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Integration of Cannabis Extract Tetrahydrocannabinol:Cannabidiol in an Interdisciplinary Therapy Setting: A Case of Chronic Multilocular Pain Disorder

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Abstract
Multilocular pain syndromes with advanced chronification lead to a significant reduction in the quality of life of patients. The administration of cannabis is currently being discussed in the context of therapy-resistant pain and increasing opiate abuse. In this case study, possible side effects from the administration of a cannabis extract tetrahydrocannabinol:cannabidiol are examined. Furthermore, the effect on pain intensity and sleep quality is recorded. Due to numerous comorbidities in the patient, interactions with other medications are documented.

Introduction

Many patients with chronic pain are prescribed opiates. However, these often do not bring the desired effect or are associated with unfavorable side effects. The use of opiates has steadily increased, leading to an increase in mortality [1]. Chronic pain patients are increasingly looking for alternative treatment options. Therapy with cannabinoids has gained in importance in recent years.

Medical cannabis refers to the use of cannabis or cannabinoids as a medical therapy to treat serious medical conditions and/or relieve symptoms. The cannabinoids include plant substances tetrahydrocannabinol (THC), cannabidiol (CBD), as well as cannabinol and cannabichromene. Plant compounds influence the cannabinoid system. Type 1 cannabinoid receptors are found in the central nervous system.

Type 2 cannabinoid receptors occur in the immune, digestive, or the reproductive system, but they are also found, for example, in bones, skin, or lungs. Cannabis is already used in many diseases. There is also increasing research into the use of cannabis, for example, in the treatment of cancer, multiple sclerosis, anxiety disorders, sleep disorders, tourette's syndrome, fibromyalgia, and other diseases [2–5].

An older meta-analysis on the effectiveness of cannabis in chronic pain shows moderate effects but also side effects [6]. Therefore, the safety of administering cannabis for various diseases is also the subject of scientific studies [7, 8]. The administration of THC can lead to an increase in heart rate and blood pressure. This can espe-

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Table 1. Previous medication

Duloxetine 120 mg (1 - - -)	Duloxetine is a drug from the group of selective serotonin-norepinephrine reuptake inhibitors and is used, among other things, in the treatment of depression and generalized anxiety disorders.
Pramipexole 0.18 mg (- - - 1)	Pramipexole is a dopamine agonist. Used here for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome.
Trazodone 100 mg (- - - 1):	The antidepressant trazodone belongs to the group of SARI and acts mainly as an antagonist at the 5-HT2A receptors and, to a lesser extent, as a serotonin reuptake inhibitor.
Levodopa/benserazide 100/25 mg (- - - 1)	A medicine that contains two active substances. Levodopa, also L-DOPA, a nonproteinogenic α-amino acid that is formed in the body from tyrosine with the help of the enzyme tyrosine hydroxylase. Benserazide is a drug from the group of L-DOPA decarboxylase inhibitors. The active ingredient benserazide inhibits the breakdown of the active ingredient levodopa in the body, so that a lower dose can be given (for the treatment of restless legs syndrome, to improve restlessness during sleep and sleep itself).
Promethazine 25 mg (- - - 1):	The active ingredient promethazine is approved for the treatment of restlessness, and agitation in the context of underlying psychiatric diseases and acute allergic reactions when a calming effect is also desired.
Metamizole 500 mg (1- 1 -)	Metamizole has an analgesic, antipyretic, and antispasmodic effect. It is a nonopioid analgesic.
Budesonide 200 µg	Budesonide is a synthetic glucocorticoid and is used by the patient as a drug for the local treatment of bronchial asthma.
Atorvastatin 10 mg (- - 1 -)	Atorvastatin is a drug from the group of statins that is used to treat hypercholesterolemia.
Magnesiocard 10 mmol (- - - 1)	Magnesiocard contains the organic compound magnesium aspartate hydrochloride. Used to treat magnesium deficiencies that require therapy; in the case of proven magnesium deficiency if it is the cause of muscle activity disorders.

