



Case Report

Cannabis for Treatment of Intractable Malignant Cough- A Case Report

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1. Introduction

Chronic cough is not uncommonly experienced by patients with cancer. Chronic cough can be a disruptive and exhausting symptom, reported as being very distressing in a quarter of those in the last year of life [1]. Severe cough has an impact on the patient and family in physical, psychological and social domains. Cough can cause issues such as urinary incontinence, syncope, headache, retinal and conjunctival haemorrhage, pneumothorax, pain from fractured ribs and injured muscles, and haemorrhoids [2]. In addition, cough is disruptive to the patient and their family, and can be embarrassing in public. It can interfere with all aspects of function and reduces quality of life [3].

Many cancer symptoms are well managed in clinical practice, but the common symptom of cough has little high level evidence to guide its management. Health professionals use inconsistent approaches to manage cough [3].

There are many possible causes of cough, which can be

- directly related to malignancy such as primary disease, metastases, and lymphangitis carcinomatosa;
- indirectly related to the malignancy such as infections, pleural effusions and pulmonary emboli; and
- conditions not related to cancer, such as asthma, chronic obstructive pulmonary disease, gastro-oesophageal reflux disease with micro-aspiration, or medications such as bleomycin, methotrexate and angiotensin converting enzyme inhibitors (ACEIs).

The range of treatments commonly offered include

- non-pharmacological options such as smoking cessation and saline nebulisers;
- treatments specific to the cause of the cough, such as anti-cancer treatment, antibiotics or beta 2 agonists; and
- non-specific treatments acting on the lungs, pharynx or nervous system such as anti-tussives, opioids, pregabalin and paroxetine [4, 5].

2. Case Report

MJ was diagnosed with adenocarcinoma of the rectum at the age of 38 after presenting with a 2 year history of altered bowel habit. He was initially treated with neoadjuvant capecitabine and radiotherapy. Surgery was delayed until 6 months after diagnosis when a robotic ultralow anterior resection with coccygectomy and IGAM (inferior gluteal artery myo-cutaneous island) flap was performed. At surgery, he was found to have 3 synchronous tumours and 1/19 lymph nodes were positive for adenocarcinoma.

Sixteen months after surgery, restaging scans demonstrated new avid retroperitoneal, retrocrural, posterior mediastinal and subpleural nodules. He was still asymptomatic and continued to work as a truck driver. Two years after surgery, he was found to have enlarging pulmonary and pleural nodules and lymphangitis carcinomatosa. He commenced palliative FOLFOX (Folinic acid, 5 fluorouracil and Oxaliplatin). He was commenced on a course of Dexamethasone which led to diabetes, which did not resolve when steroids were ceased. He stopped working at around this time.

Two months later, he complained of dyspnoea, anorexia and intractable, occasionally productive cough, which had been present for several weeks. He was found to have metastatic disease in the lungs with multiple segmental and subsegmental pulmonary emboli.

The cough was debilitating. He coughed while eating and speaking, making both difficult. He coughed while asleep and cough would disturb his sleep. Episodes of coughing could be associated with breathlessness and occasionally vomiting. It was not altered by posture and did not respond to over the counter anti-tussives, or regular use of inhaled saline, bronchodilators or steroids. Morphine liquid was commenced, even though pain was not an issue, but although it helped initially, it was soon ineffective, and he reduced the dose himself. Codeine linctus was no more effective than morphine. He was taking mirtazapine to stimulate appetite, and this was changed to paroxetine as there is limited case evidence that demonstrated efficacy in cough [4, 5]. However, three months later his cough was unchanged.

He and his wife asked about trying medicinal cannabis for his symptoms, especially poor sleep, poor appetite and vomiting. He had never used cannabis in any form in the past, consistent with survey data on the use of medicinal cannabis in cancer patients [6]. He had been a smoker, but successfully stopped in the first year post diagnosis. The possible role of medicinal cannabis in his situation was discussed. As a way of trying cannabis before investing in medicinal cannabis, a family member obtained some recreational marijuana. His wife converted it to marijuana butter following a recipe found on the internet and baked the butter into rum balls.

On a weekend night (day 0) he ate two rum balls. After noticing no effect in two hours, he ate a further three. Within another hour, he was severely intoxicated from the marijuana. His family were amused by his behaviour, but he soon went to bed and slept without disturbance until mid-morning, which had not occurred for several months. It was not until he had been awake for an hour or so, and he was having breakfast, when his partner mentioned that he had not coughed. In fact, his cough remained absent for over a week. He did not consume any further rum balls.

Eight days after eating the rum balls, another consultation occurred by telehealth. The cough had just started to return the previous day, but the difference from the previous consultation was remarkable. In the entire 30 minute consultation, he only had an occasional cough. During this time, the only other medication commenced was metronidazole for halitosis.

3. Management and Outcome

MJ decided that he did want to try medicinal cannabis to assist with his symptoms of insomnia and improve his general wellbeing. Permits were obtained to prescribe Tilray 10:10 Full Spectrum cannabis oil, which contained 10mg/ml tetrahydrocannabinol (THC) and 10mg/ml cannabidiol (CBD) with traces of other cannabinoids. The 1:1 ratio of THC and CBD is not the same ratio as would be found in most recreational marijuana, which would normally have a much higher ration of THC to CBD.

