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Medical Cannabis Alleviates Chronic Neuropathic Pain Effectively and Sustainably without Severe Adverse Effect: A Retrospective Study on 99 Cases

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Keywords
Medical cannabis · Neuropathic pain · Cannabinoids · Sleep disturbance · Side effect

Abstract
Introduction: Medical cannabis may provide a treatment option for chronic neuropathic pain. However, empirical disease-specific data are scarce. ***Methods:*** This is a retrospective observational study including 99 patients with chronic neuropathic pain. These patients received medical cannabis by means of inhaling dried flowers with tetrahydrocannabinol content of <12–22% at a maximal daily dose of 0.15–1 g. Up to six follow-ups were carried out at intervals of 4–6 weeks. Pain severity, sleep disturbance, general improvement, side effects, and therapy tolerance at the follow-up consultations were assessed in interviews and compared with the baseline data using non-parametric Wilcoxon signed-rank test. ***Results:*** Within 6 weeks on the therapy, median of the pain scores decreased significantly from 7.5 to 4.0 ($p < 0.001$). The proportion of patients with severe pain (score >6) decreased from 96% to 16% ($p < 0.001$). Sleep disturbance was significantly improved with the median of the scores decreased from 8.0 to 2.0 ($p < 0.001$). These improvements were sustained over a period of up to 6 months. There were no severe adverse events reported. Mild side effects reported were dryness in mucous tissue (5.4%), fatigue (4.8%), and increased appetite (2.7%). Therapy tolerance was reported in 91% of the interviews. ***Conclusion:*** Medical cannabis is safe and highly effective for treating neuropathic pain and concomitant sleep disturbance.

Introduction

Neuropathic pain has its origin in lesions or diseases affecting the central or peripheral nervous system [1, 2]. The primary cause of peripheral neuropathic pain is the response to damage or irritation of the nerves. Further, nociceptive afferent fibres may remain active in the absent stimulus and produce ectopic discharges at various points on the affected nerve. In addition, intact nerves close to the injury may also be activated via local transmission.

The perception of pain is subjective and differs largely in each individual. The most commonly used tool in the clinical setting to measure pain is the numeric rating

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scale, which describes pain severity from 0 to 10. According to the German Pain Society (schmerzgesellschaft.de), pain scores above 6 are defined as severe pain, which significantly affects patients' quality of life [3]. Similarly, sleep disturbance can also be measured by a numeric scale from 0 to 10. Sleep disturbance is one major comorbidity of severe pain and also a major outcome parameter for pain therapies [1].

The expression of neuropathic pain is highly individual and symptoms as well as response of patients to various analgesics, antidepressants, anti-epileptics, or opioid therapy vary greatly. Unfortunately, treatment of neuropathic pain frequently remains unsuccessful even after multiple trials with various analgesics. Strategies for stratifying neuropathic pain into subtypes and optimizing therapies accordingly did not prove as satisfactory as expected. In addition, the side effects of analgesics must always be weighed against the patients' general health and mental condition [1].

Studies demonstrated a pain-relieving effect of cannabis medication with a low side-effect profile [4–9]. An inhibition of pain impulse transmission is assumed for medical cannabis. However, the exact mechanism is not yet fully understood [10]. In 2017, medical cannabis was legalized in Germany for patients suffering from a chronic disease for which conventional treatment methods have already been exhausted. The German Pain Society (Deutsche Schmerzgesellschaft) lists neuropathic pain as one major indication for the therapy with medical cannabis [11].

The primary data-based evidence for the medical use of cannabis-based medicines is characterized by inconsistencies due to several factors. In terms of efficacy for chronic pain, the evidence suggests that cannabis-based medicines can contribute to meaningful reductions in symptom burden in some cases with chronic pain [12, 13]. At this still early stage of adoption of medical cannabis treatment in Germany, initial experience and empirical data are valuable yet scarce. The aim of our study was to retrospectively evaluate the readily available data of outcomes in a cohort of 99 patients with chronic neuropathic pain, focussing on alleviation of pain symptoms, improvement of concomitant sleep disturbance and tolerance of the therapy with medical cannabis.