SARI, serotonin antagonist reuptake inhibitor; L-DOPA, L-3,4-dihydroxyphenylalanine.

cially occur in patients with heart disease or risk factors immediately after cannabis administration. The reason for this is the stimulation of the sympathetic and the inhibition of the parasympathetic nervous system. These effects can trigger cardiac arrhythmias [9, 10]. The most reported side effects of CBD administration include diarrhea, fever, drowsiness, decreased appetite, and somnolence [11, 12].

Nevertheless, cannabis is moving into the focus of pain therapy since pain relief and the associated improvement in quality of life are desired with a medium-term reduction in opioid consumption. Two essentially different application forms are available for this: inhalation of cannabis blossoms with a medical vaporizer and oral intake of cannabis extracts (drops).

The pharmacokinetic properties of CBD are like those of THC, so that the active ingredients can be combined in a meaningful way from a pharmacokinetic point of view [13]. CBD has anticonvulsant, anxiolytic, sedative, and anti-inflammatory effects [14, 15]. THC, on the other hand, has a primarily analgesic, antispasmodic, and appetite-stimulating effect [16, 17]. The aim of this case study was to investigate the effect of a full-spectrum extract combining THC and CBD considering side effects and effects on blood pressure.

Case Report

The 63-year-old female patient was admitted to inpatient pain therapy with multilocular chronic acute exacerbated pain syndrome. In the foreground of the pain disorder were the pain diagnosis of cervicobrachial syndrome, headache, fibromyalgia, degenerative lumbar spine syndrome. The patient also had polyarthritis, carpal tunnel syndrome, and osteoarthritis.

The existing depression and anxiety were treated with duloxetine and trazodone. Due to severe idiopathic restless legs syndrome, the patient took pramipexole and levodopa/benserazide.

Due to asthma, budesonide was prescribed. To reduce high cholesterol, the patient took atorvastatin, and to treat her pain she took metamizole.

The patient also stated that she suffered from pain-related sleep disorders and tinnitus. A list of previous medical prescriptions is given in Table 1. The patient did not want to change her existing medication.

The patient (married, three children) was admitted to hospital because of massive whole-body pain (intensity of 8/10 on the visual analogue scale), which significantly restricts daily activity. The pain had increased again for 5–6 months and had steadily worsened in the last few weeks. The patient reported severe cervical pain radiating down her right arm and neck. Turning head to the right is restricted due to the pain. The pain radiated from the neck over the back of the head to the forehead and temples. The headache attacks are pronounced in the neck and back of the head and occur daily. The patient was very sensitive to touch all over her body and head. The patient continued to complain about lumbar spine complaints radiating through the sacroiliac joint into the legs. There was severe movement-dependent pain in the middle and lower thoracic spine. Furthermore, indication of a significant increase in pain in the hip on the left with known inflammation of the mucous membrane with bursitis trochanterica on the left. Severe pain in the right knee also had an immobilizing effect. Feet and hands fall asleep. The patient reported muscle cramps and restless legs at night. For the last 2 weeks, she has been suffering from dizziness that has appeared in a disorderly manner and has led to insecurity. The character of the pain was described as stabbing, pressing, pulling, spasmodic, and burning in the case of pain peaks.

The patient stated that the pain was constant and occurs regardless of the time of day. The pain was made worse by physical activity or uncomfortable head/body position and also due to stress, hectic pace, insufficient sleep, and in the cold season.

The patient was currently totally exhausted, "physically and mentally broken." She complained of feelings of insufficiency, lack of zest for life, lack of energy, difficulty concentrating, feelings of guilt, listlessness, and depression. Under the stress, her tinnitus also increased with whistling and hissing on both sides.

The patient was under permanent orthopedic care. In the last few months, she has had multiple infiltrations in the joints (hip and knee) and CT-guided injections in the lumbar and cervical spine on both sides. This treatment brought only short-term success. In January 2022, with known trochanteric bursitis on the left, cortisone shock therapy with prednisolone of 30 mg was carried out for 3 days. Below that, the condition improved only slightly, but unfortunately not permanently. The patient was also under psychiatric treatment. With therapy-resistant pain, the patient was admitted to the Waldhaus Clinic (acute clinic for internal medicine, pain therapy, and patient-centered medicine) for optimization of pain therapy and psychosomatic stabilization for multimodal therapy.

