

## Effects of Medical Cannabis on Post-Covid-19 And Post-Vaccination Syndromes

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### Abstract

Post-COVID-19 syndrome may develop after the infected patient has recovered. It is characterized by newly appearing and persistent physical or behavioral symptoms. Vaccination seems to generate similar although milder phenomena. There are currently no known drugs evidently attenuating these symptoms without causing adverse effects. This report describes the successful use of medical cannabis in ameliorating symptoms of three patients with post-COVID-19 and post-vaccination syndromes.

**Keywords:** post-COVID-19 syndrome; COVID-19-post-vaccination syndrome; fatigue; myalgia; arthralgia; neuropathic disorders; medical cannabis.

### Introduction

The present communication reports of successful use of medical cannabis (MC) in three patients with post-COVID-19 or post-vaccination syndromes after common analgesics failed ameliorating their conditions. Stable beneficial effects are proven for as long as MC is administered.

### Case 1

This 60-year-old housewife had presented to a pain clinic; she had a history of Hashimoto thyroiditis, smoking, and L<sub>5</sub>-S<sub>1</sub> disc lesion due to a traumatic fall, minor mixed anxiety/depression and obsessive-compulsive disorder. Prior to confirmation as being infected with SARS-CoV-2, those conditions had been satisfactorily controlled with occasional use of over-the-counter (OTC) compounds or single doses of non-steroidal anti-inflammatory drugs (NSAIDs). She very rarely used opioids. She now complained of intensification and persistence of muscle pain and joint tenderness, generalized fatigue, and disabling depression after minimal physical activities, all starting 2 weeks following her recovery from the COVID-19 infection delta strain. More disturbingly, night sleep became non-restorative and nothing seemed to energize her, leading her to spend most of the time in bed.

The physical examination revealed signs compatible with the patient's complaints, such as tender, painful knots produced by pressure exerted on various "trigger points". These were absent before her COVID-19 infection, and she rated the level of pain as 8-9/10 on a visual-analog scale (VAS). The medications she had used to control these symptoms in the past now barely did so. She was prescribed with new analgesics for several weeks, including tricyclic antidepressants (amitriptyline), pregabalin, duloxetine, NSAIDs, opioids (oxycodone/paracetamol) and various tranquilizers (alprazolam, mirtazapine), they all failed to ameliorate her condition.

Her request for MC was approved by the pain physician and the Israeli Medical Cannabis Agency, which authorizes the provision of medical cannabis in Israel. The patient stated that she had formerly used THC/CBD cannabis at concentrations of THC 20%/CBD 4% which was introduced to her by a family member, and that this relieved most of the symptoms for several hours. She was now provided with the same composition starting at 10 then at a maximal dose of 15 mg/kg/d as sprouts (for inhalation/smoking) divided in three daily doses. Within one week of continuous use, the patient reported significant improvement in her condition with no adverse events. Her pain VAS level decreased to 3-4/10, and she was now able to cook and do housework, feel less feeble, and, importantly, sleep well and wake up refreshed. She was much less depressed, and the spontaneous and pressure-generated myalgia and arthralgia diminished significantly as well. At 4 months since the initiation of treatment with MC, she maintains a stable and near-normal healthy life.

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Medical cannabis treatment is meant to continue for 6 months at least.

## Case 2

This 42-year-old male attorney was seeking relief of symptoms which appeared days after his recovery from COVID-19 strain alpha infection. These included sleep disturbances, alternating between insomnia or hypersomnia, diffused myalgia and arthralgia, and inability to use both palms and fingers, which sometimes seemed swollen. He also had sensations of paresthesia (mainly fingers 4-5 bilaterally). He was no longer capable to concentrate and keep alert during long judicial meetings. In addition, he failed to memorize words, phrases and keep with established schedules. He had to take an afternoon rest for the first time, and became unduly impatient with family members, clients and friends. He experienced a decline in sexual performance which intensified his already disagreeable mood. Finally, the patient described newly neuropathic pain along LT leg L<sub>2-5</sub> spread. Now, unlike then, the back pain became persistent, and he sensed that his legs were weak.

The patient had pain history of low back pain subsequent to a car accident some 22 years before, which was satisfactorily treated as needed with OTC or NSAIDs. A magnetic resonance imaging (MRI) study of his lower back had revealed mild spinal stenosis. After recovering from the COVID-19 infection, he initially consumed OTC drugs and NSAIDs, pregabalin, then opioids (oxycodone/paracetamol, tramadol/paracetamol). He also underwent physiotherapy and acupuncture; none of all afforded him adequate relief of symptoms. Physical examination confirmed the presence of peripheral neuropathic pain and weakness in both legs.

