PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Medical cannabis for severe treatment resistant epilepsy in children – A case series of ten patients
AUTHORS	Zafar, Rayyan Schlag, Anne Phillips, Lawrence Nutt, David

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Sarah Nevitt Institution and Country: University of Liverpool, Biostatistics Competing interests: None
REVIEW RETURNED	09-Aug-2021

GENERAL COMMENTS	I have conducted a statistical review of the manuscript "Medical cannabis for severe treatment resistant epilepsy in children – A case series of ten patients." I should firstly note that I have worked as a statistician in the field of epilepsy for 10 years so I am aware of how promising and important these results are. I completely agree with the authors that RCTs are very difficult to conduct within this context and that observational 'real world' evidence should be considered inform clinical decision making. My main comment is that within the discussion section the authors focus mostly on the limitations of RCTs within this population and very little mention is given to the limitations associated with this particular study. For example, given the retrospective design and the data source (i.e. a charity representing children using medical cannabis), there is scope for selection bias here. I also wonder about whether the results were as positive for the 14 children whose families did not provide consent for involvement in this study and the five children with missing data who were not included in the study. Not to take away from these very encouraging results, but limitations of the retrospective design and available data should be acknowledged more. I suggest that recommendations for future research could also include studies of prospective designs which also aim to identify children most likely to benefit from medical cannabis and also those not likely to benefit, so that they may be offered other treatments. Also just one statistical comment, the authors state that no significance testing was performed due to the lack of randomisation which is appropriate. However, I note that the correlation analyses are described in terms of a 'non-significant relationship,' so significance testing has been performed. Please rephrase either the methods, or the interpretation of the correlation analyses. I suggest the latter, i.e. interpreting the magnitude / direction of the

	estimated correlation coefficient, rather than the statistical significance (or lack of) of it.

REVIEWER	Reviewer name: Dr. Krishna Kishore Umapathi Institution and Country: Rush University Medical Center, Pediatrics Competing interests: none
REVIEW RETURNED	19-Aug-2021

GENERAL COMMENTS	Abstract: Objectives: Change "Here we report the findings of a case" to "To report..." Setting: Remove the word "carers" or change it to "caretakers" Results: change to "We also noted... Report the costs instead of telling it was high Primary outcome measure: This is different from objective. It should just be a variable. In your case, it is seizure frequency Manuscript: Line 39: Change to "...and only 2 in children" Methods: Althea 100 (<1% CBD and 10% CBD) - change to THC composition Table 1: Why are there differences in cost for the same medications for different patients? Is there a specific cost for each medication that you can document Also worth mentioning the diagnosis specif for each patient in the table How do you rule out that vagal nerve implant and ketogenic diet did not have a bias in outcomes. How long does ketogenic diet effect lasts. How long did you wait after discontinuation of the diet to start CBMP "We did not specifically ask for adverse effects, weBasked parents to note if there were any adverse effects in these interviews, but none were reported." This can induce recall bias Another significant limitation is the small sample size. The authors cannot expect their findings to drive recommendations in NICE by just reporting 10 patients

VERSION 1 – AUTHOR RESPONSE

Response to reviewers: "Medical cannabis for severe treatment resistant epilepsy in children – A case series of ten patients"

To whom it may concern,

We thank the reviewers for assessing and proving recommendations for edits on our manuscript. Below we respond in full to each of your comments in green and italic and highlight the changes we have made following reflection of your comments.

Medical cannabis access for children in the UK has become an increasingly concerning picture with only 2 NHS prescriptions having been made to date since the law changed. This was recently debated by the Health and Social care minister and several MPs where MPs expressed their frustration of their constituents, some of whom are reported in our observational data, in not being able to access these lifesaving medicines for free. The debate can be seen in the following link. https://www.theyworkforyou.com/debates/?id=2021-09-06d.102.0&s=smoking

The health and social minister and NICE have recently said that they will begin to accept forms of evidence that run outside of the traditional RCT route as they accept that this is very

difficult to do in such a rare and severely debilitated population such as those suffering with paediatric intractable epilepsy.

We hope this paper helps to provide further evidence on the potential therapeutic value of whole-plant medical cannabis to treat these patients and we welcome and encourage further research in this expanding field.

Yours sincerely,

Rayyan Zafar
Dr Anne Schlag
Prof Lawrence Phillips
Prof David Nutt

Formatting Amendments (where applicable):

1. Embedded Figures

Please remove all figures from the body of the manuscript and re-upload your figure files separately.

Please note that we do not accept figures in Word document or PowerPoint format.

All figures and images should be supplied as high quality image files, we recommend PNG,TIFF or JPG/JPEG. Please ensure images are a minimum of 300dpi and a maximum of 600dpi (resolution).