Therapy and Progress

A detailed pain history was taken, laboratory parameter, and previous medication was recorded (Table 1). The patient's laboratory values were unremarkable in the normal range.

In view of the constellation of symptoms and the resistance to outpatient therapy, an interdisciplinary, multimodal therapy was carried out with orthopedic/rheumatological and pain therapy/anesthesiologic co-supervision. The specialist in rheumatology diagnosed an additional fibromyalgia syndrome with moderate depression.

From a pain therapy/anesthesiologic point of view, the current pain exacerbation was caused by multiple factors (see diagnoses) in multimorbid chronic pain patients. The increased muscle tension and sleep disorders contributed to the inner restlessness, excitability, exhaustion, and further increase in pain.

Analgesia with Cannabis Extract THC/CBD

10:10 was carried out under the supervision and close monitoring of the pain therapist after detailed information and with the approval of the health insurance company. This was dosed up gradually. The pain therapist recommended careful dosing of the cannabis preparation with a slow dose increase according to the scheme to 0.25 mL every 3 days.

In terms of pain therapy, acupuncture, and therapeutic local anesthesia of the right cervical spine with 2 × 2.5 mL procaine, 1% were carried out to relieve pain and break through the constant pain. The patient received Magnesiocard at night to relax the muscles.

As part of the multimodal therapy, there were also high-frequency physical and physiotherapeutic units, draining procedures, relaxation procedures, phytotherapy, behavioral therapy, regulatory therapy, movement therapy, and hydro-/thermotherapy. The patient participated in the pain management group, during which work was carried out toward the modification and assessment of pain-triggering and pain-maintaining factors. The patient was taught specific relaxation techniques as well as mental methods for pain management and pain distancing. Dealing with the disease and coping strategies were focused on in the individual therapeutic sessions.

From day 4 (start of cannabis dosing) until discharge, the dosage of cannabis extract THC/CBD 10:10 was stepped from 0.25 mL twice daily to 0.5 mL twice daily. Blood pressure and heart rate were checked three times a day during the hospital stay. The result of the monitoring is shown in Figure 1. With a dose of 0.5 mL twice daily, hypotonic blood pressure values of 95–110 mm Hg systolic could be measured in the patient. At the end of the stay, the patients were able to sleep better, and better, and pain-related sleep disorders improved. A reduction in pain from VAS 8/10 to VAS-4/10 was documented by the time of discharge.

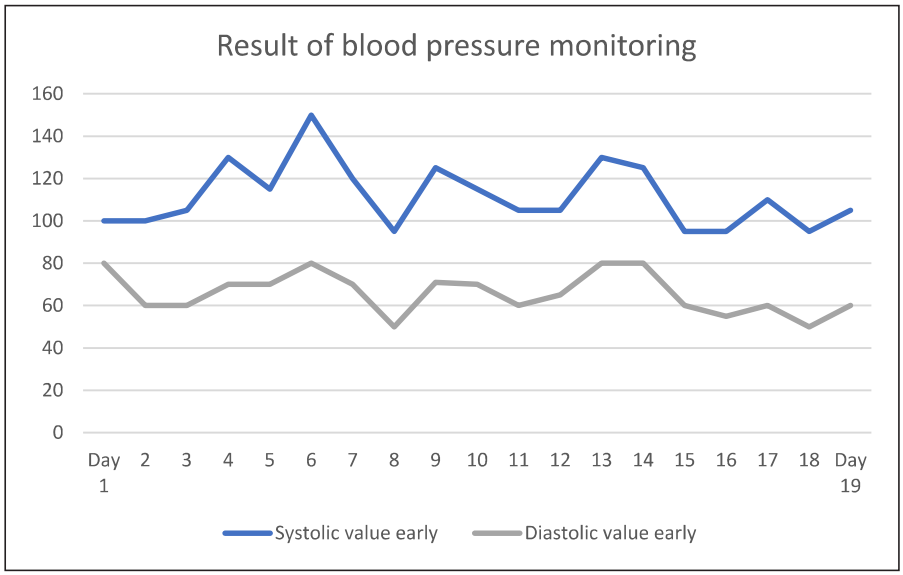

Fig. 1. Results of blood pressure monitoring under the administration of THC/CBD.

