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Cannabis and the lung

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ABSTRACT The use of cannabis is embedded within many societies, mostly used by the young and widely perceived to be safe. Increasing concern regarding the potential for cannabis to cause mental health effects has dominated cannabis research and the potential adverse respiratory effects have received relatively little attention. Studies on cannabis are challenging and subject to confounding by concomitant use of tobacco and other social factors, and while many of the studies referred to in this review are beset by the difficulties inherent in undertaking epidemiological research of the effects of cannabis, there is an emerging concern among many chest physicians who would suggest that habitual smoking of cannabis may contribute to the development of chronic obstructive pulmonary disease, pneumothorax and respiratory infections, including tuberculosis. Special attention should be given to the risk of lung cancer, particularly as biological plausibility may precede epidemiology.

KEYWORDS Cannabis, lung cancer, pneumothorax, smoking, tuberculosis

DECLARATION OF INTERESTS Dr Reid, Dr Robertson and Professor Macleod hold a grant from the Chief Scientist Office, Scotland, to investigate the respiratory effects of regular cannabis use in a primary care population.

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BACKGROUND

Cannabis sativa is a herbaceous plant that shares the botanical group Cannabaceae with the hop plant. The stems of the plant can be retted – a process of steeping or watering – to form hemp, which has been widely used in rope making and other fabrics. The plant also contains a variety of cannabinoids, including delta-9-tetrahydrocannabinol (Δ^9 THC), which acts as the principal psychoactive component contributing to the activity of cannabis as a psychotropic drug. Δ^9 THC is understood to bind to cannabinoid receptors in the brain which normally bind the natural neurotransmitter anandamide ('ananda' meaning bliss in Sanskrit).

The cannabis plant grows easily and quickly in a range of climatic and soil conditions, including both tropical and temperate regions, and is increasingly cultivated indoors using hydroponic techniques which exploit the use of nutrient-rich liquids in place of soil. These properties mean that cannabis may be grown in almost every country worldwide so it is perhaps not surprising that cannabis has emerged as the world's most commonly used illegal drug.¹ The most recent survey by the European Drugs Monitoring Centre suggests, as a conservative estimate, that cannabis has been used at least once (lifetime prevalence) by more than 70 million European adults, with around 23 million using cannabis in the past year.²

The situation in the UK is little different. Although recreational use of cannabis was rare before the 1960s,^{3,4} since then the UK has witnessed a dramatic increase in

cannabis use. Recent information from the 2007/2008 British Crime Survey,⁵ focusing on household samples of people aged 16–59 years living in England and Wales, suggests that cannabis was by far the most commonly used illegal drug, with 7.4% of this population reporting cannabis use in the preceding year. The use of cannabis is particularly prevalent in the young, with the highest levels of use generally being reported among the 15- to 24-year-old age group;² for example, in Scotland cannabis use has been reported in 13% of 15-year-old boys and 10% of 15-year-old girls.⁶

Partly as a response to the increased use of cannabis in recent years and the associated increase in the prison population sentenced for cannabis-related crimes in the UK, the Home Secretary encouraged the Advisory Council to consider rescheduling this drug under the Misuse of Drugs Act. The subsequent reclassification into class C rather than class B was intended to allow the downgrading of sentencing tariffs and reduce the prison problems; however, national and international political pressures led to a reversal of this decision within a few years.^{7,8} Further increases in the use of cannabis are anticipated over the next decade.¹

When used as a drug, cannabis is most commonly smoked; however, the form and method of smoking vary widely. For example, in Scotland, the majority of users smoke cannabis resin (a sappy substance secreted from the plant during the flowering phase supplied as a green resinous product, colloquially known as 'soap bar'), which is cut with tobacco and smoked as a handmade

unfiltered cigarette known as a 'joint'.⁹ The joint is often single skinned and unfiltered, although a roach (usually a small piece of rolled-up cardboard) may be employed to allow the user to hold the joint at a reasonable temperature. Cannabis resin, also known as hash, is smoked widely throughout Europe, but in the Americas the flowering tops and leaves of the plant (marijuana) predominate and the use of cannabis resin is limited.¹ Cannabis may also be smoked through a modified water pipe known as a bong which draws the cannabis through water cooling the inhaled vapour. This method, while used in the UK and Europe, is perhaps more common in Australasia.¹