We have added the figure as a png file titled Fig1EoP.png

Editor in Chief Comments to Author:
Abstract conclusions replace the last sentence with the 2nd statement in What this study adds

This has now been updated to delete the original statement and include the second statement in what this study adds. We have kept the second statement of what this study adds also in the box.

Introductions expand the info about cannabis-based products - how many, how they differ, etc

We have now added further details about CBMPs.

Methods list study outcomes.

A section titled 'Study outcomes' has been added to the methods section where we have included the studies primary and secondary objectives.

Study outcomes
The primary study outcome was to assess the percentage change in monthly seizure frequency in participants following initiation of medical cannabis. The secondary study

outcomes were to assess the impact of medical cannabis on changes in AED use, to report the concentrations and doses of medical cannabis used by these patients and to document the costs incurred from attaining these prescriptions.

Did you have a check list of questions you asked parents? If so, add as an appendix.

These have been added as an apendix

Discussion delete "Our patient group almost universally reported highly improved cognitive and behavioural outcomes, likely due both to reduced seizure frequency and reduced use of other AEDs." This is a result not discussion.

This has been deleted and inserted in the results section under the 'Other symptoms' paragraph

Be cautious in your interpretation of your results
Respond in full to the reviewers

Associate Editor
Comments to the Author:
Thank you for submitting this manuscript to BMJ Paediatrics Open

Please respond fully to the points raised by the peer reviewers

In addition
- Is there information available about which AED's children were prescribed initially and which ones were stopped? Could this also be included?

This information was available however it was redacted from the table through the request of the editor in order to keep the identities of the children protected. We are able to provide this data if requested.

- Could it be made clear how long children were prescribed the whole-plant cannabis medicines?

These children have been on whole-plant medical cannabis for a variable length of time. Caretakers of patients were not routinely asked on the length of time that they had been using medical cannabis. Many parents initiated the use of medical cannabis prior to the legalisation of cannabis through the black market and so it was decided to not ask these questions so as not to incriminate any of these parents. Many parents expressed they did not wish to provide these details and hence this was not recorded.

- In Figure 1 is there a reason why there is no post-treatment seizure data for patient 3?

This patient had a complete reduction of their symptoms (leading to 0 seizures per month)

- reviewer has correctly highlighted that families were not routinely asked about adverse effects and they were only noted down if mentioned, discussion section should reflect this.

We have added a section in the discussion highlighting this point.

- along these lines, overall discussion should involve more coverage of the inherent limitations to the study - observational, retrospective and subject to recall re. changes in behaviour, cognition and adverse effects (this does not take away from the clinical interest in this case series but important that they are acknowledged)

We acknowledge the limitations of observational retrospective research and have included the following into the discussion

Page 8: 'In saying this, we do acknowledge that retrospective observational research is subject to recall, and this is an inherent limitation of such designs. Given the rarity of such patient populations with these rare forms of epilepsy prospective studies would be very difficult to undertake.'

- page 4, introduction, please clarify or rephrase re. 'undiagnosable' conditions

This has been changed to 'idiopathic'.

Reviewer: 1
Dr. Sarah Nevitt, University of Liverpool
Comments to the Author
I have conducted a statistical review of the manuscript "Medical cannabis for severe treatment resistant epilepsy in children – A case series of ten patients."

I should firstly note that I have worked as a statistician in the field of epilepsy for 10 years so I am aware of how promising and important these results are. I completely agree with the authors that RCTs are very difficult to conduct within this context and that observational 'real world' evidence should be considered inform clinical decision making.

We thank the reviewer for agreeing with us in that these conditions are extremely difficult to test within the context of an RCT and therefore complimentary forms of evidence are required to support the prescribing of such medicines in a clinical setting.

My main comment is that within the discussion section the authors focus mostly on the limitations of RCTs within this population and very little mention is given to the limitations associated with this particular study. For example, given the retrospective design and the data source (i.e. a charity representing children using medical cannabis), there is scope for selection bias here.
I also wonder about whether the results were as positive for the 14 children whose families did not provide consent for involvement in this study and the five children with missing data who were not included in the study.
Not to take away from these very encouraging results, but limitations of the retrospective design and available data should be acknowledged more.

We acknowledge the limitations of observational retrospective research and have included the following into the discussion

As we do not have data for the 14 families that did not provide consent and for the for the 5 patients with missing data, we are unable to comment on the effects of medical cannabis in those. We understand that this could lead to reporting bias however these families continue

to be part of the charity and we know that they continue to use medical cannabis to treat their children so we can only speculate that even in these children there is a clinical benefit as they would not be in receipt of a prescription if there wasn't.

