Author’s response to reviews

Title: Real World Experience of Patients with Amyotrophic Lateral Sclerosis (ALS) in the Treatment of Spasticity using Tetrahydrocannabinol:Cannabidiol (THC:CBD)

Authors:

Thomas Meyer (thomas.meyer@charite.de)
Andreas Funke (kontakt@neurologie-funke.de)
Christoph Münch (christoph.muench@charite.de)
Dagmar Kettemann (kettemann@charite.de)
André Maier (andre.maier@charite.de)
Bertram Walter (bertram.walter@charite.de)
Annett Thomas (annett.thomas@charite.de)
Susanne Spittel (susanne.spittel@charite.de)

Version: 1 Date: 18 Jul 2019

Author’s response to reviews:

Dear Professor de Carvalho,

Our manuscript entitled "Real World Experience of Patients with Amyotrophic Lateral Sclerosis (ALS) in the Treatment of Spasticity using Tetrahydrocannabinol:Cannabidiol (THC:CBD)" which we submitted to BMC Neurology, has been reviewed.

Based on the most helpful comments of the reviewers we undertook a major revision of the manuscript. It follows a point-to-point description of the revision addressing the reviewers' concerns.

Reviewer: 1

Recommendation 1.1) More data about the patients should be added (time since diagnosis, ALSFRS, type of ALS, presence of cognitive impairment, etc.).
Response: For improved description of the sample, data on disease duration, ALS-FRSr, the type of onset and frontotemporal lobe degeneration were included in the methods section. A structured summary of demographic and clinical data was included (Table 1). Furthermore, the clinical data set of all individual patients was provided in the newly inserted Additional file 1.

Revision: “The following demographic data and clinical characteristics were collected for all participants: age, sex, diagnosis, type of onset (bulbar vs spinal onset), time since onset of symptoms, ALS severity as measured by the ALS functional rating scale revised (ALS-FRSr), cognitive impairment, region and severity of spasticity, and antispasmodic medication. An overview of demographic data and clinical characteristics is provided in Table 1 and the Additional file 1.” (page 7, line 28ff)

“Mean disease duration since symptom onset was 58.4 months (± 45 months; median: 42 months). 95.5% of the patients showed a spinal symptom onset. The ALS-FRS score was 23 scale points (± 9.2 scale points) as compared to the maximum number of 48 scale points. In 6.8% of the patients (n = 3) clinical signs of frontotemporal lobe degeneration were described. A summary of demographic and clinical data is summarised in Table 1. The clinical characteristics of individual patients is provided in the Additional file 1.” (page 10, line 56ff)

Recommendation 1.2) I am not sure about the retrospective nature of the study.

Response: The study was performed between May 2016 and September 2017 and was indeed retrospectively analysed.

Revision: “The investigation was confined to patients treated with THC:CBD between May 2016 and September 2017.” (page 6, line 41ff)

Recommendation 1.3) It is surprising that none patient discontinued the treatment. This could be a selection bias.

Response: We follow the valuable advice of the reviewer to provide drop-out data of THC:CBD treatment – although this aspect was not in the main focus of the investigation. In fact, discontinuation of treatment was frequent (40% of the studied THC:CBD cohort). We included detailed data about discontinuation of THC:CBD in the Methods and Results section of the manuscript and in the newly inserted table on patients´ characteristics (Additional file 1). We agree with the reviewer that the drop-out of patients may create some bias. This limitation of our study was addressed in the Discussion section of the manuscript.

Revision: “The date of discontinuation of THC:CBD treatment was record. The clinical characteristics of individual patients who terminated THC:CBD is provided in the Additional file
1. Adverse effects of THC:CBD and causes for the discontinuation of drug treatment were not collected within the scope of this study.” (page 8, line 10ff)

“40% of the studied patients (n = 16) discontinued THC:CBD treatment during the observation period.” (page 12, line 17ff)

“Remarkably, 40% of the patients discontinued the treatment of THC:CBD within the observation period. Reasons for discontinuation of treatment were not in the scope of this non-interventional cohort study.” (page 17, line 10ff)

Recommendation 1.4) Please specify if information was obtained from patients in all cases or from caregivers. Information only from patients could be also a bias because of cognitive impairment in a percentage of patients with ALS.