The widespread use of cannabis also appears to have been accompanied by an increase in the use of stronger 'skunk' cannabis or 'sinsemilla' (literally from the Spanish 'without seed'). The potency of cannabis is, at present, determined by its content of Δ^9 THC, the primary active constituent. The greatest concentrations of Δ^9 THC are harvested from the unfertilised female plant; hence, sinsemilla provides the highest concentration. This form of cannabis is most easily cultivated indoors and attracts the use of colourful names such as 'super-skunk', 'AK-47' and 'northern lights', to name but a few. Whereas the concentration of Δ^9 THC may be around 2–4% in herbal cannabis, the concentration in sinsemilla (skunk) may approach 10% or 15%. There is concern, particularly from police data on drug seizures, that the availability of skunk has increased dramatically in the UK within the past decade.¹⁰

The majority of cannabis research has focused on the psychiatric consequences and only limited attention has been given to the potential of cannabis to impact on the lung. The small number of studies that have examined the potential for cannabis to affect lung health have been undertaken in North America, Australia, New Zealand and North Africa; the remaining information is drawn from selected case reports and personal clinical experience and these have contributed to an emerging concern that cannabis may be linked to the development of chronic obstructive pulmonary disease (COPD), the presentation of pneumothorax, a predisposition to respiratory infections and, perhaps most worryingly, the development of lung cancer. Such research is particularly important when one considers that the majority of cannabis smokers are young and have yet to complete lung growth, which may make them particularly susceptible to any potential adverse effects.

CANNABIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease has assumed major importance in the world health agenda. Current estimates suggest that the condition has a prevalence of around 1% in the general population, but this is probably higher in older age groups.¹¹ The condition is characterised by an accelerated loss of lung function and life-long

disability. However, the increasing prevalence and potential impact of the disease may be most clearly seen in population mortality tables where COPD is predicted to become the world's third leading cause of mortality by 2030.¹²

The definition of COPD embraces the concept that the condition may be invoked by an abnormal inflammatory response of the lung to noxious particles and gases.¹³ In this regard, the most important aetiological factor is tobacco smoking, but epidemiological and laboratory studies support the role of other noxious particles and gases such as coal dust, silica and particulate matter from biomass fuels. As the smoke from the cannabis joint contains a mixture of potentially noxious and injurious products, it is plausible that smoking cannabis may be linked to the development of COPD.

The potential for cannabis to be detrimental to lung health was first noted in studies undertaken in California when Tashkin and colleagues recruited a convenience sample of nearly 300 subjects aged 25–49 years who smoked at least ten joints per week or the equivalent of marijuana for at least five years.¹⁴ Applying a modified version of the American Thoracic Society/National Heart, Lung and Blood Institute respiratory questionnaire they found that the symptoms of acute and chronic bronchitis were substantially and significantly more prevalent among marijuana smokers compared with non-marijuana smokers of a similar age. The results were not affected by whether an individual smoked, or did not smoke, tobacco in addition to marijuana.

Later North American studies examined the potential effects of cannabis smoking in the general population by investigating subjects enrolled in several large cohort studies.^{15–17} Bloom and colleagues reported data from a longitudinal household study from Tucson, Arizona.¹⁵ The seventh survey, undertaken from 1981 to 1983, included information on the duration and intensity of non-tobacco (assumed to be marijuana) smoking and the authors reported that the prevalence of respiratory symptoms such as phlegm and wheeze was increased in smokers of non-tobacco cigarettes. As had been observed by Tashkin and colleagues, the results were not affected by whether or not the subjects had smoked additional tobacco. A further study from Tucson reporting respiratory symptoms and pulmonary function in nearly 2,000 subjects aged 15–60 years found that compared with non-smokers, smokers of non-tobacco cigarettes were almost two times more likely to report cough, chronic phlegm and wheeze.¹⁶ Symptoms were most prevalent in those who had smoked for several years and persisted despite quitting smoking.

