different statistical approaches. These changes affect mainly

young age groups, and men rather than women. They presumably mirror the changes in use of cannabis since the 1990's. In the 2000's the views on cannabis have begun to change. The availability of cannabis products has been reduced (for example, by the closing of hemp shops, and more rigorous controls by the police), and the legalization of the sale of cannabis products with high THC content has been disapproved by parliament.

Role of the funding source

None.

Contributors

All authors listed below have contributed to this work either in data preparation and analysis (I. Warnke, C. Lauber, V. Ajdacic-Gross), in writing (V. Ajdacic-Gross, C. Lauber, W. Rössler) and in discussion and reformulation of the paper (C. Lauber, H. Haker, R. Murray, W. Rössler). All authors have reviewed the manuscript and approved its contents.

Conflicts of interest

None.

Acknowledgements

We were thankful for the comments of Michael Schaub and Hans Wydler.

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Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 22, 2015 9:19 AM
To: Public Hearing
Subject: FW: Cost of Marijuana and Mental Illness

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Thursday, May 21, 2015 10:13 PM
To: Correspondence Group, City Clerk's Office
Cc: s.22(1) Personal and Confidential
Subject: Cost of Marijuana and Mental Illness

Any future increases in cannabis-associated new cases of schizophrenia would add to the current high rate in Canada and the USA. M.J. Dealberto at Queen's University in Ontario found that the rate of new cases of schizophrenia in Canada is about 26 per 100,000 per year, considerably higher than the countries outside Canada which average about 12 new cases per 100,000 per year. Quebec is even higher at 40). In addition, such an increase in new schizophrenia cases would need to be matched by significant increases in psychiatric hospital budgets and in community-based housing and welfare.

For example, Ontario's two major psychiatric centers (Ontario Shores Centre for Mental Health Sciences in Whitby, and The Centre for Addiction and Mental Health in Toronto) have a combined budget of about 400 million dollars, with approximately half assigned for schizophrenia. Across Canada, such budgets would need major increases. Considering that Ontario, for example, receives about 1,100 million dollars each year for tobacco taxes, a cannabis tax might cover the increased needs for psychiatric hospitals and the community housing.

Almost all aspects of cannabis use and the related laws are contentious. Whatever laws are adopted by government may have to be a compromise between medical need and a reduced burden to all citizens. Philip Seeman PhD. discovered the brain's dopamine receptor for psychosis and all antipsychotic drugs

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 22, 2015 9:19 AM
To: Public Hearing
Subject: FW: Jang on Prohibition

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Thursday, May 21, 2015 10:24 PM
To: Correspondence Group, City Clerk's Office
Subject: Jang on Prohibition

"Analogies with the Prohibition era, often drawn by those who would legalize drugs, are false and inexact: it is one thing to attempt to ban a substance that has been in customary use for centuries by at least nine-tenths of the adult population, and quite another to retain a ban on substances that are still not in customary use, in an attempt to ensure that they never do become customary. Theodore Dalrymple.
March 6th, 1996 Joseph A. Califana Jr. "... alcohol consumption dropped from 1.96 gallons per person in 1919 to .97 gallons per person in 1934, the first full year after Prohibition ended. Death rates from cirrhosis among men came down from 29.5 per 100,000 in 1911 to 10.7 per 100,000 in 1929. During Prohibition, admission to mental health institutions for alcohol psychosis dropped 60%; arrests for drunk and disorderly conduct went down by 50%; welfare agencies reported significant declines in cases due to alcohol-related family problems; and the death rate from impure alcohol did not rise. Nor did Prohibition generate a crime wave. Homicide increased at a higher rate between 1900 and 1910 than during Prohibition, and organized crime was well established in the cities before 1920.

Pamela McColl
Smart Approaches to Marijuana

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 22, 2015 9:20 AM
To: Public Hearing
Subject: FW: Stevenson's question and Violence Marijuana / far from mellowing out

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From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Thursday, May 21, 2015 10:38 PM
To: Correspondence Group, City Clerk's Office
Subject: Stevenson's question and Violence Marijuana / far from mellowing out

CBS may 18th. Dr. Chris Colwell, Chief of Emergency Medicine at the Denver Health Center:

Colwell *said several times each week people enter the Denver Health emergency department after ingesting marijuana and acting suicidal.*

"We'll see several of those every week … that we have to restrain to insure they aren't a danger to themselves or other people," Colwell said.

Where do the Colorado youth get marijuana? 38% reported they got from a friend who obtains it legally, 23% reported from their parents, 22% from the black market, 9% from medical marijuana dispensaries, 4% from medical marijuana cardholders, 3% from retail marijuana stores. Data Colorado 2015. A third of high school seniors got their marijuana supply from a third party's prescription

Pamela McColl

Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 22, 2015 9:21 AM
To: Public Hearing
Subject: FW: Marijuana - PTSD and Violence - Psychosis

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Friday, May 22, 2015 6:59 AM
To: Correspondence Group, City Clerk's Office
Cc: s.22(1) Personal and Confidential
Subject: Marijuana - PTSD and Violence - Psychosis

The research on marijuana's efficacy for PTSD and other mental illnesses show how marijuana has a negative impact on PTSD symptoms. We are citing new studies from 2014 and 2015. In fact, a large study in press presented at the American Academy of Addiction and Psychiatry found that initiating marijuana use after treatment was associated with worse PTSD symptoms, more **violent behavior** and alcohol use. Researchers concluded that "Marijuana may actually worsen PTSD symptoms or nullify the benefits of specialized, intensive treatment. Cessation or prevention of use may be an important goal of treatment." And a recent review conducted by the Vermont Department of Public Health found that "marijuana is not an evidence-based treatment for PTSD and in fact has been shown to interfere with otherwise effective, evidence-based cognitive behavioral therapy protocols."

Also below this is the position of the American Psychiatric Association, where they say: **"There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders."**

American Psychiatric Association
TITLE: Position Statement on Marijuana as Medicine
ISSUE:
The medical use of marijuana has received considerable attention as several states have voted to remove civil and criminal penalties for patients with qualifying conditions. Yet, on a national level, marijuana remains a schedule I substance under the Controlled Substances Act (CSA), the most restrictive schedule enforced by the Drug Enforcement Administration (DEA)1. The Food and Drug Administration (FDA), responsible for approving treatments after appropriate and rigorous study, additionally does not support the use of marijuana for medical purposes. This juxtaposition of practice and policy has prompted many professional medical organizations to issue official positions on the topic. This statement reflects the position of the American Psychiatric Association (APA) on the use of marijuana for psychiatric indications. It does not cover the use of synthetic cannabis-derived medications such as Dronabinol (Marinol), which has been studied and approved by the FDA for specific indications.
APA POSITION:
• There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurological development.
• Further research on the use of cannabis-derived substances as medicine should be encouraged and facilitated by the federal government. The adverse effects of marijuana, including, but not limited to, the likelihood of addiction, must be simultaneously studied.
• Policy and practice surrounding cannabis-derived substances should not be altered until sufficient clinical evidence supports such changes.

• If scientific evidence supports the use of cannabis-derived substances to treat specific conditions, the medication should be subject to the approval process of the FDA.
Regarding state initiatives to authorize the use of marijuana for medical purposes:
• Medical treatment should be evidence-based and determined by professional standards of care; it should not be authorized by ballot initiatives.
• No medication approved by the FDA is smoked. Marijuana that is dispensed under a state-authorized program is not a specific product with controlled dosages. The buyer has no way of knowing the strength or purity of the product, as cannabis lacks the quality control of FDA-approved medicines.
• Prescribers and patients should be aware that the dosage administered by smoking is related to the depth and duration of the inhalation, and therefore difficult to standardize. The content and potency of various cannabinoids contained in marijuana can also vary, making dose standardization a challenging task.
• Physicians who recommend use of smoked marijuana for "medical" purposes should be fully aware of the risks and liabilities inherent in doing so. Item 2013A2 4.B Assembly November 8-10, 2013 **Attachment #1**

AUTHORS: Tauheed Zaman, M.D.; Richard N. Rosenthal, M.D.; John A. Renner, Jr., M.D.; Herbert D. Kleber, M.D.; Robert Milin, M.D.
ADOPTION DATE: TBD
BACKGROUND INFORMATION:
Medical Indications for Marijuana as Medicine:
Much of the evidence supporting marijuana use for non-psychiatric medical diagnoses remains anecdotal. The indications with the most evidence include: severe nausea and vomiting associated with cancer chemotherapy2, cachexia associated with Acquired Immune Deficiency Syndrome (AIDS)3, spasticity secondary to neurological diseases such as muscular sclerosis4, management of neuropathic pain5, and rheumatoid arthritis6. Several medical organizations have issued statements regarding indications for marijuana as medicine based on scientific evidence.
Contribution of Marijuana to Psychiatric Illness:
There is currently no scientific evidence to support the use of marijuana as an effective treatment for any psychiatric illness. Several studies have shown that cannabis use may in fact exacerbate or hasten the onset of psychiatric illnesses, as evidenced by both international trials and meta-analyses7-9. This includes the contribution of marijuana to symptoms of mood disorders, anxiety and psychosis, particularly in young adulthood10, 11. Cannabis use is associated with the emergence of mood disorders, particularly symptoms of bipolar disorder, among those with a family history of mood disorder12. Among those with major depressive disorder, co-morbid cannabis use is associated with increased rates of both suicidal ideation and attempts, raising grave safety concerns13. Among those with a predisposition to psychotic disorders, cannabis may hasten the emergence of both positive and negative psychotic symptoms14. The use of higher potency cannabis, for longer periods of time and with more frequency, is also associated with increased risk of psychosis15.
Several studies have demonstrated the link between marijuana use and mood, anxiety and psychotic disorders among adolescents. Cannabis use is associated with increased depression, suicidal ideation, use of other substances and risky behavior among adolescents16. Regular adolescent cannabis use is also associated with increased incidence of anxiety disorders17. Cannabis use significantly increases the risk of psychotic disorders among young adults18. Additionally, younger age of cannabis use is associated with an earlier onset of psychosis among those at risk19. Adolescents with a history of cannabis use tend to have higher severity of illness, lower psychosocial functioning, less insight, and longer courses of untreated psychosis compared to those without a history of cannabis use20. These findings are of particular concern as symptoms often persist into adulthood, and therefore cannabis use may increase the risk of lifelong symptoms and disability due to mental illness.
Serious Adverse Effects of Marijuana Use:
Cognitive and functional: Item 2013A2 4.B Assembly November 8-10, 2013 **Attachment #1**

Marijuana use is associated with serious cognitive problems such as short-term memory deficits, poor concentration, attention, and information processing21. These impairments might be caused by neurotoxic effects of cannabis on the developing brain, the effects of which can lead to long-term cognitive problems well into adulthood22, 23. Adolescents with daily cannabis use show deficits in learning up to six weeks after stopping marijuana use24. This may contribute to significantly decreased academic achievement, including increased rates of school dropout, failure to enter higher education or attain higher degrees25. Among both adolescents and adults, cannabis significantly impairs driving, particularly as the drug affects automatic driving functions in a highly dose-dependent fashion 26. Cannabis use,

particularly in combination with alcohol, greatly increases the risk of motor vehicle crashes due to effects on cognition and coordination27.

Addiction and burden of psychiatric illness:

Cannabis use is associated with an increased risk of developing a cannabis use disorder. Studies indicate that 9% of users become dependent on cannabis, and this number increases to 25-50% among daily users and to 1 in 6 among adolescents28. Adolescents remain at particular risk for cannabis use disorder, and can experience significant withdrawal symptoms including appetite changes, restlessness, irritability, depression, twitches and shakes, perspiration, and thoughts/cravings of cannabis29. Marijuana use is also associated with poorer outcomes among those with mental illness. Among individuals with schizophrenia, cannabis use is associated with poorer long-term clinical outcomes30. Individuals with psychotic illness may be more sensitive to both the psychosis-inducing and mood-altering effects of cannabis31. This may explain why even among those taking medications for psychotic disorders, cannabis use is associated with an increased risk of relapse into psychotic symtoms32.

Legalization of medical marijuana may reduce the perceived risks of use, the perception of societal disapproval, or the barriers to access, and potentially increase the incidence of the adverse events noted above.

Summary:

Given the gravity of concerns regarding marijuana as medicine, professionals in both neurology and psychiatry have emphasized the importance of prospective studies to understand the mechanisms by which cannabis functions, and its impact on mental health and behavior before instituting changes in practice and policy33,34.

Recommendations:

Given the general lack of evidence-based information among the public and membership, it behooves the APA to actively disseminate this position paper and background information in whatever way it seems fit to the public, policy-making entities and medical organizations.

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 22, 2015 9:36 AM
To: Public Hearing
Subject: FW: letter re advertising

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Thursday, May 21, 2015 8:49 PM
To: s.22(1) Personal and Confidential s.22(1) Personal and Confidential
Cc: Correspondence Group, City Clerk's Office;
Subject: Re: letter re advertising

Dear Minister Lake:
Ministry of Health Province of British Columbia:

I have just re-watched the transcripts from the presentation at City Hall pertaining to the proposal to license marijuana for medical marijuana stores in Vancouver and I would like to call your attention to the fact that the Vancouver Coastal Health branch have been inspecting illegal marijuana stores in the City of Vancouver.

It is not within the mandate of Coastal Health to inspect illegal operations or to charge the expenses of such services through the
Ministry of Health. It is also not the mandate of the Ministry of Health in BC to regulate marijuana in a manner that conflicts with the Government of Canada.

The problem with Coast Health taking on a responsibility in this way is that the public are now under the false impression that the products for sale in these establishments are safe for human consumption and that packaging complies with consumer
protection laws of Canada - which they do not.

The City of Vancouver should not also be soliciting the assistance of the Province Ministry of Health agencies as this puts your Ministry in conflict with the Federal Ministry of Health or to promote businesses that are conducting false and misleading advertising of their products benefits that can not be substantiated by facts of science. Marijuana for medical purposes remains an experimental drug and is not an approved medicine by the Government of Canada.

The real problem with giving a reassurance of inspecting is that they as wholly incapable of taking on the inspection of the magnitude that will be required or to test for e-coli, salmonella, fungi, molds, pesticides and other contaminates.

The fact that the most vulnerable to serious illness and even death from these contaminants is the truly sick, people with HIV and immune suppression and these are some of the very individuals being sold unregulated and untested marijuana as our pregnant women - with the fetus being also very much at risk from the damage of pesticide exposure. The public is still very misinformed over precautions for use. Something the Health Canada licensee program addresses.

This past week the Denver Health Authorities seized hundreds of millions of dollars of marijuana that was contaminated with pesticides. It has pretty well shut down the pot industry CBS reports. I spoke with the State of Washington and they are following suit.

Is this the job that you see Coast Health taking on. Denver has hired 50 employees to oversea their legalization experiment and it is failing miserably. Now over 70% of town and cities in Colorado have banned the sale of marijuana in their jurisdictions. The same goes for California were over 80% of the towns and cities, including San Jose have banned the sale of marijuana for medical purposes after 20 years of experimentation. It has been a complete failure.
The Supreme Court of California has upheld their right to place such measures in place.

The abuse rate of marijuana for medical purposes is at 98%. 33% of kids in Denver treatment centers report they had used a third
persons prescription an average of 50 times. There is no legitimate reason to have marijuana stores open in the City of Vancouver and Coastal Health should not be willing to participate in what has been called the "hoax" of the 21st. century by Mayor Michael Bloomberg. These stores are a risk no municipality should be considering taking on at this time.

If individuals wish to obtain marijuana for medical purposes their is a program in place under the Federal Government. Health Canada is not only policing production but also advertising and manufacturing and has shown capable of issuing warnings
and imposing sanctions on licensees that do not comply. Coastal Health should not be taking on this role when there is an adequate program
already in place that best protects the welfare of Canadians.

Thank you for bringing this to the attention of Coastal Health.