Response: The information was obtained from patients exclusively. Data from caregivers were not included. Seven percent of the patients showed a cognitive impairment in terms of frontotemporal lobe degeneration. The neuropsychological impairment was rather mild and limited to dysexecutive symptoms. Given the rather low grade of cognitive impairment we decided to include the data of those patients. The potential distortion of patient reported outcome data was included as study limitation in the Discussion section of the manuscript.

Revision: “Moreover, 7% of studied patients (n = 3) showed mild signs of frontotemporal lobe degeneration by means of a dysexecutive syndrome. Given the rather low grade of neuropsychological syndrome we opted to include the data of those patients. Therefore, some distortion of patient reported data cannot be excluded in this particular group of patients.” (page 15, line 23ff)

Recommendation 1.5) Statistics is only descriptive.

Response: We agree with the reviewer that – due the small sample size – statistical analysis is limited to descriptive methods. This limitation was described in the Discussion section of the manuscript.

Revision: “The study cohort was monocentric and covered a rather small sample size. Given the limited sample size the statistical analysis was therefore confined to descriptive methods.” (page 15, line 3ff)

Recommendation 1.6) A limitations section should be added in the study.
Response: The several limitations of the study where described in a point-to-point manner throughout the discussion section of the manuscript.

“Despite the advantages of the platform-based registry and substantial number of analysed patients with off-label use of THC:CBD several limitations have to be addressed. The study cohort was monocentric and covered a rather small sample size. Given the limited sample size the statistical analysis was therefore confined to descriptive methods. Furthermore, a subgroup of patients did not respond to the study invitation (n = 24; 35%). The reasons for non-responding was not explored systematically. Therefore, an observation bias in the cohort of participating patients – as compared to the group of patients who declined study participation – has to be considered. The platform-approach and the study site being a tertiary ALS centre may have created some further observation bias. Therefore, it is conceivable that more intensive THC:CBD treatment may be overrepresented in this cohort while drug treatment of less complex ALS phenotypes was provided independently from the platform, i. e. outside the analysed data set. Moreover, 7% of studied patients (n = 3) showed mild signs of frontotemporal lobe degeneration by means of a dysexecutive syndrome. Given the rather low grade of neuropsychological syndrome we opted to include the data of those patients. Therefore, some distortion of patient reported data cannot be excluded in this particular group of patients.” (page 15, line 1ff)

“The physician’s assessment of spasticity was narrowed to these main graduations as functional aspects of treatment was not the emphasis of this study. However, in further investigations a more precise classification and functional assessments of spasticity (before and after initiation of THC:CBD treatment) is of main interest.” (page 15, line 37ff)

“It is uncertain whether those patients were treated with a-priori lower-grade spasticity or THC:CBD may have achieved symptom control in those patients. In principle, an therapeutic effect of THC:CBD is conceivable as in a recent phase 2 trial (CANALS study) THC:CBD was reported to reduce spasticity in ALS [12]. However, given the non-interventional study design, our data provided little opportunity to interpret the reduced muscle tonus as response to THC:CBD.” (page 16, line 1ff)

“Cannabinoids are increasingly recognised as a treatment option in neuropathic and non-neuropathic pain [29, 30]. However, a study of NPS and TSQM-9 in the context of ALS-related pain was not subject of this registry study.” (page 16, line 17ff)

“However, the treatment modalities in this group of patients have not been studied yet. Further studies are needed to define the dose correlation and minimum effective dose of THC:CBD in ALS-related spasticity. Remarkably, 40% of the patients discontinued the treatment of THC:CBD within the observation period. Reasons for discontinuation of treatment were not in the scope of this non-interventional cohort study. In future studies, a systematic analysis of adverse events and side effects is warranted in order to determine the benefit-risk profile of THC:CBD in the treatment of ALS-related spasticity.” (page 17, line 5ff)
“Given the low case numbers, the significance in the differences of NPS between the two patient groups have to be interpreted with some caution. NPS data on THC:CBD or other medications have not yet been published in ALS. In particular, there are no comparative data for baclofen, tizanidine or other antispasmodic medication. The obtained NPS scores for THC:CBD are, therefore, to be regarded as a baseline for further studies.” (page 17, line 47ff)