Materials and Methods

This is a retrospective, observatory study using anonymized data provided by Algea Care GmbH (www.algeacare.com), a German telemedicine platform for the treatment of chronic diseases with medical cannabis. All methods were performed in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all patients for using their data in anonymized form for medical studies. There is no study-related intervention or any study-related change in the routine treatment protocol. Data of the patients were evaluated and only the statistical results were presented in the manuscript. Based on these features of the study, the Ethics Committee of the Hamburg Medical Association waivered an approval (waiver certification: 2022-300242-WF).

Patient Selection

Patients above the age of 18 with diagnosed chronic (minimum 3 months) neuropathic pain, high severity of symptoms, and exhausted treatment options were eligible for the therapy. To avoid serious side effects, patients who have or had the following contraindications were excluded from the medical cannabis therapy: severe personality disorder, psychosis, or severe cardiovascular disease. Pregnant and nursing women were also excluded. Patients were excluded if they showed criminal drug convictions.

Enrolment, Treatment, and Follow-Up

Firstly, patients registered themselves on the platform (www.algeacare.com), filled out a medical questionnaire, and submitted medical history documents. Secondly, patient data were reviewed and evaluated by the Algea Care medical staff and those considered eligible for medical cannabis treatment were further examined by a collaborating physician. Thirdly, for patients enrolled for the therapy, medical cannabis was prescribed and digital follow-up video consultations with a physician were scheduled every 4–6 weeks.

Medical cannabis was available at pharmacies as dried flowers on prescription. Patients were instructed to inhale cannabinoids via a vaporizer by heating cannabis flowers. With inhalation via vaporizer potentially harmful substances are avoided. One patient took tetrahydrocannabinol extract orally. The choice of administration scheme was left to the patients individually. Some patients inhaled at a fixed time, some inhaled when they had time and other patients inhaled when they suffered pain attack.

Data Evaluation

Patient data between July 2021 and September 2021 were selected for the evaluation in the present study and completely anonymized. Written informed consent was obtained from all patients for using their data in anonymized form for medical studies. Only the results of the statistic evaluation are presented in the publication. No information from individual cases was included.

Pain and sleep disturbance were scaled from 0 to 10. These scores at baseline were compared with those at the first follow-up using a non-parametric Wilcoxon signed-rank test with two-tailed hypothesis. The significance level was set at 0.05. The median of difference between the two time points, the 95% confidential intervals, and the effect size r was also calculated. Patients with pain scores above 6 were classified as having "severe pain" according to the German Pain Society (www.schmerzgesellschaft.de).