Health Canada has confirmed they will not regulate these illegal operations and so in the end no one will be minding these stores
and their will be damages from use and it remains to be seen who will be held responsible.

Pamela McColl
Smart Approaches to Marijuana Canada
s.22(1) Personal and Confidential

Dear Minister Lake
Minister of Health BC Government:

It has come to our attention that a number of "the illegal" marijuana stores in Vancouver are advertising on the radio
and in the print media. We have been in contact with Health Canada and they have confirmed that these ads are in violation of the
Criminal Code of Canada. Health Canada is unable to pursue this matter as they do not have a mandate to police "illegal operations".

The Vancouver Police Department will not enforce the law due at this time - this has also been confirmed in writing.

I am writing to ask that you write a letter to the RCMP in British Columbia and express your support that such advertising
be challenged by law enforcement agencies out of interest for the safety and well being of the public.

The Georgia Strait, the Westender and Fox 99.3 along with CKNW are advertising marijuana products and making claims
about their medical benefits that can not be substantiated by science and therefore constitute false and misleading advertising.

We also are of the view that the 93 marijuana store's storefronts constitute advertising and should be challenged under the
Criminal Code.

We would be able to supply you with samples of the advertising or other materials that substantiate our claim that action should
be taken against note just the storefront and home delivery operations but against the companies who have agreed to air or
print the ads in return for money.

We have filed complaints with the CRTC and with the Competition Bureau, with four federal ministries who are responsible for
Public Safety, Health, Justice and Industry Standards.

Our polling shows the public support for the advertising of marijuana to be ZERO.

Pamela McColl
Smart Approaches to Marijuana Canada
s.22(1) Personal and Confidential

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 22, 2015 2:48 PM
To: Public Hearing
Subject: FW: HEALTH CANADA RECALLS MARIJUANA FROM "LICENSED PRODUCERS" OVER BACTERIA IN POT - VANCOUVER DISPENSARIES NOT INSPECTED AS THEY ARE ILLEGAL AND NO GOVERNMENT ORGANIZATION HAS THE MANDATE TO INSPECT ILLEGAL PRODUCTS.
Attachments: List of Laboratories - MMPR - 2015-01-30.docx

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Friday, May 22, 2015 1:10 PM
To: Correspondence Group, City Clerk's Office
Cc: s.22(1) Personal and Confidential
Subject: HEALTH CANADA RECALLS MARIJUANA FROM "LICENSED PRODUCERS" OVER BACTERIA IN POT - VANCOUVER DISPENSARIES NOT INSPECTED AS THEY ARE ILLEGAL AND NO GOVERNMENT ORGANIZATION HAS THE MANDATE TO INSPECT ILLEGAL PRODUCTS.

Dear Mayor and Council

Who is going to test for bacteria in the marijuana being sold out of the dispensaries.

Here is the recall list from Health Canada who are doing their job and the lack of testing of marijuana by the City of Vancouver or by Coastal Health leaves the consumer at risk. Health Canada has forced a recall of marijuana products from the "licensees". How do you plan to handle such threats to public safety ?

Who is going to pay for all this testing and who is paying the bill to Coastal Health for using their resources to do what they alluded to in the presentation at City Hall. When I called Coastal Health I was told they are not able to do testing as these operations are illegal. I am writing to request a clear picture of the exact inspections that have taken place by Coastal Health at your request.

In answering a question put forward by Coun. Carr about who was in fact testing, a Coastal Health employee made a remark that came to the rescue of Dr. Ballem who appeared stumped by the question but it needs to be substantiated and clarified and it needs to be made clear what the plan is going to be going forward.

Here is again what happened in Denver recently - HUNDREDS OF MILLIONS OF DOLLARS OF MARIJUANA SEIZED - OVER THE ISSUE OF PESTICIDES -

http://www.cbsnews.com/news/colorado-cracking-down-on-pot-pesticides/

Pamela McColl
Smart Approaches to Marijuana Canada

From: "MMPR-RMFM" < s.22(1) Personal and Confidential
To: "PAMELA MCCOLL" s.22(1) Personal and Confidential
Sent: Friday, May 22, 2015 7:52:44 AM
Subject: Re: request for information.

Hello,

Thank you for your interest in the *Marihuana for Medical Purposes Regulations* (MMPR).

In response to your queries, Health Canada is providing you useful links and information below.

Pesticides
All queries pertaining to pesticides should be referred to the Health Canada Pest Management Regulatory Agency (PMRA). The contact information for PMRA have been provided in this email:

E-mail: pmra.infoserv@hc-sc.gc.ca
Telephone: 613-736-3799
Toll-free: 1-800-267-6315
Facsimile: 613-736-3798
Teletypewriter: 1-800-267-1245 (Health Canada)
or http://www.hc-sc.gc.ca/contact/cps-spc/pmra-arla/infoserv-eng.php

Testing
Please find attached below a list of laboratories that have demonstrated compliance and have a valid Controlled Substance Licence, under the *Narcotic Control Regulations,* allowing the possession of cannabis (marijuana) for analytical testing.:

(See attached file: List of Laboratories - MMPR - 2015-01-30.docx)

For more information on testing requirements under the MMPR, please refer to Division 4 Good Production Practices: http://www.laws-lois.justice.gc.ca/eng/regulations/SOR-2013-119/ .

Recalls
Information on recalls can be found at: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/search-recherche/result-resultat?search_text_1=marijuana

General Info on Licensed Producers under the MMPR
To obtain a producer's licence from Health Canada, interested individuals or corporations must demonstrate compliance with the requirements outlined in the MMPR.
For more information on licensed producers under the MMPR, please visit http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/index-eng.php.
Additional information such as guidance documents on product quality and security requirements are also posted at the above link to help Licensed Producers comply with the MMPR.

Compliance and Enforcement
As a regulated party, licensed producers are subject to compliance inspections conducted by Health Canada to verify that licensed producers continue to meet the requirements of the MMPR, the *Controlled Drugs and Substances Act* (CDSA) and its regulations. Inspections can happen at any reasonable time. Information on Compliance and Enforcement can be found at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/compliance-conformite/index-eng.php

Information on Advertising and compliance can be found at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/bulletin-eng.php

Dispensaries
Health Canada does not license organizations such as compassion clubs or dispensaries to possess, produce, or distribute marijuana for medical purposes. The production, sale and distribution of marijuana outside of the terms of the MMPR are illegal. Further, under the MMPR licensed producers may not operate a storefront or dispensary.

List of Laboratories in possession of a valid Controlled Substance Licence allowing the possession of cannabis (marihuana) for analytical testing

Name of Lab	Address	Name of Contact	Phone Number	Email Address
CMH Biotechnologies Inc.	9B PTH 52 West Steinbach, MB R5G 1X6	Mr. Leonard Sarna	204-371-0100	len@cmhbiotech.com
Dalton Chemical Laboratories	349 Wildcat Road Toronto, ON M3J 2S3	Mr. Ronald Angus	416-661-2102 ext: 222	rangus@dalton.com
New Brunswick Research and Productivity Council (RPC)	921 College Hill Road Fredericton, NB E3B 6Z9	Mr. Troy Smith	506-452-1270	troy.smith@rpc.ca
The Vimy Ridge Group Ltd.	16-2000 Ellesmere Road Scarborough, ON M1H 2W4	Mr. John Fanaras	416-438-6727	fanaras@nucro-technics.com
Experchem Laboratories Inc.	1111 Flint Road North York, ON M3J 3C7	Mr. Mana Sohil	416-665-2134 ext: 298 or 1-800-610-5576	sohilmana@experchemlab.com
Neopharm Labs Inc.	865 boulevard Michèle-Bohec Blainville, QC J7C 5J6	M. Michel Saulnier	450-435-8864	info@neopharm.ca
QCL Quality Compliance Laboratories Inc.	145 Konrad Crescent Markham, ON L3R 9T9	Mr. Ronald Turton	905-305-0998 ext: 202	qcl@qctest.com
MB Laboratories Inc.	2062 W. Henry Avenue, Units 4 & 5 Sidney, BC V8L 5Y1	Ms. Wendy Riggs	250-656-1334	mblabs@pacificcoast.net
Ccrest Laboratories (A Division of Europharm International Canada Inc.)	9390 boulevard Langelier Montreal, QC H1P 3H8	Dr. Ali Khamessan	514-324-1073 ext: 7227	ali.khamessan@ccrestlab.com
Laboratoire Phytochemia Inc.	555 boulevard de l'Université Chicoutimi, QC G7H 2B1	Mr. Hubert Marceau	581-306-1230	h.marceau@phytochemia.com

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Monday, May 25, 2015 9:55 AM
To: Public Hearing
Subject: FW: WORKSHOPS ON HOW TO OPEN A DISPENSARY IS THE PROBLEM NOT THE FEDERAL GOVERNMENT

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Saturday, May 23, 2015 11:01 AM
To: Correspondence Group, City Clerk's Office
Cc: s.22(1) Personal and Confidential
s.22(1) Personal and Confidential
Subject: WORKSHOPS ON HOW TO OPEN A DISPENSARY IS THE PROBLEM NOT THE FEDERAL GOVERNMENT

Dear Dr.Ballem

The reason Vancouver now has 93 pot shops open for business - pot is being promoted in this city with Sensible BC running workshops on how to open pot stores. The pot lobby are targeting the riding of Vancouver Granville in the coming election and all eyes should be on the International Pot Lobby to see who shows up and supports the candidates. All eyes ! (Globe and Mail reporting the Vancouver Granville Riding a target).

Taken off the Sensible BC Facebook Page - and link below outlines the problem.

Sensible BC
11 September 2014 ·

Speakers include Mason Tvert, who led the legalization effort in Colorado; Tonia Winchester, Outreach Director for the successful legalization campaign in Washington; and Marc Emery, Canada's 'Prince of Pot' who recently completed a five-year prison sentence in the US.

We've got political training sessions led by people including Brian Rice, former President of the Liberal Party of Canada in BC; and Andrew Radzik, former Director of Organizing for Vision Vancouver. We're even running a class on how to open a cannabis dispensary, led by Dori Dempster of the Vancouver Dispensary Society.

Get your ticket now: http://sensiblebc.ca/conference

Like · Comment · Share

http://cannabisdigest.ca/youre-invited-sensible-bc-conference/

Pamela McColl
Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Monday, May 25, 2015 9:58 AM
To: Public Hearing
Subject: FW: $500.00 per day dispensaries should be paying as stated in the by-laws of Vancouver

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From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Saturday, May 23, 2015 12:08 PM
To: Correspondence Group, City Clerk's Office
Subject: $500.00 per day dispensaries should be paying as stated in the by-laws of Vancouver

Dear Mayor of Vancouver

It is possible to charge the illegal dispensaries - all 93 of them a $500.00 per day fine for operating without a business license. That some of these stores have been allowed to stay open for years upon years is a violation by the City of the enforcement of by-laws that already exist.

The municipality of Parksville was able to close a dispensary and issue a warning to the landlord that should they rerent to an illegal operation they could be charged for receiving "Proceeds of a Crime" - and they created a new by-law to further protect their town from the unregulated and illegal selling of marijuana to the public.

You have the means to effectively close these operations without the use of the Vancouver Police Department and you should enforce the fine immediately.

A Vancouver doctor was recently offered $2,000 dollars a day to work at one of the dispensaries so they have the money to pay and they are racking in more than the entire legal marijuana for medical purposes industry under the Canada Health program.

Pamela McColl
Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Monday, May 25, 2015 10:06 AM
To: Public Hearing
Subject: FW: GROUP CALLS FOR RESIGNATION OF DR.PENNY BALLEM
Attachments: Alameda DA letter to Oakland.pdf; California crackdown by all four U.S. Attorneys.pdf; LauraDuffyDelMarLetter to City of Del mar.pdf

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From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Monday, May 25, 2015 8:07 AM
To: s.22(1) Personal and Confidential
Cc: Correspondence Group, City Clerk's Office
Subject: GROUP CALLS FOR RESIGNATION OF DR.PENNY BALLEM

Dear Mayor and Council

In the State of California over 83% of the marijuana dispensaries for marijuana for medical purposes have now been banned. Towns and cities, such
as San Jose, have placed ordinances in place to prohibit these operations after 20 years of experiencing the abuse, deceitful advertising and harm
to their cities, and citizens. California legalized medical marijuana in 1996 and it has proved to be a disaster but they are fighting back and they are winning.
23 towns were saved from going down this dangerous path as the result of letters such as the ones attached that went out reminding elected officials that they could stand criminal charges if they proceeded to break federal law by aiding and abetting criminal behavior.

From Alameda DA letter to Oakland: Excerpt: "One important caveat is that not withstanding the language of Section 5.81.100, it remains an "OPEN" question whether public officers or public employees who aid and abet or conspire to violate state or federal laws in furtherance of a city ordinance, are exempt from "criminal" liability.

In Colorado over 70% of the towns have banned marijuana dispensaries and this past month $110 million dollars of marijuana was seized by Denver
Health Authorities for pesticide contamination. The pot industry is in big trouble in Colorado.

The Governor and the Attorney General both have said repeatedly - it was all a mistake and not worth the risk. They are being sued by two
neighboring states, by sheriffs who have been put in a position of conflict of interest, and they are being sued by citizens and corporations.

The city of Parksville BC shut down a dispensary, with the help of the RCMP, and they issued warning letters to Landlords that if they resigned
leases for such operations they could themselves be charged under the Profiting from Crime act within the Criminal Code. No dispensaries have

reopened. The landlords in Vancouver could face a similar situation if a Federal Prosecutor idecides to act on this at any time.

Our organization has filed a complaint with the Federal Government over the false advertising and advertising of narcotics on store windows and on
the radio and in the print media. Ourcomplaint has been issued a file number against the dispensaries involved and four media outlets.
The investigation is now underway. The proposal to regulate the current dispensaries has a provision that calls for the banning of advertising aimed at
minors - kids walk down streets and are exposed to signage and therefore all store fronts should be banned and the proposal rejected.

We will be opposing your proposal to "license" the 93 dispensaries and we will be focusing on the rationale for this proposal as outlined in the
presentation on Aoril 28th. 2015 by Dr. Ballem to Mayor and Council. During the presentation Dr. Ballem presented information on the
benefits of marijuana use that we will be challenging with the help of scientists who are trained in the area of addiction
medicine and marijuana impact on the human body and brain. It is only as a result of the information that Dr. Ballem provided to a public
audience that we feel compelled to reply and offer a rebuttal to best inform the public of the well documented risks of harm associated with
the use of marijuana.

It is our opinion that Dr. Ballem, as the City Manager, has overstepped her jurisdiction by discussion the merits of marijuana use and also
in her elaboration on the price and access of this drug in respect to the Federal Government's licensee program.
She states that it is not the jurisdiction of the City to administer drug policy. However she goes on to say In her statement of April 28th that
they have found a window of opportunity in which the city can move forward to "license" but she adds to this a very troubling remark:

" to protect access to people who need this for their well being."

It is not the City Manager's place to advocate for patients, or to comment on the price or availability of controlled substances or to
criticize the Federal Government's Drug Policies in her official capacity or to use those opinions in an effort to influence the direction
of Mayor and Council's decision over the llicensing of dispensaries.

The City Manager, Mayor and Council should be advocating for the general public and the taxpayers of Vancouver at large
and protecting from the dangers inherent in a permissive drug culture, through law enforcement and by respecting the laws of this country.
She should not be advocating for marijuana dispensaries and "to be fair to this sector" which she did when questioned on why proximity

to daycares had not been included in the proposal. 98% of people who are accessing marijuana through marijuana dispensaries have no medical need
and this abuse is not served by treating the illegal operations "fairly". These are operations that are illegal and there is no confusion on that matter nor
is the City without methods and means of recourse.