“However, like with NPS, the limitation with this score lied in the lack of comparative TSQM-9 data for other spasticity medications such as baclofen and tizanidine. This limitation addresses a fundamental problem in clinical ALS research where no systematic studies on patient reported outcomes of symptomatic and palliative medications have been published so far. Given the lack of comparative data, the outcomes from TSQM-9 are to be regarded as pilot data.” (page 18, line 3ff)

“A comparative analysis of THC:CBD with other antispasmodic medications, particularly baclofen and tizanidine, was not in the scope of this non-interventional study. However, controlled studies are needed to achieve a head-to-head comparison of THC:CBD to other antispasmodic medicines preferably in a multicentric design. Furthermore, a dose correlation of THC:CBD to symptom control is of interest. Given the palliative treatment aim in most ALS patients, symptom control may not necessarily relate to improvement in motor function. Beyond function, the various dimensions of spasticity such as muscle tone, pain, cramps, and mobility restrictions may be modified by THC:CBD [27, 28, 33]. Contributing to this notion, future studies, as our observational study, should touched upon treatment aims beyond functional endpoints. This view is supported by the results of a systematic analysis on physical therapy in ALS demonstrating an increasing patients’ treatment satisfaction despite the continuous decline of motor function [34].” (page 18, line 43ff)

Reviewer: 2

Recommendation 2.1) How was ALS diagnosis made (in Methods, under Participants)?

Response: The diagnostic criteria in terms of revised El Escorial criteria were included in the Methods section.

Revision: “Subjects who participated in the cohort study met the following inclusion criteria: 1) diagnosis of ALS (ICD-10 G12.2) according to the revised El Escorial criteria [14];” (page 6, line 25f)

“ALS trained neurologists confirmed the diagnosis of ALS according to the El Escorial criteria and made the indication for the treatment with THC:CBD.” (page 6, line 43ff)

Recommendation 2.2) […] and how many patients had spinal and bulbar onset form?

Response: The data on type of onset (spinal vs bulbar) was provided in the newly inserted table on patients´ characteristics (Additional file 1).

Recommendation 2.3) Were the patients doing other anti-spastic medication or had done it? Had the patients done botulinum toxin?

Response: The data on other antispasmodic medication including the application of botulinum toxin were provided in the Methods section, the table on patients´ characteristics (Additional file 1) and in the newly inserted section of “Other antispasmodic medication”.

Revision: “5) participation in a case management program for ALS medication; 6) consent in electronic data capture using a digital research platform [15].” (page 6, line 30ff)

“Medication data on THC:CBD and other antispasmodic drugs were recorded on the basis of prescription data tracked on the APST platform. Data entry of prescription data was performed by data managers trained in the digital capture of medication data.” (page 6, line 56ff)

“Data on the prescription (generic name, prescribed dose) of antispasmodic drugs other than THC:CBD were recorded. The treatment with baclofen, tizanidine, dantemacrin and botulinum toxin (in combination with THC:CBD) is provided in the additional file 1.” (page 8, line 21ff)

“25% of patients (n = 10) received other antispasmodic medication in combination with THC:CBD. Baclofen was used in 25% of patients (n = 10) whereas tizanidine was observed in 5% of studied individuals (n = 2). None of the patient received dantemacrin or botulinum toxin in combination with THC:CBD.” (page 12, line 35ff)

Recommendation 2.4) Out of the 68 patients, 24 (more than 1/3) did not want to participate in the study (questionnaire) and were excluded. Had those patients started the medication? If so, how would you say the clinical efficacy of the drug was? By not including those patients you can be introducing an important bias to your results, specially if those patients were non-responders.
Response: All patients invited to the observation study were treated with THC:CBD. Given the principles of informed consent, no data were obtained from patients who did not agree in study participation. Consequentially, patient reported outcomes in the group of excluded patients were not available. We agree with the reviewer that the exclusion of THC:CBD treated patients may have created some selection bias. This limitation of our study was addressed in the Discussion section of the manuscript.