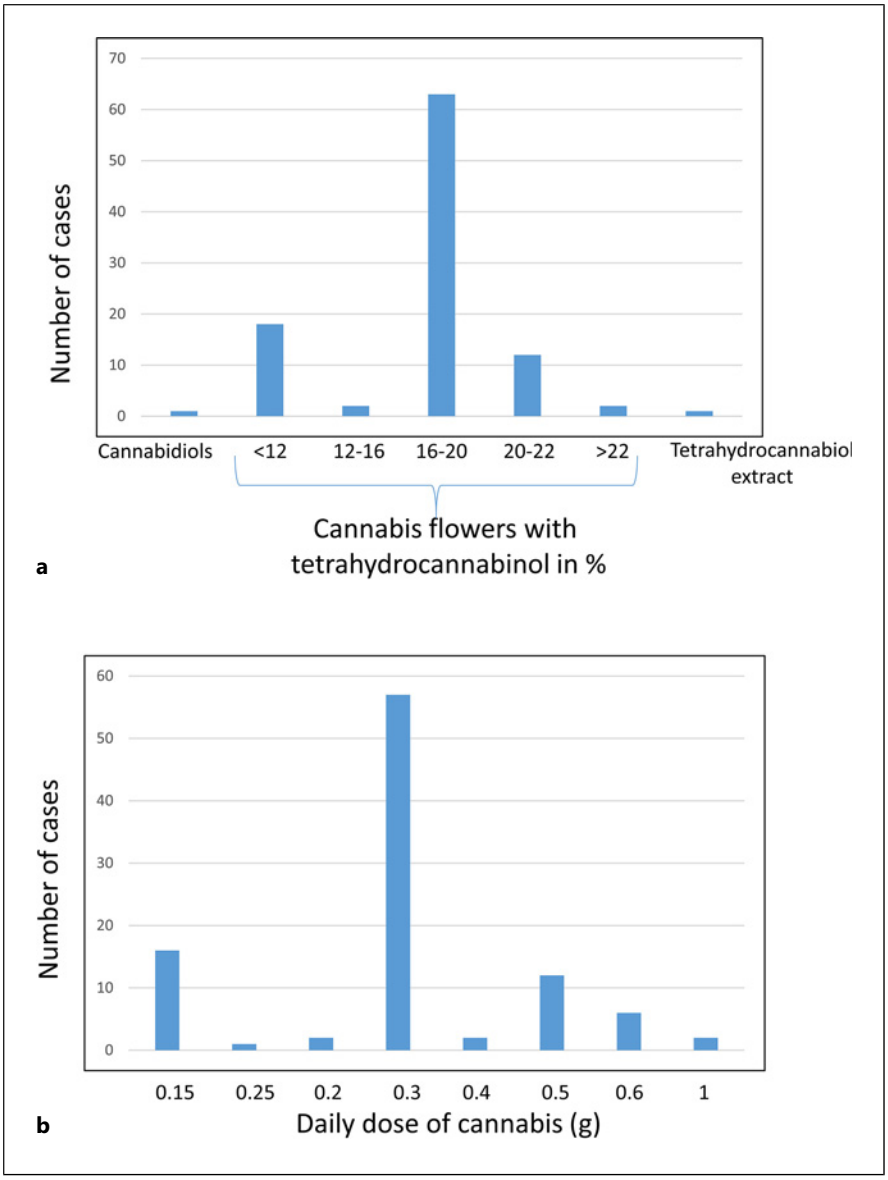

Fig. 1. Types (**a**) and dose (**b**) of medical cannabis administrated to the patients. Medical cannabis flowers were divided into groups according to their content of tetrahydrocannabinol.

Results

Between July 2021 and September 2021, 99 patients with diagnosed chronic neuropathic pain entered the treatment. Patients were between 20 and 81 years old (mean 38 years) and 87% were male. The content of tetrahydrocannabinol of the medical cannabis varied from <12 to 22% whereas the most frequently (64%) used ones had 16–22% tetrahydrocannabinol (Fig. 1a). The maximal daily dose was between 0.15 and 1 g whereas the most frequent dose was 0.3 g/day (58%) followed by 0.15 g/day (16%) and 0.5 g/day (12%) as shown in Figure 1b.

Pain

At the baseline, the majority of the patients had severe pain: the median pain score was 7.5 (out of the maximum of 10) and 96% of the patients had pain scores over 6. At the first follow-up consultation, which was within 6 weeks from start of therapy, pain was significantly ($p < 0.001$) reduced to a median pain score of 3.75. More parameters of the statistical evaluation are presented in Table 1. At the subsequent five follow-up consultations, the pain score further decreased slightly to 3.5 and 3 and stabilized as shown in Figure 2a. The proportion of patients with severe pain (pain score >6) decreased from 96% at baseline to 15% at the first follow-up consultation

Table 1. Significant improvement in pain and sleep disturbance within 6 weeks

Parameter	Sample size	*p* value	Median of scale improvement (95% confidence interval)	Effect size
Pain	39	<0.001	3.75 (3.25–4.25)	0.61
Sleep disturbance	79	<0.001	5.50 (4.75–6.00)	0.58