Table 2. Side effects and symptoms associated with cannabis administration

	Yes day 4	No day 4	Yes day 19	No day 19
Confusion		x		x
Depression		x		x
Hyperarousal		x		x
Memory disorders		x		x
Lack of concentration		x		x
Sleepiness		x		x
Dizziness		x		x
Blurred vision		x		x
Speech disorders		x		x
Change in appetite		x		x
Altered sense of taste		x		x
Dry mouth	x		x	
Constipation		x		x
Diarrhea		x		x
Nausea		x		x
Vomit		x		x
Mouth discomfort including burning		x		x
Lack of energy		x		x
Feeling weak		x		x
General malaise		x		x
Discomfort		x		x
Feeling drunk		x		x
Loss of balance		x		x
Risk of falling		x		x
Miscellaneous		x		x

The patient's body weight remained constant during administration of cannabis extracts. The side effects and symptoms associated with cannabis administration were recorded on the day of cannabis administration and on day 19 (discharge day from the hospital) and are shown in Table 2. The patient reported only a dry mouth.

Conclusion

In the present case study, the phytocannabinoids Δ9-THC and CBD were administered as a full-spectrum extract 10:10 mg (10:10 LGP Classic, little green pharma). The administration of oral THC:CBD cannabis extract

for the prevention of nausea and vomiting caused by refractory chemotherapy was investigated in a multicenter, randomized, placebo-controlled phase II/III study. A significant improvement in the control of chemotherapy-induced nausea and vomiting was observed [18]. Studies also show that the dose of opiates could be reduced by the administration of medicinal cannabis [19–21]. In this case study, after the administration of the cannabis extract, the administration of metamizole (nonopioid analgesic) could be discontinued during therapy.

In preclinical studies, full-spectrum cannabis extract shows anti-inflammatory and analgesic effects in addition to pain-relieving effects [22, 23]. Despite stopping the analgesic, the pain intensity VAS 8/10 (time of admission to the hospital) was reduced to the level of VAS 4/10 at discharge. The quality of sleep also improved over time. The mental state at the time of admission to the hospital was poor, but continuously improved until the end of the stay. This may be due to the antidepressant effect of CBD [24].

The only side effects the patient reported on day 4 (start of cannabis therapy) and day 19 (requestioning) were dry mouth. This is one of the most common side effects, along with dizziness, drowsiness, and weakness [25, 26]. Initially, the blood pressure values fluctuated, especially the systolic value, but over time the blood pressure values were in the normal range, while the diastolic value was rather low.

No interactions with the other drugs (Table 1) due to the administration of the cannabis extract could be determined. It must also be considered that the cannabis product chemotypes offered are constantly evolving (e.g., CBD-dominant, THC-dominant, and so on) [27]. Therefore, it is necessary for physicians to carefully consider the Δ9-THC and/or CBD content of the products. THC can impair cognitive function and should not be given to people with angina pectoris or myocardial infarction.

More research is needed into the effectiveness and interaction of cannabis with other medications in chronic pain patients. It is also important to involve the patient in the therapy decision and to measure patient-related outcomes.

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Statement of Ethics

This retrospective case review of patient data did not require ethical approval in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Alternative Medical Products (AMP) held out the prospect of paying the APC.

Author Contributions

Tobias Romeyke contributed to the research design, data collection, and manuscript writing. Rudolf Westfal reviewed and revised the manuscript.

Data Availability Statement

The data that support the findings of this case report are not publicly available to protect the individual's anonymity. Further inquiries can be directed to the corresponding author.

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