CBC reported 40% of the current dispensary locations do not meet the proposals criteria and will have to be closed - one of the key issues is
the proximity to schools.
Dr. Ballem has known about the proximity of the illegal dispensaries to schools and yet she has allowed them to stay open for
business for an extended period of time by not calling for law enforcement. She has also known that the products sold in these
stores are not inspected for salmonella, e-coli, molds, fungi, butane residues or other contaminants and pesticides. She also
is aware of youth entering these premises and being hospitalized. She is aware of the claims being made of the benefits of
marijuana that can not be substantiated by science and she must also be aware of the high level of THC pot that is being sold
and that poses a very real risk to the development of mental illnesses and psychotic breaks for some users.

The City Manager should be asked to resign effective immediately.

Pamela McColl
Smart Approaches to Marijuana Canada

NANCY E. O'MALLEY

1225 FALLON ST., ROOM 900, OAKLAND, CA 94612
SPECIAL TEAMS TEL: 510-272-6261 FAX: 510-208-4965

FACSIMILE TRANSMITTAL SHEET

TO: Jean Elle
FROM: Teresa Deuel
COMPANY:
DATE:
FAX NUMBER:
TOTAL NO. OF PAGES INCLUDING COVER:
PHONE NUMBER:
RE:

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

***** PLEASE DELIVER AS SOON AS POSSIBLE *****

NOTES/COMMENTS:

per your request -

THIS FAX WAS SENT BY THE SPECIAL TEAMS OF THE ALAMEDA COUNTY DISTRICT ATTORNEY'S OFFICE. ANY PROBLEMS SHOULD BE REPORTED TO OUR TEAM SECRETARY LIZ CAZESSUS AT 510-272-6261.

December 8, 2010

Mayor-Elect Jean Quan
Oakland City Hall
Frank Ogawa Plaza
Oakland, CA 94607

Dear Mayor-Elect Quan:

Congratulations on your election. I hope this letter finds you well. I look forward to joining together in our work towards a safe, healthy and thriving Oakland in the New Year.

I am writing to you regarding Oakland's Ordinance amending Title 5 of the Oakland Municipal Code, Entitled Business Licenses And Regulations, to add Chapter 5.81, pertaining to Medical Cannabis Cultivation Facility Permitting and amending the master fee schedule (Ordinance No. 9336, as Amended) to establish regulatory fees regarding this activity. The Alameda County District Attorney's Office has a long-standing policy of declining to issue advisory opinions as to the legality of any particular conduct. To that end, this letter is not, nor should it be interpreted, as an advisory opinion on the legality of the Ordinance, or any part contained therein.

I make the point that this Office has always taken a very reasonable approach to enforcement of the marijuana laws in light of the Compassionate Use Act and the Medical Marijuana Program. As a cancer survivor myself, I certainly understand the benefits for those in need of the medicinal use of marijuana in various forms. This reasonable policy and approach should not be taken as an endorsement of the Ordinance, or as a declaration that those engaging in conduct outside the parameters of the law as it pertains to marijuana, will be ignored.

Earlier this year, my Staff was in discussion with Council staff regarding legal concerns the DA's Office had with the Ordinance, if it passed. At that time, we were told that with respect to the Ordinance, Council would wait until the outcome of Proposition 19. Obviously, Prop 19 failed to pass. It is my understanding that Council is now moving forward with your Ordinance. This letter is being written to alert you to legal concerns still held by the Alameda County District Attorney's Office regarding the Ordinance, particularly in light of recent case law opinions regarding the Compassionate Use Act (CUA) and the Medical Marijuana Program Act (MMP).

The CUA and MMP define "primary caregiver" as the individual designated by the person exempted under this section who has *consistently assumed responsibility for the housing, health, or safety of that person* (emphasis is mine). The definition becomes

very significant in terms of who is allowed by California law to cultivate and provide marijuana to others. I would point out that most recently, the California Court of Appeals, in ***People* v. *Hochanadel*** (2010) 176 Cal.App.4th 997, relying on the California Supreme Court case of ***People v. Mentch*** (2008) 45 Cal.4th 274, found that operators of storefront medical marijuana dispensary were not "primary caregivers" exempted from liability for certain narcotics offenses under Compassionate Use Act and Medical Marijuana Program Act, despite them being designated as such by medical marijuana patients who purchased medical marijuana from them. The Court found that where there was no evidence of an existing, established relationship providing for housing, health or safety independent of the administration of medical marijuana, the dispensary operators did not qualify as "caregivers" under the legal definition set forth in the law. The MMP set limits on the number of plants that could be possessed or cultivated. The same section of the code, but a different subsection, authorizes possession and/or cultivation in amounts for reasonable use for the patient. In striking down the "limits" language as it pertains to medicinal use or cultivation for medicinal use, the Supreme Court did not extend its ruling to H&S Sections 11359 and 11360 (possession for sale and sale of marijuana) outside the CUA and MMP. See ***People v. Kelly,*** (2010) 24 Cal.4th 1008.

The Alameda County District Attorney's office makes the point that enactment of this Ordinance does **not** provide a defense over and above the defense provided by the Compassionate Use Act (Health and Safety Code section 11362.5 aka Prop 215) or the Medical Marijuana Program (Health and Safety Code sections 11362.7 et seq.) to any criminal charge. In other words, *notwithstanding* pronouncements by city officials or the enactment of the Ordinance, the prosecuting agency in Alameda County is not providing any assurances that activities authorized by the Ordinance, but not authorized under state law or federal law, are permissible. Persons should **not** rely solely upon pronouncements by city officials or enactment of the Ordinance as providing any legal or equitable defense to a criminal prosecution. Nor should persons rely on pronouncements of city officials or the Ordinance as an accurate ***interpretation*** of the state laws regarding marijuana cultivation, possession, sale, etc., and/or the defenses available to those charges.

In California, as you know, cultivation of marijuana for medicinal or compassionate use must be 'not-for-profit'. The law is quite specific in what can and cannot be the basis of exchange of money from the primary caregiver and the patient as it pertains to marijuana. Potential difficulties might arise in assessing the appropriate amount of taxes that can be imposed on transactions undertaken by these large-scale marijuana growing operations. This concern is not only with potential difficulties in cases of tax evasion, but also persons relying on the Ordinance may be placed at risk of prosecution for tax evasion due to the lack of clear guidelines in assessing when and how much tax need be paid.

One important caveat is that notwithstanding the language of Section 5.81.100, it remains an **open** question whether public officers or public employees who aid and abet or conspire to violate state or federal laws in furtherance of a city ordinance, are

exempt from criminal liability.

The District Attorney's Office will uphold and enforce the laws of this State. As is the policy in this Office, alleged violations of the law will be reviewed on a case-by-case basis.

Thank you for your attention to these issues. I am not providing to you an advisory opinion on the legality of your Ordinance, that is the purview of your City Attorney. However, if you would like to discuss this further, please don't hesitate to contact me.

Sincerely yours,

Nancy E. O'Malley
District Attorney

Cc: City Attorney John Russo

Department of Justice

United States Attorney Benjamin B. Wagner
United States Attorney André Birotte Jr.
United States Attorney Laura E. Duffy
United States Attorney Melinda Haag

FOR IMMEDIATE RELEASE
October 7, 2011

California's Top Federal Law Enforcement Officials Announce Enforcement Actions Against State's Widespread and Illegal Marijuana Industry

SACRAMENTO, Calif. – The four California-based United States Attorneys today announced coordinated enforcement actions targeting the illegal operations of the commercial marijuana industry in California.

The statewide enforcement effort is aimed at curtailing the large, for-profit marijuana industry that has developed since the passage of California's Proposition 215 in 1996. That industry has swelled to include numerous drug-trafficking enterprises that operate commercial grow operations, intricate distribution systems and hundreds of marijuana stores across the state — even though the federal Controlled Substances Act makes illegal the sale and distribution of marijuana.

While the four United States Attorneys have tailored enforcement actions to the specific problems in their own districts, the statewide enforcement efforts fall into three main categories:

- Civil forfeiture lawsuits against properties involved in drug trafficking activity, which includes, in some cases, marijuana sales in violation of local ordinances;
- Letters of warning to the owners and lienholders of properties where illegal marijuana sales are taking place; and
- Criminal cases targeting commercial marijuana activities, including arrests over the past two weeks in cases filed in federal courts in Los Angeles, San Diego, Sacramento and Fresno.

The enforcement actions being announced today are the result of the four United States Attorneys working with federal law enforcement partners and local officials across California to combat commercial marijuana activities that are having the most significant impacts in communities.

"The actions taken today in California by our U.S. Attorneys and their law enforcement partners are consistent with the Department's commitment to enforcing existing federal laws, including the Controlled Substances Act (CSA), in all states," said Deputy Attorney General James Cole. "The department has maintained that we will not focus our investigative and prosecutorial resources on individual patients with serious illnesses like cancer or their immediate caregivers. However, U.S. Attorneys continue to have the authority to prosecute significant violations of the CSA, and related federal laws."

Benjamin B. Wagner, the United States Attorney for the Eastern District of California stated: "Large commercial operations cloak their moneymaking activities in the guise of helping sick people when in fact they are helping themselves. Our interest is in enforcing federal criminal

law, not prosecuting seriously sick people and those who are caring for them. We are making these announcements together today so that the message is absolutely clear that commercial marijuana operations are illegal under federal law, and that we will enforce federal law."

André Birotte Jr., the United States Attorney for the Central District of California, stated: "The federal enforcement actions are aimed at commercial marijuana operations, including marijuana grows, marijuana stores and mobile delivery services - all illegal activities that generate huge profits. The marijuana industry is controlled by profiteers who distribute marijuana to generate massive and illegal profits."

Laura E. Duffy, the United States Attorney for the Southern District of California, commented: "The California marijuana industry is not about providing medicine to the sick. It's a pervasive for-profit industry that violates federal law. In addition to damaging our environment, this industry is creating significant negative consequences, in California and throughout the nation. As the number one marijuana producing state in the country, California is exporting not just marijuana but all the serious repercussions that come with it, including significant public safety issues and perhaps irreparable harm to our youth."

Melinda Haag, the United States Attorney for the Northern District of California, said: "Marijuana stores operating in proximity to schools, parks, and other areas where children are present send the wrong message to those in our society who are the most impressionable. In addition, the huge profits generated by these stores, and the value of their inventory, present a danger that the stores will become a magnet for crime, which jeopardizes the safety of nearby children. Although our initial efforts in the Northern District focus on only certain marijuana stores, we will almost certainly be taking action against others. None are immune from action by the federal government."

Dozens of letters have been sent over the past few days to the owners and lienholders of properties where commercial marijuana stores and grows are located. In the Southern and Eastern Districts, the owners of buildings where marijuana stores operate have received letters warning that they risk losing their property and money derived from renting the space used for marijuana sales. In the Central District, where more than 1,000 stores are currently operating, prosecutors have sent letters to property owners in selected cities where officials have requested federal assistance, and they plan to continue their enforcement actions in other cities as well. In the Northern District, owners and lienholders of marijuana stores operating near schools and other locations where children congregate have been warned that their operations are subject to enhanced penalties and that real property involved in the operations is subject to seizure and forfeiture to the United States.

In the Central District and Eastern District, prosecutors this week filed a total of seven civil forfeiture complaints against properties where landlords are knowingly allowing marijuana stores to operate. One complaint filed against a south Orange County strip mall, for example, alleges that eight of the 11 second-floor suites in the buildings are occupied by marijuana stores and that one small city has spent nearly $600,000 in legal fees in its attempt to eradicate the illegal operations.

Criminal cases recently unsealed across the state reveal marijuana operations that produce huge profits, send their money and illegal narcotics to other states, and market products to young people. In a case involving a now-closed marijuana store in the San Fernando Valley, two conspirators allegedly used encrypted smartphones to coordinate marijuana sales to places as far away as New York and estimated that they would each receive $194,000 in profits per month. In

a San Diego dispensary case unsealed last week, six defendants were charged in a 77-count indictment that alleges a wide-ranging conspiracy that included numerous marijuana sales to under-aged persons.

"The DEA and our partners are committed to attacking large-scale drug trafficking organizations, including those that attempt to use state or local law to shield their illicit activities from federal law enforcement and prosecution," said DEA Administrator Michele M. Leonhart. "Congress has determined that marijuana is a dangerous drug and that its distribution and sale is a serious crime. It also provides a significant source of revenue for violent gangs and drug organizations. The DEA will not look the other way while these criminal organizations conduct their illicit schemes under the false pretense of legitimate business."

Victor S.O. Song, Chief, IRS Criminal Investigation, stated: "IRS Criminal Investigation is proud to work with our law enforcement partners and lend its financial expertise to this effort. We will continue to use the federal asset forfeiture laws to take the profits from criminal enterprises."

Across California, the federal government will continue to investigate and prosecute those whose actions not only violate federal laws, but also the state laws regarding the use of marijuana. The problems associated with the marijuana business have dramatically increased over the past two years, even in areas where local governments and citizens actively oppose these businesses.

The statewide coordinated enforcement actions were announced this morning at a press conference in Sacramento.

CONTACTS:

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Thom Mrozek – thom.mrozek@usdoj.gov
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Northern District of California (San Francisco)
Jack Gillund - Jack.Gillund@usdoj.gov
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U.S. Department of Justice

LAURA E. DUFFY
United States Attorney
Southern District of California

(619) 557-5690
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880 Front Street, Room 6293
San Diego, California 92101-8893

Imperial County Office
516 Industry Way, Suite C
Imperial, California 92251-7501

July 17, 2012

Ms. Leslie Devaney
City Attorney
City of Del Mar
STUTZ ARTIANO SHINOFF & HOLTZ, APC
2488 Historic Decatur Road, Suite 200
San Diego, CA 92106

Re: **The City of Del Mar Medical Marijuana Ballot Initiative**

Dear Ms. Devaney,

This letter acknowledges receipt of your office's request dated June 26, 2012, concerning the Department of Justice's guidance on investigations and prosecutions in states and cities that authorize the medical use of marijuana. This letter is written to clarify the U.S. Department of Justice's guidance on this issue.

The United States Congress has determined that marijuana is a controlled substance, and it has placed marijuana on Schedule I of the Controlled Substances Act, 21 U.S.C. § 801, *et. seq.* (the "CSA"). As such, growing, distributing, and possessing marijuana, in any capacity, other than as part of a federally authorized research program, is a violation of federal law regardless of state laws permitting such activities. Moreover, those who engage in financial transactions involving the proceeds of such activities may also be in violation of federal money laundering statutes and other federal financial laws.

As stated in the October 2009 Ogden Memorandum, "the prosecution of significant traffickers of illegal drugs, including marijuana, and the disruption of illegal drug manufacturing and trafficking networks continues to be a core priority" of the Department. This Department's commitment to the enforcement of the CSA was reiterated in the June 2011 Cole Memorandum which advised that the prosecution of business enterprises that unlawfully cultivate, distribute, or sell marijuana remains a core priority, regardless of state law. The Cole Memorandum is consistent with, and a further explanation of, the Ogden memorandum.

Both the Ogden and Cole Memoranda state that the Department of Justice will likely not focus its limited resources on the prosecution of seriously ill individuals who use marijuana as part of a medically recommended treatment regimen consistent with state laws, or on their individual caregivers. The Cole Memorandum further clarifies that the "term 'caregiver'...means just that: *individuals* providing care to individuals with cancer or other serious illnesses." (Emphasis added).

You raised concerns with respect to the citizen-drafted City of Del Mar Compassionate Use Dispensary Regulation and Taxation Ordinance ("Ordinance") which has qualified with sufficient signatures to be placed on the November 2012 ballot in the City of Del Mar, California. Although the Department does not offer advisory opinions, as indicated above, enterprises engaged in the cultivation, manufacture, and sale of marijuana directly violate federal law. Accordingly, individuals and organizations that participate in the unlawful cultivation and distribution of marijuana could be subject to civil and criminal remedies. State and City employees who conduct activities mandated by the Ordinance are not immune from liability under the CSA. The United States Attorney's Office (USAO) will evaluate all potential civil and criminal enforcement actions on a case-by-case basis in light of the priorities of the Department of Justice and the USAO's available resources.