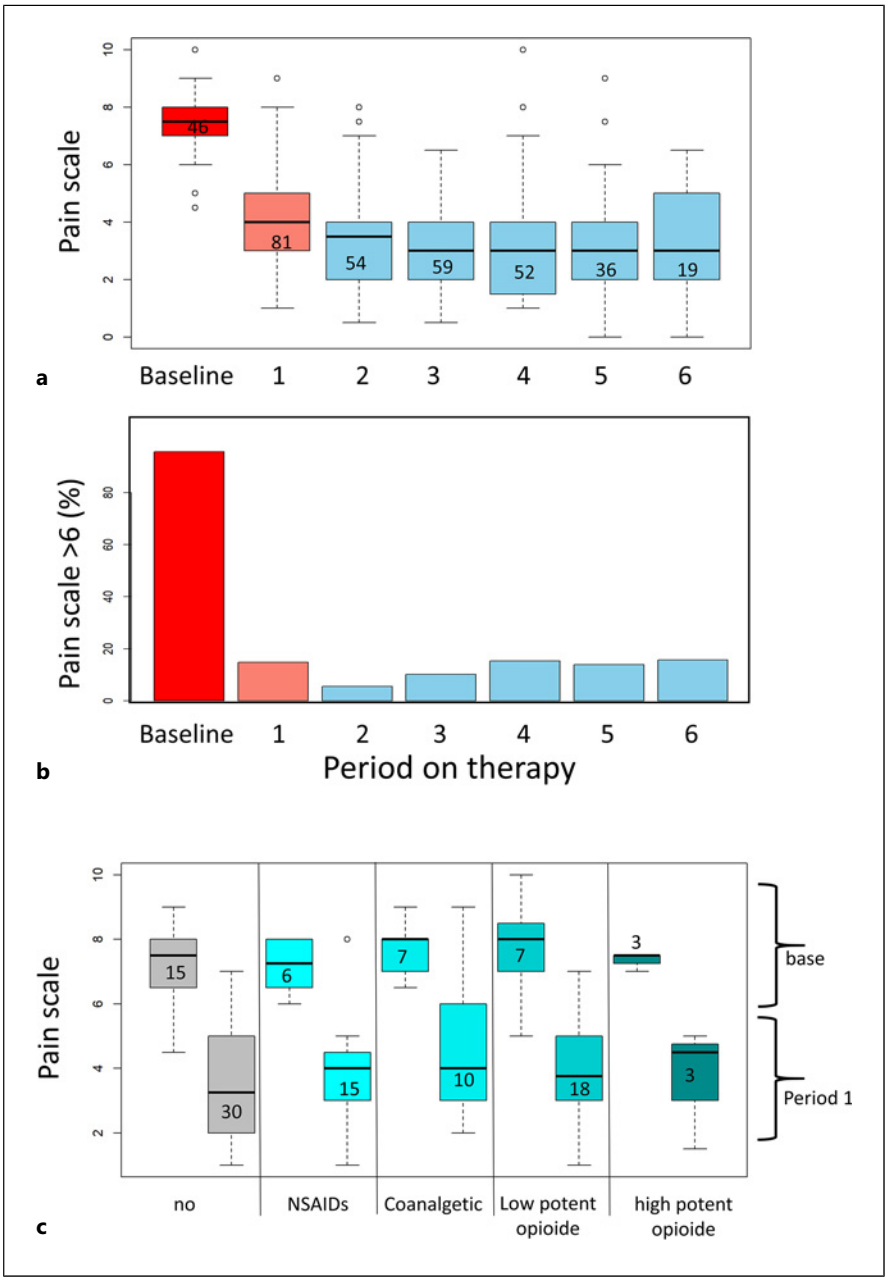

Fig. 2. Pain alleviation with medical cannabis. **a** Boxplots of pain scores at baseline (before therapy) and at each follow-up consultation during therapy. **b** Proportion of cases with severe pain (defined by scores >6 on NRS) at baseline and at each follow-up consultation during therapy. **c** Pain scores at baseline (left in each group) and first follow-up consultation (right in each group) in each group of patients with different categories of analgesics (indicated in the graph). Numbers of cases with available data are given in the respective boxes.