The third National Health and Nutrition Examination Survey (NHANES III) was used to report a much larger North American general population study in which

Moore and colleagues were able to include nearly 7,000 adults aged 20–59 years.¹⁷ The use of marijuana (defined as self-reported 100+ lifetime use and at least one day of use in the past month) was accompanied by a variety of respiratory symptoms, including chronic bronchitis, coughing on most days, phlegm production, wheezing and chest sounds without a cold. Those who smoked both tobacco and marijuana had a greater prevalence of respiratory symptoms than those who smoked only tobacco. A potentially important public health message was that the marijuana users had similar rates of respiratory symptoms as tobacco users even though they were ten years younger.

While the data on chronic bronchitis and other respiratory symptoms appear reasonably consistent between these different centres, the relationship between smoking cannabis and lung function remains less clear. In a longitudinal study of nearly 400 healthy Caucasian adults who smoked marijuana on a regular basis, Tashkin and colleagues found no significant adverse effect on lung function. The subjects in this study were predominantly men in their early thirties who had consumed an average of 3.5 joints per day for around five years.¹⁸ Although Moore and colleagues reported an initial observation that marijuana smoking was associated with an obstructive ventilatory defect, this disappeared when corrected for other potential confounding factors. However, both of the Tucson studies have suggested that smoking non-tobacco cigarettes was associated with airways obstruction. A more detailed analysis of nearly 900 people studied as part of a population-based study of obstructive lung disease being undertaken in Vancouver, Canada, has shown that regular cannabis smokers were nearly three times more likely than non-smokers to have COPD as defined by spirometric testing.¹⁹

The data from New Zealand, where the other main body of literature on cannabis emerges, are similar. Taylor and colleagues selected a group of 20-year-old cannabis-dependent individuals who had been enrolled in the Dunedin Multidisciplinary Health and Development Study.²⁰ After correcting for tobacco use the authors reported that compared with non-tobacco users, cannabis dependence was associated with an increased odds ratio of reporting respiratory symptoms such as cough and sputum, wheezing apart from colds, exercise-induced shortness of breath and sputum production, nocturnal waking and chest tightness. The frequency of reported symptoms was similar to subjects who smoked between one and ten cigarettes per day. Just over one-third of cannabis-dependent subjects had an obstructive ventilatory defect compared with around one-fifth of non-smokers; the outcomes were independent of co-existing bronchial asthma. A further longitudinal study from the same authors collected data at ages 18, 21 and 26.²¹ For each age an increasing use of cannabis was associated with a decline in first-second

expiratory volume (FEV₁)/vital capacity (VC); however, after controlling for possible confounding factors, only a marginal effect remained. There was no significant interaction between cannabis use and cigarette smoking, which suggested to the authors that cumulative cannabis use and daily cigarette smoking act in an additive fashion.

Investigators from the Greater Wellington region reported data pertaining to symptoms, lung function and the prevalence of emphysema as measured by high-resolution computed tomography (CT) scan in a convenience sample of just over 300 adult subjects.²² Smoking cannabis (predominantly in the form of joints) was accompanied by chest tightness, wheeze, cough and chronic bronchitis and the presence of asthma diagnosed after the age of 16 years. The effects of cannabis smoke and tobacco smoke were additive. Smoking cannabis was also associated with a dose-related impairment of airflow obstruction, large airways function and hyperinflation. The authors estimated that, for measures of airflow obstruction, one cannabis joint had a similar effect to 2.5–5 tobacco cigarettes. However, while cannabis smoking was associated with decreased lung density on a high-resolution CT scan, in contrast to tobacco smoking, macroscopic emphysema was seldom observed.