Three weeks after taking the rum balls MJ had another telehealth consultation. During the telehealth consultation MJ was coughing persistently, holding a towel to his face and occasionally retching after coughing.

Four weeks after day 0, he commenced the medicinal cannabis at 0.25 ml nocte and slowly up titrated the dose. At the next consultation, 6 weeks after day 0, he was taking 0.25 mls mane and 0.5 mls nocte. He reported a significant improvement in the cough. He found higher doses made him feel drugged and drowsy during the day. By altering the dosing schedule, taking a lower dose in the morning and a higher dose at night, he was able to function during the day and suppress the cough so that he was also sleep at night. Medical notes at the time report that the reduction in cough was an unexpected effect of the medicinal cannabis and that “the cough reduction shows dose dependency”. The dose of slow release Morphine which had been commenced for cough was reduced at this consultation.

MJ reported that when his supply of medicinal cannabis at home was running out, he had reduced the dose himself for a period of time. During that time, the cough worsened. At the next consultation, 8 weeks after day 0, the cough was still present, but not as severe as prior to using the cannabis oil. Over time, the dose of cannabis oil increased. At his last consultation, 12 weeks after day 0, he was taking Tilray 25:25 Full Spectrum cannabis oil (THC 25 mg/ml and CBD 25 mg/ml), 0.25mls mane and 0.5 mls nocte with an occasional dose of 0.25 – 0.5mls in the middle of the day. MJ died peacefully at home 4 months after commencing medicinal cannabis.

4. Discussion

The cough is a common symptom in many diseases and its aetiology can includes benign and malignant causes in multiple systems. Often by the time a patient with severe cough first presents for specialist review, they have already tried several over-the-counter anti-tussives, and some of the commonly used prescribed drugs such as beta-2 agonists,

inhaled corticosteroids, and opioids. A Cochrane review titled “Interventions for cough in cancer” [7] in 2015 could not offer any practice guidelines ‘as evidence was limited and of the lowest quality.’ The 2010 and 2015 Cochrane reviews suggested that further studies of cough treatments were urgently needed. The American College of Chest Physicians in 2017 [3], suggested the following graded intervention, although none with strong evidence.

1. Comprehensive assessment to identify co-existing causes linked with cough and treat accordingly.
2. Cough suppression exercises as an alternative treatment or in addition to pharmacological intervention.
3. Endobronchial brachytherapy for suitable tumours.
4. Demulcents (agents that form soothing protective films when administered onto a mucous membrane e.g. butamirate linctus, simple linctus or glycerin-based linctus.
5. Opiate derivatives e.g. codeine, morphine, methadone, dextromethorphan, pholcodine.
6. Nebulised lidocaine or bupivacaine.
7. N-of-1 trials of other drugs, which have not been definitively shown to be effective nor devoid of adverse effects e.g. diazepam, gabapentin, carbamazepine, baclofen, amitriptyline, thalidomide.

Other agents with limited evidence include aprepitant [8, 9] and paroxetine [4, 5]. There are no recent human studies or case series using cannabis in the management of cough, in spite of pre-clinical evidence suggesting a role for cannabinoids in cough. Short-term smoking of marijuana is associated with bronchodilatation while long-term smoking is associated with increased respiratory symptoms suggestive of obstructive lung disease [10].

There is a physiological rationale as to why cannabis may have a role in the suppression of cough. The cough reflex is regulated by G-protein coupled receptors. Agonists of prostanoid receptors and agonists of bradykinin receptors stimulate cough, whereas beta-adrenoceptor agonists and cannabinoids suppress cough [11]. The CB2 receptor is particularly implicated as a site of action for anti-tussives as selective blockade of the CB2 receptor reduces the anti-tussive effect in guinea pigs and human sensory nerves in the airways [12]. This has implications for the development of novel anti-tussives, as CB2 receptors are not expressed in the CNS to the same extent as CB1 receptors [13]. Hence selective CB2 agonists may avoid the psycho-stimulatory adverse effects of non-specific cannabinoids [14].

The case of MJ is interesting, not only because the effect of cannabis on cough was unexpected to both patient and clinician, but also because the effects of recreational marijuana and medicinal cannabis could be compared. In addition, the effect seemed to be dose responsive over time, with the patient and wife reporting that when they decreased the dose, the cough increased in severity. The anti-tussive effect was seen with both recreational and medical forms of cannabis, and the patient was clear that there was a dose response with higher doses causing more adverse effects, but also being more effective for cough.

It can be difficult to assign causation in the setting of a single retrospective case report. However, in MJ, who had not used any form of cannabis previously, only two changes occurred around the time of the dramatic improvement in his cough-the introduction of metronidazole for management of halitosis and introduction of cannabis for management of poor appetite and insomnia. The fluctuation in the impact of the cough mirrored the dose of cannabis, as

did the adverse effects of feeling drugged and sedated. Chronic cough in the setting of malignant disease is a common problem that has a significant impact on the person's quality of life, with little evidence to guide therapy to reduce its severity. Further investigation of the role of medicinal cannabis in the management of intractable cough is warranted.

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