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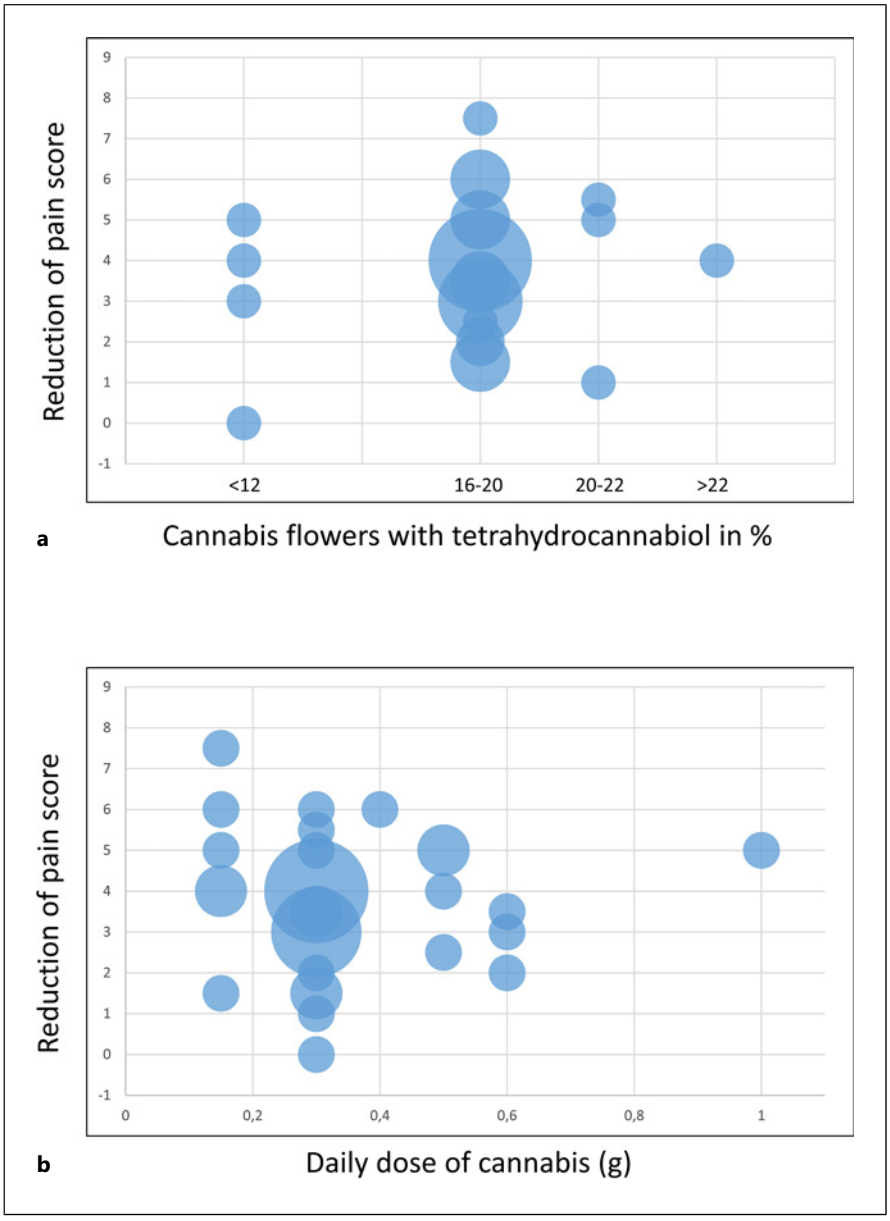

Fig. 3. Lack of correlation between the improvement of pain with neither type (**a**) nor daily dose (**b**) of cannabis. Data points consisting of multiple cases are in larger circles.

($p < 0.001$) and was sustained until the end of the observation period of 6 months as shown in Figure 2b. This shows an improvement rate of 84%.

When patients were allocated into groups according to their prescribed analgesics before the medical cannabis therapy, similar alleviation of pain was achieved in all groups as shown in Figure 1c. Due to the small sample size, no statistic evaluation was performed. Alleviation of pain was neither correlated with the categories of cannabis flowers according to the content of tetrahydrocannabinol nor with the maximal daily dose as shown in Figure 3.

Regarding the status of taking additional analgesics, information from 91 patients was available. Forty-six (50%) did not take any beside the medical cannabis and had a decrease of pain scores of 4.0, compatible with the 3.5 in patients who continued their additional analgesics beside the medical cannabis.

Sleep Disturbance

Before the therapy with medical cannabis, a majority of the patients suffered from severe sleep disturbance with a median score of 8 (out of the maximum of 10). At the first follow-up consultation, a significant ($p < 0.001$)