Most recently, a population-based cohort study from Dunedin, New Zealand, has reported the effects of cannabis on the lung function of just over 1,000 subjects aged 32 years.²³ Cannabis use was associated with higher lung volumes, hyperinflation and increased large-airways resistance, but there was little evidence for airflow obstruction or impairment of gas transfer, as seen with tobacco smoking. The authors suggested that cannabis appears to have different effects on lung structure and function from tobacco and is less likely to result in emphysema.

These observations, although containing some contradictions and inconsistency, have contributed to an emerging concern among respiratory physicians that regular cannabis smoking may promote the development of COPD. Nonetheless, it remains uncertain whether cannabis smoking contributes to the development of emphysema. The data from New Zealand would suggest that the occurrence of emphysema is unusual in cannabis smokers; however, this appears to be frequently observed by UK chest physicians²⁴ and selected case reports have published dramatic bullous disease.^{25,26}

Issues of ethnicity aside, one possible explanation for the apparent differences in the spectrum of pulmonary disease associated with cannabis use may relate to the type of cannabis available and the method of smoking. As mentioned, the most common form of cannabis used in Scotland is cannabis resin, imported from North Africa, which is cut with tobacco and smoked as an unfiltered joint. The resin is often impure, being adulterated with a

range of other contaminants. In North America, cannabis is more usually supplied as marijuana, typically imported from Mexico and, particularly in the earlier studies, the herbal cannabis available is likely to have been of low potency compared with that available today. New Zealand imports very little cannabis, with much of it being grown wild or at home using hydroponic plants, and a greater number of users employ bong. These and other differences may be important in the pattern of disease observed and further studies are needed to investigate the effects of cannabis, given the potential public health agenda if so many young people smoke the drug.

CANNABIS AND PNEUMOTHORAX

Selected case reports and small case series have hinted at an association between pneumothorax and cannabis smoking.^{27–29} In one series, 13 of 15 consecutive patients with spontaneous pneumomediastinum or subcutaneous emphysema admitted to using marijuana extensively before coming to hospital.³⁰ More recently, Beshay and colleagues have reported the findings in 17 young regular marijuana smokers presenting with spontaneous pneumothorax with bullous emphysema, comparing them with the findings of non-marijuana smoking patients presenting during the same 30-month period.³¹ Computed tomography imaging of the lungs revealed multiple bullae at the apex or significant bullous emphysema. Also, in common with other reports, this dramatic emphysema occurred largely in the absence of spirometric abnormalities. Only two patients had reduced FEV₁ and one reduced VC below 50% of predicted. This correlated with the subjectively asymptomatic condition of the patients. Histology showed severe lung emphysema, inflammation and heavily pigmented macrophages.

This pathological description by Beshay and colleagues is reminiscent of the Australian experience of 'bong lung'. Gill reviewed the histopathology of ten known cannabis smokers (although several also used cocaine) who underwent video-assisted thoracoscopic surgery and resection of bullae.³² All the marijuana smokers showed features of 'irregular emphysema' with prominent irregularly dilated airspaces, cysts, blebs and bullae. In addition, they observed massive accumulation of intra-alveolar pigmented histiocytes ('smokers' macrophages') with a desquamative interstitial pneumonia (DIP)-like appearance. However, in contrast to DIP, interstitial scarring and bullous disease were very prominent and there was no radiographical evidence of interstitial lung disease. Gill proposed that this DIP-like pattern with massive accumulation of pigmented histiocytes and pulmonary apical cystic disease may be strongly suggestive of illegal drug use.

The occurrence of pneumothorax and the descriptions of bullous lung disease may lend some weight to the concerns that cannabis smoking is linked to bullous

emphysema; however, not all of the subjects reported in these studies showed evidence of emphysema.

CANNABIS AND PULMONARY INFECTIONS

Cannabis exerts a variety of effects on inflammatory and immune cells and it seems credible to suggest that, as with regular tobacco smoking, regular cannabis smoking may be accompanied by an increased risk of respiratory infections. Moore and colleagues reported an increased odds ratio of self-reported pneumonia,¹⁷ but none of the other studies appear to have reported this endpoint.