I hope that this letter assists the City of Del Mar in making informed decisions about the cultivation, manufacture, and distribution of marijuana.

Very truly yours,

LAURA E. DUFFY
United States Attorney

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Tuesday, May 26, 2015 11:13 AM
To: Public Hearing
Subject: FW: San Jose medical marijuana crackdown begins after council vote on regulations

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Tuesday, May 26, 2015 8:03 AM
To: Correspondence Group, City Clerk's Office
Subject: Fwd: San Jose medical marijuana crackdown begins after council vote on regulations

Dear Mayor of Vancouver,

Here is "best practices" in action. California has had marijuana dispensaries and they have shut down 83% of them.
Here is the first of a series of emails I will send to you regarding San Jose and what they eventually had to do to get the
dispensaries under control. The complaints came from businesses and citizens over damage to their property and businesses.
I will also be sending you the court cases under way in Colorado that claim loss of property value and of again business loss
as a result of marijuana dispensaries.

Where is the economical impact study for your proposal regulatory model that does not provide for a cap on the number of
dispensaries ?

Why are daycares and "sensitive" housing and vulnerable neighborhoods not dealt included in the proposal - and only
schools ?

San Jose medical marijuana crackdown begins after council vote on regulations

http://www.mercurynews.com/crime-courts/ci_24703545/san-jose-medical-marijuana-crackdown-begins-after-council?source=pkg

By Mike Rosenberg
mrosenberg@mercurynews.com

POSTED: 12/11/2013 01:04:58 PM PST130 COMMENTS | UPDATED: ABOUT A YEAR AGO

RELATED STORIES

- Dec 10:

- Legal pot supported by California majority for first time, Field Poll shows
- Dec 7:
- San Jose to take new shot at limiting medical marijuana shops

SAN JOSE -- City officials on Wednesday began the process of shutting down medical marijuana shops next to homes as part of strict new regulations to be rolled out next year.

A minute before midnight, the San Jose City Council late Tuesday ended an hours-long discussion and voted 8-3 to support a package of pot shop laws that they expect to take a final vote on in March.
The regulations would limit the city's 82 medical marijuana dispensaries to operate in less than 1 percent of the city -- mostly in the industrial northern tip of San Jose, away from homes, schools and drug rehab centers. Those new rules could take effect next spring or summer.
In the meantime, the council told city code officials to begin sending letters to pot shops situated next to homes, telling them that they are illegal and need to shut down, and expect all of those dispensaries to be closed within a month or two. Even though San Jose has no laws expressly banning pot shops, it has no laws allowing them, either -- meaning city officials have the authority to shut them down. While the city has gone after clubs that drew complaints, it is now broadening enforcement.
The council's decision comes after complaints from youth groups, neighborhood leaders, schools and local government agencies who said kids are getting their weed from the pot shops.

The Santa Clara County Public Defender's Office said drug-related suspensions were up 243 percent at east San Jose schools since the pot shops began multiplying a few years ago.
Councilwoman Rose Herrera led the charge at the meeting to ban the pot shops altogether, but that effort failed by a 7-4 vote, with only Councilmen Xavier Campos, Kansen Chu and Pete Constant joining Herrera.
On the other end were pot shop owners who have promised to once again gather signatures to put strict regulations on the ballot, as they did when council members tried passing new rules in 2011. They said the dispensaries create jobs, produce more than $5 million annually in tax revenue for the city and try to work with neighborhoods, and that it was wrong to blame the shop owners.
"What happened to parents taking responsibilities for their children and their children's actions?" Doug Chloupek, co-founder of the MedMar Healing Center pot shop in downtown San Jose.

Submitted by Pamela McColl
Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Tuesday, May 26, 2015 4:28 PM
To: Public Hearing
Subject: FW: Inspection of retail operations.

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Tuesday, May 26, 2015 2:50 PM
To: Correspondence Group, City Clerk's Office
Subject: Fwd: Inspection of retail operations.

From: "Feedback [VC]" s.22(1) Personal and Confidential
To: "PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Tuesday, May 26, 2015 2:31:24 PM
Subject: FW: Inspection of retail operations.

Dear Pamela,

Further to your response below, Feedback has received the following from Dr. Daly's office that:

"My instructions to staff to undertake inspections was in reference to complaints only, not routine inspections. I apologize if this was not clear.

At the time of my statements, I thought my staff may have inspected one or two of these facilities in response to complaints. I have since confirmed with my staff that that is not the case, and no such inspections have occurred.

The information in my letter is accurate. I hope this clarifies my responses to your questions."

Best regards, VCH Feedback on behalf of Dr. Patricia Daly

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Monday, May 25, 2015 7:10 PM
To: Feedback [VC]
Cc: VCH Board Chair
Subject: Re: Inspection of retail operations.

Dear Dr. Daly

I thank you for your response and I also revisited the transcript and this is what you said on April 28th. 2015 at 1 hour and nineteen minutes into the presentation:

" I have instructed my staff to inspect those facilities right now because regardless whether they are legal or illegal we would expect them to follow these standards."

Prior to this statement you made a remark about responding to a complaint regarding labeling and you discussed the

need to protect the public from nut allergies.

I do not see in your letter a reference to the inspection for mislabeling. I would ask that you review your full statement and confirm that Vancouver Coastal Health has not inspected these facilities but has only ever responded to the health issues you have cited in your letter to me.

Given that Health Canada, and by your letter Vancouver Coastal Health will not be inspecting these illegal operations for contaminates and pesticides is it your position that the very serious risks of harm associated with contaminates and pesticides, possible to the most vulnerable users of medical marijuana - those who suffer from immune suppression are to be well served by allowing these facilities to continue on under a licensing schematic without anyone testing for the THC levels and the other aspects of product safety and drug testing safety that the consumer has come to expect ?

Thank you Pamela McColl

From: "Feedback [VC]" s.22(1) Personal and Confidential
To: "PAMELA MCCOLL
Sent: Monday, May 25, 2015 1:43:21 PM
Subject: FW: Inspection of retail operations.

Dear Pamela,

Further to your email below, please see the attached response from Dr. Patricia Daly our Chief Medical Health Officer.

Best regards, VCH Feedback

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Saturday, May 23, 2015 11:52 PM
To: VCH Board Chair
Subject: Inspection of retail operations.

Dear Board of Directors of Vancouver Coastal Health.

I am writing on behalf of a national organization Sam Canada - Smart Approaches to Marijuana Canada. We are a group of concerned citizens from the medical, legal, judicial and academic community.

The purpose of this letter is to bring to your attention our concern over the recent proposal for the City of Vancouver to entertain a licensing of illegal marijuana businesses and to involve Vancouver Coastal Health in the inspecting of these illegal businesses, and therefore place the responsibility of protecting the health and well being of the public with a Provincial Government agency.

Vancouver currently has in excess of ninety-three illegal marijuana stores retailing marijuana for medical purposes to the public. Many of the outfits are also advertising and making unsubstantiated claims about the health or medicinal benefits of their products. They are being supplied product by illegal dealers. They have not displayed a willingness to recognize and acknowledge reputable science and the mountain of evidence that now exists that marijuana is not safe for human consumption.

Licensing would create the situation of "in the back door illegally and out the front door with an air of legitimacy" but still illegal.

Licensing might temporarily reduce the total number of stores but it is likely the number of stores will grow back to close to what we are experiencing now or possible exceed the current total. There has also been a rise in "home delivery" services from these outfits and as with the experience in Colorado and Washington it has aided the black markets ability to mesh with the crowd. This poses a very real risk to the safety of the public. By controlling the delivery of marijuana for medical purposes through the mail service, as is the case with the program for delivery run by Health Canada, this risk has been mitigated. One only has to learn of incidents like the 16 year old girl and her dog who were shot after meeting up with a "home delivery" to understand the depth of consideration that must go into any move to "retail" marijuana for any purpose.

Any marijuana products sold through storefronts must be tested for contamination and for pesticides, for bacteria, for fungi, molds, salmonella and e-coli as they should be held to standards of packaging, labeling and child-proof closures that all narcotic drug products are held to in Canada. There should also be marketing on these products that they are all GMO products.

THC levels must also be monitored and products tested as reports now show that 50% of the marijuana sold in North America exceeds 15% THC. In Holland any product over 15% remains an illegal substance.

Un-monitored THC levels in marijuana retailed through storefronts is unacceptable.

We are writing to also firmly object to inspectors within the Environment Division of Vancouver Coastal Health going into these establishments and being involved in any inspections that would offer legitimacy to these operations. Such involvement unless it was complete and thorough would further expose the public to harm by creating a false sense of security and protection. The public is already very confused over the legality of these operations, as they are over the usefulness of marijuana as a medicine. They do not need to think they are being protected by the services of Vancouver Coastal Health when in all probability they will not be at the level other consumer products are held to.

Minister Ambrose and other elected federal officials and Health Canada have made it clear that there is no dispute over the illegal status of the retail "dispensary" stores and it is our organization's position that no BC government agency or agency funded by BC taxpayers should not be endorsing or involved in these illegal operations in any way. They should be shut down and law enforced as has been the case in other British Columbia jurisdictions.

Dr. Patricia Daly, involved in a public presentation to the Mayor and Council of Vancouver, answered a question posed by Councillor A. Carr, regarding who was going to inspect the dispensaries. Dr. Daly reported that she had already instructed Coastal Health staff to inspect . The level of inspection was not provided in detail but it has been requested by our organization in a letter this past week.

In Colorado in recent weeks hundreds of millions of dollars of marijuana that was discovered to be contaminated with pesticides was seized out of concern for the public's safety by the Denver Health Authorities. This recent development has very serious consequences for the marijuana industry there. We spoke with Washington State this week and they will be following on the same course of action.

Since the legalization of marijuana in Colorado an elaborate testing program has been set up and 50 employees have been hired. Vancouver Coastal Health it is suggested will not have such a ready manpower to oversea the supply of marijuana that is likely to result from the stores that will obtain a Vancouver license. Colorado also has a very elaborate system of tracking all marijuana sold and collecting other data on the industry.

Overall the experience of Colorado has been a problematic. So problematic that both the Governor and the Attorney General of the State have said it was reckless to move to legalization and not worth it. Colorado is currently being sued by both Oklahoma and Nebraska, by the Sheriffs Association, by citizens and by corporations for damages. Over 70% of towns and cities have now banned the sale of marijuana for any purpose in their jurisdictions.

The current stores in Vancouver, according to a Georgia Strait investigation, are moving more marijuana than all the legal licensees that have been granted permission through the 2014 Federal Government Program run through Health Canada.

In the past six months Health Canada has instructed several of the legal licensees to issue recalls of their marijuana products as a result of bacteria being discovered after routine testing.

Health Canada should be the only agency that is responsible for the testing of marijuana for medical purposes as they should be responsible for a control of advertising and other aspects of marijuana selling and marketing and promotion. This is not something that any city should take on as a trial as the infrastructure required would prohibit such an "experiment".

In reviewing the business license requirements that are required currently for applicants wishing to sell food in the City of Vancouver the bylaw specifies that the establishments must be inspected by Vancouver Coastal Health.The products being sold by the marijuana for medical purposes are not food products but are sold as medical products and are illicit drugs. No new bylaw should be allowed to be written that would extend the provision to include illicit drug products that solicit the resources of Vancouver Coastal Health.

The City Bylaw requirements also state that incorporated companies must have registration papers from the BC Government to be able to qualify for a business license. These businesses can not be granted Provincial Incorporation documents and they should therefore not be inspected by any other agency of the same level of government that denied their
right to exist as corporate entities.

We object to the use of Provincial tax payer funds to finance inspections conducted of illegal businesses under the laws of Canada.

We object to the City of Vancouver issuing business licenses to company's that can not be inspected by Health Canada because of their illegal status and we do not believe there is another agency equipped in this country to take on this responsibility.

We are asking for a letter stating the Board of Directors position on this matter and we would ask for a commitment that Vancouver Coastal Health will make it explicitly known that they will not be testing the products, tracking the supply and source of products, regulating packaging, labeling, and all the other aspects of inspections in regards to these illegal operations.

In closing our organization does not support the promotion of narcotic drugs for recreational purposes, or the commercialization
of marijuana. We welcome discussions of legal review and we support public education on the adverse impact of using drugs at any age. The abuse rate for medical marijuana has been established to be 98% with only 2% obtaining marijuana for a medical complaint or ailment.

The City of Vancouver will be hearing from the public on this issue on June 10th. and we do hope you will be able to relay your position on this matter
prior to that date.

Respectfully
Thank you,

Pamela McColl
Smart Approaches to Marijuana Canada.

Nancy Morrison, Lawyer - retired Judge
Dr. Harold Kalant - Toronto
Dr. Andra Smith Ottawa
Dr. Meldon Kahan Toronto
Dr. Philip Seeman Toronto
Chuck Doucette - Vancouver
Dr. Wayne Jeffrey Vancouver
David Berner - Vancouver
Dr. Charles Ratzlaff Vancouver
Jim Stimson Delta

Dr. Elizabeth Osuch Toronto
Connor Fesenmaier Surrey
Duncan Fesenmaier Surrey

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 29, 2015 2:32 PM
To: Public Hearing
Subject: FW: California bans dispensaries in excess of 86% of cities THEY TRIED IT AND THEN SAID NO MORE - BEST PRACTICE - SAY NO.

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Friday, May 29, 2015 8:55 AM
To: Correspondence Group, City Clerk's Office
s.22(1) Personal and Confidential

Subject: California bans dispensaries in excess of 86% of cities THEY TRIED IT AND THEN SAID NO MORE - BEST PRACTICE - SAY NO.

Dear Mayor and Council

In studying best practices of American examples the best state would be California as they were the first state to legalize marijuana for medical purposes which they did in 1996. They rejected recreational marijuana in 2010.

With close to twenty years of direct experience in best practice it is questioned why they were not used to the preparation of the Vancouver proposal.

In San Jose, the 11th. largest city in America and the third largest in California, the experiment has not gone well and after great trials and efforts the City Council now have adopted an ordinance that limits marijuana dispensaries to industrial locations after the negative impact on commercial areas was identified.

Here is a transcript from the City of San Jose, in which citizens and business owners, bring their very real concerns to the City Management. Here you will hear impact statements from dentists, doctors, and other professional who have seen their businesses suffer as as result of parents not wanting to expose their children the close proximity of these offices to marijuana dispensaries. There are also cases of businesses who were forced to move, including a dance studio frequently visited by children who that found the proximity to a dispensary not in the interests of these youngsters and in turn bad for their businesses.

http://sanjose.granicus.com/DocumentViewer.php?file=sanjose_44a0bd3bd438a66b94b371228a35d690.pdf&view=1

I spoke to a senior analyst with the City of San Jose - s.22(1) Personal and Confidential and she was very knowledgeable about the problems associated with the medical marijuana dispensary location issues. Her number in California is s.22(1) Personal and Confidential

In the State of California by 2012 the majority of towns and cities had placed bans on the operation of marijuana for medical purposes dispensaries.

As of August 2012 there were bans against marijuana dispensaries in 26 counties and 247 cities in the state of California. With moratoriums on dispensaries in place in 9 counties and 80 additional cities. Only 8 counties and 53 cities allow for dispensaries. Percentage ban or moratoriums 79.1% counties 86.1% of cities.

California has not legalized recreational marijuana and they would have been the best place to find best practices and research this proposal - not Colorado or Washington that are dealing with very different

scenario - as they are dealing with both legalized pot for both medical and recreational purposes.

Who ever did the research looked in the wrong place.

Pamela McColl
Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 29, 2015 2:31 PM
To: Public Hearing
Subject: FW: MAJORITY OF TOWNS AND CITIES IN COLORADO HAVE REJECTED MEDICAL MARIJUANA DISPENSARIES

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Friday, May 29, 2015 7:53 AM
To: Correspondence Group, City Clerk's Office
Subject: MAJORITY OF TOWNS AND CITIES IN COLORADO HAVE REJECTED MEDICAL MARIJUANA DISPENSARIES

Dear Mayor and Council

In reviewing the proposal before you in regards to licensing the marijuana dispensaries you may wish to review the use of Colorado as a best practice model.