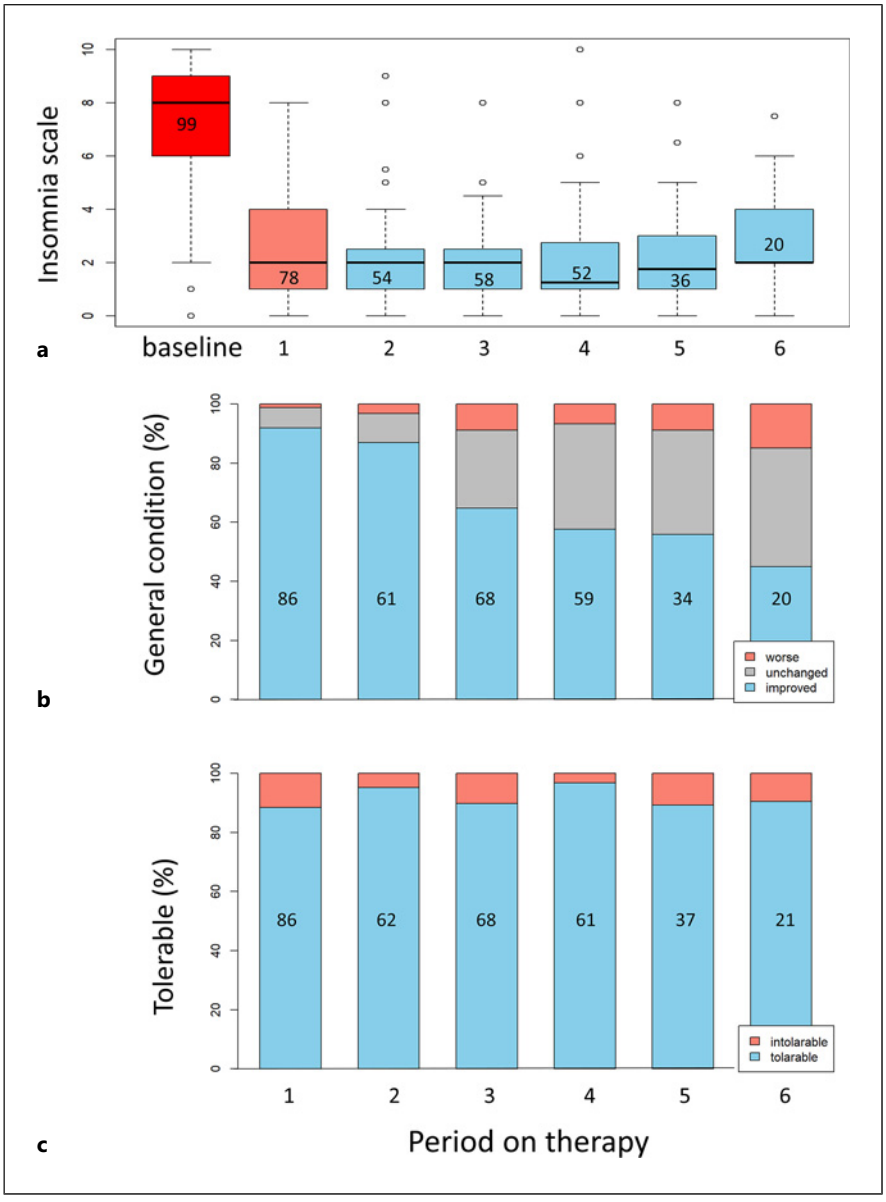

Fig. 4. Changes in sleep disturbance score (**a**), general condition (**b**), and tolerance (**c**) to the therapy. Numbers of cases with available data are given in the boxes.

improvement in sleep was reported as can be seen in Figure 4a and in Table 1. The median sleep disturbance score dropped from 8.0 to 2.0 and this improvement was sustained until the end of the observation period of 6 months.

General Condition and Side Effects

At the first follow-up video consultation, 90% of the patients reported an improvement in their general condition. Cumulatively over the entire observation period of 6 months, 97 (99%) patients reported an improvement in their general condition at one or more follow-up interviews, as shown in Figure 4b.

Over the six follow-up consultations, good therapy tolerance was reported in 279 (91%) out of the cumulative 307 available answers as shown in Figure 4c. Reports regarding side effects were available cumulatively in 335 interviews over the six follow-up consultations. No serious adverse events were reported, e.g., psychosis, heavy tachycardia, breathing problems, or deficits in vital activities such as sleep and sexuality. Mild side effects were reported infrequently as summarized in Table 2. These included dryness of the mucous tissue (5.4%), fatigue (4.8%), and increased appetite (2.7%). The rate of all reported mild side effects was 12.9% with an error margin of 3.6%. There were single reports of

Table 2. Side effects of the medical cannabis in the total of 6 follow-up consultations

Mild side effect	Counts	Frequency, %
Dryness in mucous tissue	18	5.4
Fatigue	16	4.8
Change in appetite	9	2.7
Dizziness	3	0.9
Intoxication	3	0.9
Nausea	3	0.9
Restlessness	3	0.9
Others	12	3.6

rare adverse events such as dizziness, intoxication, restlessness, and nausea. Also, there were single reports of unusual experiences such as unpleasant smell of the medical cannabis, shortness of memory, stress, strong sedating effects.