Revision: “Furthermore, a subgroup of patients did not respond to the study invitation (n = 24; 35%). The reasons for non-responding was not explored systematically. Therefore, an observation bias in the cohort of participating patients – as compared to the group of patients who declined study participation – has to be considered.” (page 15, line 6ff)

Recommendation 2.5) Can you clarify why the Ashworth modified scale was not used? Why is the presence of lower limb symptoms (weakness) a limitation of the scale if it should be assessed passively?

Response: The Ashworth scale was not applied given to its limitations as described previously: Ashworth NL, Satkunam LE, Deforge D. Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2012;2:CD004156.doi:10.1002/14651858.CD004156. The justification not to use the Ashworth scale was discussed in the manuscript: “The Ashworth Scale, which has been used in some previous ALS studies, was not applied given its limitations [6]. The score does not reflect the possible co-existence of spasticity with lower motor neuron involvement which is specific for ALS. Furthermore, this score might not represent the patients’ subjective perception of spasticity. In an attempt to overcome these limitations, a disease--specific self--reported scale, the ALS spasticity index (SI-ALS) has been developed. However, the SI-ALS was released only recently, well after our study had been completed [25].” (page 15, line 45ff)

Recommendation 2.6) How can you adequately classify spasticity in mild, moderate, severe?

Response: We agree with the valuable comment of the reviewer that the physician’s assessment of spasticity was based on a rather gross graduation. Given the main focus on the patient’s perception of THC:CBD (independent of spasticity related motor function), a distinction of three main spasticity grades was considered to be sufficient. However, a more precise classification of spasticity is of interest in future studies. We added this limitation to the Discussion section of the manuscript.

Revision: “The physician’s assessment of spasticity was narrowed to these main graduations as functional aspects of treatment was not the emphasis of this study. However, in further
investigations a more precise classification and functional assessments of spasticity (before and after initiation of THC:CBD treatment) are of main interest.” (page 15, line 37ff)

Recommendation 2.7) Was it assessed always by the same evaluators?
Response: Spasticity was graded by the same evaluator. We added the information to the Methods section of the manuscript.

Revision: “The anatomic region and severity of spasticity were classified by the neurologist (observer reported outcome). The physician’s classification of spasticity was assessed by the same investigator.” (page 6, line 47ff)

Recommendation 2.8) How could patients perceive spasticity? How was it explained to them?
Response: Before self-assessment of spasticity, the patients received an introduction into the method and a short training session how to use the NRS scale.

Revision: “The patient’s perception of spasticity (patient reported outcome) was obtained during the course of treatment. Before the patient’s assessment an instruction to the method of numeric rating scale (NRS) was performed by the investigator.” (page 6, line 50ff)

Recommendation 2.9) Was it correlated with the neurologists’ own perception/evaluation of spasticity?
Response: Given the limited sample size, a correlation analysis between those parameters was not performed.

Recommendation 2.10) A functionality scale could have been included.
Response: We agree with the valuable recommendation of the reviewer that functionality scales are of interest. However, the patients’ perception of THC:CBD was the main objective of this study whereas functional aspects of treatment were not in the focus. In further investigations functional assessments of spasticity (before and after initiation of THC:CBD treatment) will contribute to a more comprehensive picture of THC:CBD treatment in ALS.

Revision: “The physician’s assessment of spasticity was narrowed to these main graduations as functional aspects of treatment was not the emphasis of this study. However, in further
investigations a more precise classification and functional assessments of spasticity (before and after initiation of THC:CBD treatment) is of main interest.” (page 15, line 37ff)

Recommendation 2.11) How many patients in your study had only spasticity in the upper limbs (as mentioned by you)? What was their onset form?