Colorado is being sued by two neighboring states, by a individual law enforcement officers who have been put in a conflict of interest with their responsibility to uphold federal law.

The State is being sued by individual citizens for damage to property value and by corporations, including the Holiday Inn who are claiming damages to revenue and costs for having in increase security.

Suppliers are being sued for aiding and abetting, including construction workers who worked in any lease hold improvements, telephone providers and anyone else who contributed to the operation of these illegal enterprises. Most relevant is the claims for damages being made by business owners and individuals who have suffered losses due to the proximity of a medical marijuana dispensary.

The Governor of Colorado and the Attorney General have repeatedly made public statements criticizing the sale legalization of medical and recreational marijuana in their state and they have repeated advised other jurisdictions not to precede down this path.

The true state of affairs in current day Colorado:

In the State of Colorado as of 2015 of the 321 total local jurisdictions 228 now prohibit any medical or recreational marijuana business - 67 allow medical and recreational and 26 allow either medical or recreational marijuana, not both.

The best practice in Colorado is to ban medical marijuana and protect the citizens, corporations and youth from the risk associated with the use of marijuana.

http://m.dailytelegraph.com.au/news/world/colorado-is-facing-a-barrage-of-lawsuits-over-its-legalisation-of-marijuana/story-fni0xs63-1227260897065

https://www.scribd.com/doc/256277197/Colorado-marijuana-legalization-lawsuit-Civil-Action-No-15-349-Safe-Streets-Alliance-lawsuit-1

Plaintiffs the Safe Streets Alliance ("Safe Streets"), Phillis Windy Hope Reilly, and Michael P. Reilly file this suit to vindicate the federal laws prohibiting the cultivation and sale of recreational marijuana and their rights under the Racketeer Influenced and Corrupt OrganizationsAct ("RICO"). The Reillys are Colorado property owners who have been injured by a conspiracy to cultivate recreational marijuana near their land, and they are members of SafeStreets. Plaintiffs seek redress under RICO, which requires those who engage in racketeering activity—including the commercial production of marijuana—to pay those they injure treble damages, costs, and attorneys' fees. Plaintiffs also seek an injunction under RICO directing the marijuana operations affecting their land to stop violating the federal drug laws. In addition to their RICO claims, **Plaintiffs are also suing the state and local officials who are facilitating and encouraging Colorado's recreational marijuana trade, including the racketeering activity that is injuring their property,** through a licensing regime that purports to authorize federal drug crimes. Because state and local government actions that promote the marijuana industry directly conflict with the federal Controlled Substances Act ("CSA"), those actions are preempted under the Supremacy Clause of the United States Constitution and must be set aside

https://www.scribd.com/doc/256279229/Colorado-marijuana-legalization-lawsuit-Civil-Action-No-15-350-Safe-Streets-Alliance-lawsuit-2

Olson's racketeering activities (medical marijuana store) directly and proximately injured New Vision's business and property. Those activities have discouraged prospective guests from booking stays at New Vision's hotel and forced New Vision to incur additional expense in attempting to mitigate the resulting decline in revenue. Furthermore, the prospect of lost revenue and increased security costs in the future has reduced the market value of New Vision's business and property,

Pamela McColl

Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 29, 2015 2:38 PM
To: Public Hearing
Subject: FW: Police challenged by lack of ability to enforce the law over dispensaries.

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Friday, May 29, 2015 9:50 AM
To: Correspondence Group, City Clerk's Office
Subject: Police challenged by lack of ability to enforce the law over dispensaries.

http://www.usatoday.com/story/news/2015/03/05/sheriffs-from-three-states-sue-colorado-over-marijuana/24385401/

DENVER — Sheriffs from Colorado and neighboring states Kansas and Nebraska say in a lawsuit to be filed Thursday that Colorado's marijuana law creates a "crisis of conscience" by pitting the state law against the Constitution and puts an economic burden on other states.

The lawsuit asks a federal court in Denver to strike down Colorado's Amendment 64 that legalized the sale of recreational marijuana and to close the state's more than 330 licensed marijuana stores.

Lead plaintiff, Larimer County, Colo., Sheriff Justin Smith, calls the case a "constitutional showdown." Each day, he says, he must decide whether to violate the Colorado Constitution or the U.S. Constitution. Colorado legalized recreational marijuana sales Jan. 1, 2014, but marijuana remains illegal at the federal level.

Colorado is "asking every peace officer to violate their oath," Smith said. "What we're being forced to do ... makes me ineligible for office. Which constitution are we supposed to uphold?"

Pamela McColl

Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, May 29, 2015 2:39 PM
To: Public Hearing
Subject: FW: Denver - impact studies needed.

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s.22(1) Personal and Confidential

From: PAMELA MCCOLL
Sent: Friday, May 29, 2015 12:49 PM
To: Correspondence Group, City Clerk's Office
Subject: Denver - impact studies needed.

Colorado - presented as Best Practice Example - What is missing is the impact studies and the results of both the legalization of
marijuana for medical purposes and recreational purposes. Here are some of the more interesting and telling statistics coming out
of Colorado.

20% of grade eight students in Denver Colorado report being regular users of marijuana.

Data Crime All Reported Crime in Denver 2012 43,867 reported crimes 2013 48,147 reported crimes 2014 49,258 reported crimes 5,391 reported crimes increase from 2012 through 2014 (+12.3
percent) SOURCE: http://www.rmhidta.org/

Colorado Public Radio December 15th. 2014 - Arrests for pot-related incidents spiked nearly 40% at Denver Public Schools following the opening of recreational marijuana
stores in January.

The best quantifiable evidence the state has yet to indicate that marijuana is a significantly growing problem from the 2012-2013 report that shows why 720 students
were expelled from public schools across Colorado. For the first time, marijuana was separated from other drugs when school officials were asked to identify students
expulsions. Marijuana came in first. It was listed as the reason for 32 percent of expulsions. Denver Post reporting.

It is not worth it - said Colorado Attorney General Cyntha Coffman.

In just one year when Colorado legalized marijuana (2013), past month marijuana use among college age 18+ to 25 years use increasd by 8.4%

In just one year when Colorado legalized marijuana (2013) past month marijuana use among those ages 12-17 increased by 6.6%

In Colorado 40% of purchases are being made from out of state visitors to Colorado and 40% of all purchases of marijuana continue to go through illegal
channels. With an increased market - more crime not less, more illegal selling not less.

In Colorado, Legalization has done nothing more than enhance the opportunity for the black market, said Lt. Mark Conte of the Colorado Springs Police Vice and
Narcotics Units - Associated Press

(Colorado Springs has now banned marijuana sales in their jursidiction)

Pamela McColl

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Monday, June 01, 2015 2:16 PM
To: Public Hearing
Subject: FW: If we can raise $4000 before June 10th we'll be able to make sure that medicinal cannabis patients get their voices heard.

s.22(1) Personal and Confidential

From: PAMELA MCCOLL
Sent: Saturday, May 30, 2015 6:48 AM
To: Correspondence Group, City Clerk's Office
Subject: If we can raise $4000 before June 10th we'll be able to make sure that medicinal cannabis patients get their voices heard.

Dear Mayor and Council

Please see email below - here are some direct quotes that should be of concern to you:

If we can raise $4000 before June 10th we'll be able to make sure that medicinal cannabis patients get their voices heard.
We need to raise $4000 before June 10th to help coordinate our efforts before the hearings begin. Click here to make donation of $25 and help us plan and coordinate better.
Dana Larsen - Sensible BC

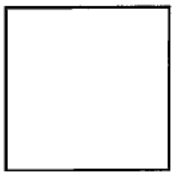
These new city laws will have a profound effect on the future shape of medical access and eventual legalization across Canada.
Dana Larsen.

Our response:

The pot lobby understands the significance of what this proposal would do. The City of Vancouver does not have the jurisdiction to deal with drug access in this country. As Minister Ambrose advised - DO NOT DO THIS. Legalization of marijuana should be a national conversation and decision
and given that only 31% of Canadian women and 40% of Canadian men support legalization it will be fought ever step of the way by organizations
such as our who come at this from a public health perspective and want to reduce the use of drugs in our society not increase use - and we are
will get there.

"Pamela McColl
Smart Approaches to Marijuana Canada

Date: Sat, 30 May 2015 01:15:35 +0000
From: s.22(1) Personal and Confidential
Subject: We're still fighting hard



People can now register to speak at the Vancouver public hearings on medical cannabis dispensaries. To have an impact, we need many voices to be heard! At Sensible BC, we're working to make that happen.

These new city laws will have a profound effect on the future shape of medical access and eventual legalization across Canada.

We've been coordinating with patients and groups across the city and around the province, to make sure that the City of Vancouver understands the impact these regulations will have across the lower mainland.

We're working right now to identify speakers, run training sessions, and make sure that patients make it out to the public hearings in record numbers. We need your help to make that happen!

We need to raise $4000 before June 10th to help coordinate our efforts before the hearings begin. Click here to make donation of $25 and help us plan and coordinate better.

This is an important issue for everybody.

Don't get us wrong, **we are also still working to get British Columbians out to vote for candidates who support marijuana reform in the upcoming federal election.** But these new regulations are going to set the precedent for what a legal framework will look like at the local level, and we need to be part of that conversation.

The City of Vancouver needs to see a solid showing from the medicinal cannabis community.

If we can raise $4000 before June 10th we'll be able to make sure that medicinal cannabis patients get their voices heard.

With a $25 donation, you can help make that happen.

Dana Larsen

Dana Larsen, Sensible BC
s.22(1) Personal and Confidential

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Monday, June 01, 2015 9:40 AM
To: Public Hearing
Subject: FW: Dr. Ballem - not a single bit of medical evidence that cannabis is a treatment for substance use disorder as stated in presentation.
Attachments: MJ as RX review.pdf

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Sunday, May 31, 2015 7:39 AM
To: Correspondence Group, City Clerk's Office
s.22(1) Personal and Confidential

Subject: Dr. Ballem - not a single bit of medical evidence that cannabis is a treatment for substance use disorder as stated in presentation.

Please see the attachment which is an excellent review of the medical evidence or lack thereof of the various uses of marijuana for a list of conditions - please note insufficient evidence in every single case.

NO COUNTRY IN THE WORLD HAS LEGALIZED MARIJUANA -
WE ARE THE ONLY COUNTRY WERE THE COURT HAS ORDERED ACCESS TO MARIJUANA UNDER CONTROLLED CONDITIONS.
THIS IS NOT A DECISION THAT HAS SUPPORT IN THE MEDICAL ESTABLISHMENT OR THE REST OF THE WORLD.

I received this information and this comment which you will find of interest.

This is a fairly good current review as cannabis as medical treatment option for the commonest conditions it is being used.
The City Manager implied in her talk there was experimental evidence that to the best of my knowledge does not exist.
With respect to her claim that cannabis is a treatment for substance use disorders,
I am aware of not a single bit of medical evidence to this effect and that is my specialty.

Pamela McColl
Smart Approaches to Marijuana Canada

Addiction Science & Clinical Practice

BioMed Central
The Open Access Publisher

Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders

Addiction Science & Clinical Practice (2015) 10:10

doi:10.1186/s13722-015-0032-7

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Published online: 21 April 2015

ISSN 1940-0640

Article type Review

Submission date 29 August 2014

Acceptance date 15 April 2015

Article URL http://dx.doi.org/10.1186/s13722-015-0032-7

Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders

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[4] Center for Innovation to Implementation and National Center for PTSD, VA Palo Alto Health Care System, 795 Willow Road (152-MPD), Menlo Park, CA 94025, USA

[5] Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, 3440 Market Street, Philadelphia, PA 19104, USA

[*] Corresponding author. Center for Innovation to Implementation and National Center for PTSD, VA Palo Alto Health Care System, 795 Willow Road (152-MPD), Menlo Park, CA 94025, USA

Abstract

The present investigation aimed to provide an objective narrative review of the existing literature pertaining to the benefits and harms of marijuana use for the treatment of the most common medical and psychological conditions for which it has been allowed at the state level. Common medical conditions for which marijuana is allowed (i.e., those conditions shared by at least 80 percent of medical marijuana states) were identified as: Alzheimer's disease, amyotrophic lateral sclerosis, cachexia/wasting syndrome, cancer, Crohn's disease, epilepsy and seizures, glaucoma, hepatitis C virus, human immunodeficiency virus/acquired immunodeficiency syndrome, multiple sclerosis and muscle spasticity, severe and chronic pain, and severe nausea. Post-traumatic stress disorder was also included in the review, as it is the sole psychological disorder for which medical marijuana has been allowed. Studies for this narrative review were included based on a literature search in PsycINFO, MEDLINE, and Google Scholar. Findings indicate that, for the majority of these conditions, there is

insufficient evidence to support the recommendation of medical marijuana at this time. A significant amount of rigorous research is needed to definitively ascertain the potential implications of marijuana for these conditions. It is important for such work to not only examine the effects of smoked marijuana preparations, but also to compare its safety, tolerability, and efficacy in relation to existing pharmacological treatments.

Keywords

Cannabis, Medical marijuana, Marijuana, Medicine, Treatment, Alzheimer's disease, ALS, Cachexia, Cancer, Crohn's disease, Epilepsy, Seizures, Glaucoma, Hepatitis C virus, HCV, HIV, AIDS, Multiple sclerosis, MS, Pain, Nausea, Vomiting, Post-traumatic stress disorder, PTSD

Introduction

National estimates suggest that 5.4 million people in the United States above the age of 12 have used marijuana daily or regularly within the past year [1]. This represents an increase of approximately 74.2 percent since 2006 [1]. Similar increases have also been noted among vulnerable populations in the U.S. (e.g., veterans and adolescents) [2,3].

Marijuana is currently illegal in every country in the world. In 2012, Uruguay voted to legalize state-controlled marijuana sales but implementation of the law has been postponed until 2015. The policy in the Netherlands is mixed, with permissible retail sale of marijuana at coffee shops, but restrictions on production and possession. Notably, as the concentration of THC in marijuana has increased, Dutch coffee shops have begun to close, as perception of marijuana as a "soft" drug transitions to perceptions of marijuana as a "hard" drug.

Like the Netherlands, the United States currently has a mixed drug policy; marijuana is an *illegal* Schedule I drug under U.S. Federal law. However, marijuana policies vary by state, with some states (e.g., Colorado and Washington) *legalizing* the use of recreational marijuana (i.e., allowing the legal possession and use of marijuana under state law), and other states *decriminalizing* marijuana (i.e., reducing the penalties for possession and/or use of small amounts of marijuana to fines or civil penalties). Furthermore, as of this review, 23 states and the District of Columbia have passed legislation allowing medical marijuana (i.e., individuals can defend themselves against criminal charges related to marijuana possession if a medical need is documented) for the treatment of a variety of medical and psychological conditions. Though the list of conditions for which medical marijuana has been allowed varies at the state level, the majority of states agree on its use for Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), cachexia/wasting syndrome, cancer, Crohn's disease (CD), epilepsy and seizures, glaucoma, hepatitis C virus (HCV), human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), multiple sclerosis (MS) and muscle spasticity, severe and chronic pain, severe nausea, and post-traumatic stress disorder (PTSD).

The aim of the present review is to provide a summary of the existing empirical literature regarding the effects of marijuana/cannabinoids on each of the above-noted conditions. Though some recent work has reviewed the adverse effects of marijuana [4] or the efficacy of marijuana for certain conditions (e.g., neurologic) [5], there has yet to be a comprehensive review of the effects of marijuana for each of the medical and psychiatric conditions for which it is currently used.