Discussion

The results of this study demonstrated that chronic neuropathic pain can be effectively, sustainably, and safely treated with medical cannabis. The largest pain relief was achieved within 6 weeks. Considering the plastic feature of chronic neuropathic pain, which cannot be corrected in a short time, the effect of medical cannabis is swift in comparison. The over 40% improvement is also a success especially as other analgesic drugs used before had limited or no effects in this cohort.

Sustainability and stability of the effect is a key issue for pain therapies. In the present study, follow-ups were performed for up to 6 months showing the pain scores were stable at a largely reduced level.

The pain-relieving effect was achieved regardless of the previous analgesics used before the cannabis therapy. In conventional cases where co-analgesic drugs do not deliver the desired effect, medical cannabis may provide a powerful alternative. A combination with other drugs may also be an option. All these issues need to be further addressed in future studies.

The large improvement in sleep disturbance of the patients in the present study is likely due to the improvement in pain symptoms. However, it is also possible that a direct effect of the medical cannabis plays a role. In any case, the therapy achieved an adequate quality of sleep for a majority of the patients, which is a crucial parameter for life quality.

Another major observation in our study is the lack of serious adverse events. This is in concordance with a previous retrospective publication [6]. Dryness in the aspiration track, fatigue, and increased appetite are the most frequently reported mild side effects, which are familiar side effects of cannabis. Several other rare adverse events such as nausea and short memories were reported. However, these may not necessarily be related to the cannabis therapy. Some of these may also be related to the neuropathic pain itself.

Data in the present study are from a single centre, which has the advantage of relatively homogeneous treatment and follow-up protocol. Chronic (neuropathic) pain is more common in women than in men. In addition, most patients seeking cannabis-based medication prefer oral treatment [14]. However, the majority (86 out of 99) of patients in our study was male. There is a possible bias in selecting patients who are more open-minded for inhaling medical cannabis. Nevertheless, our data show a strong and lasting effect of medical cannabis for relieving chronic neuropathic pain in our cohort. As an intrinsic weakness of a retrospective and observatory study, the data sets were not complete and frequently, there were missing data points. Nevertheless, with an adequate sample size, effect of the therapy could be solidly assessed with regard to the two major parameters: pain and sleep disturbance. Further studies including more cases, covering longer periods and addressing additional issues are needed to continuously improve our understanding and to optimize the therapy with medical cannabis, not only for neuropathic pain but potentially also for other pain diseases and symptoms.

Acknowledgments

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Statement of Ethics

The research was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all patients for using their data in anonymized form for medical studies. This is a retrospective observational study whereas no study-related intervention or any study-related change in the routine treatment protocol was conducted. Data of the patients were retrospectively evaluated and only the statistical results were presented in the publication. Based on these features of the study, the Ethics Committee of the Hamburg Medical Association waivered an approval: 2022-300242-WF.

Conflict of Interest Statement

Christian Scholze, Lisa Marie Schmidberg, Julian Lukas Wichmann, Mihail Gemkov, and Martin Julian Keller are employees of the Algea Care GmbH. Lan Kluwe and Said Fartschschi do not have any conflict of interest to declare.

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Author Contributions

J.L.W. and S.C.F. conceived the study; C.S., L.M.S., M.G., and M.J.K. acquired and validated the data; L.K. and S.C.F. analysed the data, conceived the structure of the manuscript, and drafted and contributed to completing the manuscript. C.S., M.G., J.L.W., and M.J.K. contributed to completing the manuscript. S.C.F. supervised the data analysis and drafting/completing the manuscript. All authors reviewed the manuscript.

Data Availability Statement

The original data are not publicly available due to ethical reasons. Specified requests can be sent to the corresponding author Dr. Said Farschtschi (nfambulanz@uke.de.)

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