Smoking tobacco is known to be associated with an increased risk of developing tuberculosis (TB). To date, no studies have suggested the same from cannabis smoking, but there is evidence that the spread of TB may be facilitated by the shared smoking of cannabis. Munckhof and colleagues reported a cluster of cases of TB occurring in young males from Queensland, Australia, in whom marijuana smoking through bong was common among cases and contacts.³³ Although the most important risk factor for acquiring TB was close household contact with a case, sharing a bong with a case was associated with a more than doubled risk of pulmonary TB.

Variants on the method of cannabis smoking have also been linked to an increased risk of TB transmission. For example, 'hotboxing' describes the behaviour of smoking marijuana inside a car with the windows closed so that users may repeatedly inhale exhaled smoke. Among users who reported or were observed hotboxing, the majority who received a tuberculin skin test had a positive result. 'Shotgunning' refers to inhaling smoke from illicit drugs, then exhaling it directly into another person's mouth. Perhaps not surprisingly, this practice is associated with a high risk of TB transmission.³⁴

The identification of fungal spores in cannabis plants has led to suggestions that smoking the drug may increase the risk of fungal respiratory infections. Pulmonary aspergillosis as a complication of bone marrow transplantation for chronic myeloid leukaemia has been reported in a patient who had smoked marijuana heavily.³⁵ Cultures of the marijuana used by the individual revealed *Aspergillus fumigatus* with morphology and growth characteristics identical to the organism grown from open lung biopsy. Similar reports emphasise the potential importance of smoking cannabis in other immunosuppressed subjects.^{36,37}

CANNABIS AND LUNG CANCER

The cannabis joint is qualitatively similar in terms of tar and carcinogen content to a standard cigarette. Several studies have demonstrated pre-cancerous histological and molecular abnormalities in the respiratory tracts of cannabis smokers, and the carcinogenic effects of

cannabis smoke have been demonstrated in *in vitro* and *in vivo* animal models. However, the problems inherent in the design and power of clinical studies that would provide strong evidence of an association between cannabis smoking and the subsequent development of lung cancer mean that robust evidence may be some way off. Nonetheless, the subject is attracting the attention of researchers. While some studies have failed to identify such links,³⁸ several smaller studies have reported an increased risk of developing lung cancer in relation to smoking cannabis, as hinted at by the basic science.

Investigators from Tunisia reported a hospital-based case-control study including 149 cases of lung cancer and 188 controls.³⁹ As expected, tobacco smoking was significantly associated with an increased risk of lung cancer, with the greatest risks being seen in those that smoked the most; however, lung cancer was seen almost four times more frequently in individuals with past cannabis use (odds ratio 3.7, 95% confidence interval [CI] 1.8–7.5). The association remained statistically significant after adjustment for age, tobacco smoking and occupational exposure.

A hospital-based case-control study from Casablanca, Morocco included 118 incident lung cancer cases and 235 age-, sex- and residence-matched controls.⁴⁰ While tobacco smoking and a history of chronic bronchitis were the strongest risk factors for lung cancer the combined use of hashish/kiff and snuff had an odds ratio of 6.67 (95% CI: 1.65–26.90) and the odds ratio for hashish/kiff (without snuff) was 1.93 (95% CI: 0.57–6.58). A further pooled analysis of three hospital-based case-control studies in Tunisia, Morocco and Algeria identified a total of 430 cases and 778 controls (all male).⁴¹

Adjusting for country, age, tobacco smoking and occupational exposure, the odds ratio for lung cancer was 2.4 (95% CI: 1.6–3.8) for ever cannabis smoking. This association remained after adjustment for lifetime tobacco pack-years as continuous variable. The odds ratio adjusted for intensity of tobacco smoking (cigarette/day) among current tobacco smokers and never cannabis smokers was 10.9 (95% CI: 6.0–19.7) and the odds ratio among current tobacco users and ever cannabis smokers was 18.2 (95% CI: 8.0–41.0). The risk of lung cancer increased with increasing joint-years, but not with increasing dose or duration of cannabis smoking.