Methods

The list of all conditions for which medical marijuana is allowed, according to the legislation of each U.S. state for which medical marijuana has been approved, was obtained and examined [6]. From this list, common conditions for which medical marijuana is allowed (i.e., those conditions shared by at least 80 percent of medical marijuana states) were identified as: AD, ALS, cachexia/wasting syndrome, cancer, CD, epilepsy and seizures, glaucoma, HCV, HIV/AIDS, MS and muscle spasticity, severe and chronic pain, and severe nausea. Though not presently a qualifying condition in at least 80 percent of states with medical marijuana laws, PTSD was also included in the review, as it is rapidly gaining attention and recognition as the sole psychological disorder for which medical marijuana is allowed.

Studies for this narrative review were included based on a literature search in the following databases: PsycINFO, MEDLINE, and Google Scholar. Within each database, each combination of the following key marijuana terms and the above-listed conditions were used to conduct a search: cannabis, marijuana, marihuana, cannabinoid, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, cannabinol, cannabigerol, Marinol, dronabinol, Sativex, Nabilone, and Nabiximols. References within each obtained article were also examined to assure that no studies were overlooked. Only published, English-language studies were included in this review.

Though the primary focus of this review is on studies of marijuana plant effects, as these are most relevant to recent medical marijuana legislation, synthetic or plant-derived cannabinoids (e.g., dronabinol, Nabilone) were also included due to the general dearth of marijuana plant studies for a number of conditions. Indeed, for purposes of the review, references to oral administrations of marijuana constitute a pharmaceutical grade extraction administered in tablet or liquid form (e.g., dronabinol, Nabilone, nabiximols), while references to smoked administration of marijuana constitute the inhalation of smoke from burned marijuana leaves and flowers. Finally, the present review is organized alphabetically by condition for which marijuana is allowed, rather than in order of disorder for which it is most to least commonly recommended, or strength of the evidence. We chose this approach as there is currently only state-level data [7-9], rather than national, representative data on the primary conditions for which medical marijuana is used or recommended, and the existing literature and state of the evidence for many conditions remains relatively poor.

Results

Alzheimer's disease

AD, the leading form of dementia in the elderly, is a progressive, age-related disorder characterized by cognitive and memory deterioration [10]. AD has several neuropathological markers, including neuritic plaques and neurofibrillary tangles [11]. Although several researchers have suggested dronabinol and Nabilone may act on these mechanisms to confer therapeutic effects for patients with AD [12,13], a recent Cochrane systematic review found no evidence that dronabinol was effective in reducing symptoms of dementia [14]. The authors of a placebo-controlled crossover study of 15 patients with AD who were refusing to eat suggest that dronabinol increases weight gain and decreases disturbed behavior [15], but there is insufficient quantitative data to support this conclusion [14], and one study

participant had a grand mal seizure following dronabinol administration [15]. Another pilot study of two patients with dementia found that dronabinol reduced nocturnal motor activity [16]. No studies have examined the effects of smoked marijuana in patients with AD. In sum, there is insufficient evidence to recommend marijuana for the treatment of AD. Future directions should include conducting randomized controlled trials (RCTs) comparing both smoked and oral marijuana to placebo and existing treatments, with sample sizes large enough to detect treatment effects and the safety and tolerability of marijuana.

Amyotrophic lateral sclerosis

ALS is a fatal neurological disease with symptoms that include weakness, spasticity, and respiratory difficulties. Cannabinoids are hypothesized to act in the regions of established pathophysiology for ALS [17] and could be used for symptom management (e.g., pain, spasticity, wasting, respiratory failure, dysphagia, negative mood, and dysautonomia) [18]. Although there is limited evidence from a survey of patients with ALS that marijuana consumed in a variety of forms (i.e., oral, smoked, vaporized, and eaten) improves speech and swallowing [19], the anti-salivatory components of marijuana may reduce the risk of aspiration pneumonia, while also increasing patient comfort [18,19]. These survey findings indicate that up to 10 percent of patients use marijuana for symptom management, and these self-reports suggest efficacy in increasing appetite and mood and decreasing pain, spasticity, and drooling. However, as is consistent with the half-life of smoked marijuana, the beneficial effects of marijuana on symptoms of ALS were fewer than 3 hours in duration [19]. The only randomized, double-blind, placebo-controlled crossover trial of marijuana in patients with ALS has a small sample size (N = 27) and indicates that while 5 mg of dronabinol is well-tolerated, there was no effect on number or intensity of cramps, quality of life, appetite, sleep, or mood [20]. There is currently insufficient clinical evidence in humans with ALS to recommend cannabinoids as primary or adjunctive therapy.

Cachexia/wasting syndrome

Cachexia is the general wasting and malnutrition that occurs in the context of chronic diseases such as HIV/AIDS and cancer. In patients with HIV or cancer, smoked marijuana and dronabinol have been shown to increase weight gain [21,22] and food intake [22,23] compared to placebo. In a within-subject, double-blind, staggered, double-dummy study of nine individuals with muscle mass loss, dronabinol resulted in significantly greater calorie consumption than smoked marijuana [24]. A within-subject, double-blind, placebo-controlled trial with seven HIV-positive marijuana smokers taking antiretroviral medications found that compared to placebo, dronabinol increased caloric intake [25]. Additional studies indicate that dronabinol administration increases appetite, decreases nausea, and protects against weight loss [26], with effects on appetite and weight stability enduring in long-term follow-up [27].

Both dronabinol and smoked marijuana increase the number of eating occasions [22,25], and smoked marijuana may also affect weight gain and calorie intake by modulating appetite hormones [28]. Importantly, weight gain in one study was greater than would have been expected based on increased calorie consumption alone [23], which may be particularly relevant for those who have impaired food intake and/or nausea. These studies demonstrated that marijuana has positive effects on cachexia resulting from a medical condition, but are largely limited by small sample sizes. Additionally, studies comparing THC to FDA-approved medication (i.e., megestrol) indicate that THC is less effective in promoting

appetite and weight gain [29]. In sum, there is moderate support for the use of cannabinoids for cachexia/wasting, and dronabinol has been FDA-approved for anorexia associated with weight loss in individuals with AIDS. Additional studies with larger sample sizes that examine the efficacy of marijuana compared to nutritional support/calorie augmentation in the treatment of cachexia are indicated.

Cancer

Cancer is a qualifying medical condition in every state that has approved marijuana for medical use [30]. The majority of clinical research examining the relation between THC and cancer has evaluated the effect of smoked THC on the risk for cancer, or the palliative effects of THC on chemotherapy-related nausea and emesis, chronic pain, and wasting (reviewed in respective sections); few studies have studied the effect of marijuana in any form on the treatment of primary cancer pathology. *In vitro* and *in vivo* research suggests that cannabinoids inhibit tumor growth [30] via several proposed mechanisms (e.g., suppression of cell proliferation, reduced cell migration, increased apoptosis) [31]; however, *in vitro* and *in vivo* studies also have shown that THC increases tumor growth due to reduced immune response to cancer [32]. The only clinical trial of THC on cancer examined intracranial administration of THC to nine patients with recurrent glioblastoma multiforme who had failed surgical- and radiotherapy, and results indicated that THC decreased tumor growth, while being well-tolerated with few psychotropic effects [33]. This study is limited by lack of generalizability, and clinical trials with larger representative samples that examine oral or smoked administration of THC are essential to elucidate the effects on cancer pathology. There is currently insufficient evidence to recommend marijuana for the treatment of cancer, but there may be secondary treatment effects on appetite and pain.

Crohn's disease

CD is an inflammatory bowel disease (IBD) that has no cure; treatment targets include reducing inflammation and secondary symptoms. Between 16 percent and 50 percent of patients use marijuana to relieve symptoms of IBD [34-36], and patients using marijuana for 6 months or longer are five times more likely to have had surgery for their IBD [34]; whether marijuana exacerbates disease progression or more severe disease results in self-medication is unclear. Only one placebo-controlled study of the effects of marijuana in patients with CD has been conducted [37]. This study found that there was no difference between placebo and smoked marijuana on CD remission (defined as a CD Activity Index (CDAI) of less than 100), and that marijuana was superior to placebo in promoting clinical response (a decrease in CDAI score greater than 100), reducing steroid use, and improving sleep and appetite [37]. Importantly, this study did not include objective measurement of inflammatory activity, and there was no significant difference in placebo and treatment groups 2 weeks after treatment cessation [37]. Until clinical trials with objective measurement of treatment effects over an extended period of time have been completed to examine the safety and efficacy of marijuana for the treatment of IBD have been conducted, there is insufficient evidence for the use of marijuana for the treatment of IBD.

Epilepsy and seizures

The known effects of cannabinoids on epilepsy and seizures are largely from animal studies, surveys, and case studies. Several animal studies indicate that marijuana and its constituents exhibit anticonvulsant effects [38-41] and reduce seizure-related mortality [39], but there is

also evidence that cannabinoids can lower the threshold for seizures [42], and THC withdrawal increases susceptibility for convulsions [42]. Cross-sectional surveys indicate that 16–21 percent of patients with epilepsy smoke marijuana [43,44], with some reporting positive effects (e.g., spasm reduction) and a belief that marijuana is an effective therapy [44], and others reporting increased seizure frequency and intensity [43]. Based on a Cochrane review, the few RCTs that have been conducted in humans include a total of 48 participants [45] and only examine treatment with cannabidiol. These trials exhibited heterogeneity of effects: some indicated a reduction in seizure frequency [46,47], while others demonstrated no effect compared to placebo [48]. In addition, none of the studies examined response at greater than 6-month follow-up [45]. Systematic reviews of the literature have concluded that there is insufficient clinical data to support or refute the use of cannabinoids for the treatment of epilepsy and seizures [5,45].

Glaucoma

Glaucoma is a neurodegenerative eye disease that can cause blindness by damaging retinal ganglion cells and axons of the optic nerve. Intraocular pressure (IOP) can influence both onset and progression of glaucoma and is often a target for intervention. Small samples have demonstrated reduced IOP following smoked marijuana [49,50], but the effect is only present in 60–65 percent of individuals [51] and lasts for 3–4 hours, requiring repeated dosing throughout the day [52]. Furthermore, patients discontinue marijuana use due to side effects (e.g., dizziness, anxiety, dry mouth, sedation, depression, confusion, weight gain, and distortion of perception [53]), and this treatment discontinuity may exacerbate optic nerve damage and obviate the benefits of reduced IOP [54]. Limited research and documented toxicity have resulted in the American Glaucoma Society [54], Canadian Opthalmological Society [55], and the American Academy of Ophthalmology's Complementary Therapies Task Force [52] determining that there is insufficient evidence to indicate that marijuana is safer or more effective than existing pharmacotherapy or surgery for the reduction of IOP. Development of eye drops for topical application of THC would minimize psychoactive and other side effects but is complicated by the high lipophilicity and low water solubility of cannabinoids [52,56]. Additionally, the distance from the application site to the retina may be too great to afford neuroprotective benefits [52], given that only 5 percent of an applied dose penetrates the cornea to the intraocular space [56].

Hepatitis C virus

There have been no RCTs examining the use of cannabinoids on HCV infection. Of the studies that have been conducted, one longitudinal study demonstrates that smoked marijuana has no effect on HCV progression in individuals with HIV [57]. In contrast, individuals with HCV who smoke marijuana have a higher fibrosis progression rate [58] and more severe steatosis [59], with daily smokers having a more rapid rate of progression and greater severity [60] than occasional marijuana users [58,59]. Marijuana may have independent negative effects on steatosis [59], but because none of these findings were in the context of a clinical trial, these correlations are not causal and it is possible that individuals who use marijuana do so to manage greater symptom severity [60].

There may be secondary effects of cannabinoids on HCV treatment side effects: dronabinol and Nabilone stabilized treatment-induced weight-loss [61]; and dronabinol, Nabilone, and marijuana procured from a marijuana club (dose and method of administration unspecified) increased HCV treatment duration and reduced post-treatment virological relapse [61,62].

However, there is also a potential drug-drug interaction between ribavirin, a traditional HCV treatment, and marijuana due to shared cytochrome 450 metabolism [63]. Because 90 percent of HCV infections are the result of injection drug use [64], treatment of symptoms with marijuana may be contraindicated for this subpopulation, particularly because marijuana use in the context of other substance use (i.e., alcohol) has multiplicative effects on the odds of fibrosis severity [60]. Given that newer treatments for HCV (e.g., sofosbuvir) are replacing ribavirin, there will likely be less need for use of marijuana in management of treatment-related side effects. In sum, there is currently insufficient empirical support to recommend marijuana for the treatment of HCV.

HIV/AIDS

Marijuana use in HIV-infected patients is typically for the management of side effects (e.g., nausea) of older antiretroviral treatments and AIDS-related symptoms, including weight-loss and HIV-associated neuropathy (covered in cachexia and pain sections, respectively). Survey studies indicate that 23 percent of patients with HIV/AIDS smoked marijuana in the past month and do so largely to improve mood and appetite and reduce pain [65]; these patients may exhibit tolerance and need higher doses of THC than are currently approved by the FDA for use in clinical trials [25] to experience treatment effects. The few RCTs that have been conducted in a small number of patients with HIV/AIDS largely examined the effects of marijuana (synthetic or natural marijuana that is smoked or ingested) on symptoms (e.g., nausea and appetite) over a short treatment window (21–84 days; see [66] for systematic review). Studies examining the effects of marijuana on the pharmacokinetics of antiretroviral medication demonstrated that neither smoked marijuana nor dronabinol affects short-term clinical outcomes (e.g., viral load, CD4 and CD8 counts [67]), influences the efficacy of antiretroviral medication [68], or indicates that dose adjustments for protease inhibitors are necessary [21]. However, individuals who are dependent on marijuana have demonstrated poorer medication adherence and greater HIV symptoms and side effects than nonusers and nondependent users [69]. Furthermore, while some studies have no participant withdrawal due to adverse events [21,70,71], others reported treatment-limiting adverse events [26,72,73]. Finally, because drug use is a risk factor for HIV infection [74], treatment of symptoms with marijuana may be contraindicated for this subpopulation. In sum, there is variability in short-term outcomes and insufficient long-term data addressing the safety and efficacy of marijuana when used to manage symptoms of HIV/AIDS and its role in those also using newer, better-tolerated antiretroviral agents.

Multiple sclerosis and muscle spasticity

Muscle spasticity, a common feature of MS, is disordered sensorimotor control that leads to involuntary muscle activation [75] that results in pain, sleep disturbance, and increased morbidity [76]. The majority of studies examining spasticity have compared oral or sublingual forms of cannabinoids to placebo and found reduced spasm severity [77-84], with symptom improvement enduring at long-term follow-up [85-87], and also reduced spasm frequency and spasm-related pain and sleep disturbances [77,88,89]. With regard to smoked marijuana, one study found reductions in muscle spasticity [90]; however, another study showed that smoking marijuana impaired posture and balance in individuals with spasticity [91], so there is currently insufficient evidence to determine the efficacy of smoked marijuana on spasticity [5].

Surveys of patient populations show that between 14 and 16 percent of patients with MS report using marijuana for symptom management [92,93] and that compared to non-marijuana-using individuals with MS, marijuana-using individuals with MS have decreased cognitive functioning [90,94,95]. Because cognitive dysfunction is present in 40–60 percent of individuals with MS before marijuana administration [96], marijuana use may further compromise impaired cerebral functioning in a neurologically vulnerable population. Additionally, future studies should carefully consider outcome assessment. The primary methods of measuring spasticity, the Ashworth Scale and patient self-report, may not be appropriate measures because antispastic drugs do not decrease Ashworth ratings, and patient-reported spasticity severity may be poorly correlated with patient functioning (i.e., a patient whose spasticity compensated for motor weakness may be unable to ambulate with reduced spasticity) [97]. Importantly for both MS and other neurological disorders, the American Academy of Neurology does not advocate the use of marijuana for the treatment of neurological disorders, due to insufficient evidence regarding treatment efficacy [98].