After receiving legal permission as for Case 1, he was provided with amounts of THC/CBD 15%/3% MC at a daily maximal dose of 12 mg/kg as sprouts divided into three daily doses. He reported significant improvement in all symptoms as early as few days of this treatment. At 1.5 months after starting treatment with MC, he rated all memory, behavioral, sexual and sleeping disturbances as 4-5/5 (almost optimal/optimal) compared to 1/5 (bad and incessant/optimal) before initiating treatment. He also reported being able to concentrate in discussing legal issues, put in an almost full working day, and reported being calm and friendly, and he could enjoy a full and restoring night's sleep. His back pain VAS levels decreased from 8 to 3-4/10. He still continued to sense sometimes minimal myalgia and arthralgia, but neuropathic pain disappeared. He described feeling much less depressed, and his former quality of life had been greatly restored. Treatment is still ongoing.

## Case 3

A 43-year-old fashion stylist visited the clinic due to diffused pain, which started several days after receiving the 3<sup>rd</sup> coronavirus vaccination dose ("booster"). She had become unable to grasp fabrics and to use the sewing machine. She had a 6-year history of low thoracic, lumbar and knee pain caused by a fall after having been accidentally tripped. Ordinary OTC drugs satisfactorily helped to manage

backache as needed. The recent vaccination appeared to have induced severe disabling pain at the lumbar region and right knee that even caused a sensation of spontaneous local burning, which spread deep into muscles and bones. She had no strength in her hands to the point of not being able to grasp a glass of water, and had to use a cane for walking due to foot weakness.

Treatment with OTC drugs, NSAIDs or pregabalin, which had been effective before, no longer had any effect. Her family physician then prescribed opioids, including tramadol, tramadol/paracetamol, and oxycodone/paracetamol. When these medications failed to relieve her symptoms but rather caused gastrointestinal and mood-altering side effects, she was prescribed patches of buprenorphine followed by fentanyl which also provided no pain relief, even with increasing dosages. She slept poorly and had become querulous and moody.

Physical examination confirmed myalgia and arthralgia as well as diffused neuropathic pain along the right limb and knee. Computerized tomography (CT) demonstrated a mild L<sub>5-4</sub> bulging disc that, however, did not produce pressure on the thecal sack, while an MRI showed degenerative processes at the right knee. The muscular strength of her hands, especially the right one, were below normal, with the grip of the right hand being weaker than that of the left one. The examination also revealed bilateral foot weakness and unstable walking, as well as limited right knee flexion and rotation. She appeared to be emotionally desperate.

This patient was granted legal permission to use MC, starting at 10 mg and increasing it to a maximal dose of 15 mg/kg/d. Since she had experienced its use in the past, the concentration prescribed to her was 20% THC/4% CBD. Within one week after starting inhaling it, she reported significant attenuation of the neuropathic pain, better night sleep, and substantial increase in the strength of her hands. Her VAS back pain decreased from 8/10 (when using fentanyl patch) to 4/10. She slowly discontinued opioids and NSAIDs. Seventy days into treatment with MC, the patient returned to her pre-vaccination physical status, most notably resuming her work as a stylist and celebrating the return of normal sensation in her palms and fingers and no need of a cane to walk confidently. There were no adverse events associate with the cannabis protocol. Treatment is planned to be weaned off soon.

## Discussion

Most patients who had experienced various forms of COVID-19 infection recover completely within weeks. However, some will experience a continuation of symptoms, their intensification or newly emerging ones shortly after being declared virus free. These symptoms can appear even if illness had been mild or altogether asymptomatic. Warning signs include fatigue, joint and muscle pain, memory loss, inability to concentrate, sleep problems, headache, depression and anxiety, dizziness, and more [1,2]. This post-COVID-19 syndrome (also known as long COVID-19, long-haul COVID-19, post-acute COVID-19, long-term effects of COVID, or chronic COVID) may leave patients incapacitated for many months.

Vaccination is known to sometimes generate undesired effects of varying degrees, such as those after influenza vaccination [3] or as reported after immunization with the SARS-CoV-2 BNT162b2 vaccine (the Pfizer-BioNTech vaccine) [4-6]. The pathophysiological mechanisms that connect the post-COVID-19 syndrome to the above-mentioned symptoms are probably late nociceptive activation and central anomalous sensitization. Pennisi et al [7] observed that post-COVID-19 syndrome could intensify by repercussions of earlier nociceptive anomalies, social isolation, hospitalization-related stress, anxiety, and fear of dying, also resulting in depression or post-traumatic stress disorder-related phenomena. Although yet unproven by random controlled trials, over 30% of the elderly as well as individuals of all ages with pre-existing pathological conditions, reportedly complained of debilitating conditions for weeks or months after infection by COVID-19 [8]. These explain why the mentioned physical and neurological ailments that linger over time may worsen after minimal physical or mental activities, including unexplained depressive states and anxiety [1,2,9,10]. Indeed, as reported very recently by Oaklander and colleagues, long COVID sickness is associated with characteristic small-fiber neuropathy, due to the infection-triggered dysregulation [11]. Vaccination can also be the cause to similar multi-symptom conditions.