Page 8: 'In saying this, we do acknowledge that retrospective observational research is subject to recall, and this is an inherent limitation of such designs. Given the rarity of such patient populations with these rare forms of epilepsy prospective studies would be very difficult to undertake.'

I suggest that recommendations for future research could also include studies of prospective designs which also aim to identify children most likely to benefit from medical cannabis and also those not likely to benefit, so that they may be offered other treatments.

We acknowledge that such a study would greatly improve the outcomes of these patients as early intervention leads to better outcomes and so if this was possible then a prospective study to determine those that would benefit from this intervention would be warranted. We have included the following within the manuscript.

'Whilst we note the difficulty in conducting prospective studies, these could be designed to identify children who are most likely to benefit from medical cannabis and those that aren't in order to stratify treatment packages earlier during their disorders. Such a study would serve to ameliorate the current poor prognosis within this severely ill population.'

Also just one statistical comment, the authors state that no significance testing was performed due to the lack of randomisation which is appropriate. However, I note that the correlation analyses are described in terms of a 'non-significant relationship,' so significance testing has been performed. Please rephrase either the methods, or the interpretation of the correlation analyses. I suggest the latter, i.e. interpreting the magnitude / direction of the estimated correlation coefficient, rather than the statistical significance (or lack of) of it.

We agree with the reviewers' comments re statistical analysis and have redacted any statement to significance testing. The manuscript has now been reflected to reflect this

We correlated the THC: CBD dose ratio against the percent reduction in monthly seizure frequency to see if there were any effects of dosage on reported outcomes. Spearman's rho revealed a moderate correlation between THC:CBD ratio and changes in seizure frequency (rs =0.271). The trend in the data indicated higher THC dose to be associated with greater reductions in seizure frequency.

Reviewer: 2
Dr. Krishna Kishore Umapathi, Rush University Medical Center
Comments to the Author
Abstract:
Objectives: Change "Here we report the findings of a case" to "To report..."
This has been updated

Setting: Remove the word "carers" or change it to "caretakers"
Been changed to caretakers

Results: change to "We also noted... Report the costs instead of telling it was high
We also noted significant financial costs of £874 per month to obtain these medicines through private prescriptions.

Primary outcome measure: This is different from objective. It should just be a variable. In your case, it is seizure frequency
This has been changed to 'The primary outcome measure was seizure frequency'

Manuscript:
Line 39: Change to "...and only 2 in children"
This has been updated

Methods: Althea 100 (<1% CBD and 10% CBD) - change to THC composition
This has been updated

Table 1: Why are there differences in cost for the same medications for different patients? Is there a specific cost for each medication that you can document
Differences in costs are related to the quantity of medicine used in each prescription plus each individual private clinic that prescribes the drugs having varied overhead costs that are included to sum up the total prescription amount. There is no specific documented cost for each medicine as this is calculated independently through negotiations between the supplier and prescribing clinic. These costs are also very dynamic and are subject to ever changing governmental taxation/business laws that we cannot account for.

Also worth mentioning the diagnosis specific for each patient in the table
Following recommendations from the editor we have redacted the diagnosis in the table to maintain patient confidentiality.

How do you rule out that vagal nerve implant and ketogenic diet did not have a bias in outcomes. How long does ketogenic diet effect lasts. How long did you wait after discontinuation of the diet to start CBMP?
Only 1 patient had a VNS implant and this was implanted prior to initiation of medical cannabis and was continued throughout medical cannabis treatment. There were 4 patients that had a ketogenic diet prior to initiation of medical cannabis treatment but this was discontinued while the initiation of medical cannabis. There was an overlap between discontinuing ketogenic diet and initiating medical cannabis treatment which was not recorded. Given that these interventions were present whilst using standard AEDs and then given the remarkable improvements on medical cannabis that mirrored that seen in other patients it would see unlikely that these interventions were a major factor in biasing outcomes.

"We did not specifically ask for adverse effects, we asked parents to note if there were any adverse effects in these interviews, but none were reported." This can induce recall bias
We agree here that this could lead to recall bias, we have conducted a narrative research study in 11 patients spread across our previous study (https://journals.sagepub.com/doi/full/10.1177/2050324520974487) and this current study which is published here (https://journals.sagepub.com/doi/full/10.1177/20503245211034930) where we have discussed parental reporting of adverse outcomes

Another significant limitation is the small sample size. The authors cannot expect their findings to drive recommendations in NICE by just reporting 10 patients
We now have a group of N=20 in a rare population group when combined with our previous paper https://journals.sagepub.com/doi/full/10.1177/2050324520974487)

We also draw the reviewers attention to the licensing of Zolgensma for SMA in which 15 patients were recruited for a study in this paediatric population and the results of which were convincing enough to have it licensed through NICE https://www.nejm.org/doi/full/10.1056/nejmoa1706198