Post-traumatic stress disorder

There has been a recent emergence of empirical studies of the effects of marijuana on symptoms of PTSD, borne primarily out of the observation that individuals with PTSD report using marijuana to cope with PTSD symptoms; specifically, hyperarousal, negative affect, and sleep disturbances [99-101]. Empirical work has consistently demonstrated that the endocannabinoid system plays a significant role in the etiology of PTSD, with greater availability of cannabinoid type 1 receptors documented among those with PTSD than in trauma-exposed or healthy controls [102,103]. Though the use of marijuana and oral THC [104,105] have been implicated as a potential mechanism for the mitigation of many PTSD symptoms by way of its effects on the endocannabinoid system, some researchers caution that endocannabinoid activation with plant-based extracts over extended periods may lead to a number of deleterious consequences, including receptor downregulation and addiction [102].

There have been no RCTs of marijuana for the treatment of PTSD, though there has been one small RCT of Nabilone that shows promise for reducing nightmares associated with PTSD [106]. One pilot study of 29 Israeli combat veterans showed reductions in PTSD symptoms following the administration of smoked marijuana, with effects seen up to one year post-treatment [107]. Remaining studies have been primarily observational in nature, documenting that PTSD is associated with greater odds of a cannabis use disorder diagnosis [108] and greater marijuana craving and withdrawal immediately prior to a marijuana cessation attempt [109]. Indeed, sleep difficulties (a hallmark of PTSD) have been associated with poor marijuana cessation outcomes [110,111], while cannabis use disorders have been associated with poorer PTSD treatment outcomes [112]. Given the lack of RCTs studying marijuana treatment for PTSD, there is insufficient scientific evidence for its use at this time.

Severe and chronic pain

Clinical trials have examined smoked and oral administration of cannabinoids on different types of pain (e.g., neuropathic, post-operative, experimentally induced) in multiple patient populations (e.g., HIV, cancer, and fibromyalgia). Two meta-analyses have been conducted examining the association between marijuana and pain. In the first, 18 RCTs demonstrated that any marijuana preparation containing THC, applied by any route of administration, significantly decreased pain scores from baseline compared to placebo [113]. The second examined 19 RCTs of smoked marijuana in individuals with HIV, which also indicated

greater efficacy in reducing pain (i.e., sensory neuropathy) compared to placebo [114]. Importantly, the first meta-analysis showed that marijuana increased the odds of altered perception, motor function, and cognition by 4 to 5 times [113], and the second study did not recommend marijuana as routine therapy [114]. Dosage is an important factor to consider for administration of cannabinoids for pain management, as some studies have found that higher doses of smoked marijuana are associated with improved analgesia [115], whereas other studies show that higher doses of smoked marijuana increase pain response [116]. Because the analgesic effects of marijuana are comparable to those of traditional pain medication [117], future research should aim to identify which analgesics provide the lowest risk profile for the management of severe and chronic pain. Although there is preliminary support to suggest that marijuana may have analgesic effects, there is insufficient research on dosing and side effect profile, which precludes recommending marijuana for the management of severe and chronic pain.

Severe nausea

The majority of research related to the effects of marijuana on severe nausea has involved oral administration of marijuana to individuals with chemotherapy-induced nausea and vomiting (CINV). Oral marijuana (i.e., THC suspension in sesame oil and gelatin) has been shown to be more effective in reducing CINV than placebo [118], including the number and volume of vomiting episodes, and the severity and duration of nausea [119]. When compared to traditional anti-emetics, some meta-analytic reviews indicate that oral THC is more effective in reducing CINV [120-123], others find no significant difference [122,124-126], and another suggests that combining both is the most effective at reducing the duration and severity of CINV than either alone [127]. Recent advances in both anti-emetic agents and the mechanisms of cannabinoid administration (i.e., sublingual application) warrant future research.

Importantly, patients receiving cannabinoids for severe nausea reported toxicities, including paranoid delusions (5%), hallucinations (6%), and dysphoria (13%) [122]. Additionally, cannabinoid hyperemesis syndrome has been documented, in which persistent and regular marijuana use (i.e., daily or weekly use for more than 1 year) is associated with cyclic vomiting (i.e., episodic nausea and vomiting) [128] and nonresponse to treatment for cyclic vomiting [129]. Dronabinol has been FDA-approved for CINV in individuals who have not shown a treatment response to traditional anti-emetics, but in line with recommendations from the American Society of Clinical Oncology [130] and the European Society for Medical Oncology [131], cannabinoids should not be utilized as a first-line treatment for nausea and vomiting.

Conclusions

The reviewed literature highlights the dearth of rigorous research on the effects of marijuana for the most common conditions for which it is currently recommended. It is paramount that well-designed RCTs with larger sample sizes be conducted to determine the actual medical benefits and adverse effects of marijuana for each of the above conditions. Indeed, recent reviews [4,132] comprehensively discuss adverse events associated with marijuana use, and while it is beyond the scope of the current paper to review these effects in-depth, they are important to consider when evaluating whether or not to recommend marijuana for a medical or psychiatric disorder in place of other existing treatment options.

Given the extensive literature speaking to the harms associated with marijuana use, research on the comparative safety, tolerability, efficacy, and risk of marijuana compared to existing pharmacological agents is needed. The present literature also illuminates the need for research into the effects of isolated cannabinoids (e.g., THC, CBD) as well as species of smoked marijuana (e.g., indica and sativa), as the majority of medical marijuana users ingest marijuana by smoking the marijuana plant [133,134], which contains a wide variety of phytocannabinoids at varying potencies [135,136]. Furthermore, improved and objective measurement of clinical outcomes should be implemented in clinical trials to determine treatment efficacy. Finally, little research has considered the issues of dose, duration, and potency. If research identifies a therapeutic effect of marijuana for medical or psychiatric conditions, there will need to be revisions in marijuana policy to increase quality control so that dose and potency are valid and reliable. Additionally, risk of abuse and diversion can be decreased by developing prescribing practices with continued supervision of a medical professional, creating prescription monitoring programs to reduce the risk of "doctor shopping" and identifying provisions for the safe disposal of unused cannabinoids. In sum, the current literature does not adequately support the widespread adoption and use of marijuana for medical and psychiatric conditions at this time.

Abbreviations

THC, Δ^9-tetrahydrocannabinol; HIV, Human immunodeficiency virus; AIDS, Acquired immunodeficiency syndrome; RCTs, Randomized controlled trials; IOP, Intraocular pressure; MS, Multiple sclerosis; CINV, Chemotherapy-induced nausea and vomiting; HCV, Hepatitis C virus; ALS, Amyotrophic lateral sclerosis; CD, Crohn's disease; IBD, Inflammatory bowel disease; AD, Alzheimer's disease; PTSD, Post-traumatic stress disorder; CB1, Cannabinoid type 1; CBD, Cannabidiol.

Competing interests

Dr. Belendiuk holds stock in Shire Pharmaceuticals.

Authors' contributions

Dr. KAB synthesized the literature and authored sections of the manuscript. Ms. LLB assisted with the literature search and synthesis. Dr. MOB-M conceived the review, assisted in the search and synthesis of existing literature, and authored sections of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Dr. Belendiuk's salary was supported by National Institute of Mental Health R01 MH40564.
Dr. Bonn-Miller's salary was supported by the VA Center of Excellence for Substance Abuse Treatment and Education.
Literature review and synthesis was supported by a grant from the VA Substance Use Disorder Quality Enhancement Research Initiative (SUDQ-LIP1410).
The above funding agencies played no role in the writing of the manuscript or decision to submit the manuscript for publication. The expressed views do not necessarily represent those of the Department of Veterans Affairs.

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Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Monday, June 01, 2015 5:24 PM
To: Public Hearing
Subject: FW: EMPLOYEE SHOT MARIJUANA DISPENSARY ROBBERY

s.22(1) Personal and Confidential

From: PAMELA MCCOLL
Sent: Monday, June 01, 2015 5:03 PM
To: Correspondence Group, City Clerk's Office
s.22(1) Personal and Confidential
Subject: EMPLOYEE SHOT MARIJUANA DISPENSARY ROBBERY

CALL OFF THE LICENSING AND ENFORCE THE LAW - THE POLICE WANT YOU TO DO PRECISELY THAT.
USE THE CIVIL FORFEITURE ACT OF BC TO ACT ON INVESTIGATIONS - YOU DO NOT EVEN NEED THE
COURTS - YOU HAVE A JUDICIAL OBLIGATION TO DO SO. THIS IS NOW HIGH PRIORITY.

http://bc.ctvnews.ca/smash-and-grab-thief-targets-vancouver-pot-dispensaries-1.2399851

http://www.cannabisculture.com/content/2015/05/25/Employee-Shot-LA-Medical-Marijuana-Dispensary-Robbery

Pamela McColl
Smart Approaches to Marijuana Canada

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Monday, June 01, 2015 5:14 PM
To: Public Hearing
Subject: FW: Plan to oppose Vancouver's Plan
Attachments: June 10th. final notes for City Presentation.docx

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From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Monday, June 01, 2015 12:03 PM
To: Correspondence Group, City Clerk's Office
s.22(1) Personal and Confidential
Subject: Fwd: Plan to oppose Vancouver's Plan

Please find attached our organizations position in opposition to the City of Vancouver's plan to license marijuana dispensaries. In it you will understand our rationale for calling for the resignation of Dr. Penny Ballem as City Manager effective immediately.

Pamela McColl
Smart Approaches to Marijuana Canada
s.22(1) Personal and Confidential

Pamela McColl –Opposition to call to license illicit marijuana dispensaries.
Smart Approaches to Marijuana Canada

There is a program in place under which Canadians can access marijuana for medical purposes. The MMPR program, run by Health Canada, in compliance with the courts that have required reasonable access to a legal source of marijuana for medical purposes.

These dispensaries are not in compliance and it is illegal to sell marijuana for any purpose from a storefront in Canada.

Health Canada has the expertise to monitor production, conduct testing, issue demands for recalls for contaminated or inaccurately labelled product and vigorously control advertising. They have a watchful eye on any misrepresentations being made by the federally "licensees" - with the power of the federal judicial system to take action against those who do not comply.

Health Canada can deliver on consumer protection and safety – both things the City of Vancouver cannot do. This plan on implementation would increase health and safety risks. It should be rejected.

The Governor of Idaho recently rejected a bill to legalize medical marijuana: "In our quest to relieve suffering, it is vital we ensure the solutions employed do not exacerbate health problems to the critically ill or decrease public safety."

This proposal has the potential of doing both of these things – exacerbating the health problems of the critically ill and decreasing public safety.

There now exists thousands of studies that establish the very clear risk of damage of using marijuana at any age - even for short periods of time.

There is confusion in the minds of the public over risks associated with using marijuana.

This country needs a broad based prevention program. We should not give up on our quest to reduce demand and supply when it comes to the use of illicit drug use. No country in the world has legalized marijuana use and our goal should be less drug abuse not the facilitation of more through the adopting of permissive drug policies.

Individuals associated with these dispensaries advance claims of benefit of use that cannot be substantiated by evidence based science. We are in terms of public awareness of the risks of the use of marijuana we were with tobacco products in the 1960's – we have the evidence of harm but it is not getting out to the public.

"Those treated for addiction to cannabis (marijuana) had a higher mortality rate (3.85 times higher than controls), higher if compared to death rate risk of cocaine use disorder (2.96), alcohol use disorder (3.83).... Callaghan et al.

Manuscript Safety D 13 00224R1 Rosebelle Macdonald
There were 38 traumatic fatalities among forestry workers. Employed by small businesses. (BC). Toxicology screen data were available for 23 of them, 22% were positive to cannabis, 9% were positive for cocaine and cannabis. There were no instances of alcohol intoxication.

Marijuana is not an approved medication, does not come in specific dosages or concentrations, and cannot be prescribed. However, there is antidotal evidence which suggests that some component or components of marijuana may be useful for patients with chronic pain, side effects of chemo-therapy, and with varying symptoms secondary to HIV infections. In no case have any double-blind placebo-controlled trials demonstrated objectively measurable benefits from the whole plant, either for these purposes or for any medical application. "Stuart Gitlow, MD MPH MBA President American Society of Addiction Medicine.

These dispensary operators support, encourage, promote and profit off untested and experimental drug use. By alluring customers under false presentations they could be contributing to a delay in a person seeking appropriate and effective medical treatment.

In May 2015 Colorado Health Authorities seized $110 million worth of marijuana, contaminated with pesticides. Washington test results show 13% of marijuana sold through legal operations are contaminated with bacteria.

The illegal dispensaries are selling marijuana that is not tested. Smart Approaches to Marijuana has confirmed that Health Canada nor Vancouver Coastal Health will be inspecting the products these dispensaries peddle.

There have been complaints from the public regarding the products being sold in these stores and it has been confirmed that Vancouver Coastal Health has never

inspected any of these dispensaries nor have they responded to public complaints concerning the safety of the products or the accuracy of the labeling under which they are being sold.

Dr. Ballem on April 28th, was asked about the responsibility of testing: "No one – eventually the Federal Government".

This is not an accurate statement. The Federal Government will not inspect these illegal operations.

Dr. Daly to Mayor and Council ;" I have instructed my staff to inspect these facilities right now because regardless whether they are legal or illegal we would expect them to follow these standards." April 28th. 2015

In a letter to SAM CANADA she states. May 26th. 2015 Letter from Dr. Daly

Comment [pm1]:

"My instructions to my staff to undertake inspections was in reference to complaints only, not routine inspections. I apologize if this was not clear. At the time of my statements, I thought my staff may have inspected one or two of these facilities in response to complaints. I have since confirmed with my staff that that is not the case, and no inspections have occurred. "

"Heather Miller Coyle, a forensic botanist and associate professor at the university (Univ. of New Haven), says all sorts of nasty things not visible to the naked eye have been found in marijuana – mold, mildew, insect parts, salmonella and E.coli, to name a few. ..."If there's no certification... it's like saying we don't check our meat for mad cow disease."

The illegal "drug" dispensary operations expose consumers to an increased risk or threat of E-coli and salmonella – with special concern for the most vulnerable of users – those with immune suppression including those individuals suffering with HIV-AIDS.

The products being supplied to these dispensaries are GMO engineered to have a high THC level – natural marijuana is below 3% THC. Who will test the level of THC against the amount specified on the packaging?

Tests done on US dispensaries have discovered that in some cases no CBD in products that claimed the benefit of CBD for specific ailments. Who will test for such deception in the product supplied to these dispensaries in Vancouver?

Health Canada licensees must send out a Health Canada document that list the contraindications of use. The dispensaries are in fact make claims of benefit in contradiction of the warnings provide by Health Canada, an example being the case of pregnant women.

It's not the true medical cases anyone wants to stop, it's what law enforcement tells us are the 90% plus (as many as 99%) non-sick people who also come into the clinic feigning illness with a makeshift letter just to get drugs. R.Weiner, former White House Drug Policy Spokesman.

Researchers at the University of Colorado found that about 74% of teens reporting using marijuana they had obtained from a medical-marijuana license holder

In Canada as of March 31st. 2014 there were less than 40,000 medical marijuana cardholders

Between 30-53% of grade twelve students report regular use in Canada – clearly the priority must be addressing the use by youth and these storefront dispensaries are providing another point of access and
they are engaging in advertising in local newspapers and on at least two popular radio stations.

Canada has the highest rate for the use of marijuana in the Western World and we are the only country in the world that has legalized access to marijuana for medical purposes. Canadians kids have been pushed into pot use – high rates of use are not a failed system but the direct result of a heavily funded and aggressive pro pot lobby group and an emerging industry – predatory in nature and after one thing – to make a great deal of money. We have lived this story before – with Big Tobacco – this time it is Big Pot.

Dr. Ballem may not like current federal drug policies or not particularly like the way marijuana for medical purposes is delivered under Health Canada. It is however not within the jurisdiction of the office of the City Manager to advance including the avail of access through any "window" of opportunity.