Aldington and colleagues conducted a case-control study of lung cancer in adults under the age of 55 years using the New Zealand Cancer Registry and hospital databases.⁴² Interviewer-administered questionnaires were used to assess possible risk factors, including cannabis use. In total, 79 cases of lung cancer and 324 controls were included in the study. In this study those with the heaviest cannabis use (>10.5 joint-years of cannabis use) displayed an increased risk of lung cancer (relative risk 5.7 [95% CI 1.5–21.6]), after adjustment for confounding variables including cigarette smoking.

SUMMARY

Cannabis is a commonly used illegal drug that is mostly smoked. Although the potential adverse respiratory effects have received relatively little attention the studies that have been reported suggest that habitual smoking of cannabis may contribute to the development of COPD, pneumothorax, respiratory infections, including tuberculosis, and lung cancer.

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SELF-ASSESSMENT QUESTIONS

1. The predominant method of taking cannabis in the UK is?

- A. Eating as hash cakes.
- B. Smoking resin with tobacco rolled as a joint.
- C. Smoking resin alone without tobacco rolled as a joint.
- D. Smoking marijuana with tobacco rolled as a joint.
- E. Smoking marijuana without tobacco rolled as a joint.

2. Which one of the following is not true of cannabis?

- A. Δ^9 THC may act to induce bronchial smooth muscle relaxation when taken acutely.
- B. Δ^9 THC binds to naturally occurring receptors in the brain.

- C. The plant grows slowly in a limited range of climatic conditions.
- D. The plant can be difficult to cultivate indoors.
- E. The most potent forms of the drug are derived from female plants.

3. Which of the following is consistently reported in studies investigating regular cannabis smokers?

- A. Symptoms of chronic bronchitis.
- B. An accelerated decline in FEV₁.
- C. The presence of bullous emphysema.
- D. A decreased risk of pneumothorax.
- E. A decreased risk of lung cancer.

4. Which of the following has not been reported in association with cannabis use?

- A. Tuberculosis.
- B. Pneumomediastinum.
- C. Fungal lung infection.
- D. Pneumonia.
- E. Pulmonary carcinoid.

5. Which one of the following statements is accurate?

- A. The cannabis smoked in California is similar to that smoked in Scotland.
- B. Cannabis resin is a predominantly pure drug.
- C. Pneumothorax has not been described in persons smoking cannabis through bongs.
- D. The risk of contracting tuberculosis may be increased by hotboxing.
- E. The use of skunk is declining.

For the answers, please turn to page 382.

INVITATION TO SUBMIT PAPERS

We would like to extend an invitation to all readers of *The Journal of the Royal College of Physicians of Edinburgh* to contribute original material, especially to the clinical section. The *JRCPE* is a peer-reviewed journal with a circulation of 8,000. Its aim is to publish a range of clinical, educational and historical material of cross-specialty interest to the College's international membership.

The *JRCPE* has recently been accepted for Medline indexing and is also currently indexed in Embase, Google Scholar and the Directory of Open Access Journals. The editorial team is keen to continue to improve both the quality of content and its relevance to clinical practice for Fellows and Members. All papers are subject to peer review and our turnaround time for a decision averages only eight weeks.

We would be pleased to consider submissions based on original clinical research, including pilot studies. The *JRCPE* is a particularly good forum for research performed by junior doctors under consultant supervision. We would also consider clinical audits where the 'loop has been closed' and a demonstrable clinical benefit has resulted.

For further information about submissions, please visit: <http://www.rcpe.ac.uk/journal/contributors.php> or e-mail editorial@rcpe.ac.uk. Thank you for your interest in the College's journal.

The editorial team,
The Journal of the Royal College of Physicians of Edinburgh