Medical cannabis was shown to relieve intense pain, such as arthralgia, myalgia, arthritis and other bone- or ligament-associated sufferings [12,13], as well as deterioration in mood and emotional states [14]. The mechanism by which the neurophysiological network responds to the compound remains partly unclear.

The feasibility of MC to attenuate the post-COVID-19-associated persistent symptoms, and to allow patients to return to their earlier lifestyles, has not been described before. The three patients described in this report had histories of satisfactorily controlled mild malaise before being infected. They all had been physically and mentally active; the chronic-COVID phenomena changed their lives to the point of rendering them too weak to even minimally manage their habitual daily activities. All these correlate to emerging evidence suggesting infection-triggered immune or small-fiber dysregulation as common mechanisms to post-COVID or vaccination symptoms.

Especially interesting is the applicability of MC for alleviating post-vaccination syndrome, which prove restorative for months, with no relapses or adverse effects whatsoever. Various drugs were provided to patient 3, including powerful opioids. While MC is not advocated as the first-line analgesic in post-vaccination patients, the results of its use in this patient point to its efficacy in alleviating pain, restoring daily functionality and minimizing neuropathic disturbances.

We reckoned that post-long-COVID or post-vaccination abnormal neural arousal would respond similarly to neuropathic pain as after trauma that can be treated with MC [15]. This was the basis of the decision to grant MC to the three patients in this report. Ware et al showed that a

concentration dose of 9.4% tetrahydrocannabinol (THC) herbal cannabis tid adequately reduced intense pain and improved functionality and sleep, while being well tolerated by patients with chronic neuropathic pain [16]. The reasons for prescribing the patients with higher doses were threefold. First, higher doses are frequently prescribed to non-post-COVID-19 patients complaining of weakness, myalgia, arthralgia, and correlated syndromes. Reasonably, long-COVID or vaccination-induced PNP could involve neuromechanisms similar to those up-and-coming in chronic pain sufferers. Second, the useful protocol was arbitrarily, but successfully used by the first patient before being cared in the clinic. Finally, THC was combined with CBD, which would moderate psychoactive effects that could be induced by high THC concentrations.

This report is the first of its kind and is of clinical importance, since there are no documented compounds that effectively attenuate various neuropathological complaints following long COVID-19 infection or vaccination. As recommended by Hill et al [17], this line of therapy was chosen after the first- and second-line analgesics and tranquilizers, including opioids, had not ameliorated patients' conditions but rather produced adverse effects. Indeed, Herkenham et al demonstrated that cannabis possesses a superior safety profile compared to many other line 1 or 2 analgesics used in the community for chronic pain, even in cases of overdose, due to the lack of CB1 receptors in the brainstem or cardiorespiratory centers [18]. Although THC-mediated side effects are dose-dependent, the lack of such occurrences in the current three patients supports the use of the reported protocols. Gradual increase in dose and concentration of combined CBD/THC is important in preventing adverse effects. Since quick tolerance to psychoactive effects of cannabis is also obtained within days, without inducing tolerance to the benefits, uninterrupted maintenance of the same daily dose is most essential [19], as maintained in the current patients. This is in stark contrast to opioids where treatment protocols characteristically require augmentation. Since a single dose of MC is ineffective in generating sustained neuropharmacological effects over time [20], continuous use is mandated and evaluation of its therapeutic efficacy should start not earlier than 5-6 days [16] into treatment, as deemed appropriate by the treating physician.

Finally, the reason for prescribing the Patient 1 with the mixture of THC 20%/CBD 4% was her earlier exposure to that mixture. The rationalization was that it would be pharmacologically unwise to prescribe her with lower concentrations after her brain had already been reliant upon that therapeutic protocol. Had the earlier "introduction" of the patient to cannabis not taken place, as was the case in patient 2, it would have been more prudent to start treatment with a lower concentration and quantity ("start low, go slow").

## Conclusions

Medical cannabis, at a mixtures of THC 15%-20% and CBD 3-4%, administered twice to three daily times at a maximal daily dose of 12-15 mg/kg, proved to be an optimal protocol for attenuating post-COVID-19 physical and mental sequelae as well as post-vaccination malaise, without evoking

adverse effects. The worldwide COVID-19 pandemic will probably be around for many years, thus doses and compositions of MC need to be tested with the aim of identifying the optimal therapeutic protocol in such occasions.

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