Dr. Ballem has shared her opinion as to where blame should lie for the rapid rise of the number of the number of dispensaries in Vancouver. The question is did the development of this proposal prompt the opening of more dispensaries?

In Vancouver there are 93 illegal marijuana stores. As provided by the RCMP as of May 25th. 2015 Manitoba 1 Alberta 2 Quebec 4 Ontario 13 Nova Scotia none

Page 4 Dr. Ballem "In 2013 the Federal Government amended the rules to restrict the suppliers of medical marijuana. "It is in this context that there has been a rapid growth in the establishment of new marijuana-related businesses in the city."

Is the rise in dispensaries not rather the lack of enforcement by this civic administration?

In October of 2014 Sensible BC Dana Larson
"We've got political training sessions led by people including Brian Rice, former president of the Liberal Party of BC, and Andrew Radzik, former director of Organizing for Vision Vancouver. We've even running a class on how to open a cannabis dispensary, led by Dori Dempster of the Vancouver Dispensary Society. "September 11 2014 Sensible BC.

Is the rise in the number of marijuana dispensaries not the plan and fault of Sensible BC?

In California as of August 2012 there were bans against marijuana dispensaries in 26 counties and 247 cities, with moratoriums on dispensaries in 9 counties and 80 additional cities. Only 98 counties and 53 cities allow for dispensaries. Percentage bans or moratoriums on marijuana dispensaries 79.1% counties and 86.1% of cities.

Colorado bans – as of 2015 321 total jurisdictions 228 or 71% prohibit any medical or recreational marijuana business, 67 or 21% allow any medical and recreational business, 8% allow either medical or recreational but not both.

Court cases holiday inn, 2 neighboring states, sheriffs, citizen's property values and security costs.
They citizens of San Jose forced local council to limit dispensaries to industrial areas.

You turn on the local Vancouver news on May 31st. robberies smash and grabs – would you really want that activity beside your business?

The owner of the Holiday Inn in Frisco claims its business is already suffering because of a recreational marijuana shop they say is planning on opening 75 yards

from the hotels front door. Many of its guests are youth ski teams and families with children, the lawsuit says. Many parents and coaches will avoid booking with a hotel that is within a short walking distance and direct sight of a recreational marijuana store and grow facility. The Governor, politicians, public servants and businesses are the defendants.

Other factors to consider:

Colorado "The shelter did an informal survey of the roughly 500 new out-of-towners who stayed there between July and September and found as many as 30 percent had relocated for pot, he said. CBS

Seattle Times Editorial: The world is watching Washington's historic experiment with marijuana legalization and we are screwing it up. December 6, 2014: The city already has a law but that bans major medical marijuana operations from opening after November 2013. But there is no excuse to ignore existing authority, including criminal charges against black market dealers masquerading as dispensaries.

Brian Montague, the VPD spokesperson, told the Georgia Strait, that the VPD has found evidence that organized crime is taking an interest in the Vancouver dispensaries.

THE ILLICIT DRUG TRADE IS FLOURISHING New York Times Jan.2 2015
In Washington the black market has exploded since voter's legalized marijuana in 2012 with scores of legally dubious medical dispensaries opening and some pot dealers brazenly advertising that they sell outside the legal system.

There is no reasonable justification to allow for dispensaries in the Downtown Eastside on Hastings or Main Street.

There is no reasonable justification to not limit the proximity to daycares.

Breathing second hand marijuana smoke could damage your heart and blood vessels as much as second hand cigarette smoke. Preliminary research – America Heart Association 2014

Children who have a history of asthma are prone to severe asthma attacks following exposure to marijuana smoke either via inhalation or contact with contaminated clothing. Blood levels of THC above 3.5ng-ml have been repeatedly

documented in adults exposed to second-hand marijuana smoke for at least three hours. (Rohrick JJ Anal Toxicol 2010; 34 (4) 196-203)

Dr. Harold Kalant (MD, PhD, FRSC) Professor Emeritus Pharmacology and Toxicology, University of Toronto.

Evidence available to date suggests that there has been a large increase in use in Colorado, beginning in the period of expansion of the medical marijuana program and accompanied by increases of use by adolescents, fatalities among drivers under the influence of cannabis, cannabis-related emergency room visits and deviation of Colorado marijuana to other states. The results are still early, and it will take several years to learn what the full extent of social costs will be to school and work performance, physical and mental health, automobile accidents and death etc. Without such knowledge we have no basis of saying prohibition is a failure.

In Dr. Ballem's presentation of April 28th:

Councillor Jang asks why daycares have not been included in the provisions for proximity regulations:

Response from Dr. Ballem: "Every time we add another criteria it makes it much more complex – in fairness to this sector – trying to make it transparent and fairly reasonable for them to decide what are the sensitive uses they have to adhere to. .... Stick to best practices."

Washington Best Practice Appendix A
Requires 1,000 ft. (300 m) from school, playground, recreation center, child care, public park, public transit center, library, or game arcade. Colorado requires 1,000 (300 m) from school, preschool, child care establishment, medical marijuana center, or alcohol or drug treatment facilities.

"Marijuana stores operating in proximity to schools, parks, and other areas where children are present send the wrong message to those in our society who are the most impressionable. In addition, the huge profits generated by these stores, and the value of their inventory, present a danger that stores will become a magnet for crime, which jeopardizes the safety of nearby children." Melinda Haag

It is not Dr. Ballem's job, as the City Manager to advocate for patients nor is it her job to be an advocate for illegal operations who feel that they are not being treated fairly.

Page 2 Report Summary
"This report recommends regulations for an emerging sector of retail businesses related to the provision of advice for medicinal marijuana. The regulations will ensure the availability of these services is sufficient to meet local needs and, as in all areas of business activity in the city, that business is conducted appropriately in the context of health, safety, and the public interest. "

Power Point
Slide 3 "Treat all businesses consistently and fairly".

April 22nd City proposes:
"The City is proposing a balanced approach on best practice research and input from key partners such as the VPD, Vancouver School Board, Vancouver Coastal Health, business improvement areas, and several key stakeholders in the industry.

Page 5 "In considering an appropriate approach, we have built on Best Practice from other jurisdictions and endeavoured to achieve a careful balance between ensuring adequate availability for those in need and ensuring community health, safety, security, aesthetics and enjoyment of property."

Patient access as the rationale: "to protect access to people who need this for their wellbeing."

Page 12 – Continuing to have a proliferation of unregulated businesses poses a significant risk to youth, public health and general quality of life as well as an impact on the local economy and health of our community. If however, they are carefully managed and regulated, these businesses can play a role in ameliorating health conditions that affect numerous people.

Page 7 "Treat all businesses consistently and fairly"

Page 5 "The rapid growth in marijuana-related business over the past two years has also generated some community feedback.... The majority of concerns are related to impact on youth, with other areas of concern including criminality, declining area character and lack of fairness in the regulatory framework for marijuana-related businesses in contrast."

It remains an open question as to whether or not the actions as outlined in this proposal, if acted upon, would amount to civic employees being deemed to be

aiding and abetting criminal activity or conspiring to violate laws. It remains open whether charges could be brought, now or in the future, against civic employees or others in relation to this course of action.

Dr. Ballem should resign and if not this Council and Mayor should terminate her contract.

I was not paid to be here – I am not associated with any pharmaceutical or marijuana company. I graduated from Point Grey in 1975 and went to university at the height of the pot era – I have seen what 3% THC marijuana use can do to some ones potential – I now know what oils – 90-% THC – can do to young developing brains - Our organization is simply trying to minimize the damage to kids – this proposal is dangerous.

Comment [pm2]:

Dana Larsen May 30th. Email blast – and on Facebook page.
"If we can raise $4000 before June 10th we'll be able to make sure that medicinal cannabis patients get their voices heard.
"These new city laws will have a profound effect on the future shape of medical access and eventual legalization across Canada".

The result of this manipulation is more people using marijuana for any purpose without understanding the consequences.

(References on request) samcanadanet@gmail.com

http://former.vancouver.ca/ctyclerk/cclerk/20150428/documents/rr1presentation.pdf

http://cannabisincanada.ca/blog/ballem-speaks-city-council-regulating-dispensaries/

http://www.cannabisculture.com/content/2015/05/20/Public-Hearing-Vancouver-Medical-Marijuana-Dispensary-Rules-Set-June-10

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Tuesday, June 02, 2015 3:19 PM
To: Public Hearing
Subject: FW: DISPENSARIES IN BREACH OF FOOD AND DRUG ACT AND CAN NOT BE MADE AVAILABLE TO VANCOUVER CONSUMERS THROUGH LICENSING

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Tuesday, June 02, 2015 2:36 PM
To: Correspondence Group, City Clerk's Office
s.22(1) Personal and Confidential
Subject: DISPENSARIES IN BREACH OF FOOD AND DRUG ACT AND CAN NOT BE MADE AVAILABLE TO VANCOUVER CONSUMERS THROUGH LICENSING

http://www.laws-lois.justice.gc.ca/eng/regulations/SOR-2013-119/

GOOD PRODUCTION PRACTICES

Marginal note:Prohibition — sale or provision

- **52. (1) A licensed producer must not sell or provide dried marihuana under subsection 12(4) unless the requirements of this Division have been met.**

- Marginal note:Prohibition — export

(2) A licensed producer must not export dried marihuana unless the requirements of this Division have been met.

Marginal note:Microbial and chemical contaminants

- **53. (1) The microbial and chemical contaminants of dried marihuana must be within generally accepted tolerance limits for herbal medicines for human consumption, as established in any publication referred to in Schedule B to the *Food and Drugs Act*.**

- Marginal note:Analytical testing

(2) Analytical testing for those contaminants and for the percentages of delta-9-tetrahydrocannabinol and cannabidiol referred to in these Regulations must be conducted using validated methods.

Marginal note:Pest control product

54. Marihuana must not be treated — before, during or after the drying process — with a pest control product unless the product is registered for use on marihuana under the *Pest Control Products Act* or is otherwise authorized for use under that Act.

- SOR/2014-51, s. 7.

Previous Version

Marginal note:Premises

- **55.** (1) Dried marihuana must be produced, packaged, labelled and stored in premises that are designed, constructed and maintained in a manner that permits those activities to be conducted under sanitary conditions, and in particular that
    - (*a*) permits the premises to be kept clean and orderly;
    - (*b*) permits the effective cleaning of all surfaces in the premises;
    - (*c*) permits the dried marihuana to be stored or processed appropriately;
    - (*d*) prevents the contamination of the dried marihuana; and
    - (*e*) prevents the addition of an extraneous substance to the dried marihuana.

Marginal note:Storage

(2) Dried marihuana must be stored under conditions that will maintain its quality.

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Marginal note:Equipment

56. Dried marihuana must be produced, packaged, labelled and stored using equipment that is designed, constructed, maintained, operated and arranged in a manner that

- (*a*) permits the effective cleaning of its surfaces;
- (*b*) permits it to function in accordance with its intended use;
- (*c*) prevents it from contaminating the dried marihuana; and
- (*d*) prevents it from adding an extraneous substance to the dried marihuana.

Marginal note:Sanitation program

57. Dried marihuana must be produced, packaged, labelled and stored in accordance with a sanitation program that sets out

- (*a*) procedures for effectively cleaning the premises in which those activities are conducted;
- (*b*) procedures for effectively cleaning the equipment used in those activities;
- (*c*) procedures for handling any substance used in those activities; and
- (*d*) all requirements, in respect of the health, the hygienic behaviour and the clothing of the personnel who are involved in those activities, that are necessary to ensure that those activities are conducted in sanitary conditions.

Marginal note:Standard operating procedures

58. Dried marihuana must be produced, packaged, labelled and stored in accordance with standard operating procedures that are designed to ensure that those activities are conducted in accordance with the requirements of this Division.

Marginal note:Recall

59. A licensed producer must establish and maintain a system of control that permits the rapid and complete recall of every lot or batch of dried marihuana that has been made available for sale.

Marginal note:Quality assurance

- **60. (1) A licensed producer must**
  - **(*a*) have a quality assurance person who**
    - (i) is responsible for assuring the quality of the dried marihuana before it is made available for sale, and
    - (ii) has the training, experience and technical knowledge relating to the activity conducted and the requirements of this Division; and
  - **(*b*) investigate every complaint received in respect of the quality of the dried marihuana and, if necessary, take corrective and preventative measures.**

- Marginal note:Methods and procedures

  (2) Dried marihuana must be produced, packaged, labelled and stored using methods and procedures that, prior to their implementation, have been approved by a quality assurance person.

- Marginal note:Approval prior to sale

  (3) Every lot or batch of dried marihuana must be approved by a quality assurance person before it is made available for sale.

- Marginal note:Returns

  (4) Dried marihuana that is sold or provided under subsection 12(4) and subsequently returned to the licensed producer must.

submitted Pamela McColl
Smart Approaches to Marijuana Canada

Isfeld, Lori

From: Correspondence Group, City Clerk's Office
Sent: Wednesday, June 03, 2015 11:39 AM
To: Public Hearing
Subject: FW: June 2nd 2015 Californians defeat the pot lobby and denying marijuana dispensaries and mobile dispensaries within their city limits

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From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Wednesday, June 03, 2015 7:54 AM
To: Correspondence Group, City Clerk's Office
s.22(1) Personal and Confidential
Subject: June 2nd 2015 Californians defeat the pot lobby and denying marijuana dispensaries and mobile dispensaries within their city limits

After legalization in 1996 of marijuana for medical purposes now over 88% of cities have bans or moratoriums in place. Results show the experiment of dispensaries does not work. The public will not support dispensaries,
The place to watch is California - the first state to permit medical marijuana.

Sent: Tuesday, June 2, 2015 11:17:14 PM
Subject: Town of Yucca Valley defeats Measure A and denying marijuana dispensaries and mobile dispensaries within their city limits

Dear All,

Tonight, the Town of Yucca Valley held a special election to consider their Measure A, to allow store front marijuana dispensaries and mobile marijuana sales.

As you can see from the voter results below, the Citizens of Yucca Valley overwhelmingly defeated Measure A, put forth by the Pro-Marijuana Advocates, and voted [60.51% to 39.49%] to deny allowing store front marijuana dispensaries or mobile marijuana dispensaries within their jurisdiction.

Such is the popularity of marijuana in the State of California.

This follows the results after the 2014 election when four California cities [three cities located near San Diego and the City of Palo Alto] had the issue on their ballots and their citizens all voted overwhelmingly to deny marijuana dispensaries in their cities.

Pamela McColl
Smart Approaches to Marijuana Canada

SAN BERNARDINO COUNTY

Elections Office of the
Registrar of Voters

www.SBCounty.gov

Michael J. Scarpello
Registrar of Voters

8:05 p.m. Posting of Unofficial Election Night Results

777 East Rialto Avenue, San Bernardino, CA 92415 | Phone: 909.387.8300 Fax: 909.387.2022

Town of Yucca Valley Special Election – June 2, 2015 Total Registered

Measure A – Store Front and Mobile Marijuana

	Vote Count	Percentage
Yes	8,639	39.49%
No	13,240	60.51%
Total	21,879	100.00%

Kazakoff, Laura

From: Correspondence Group, City Clerk's Office
Sent: Friday, June 05, 2015 2:41 PM
To: Public Hearing
Subject: FW: OPCC Online Complaint Submission Receipt

From: PAMELA MCCOLL s.22(1) Personal and Confidential
Sent: Friday, June 05, 2015 12:06 PM
To: Correspondence Group, City Clerk's Office
s.22(1) Personal and Confidential
Subject: Fwd: OPCC Online Complaint Submission Receipt

Smart Approaches to Marijuana Canada has filed a complaint with the OPCC against the Vancouver Police Department for failing to enforce the laws of Canada.

From: s.22(1) Personal and Confidential
To: s.22(1) Personal and Confidential
Sent: Friday, June 5, 2015 11:27:39 AM
Subject: OPCC Online Complaint Submission Receipt