Response: The data on region of spasticity (including patients with spasticity confined to the upper extremities) and type of onset (spinal vs bulbar) was provided in the Results section and in the newly inserted table on patients’ characteristics (Additional file 1), respectively. This table encompasses the clinical data set of all individual patients allowing the “tracking” of characteristics of each participating patient.

Revision: “The majority of the patients in the study (95.5%; n = 42) showed spasticity of the lower extremities, either limited to the legs or in combination to spasticity of the upper extremities. 29.5% of the patients (n = 13) had only spasticity in the lower extremities, all of whom had a spinal onset. Spasticity of the arms, either limited to the arms or in combination to spasticity of the lower limbs, was found in 68.2% (n = 30) of patients. Only one of the study patients showed spasticity confined to the upper extremities (2.3%).” (page 11, line 8ff)

Recommendation 2.12) For each patient, was the amount of daily dose constant over the 4-mo course? When were the scales done? When a 7 consecutive-day period with the same dosage was reached? What happened thereafter?

Response: The study was designed as a cross-sectional study. A dose control of THC:CBD and a harmonisation of longitudinal data points (e.g. after 4 months of THC:CBD treatment) would have been highly valuable but were beyond the scope of this observation study. Given the pilot character (in a palliative environment) and the cross-sectional design of the investigation, medication data (and corresponding patient reported outcomes) were obtained at different time points in the course of THC:CBD treatment. This limitation was addressed in the Discussion section of the manuscript: “Further studies are needed to define the dose correlation and minimum effective dose of THC:CBD in ALS-related spasticity.” (page 17, line 7f)

Recommendation 2.13) It is really not clear if the patients in your retrospective study did a max of 20 applications per day or 12. Can you please clarify?

Response: Two patients used up to 20 actuations per day. These data were added to the Results section of the manuscript.
Recommendation 2.14) What side effects, if any, did you encounter?

Response: Given the non-interventional scope of this study, adverse events and side effects of THC:CBD were not recorded and analysed. We agree with the reviewer that a systematic analysis of adverse events and side effects is warranted in order to determine the benefit-risk profile of THC:CBD in the treatment of ALS-related spasticity. We included this important aspect in the Discussion section of the manuscript.

Revision: “Adverse effects of THC:CBD and causes for the discontinuation of drug treatment were not collected within the scope of this study.” (page 8, line 14ff)

“In future studies, a systematic analysis of adverse events and side effects is warranted in order to determine the benefit-risk profile of THC:CBD in the treatment of ALS-related spasticity.” (page 17, line 14ff)

Recommendation 2.15) Did any patients discontinue the medication?

Response: This aspect was also addressed by reviewer 1. See our response and revision concerning recommendation 1.3.

Recommendation 2.16) How can you warranty that the perception of spasticity amelioration was indeed not simply a diminishing on the pain level?

Response: We agree with the reviewer that the perceived amelioration of spasticity may be interrelated to improved pain control. It was beyond the scope of this pilot study to differentiate the various potential treatment modalities of THC:CBD. This limitation was addressed in the Discussion section of the manuscript: “Beyond function, the various dimensions of spasticity such as muscle tone, pain, cramps, and mobility restrictions may be modified by THC:CBD [26, 27, 32]. Contributing to this notion, future studies, as our observational study, should touched upon treatment aims beyond functional endpoints.” (page 18, line 54ff)

Recommendation 2.17) Were TSQM-9 and NPS correlated?

Response: Given the limited sample size, the correlation between those parameters was not analysed.
Reviewer 3:

Recommendation 3.1) Even though a comparison of different antispastic treatments was not the aim of this study, it should however be presented if/how many of the patients also used other concomitant medications to alleviate spasticity, pain or muscle cramps.

Response: This aspect was also addressed by reviewer 2. See our response and revision concerning recommendation 2.3.

I hope that we were able to address all the reviewers' concerns and thank you for reviewing the revised manuscript. I would be most grateful if you kindly considered our manuscript for publication in BMC Neurology.

Prof. Dr. Thomas Meyer
- Head, Department for ALS
and other Motor Neuron Disorders -