PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	So near yet so far – why won't the UK prescribe medical cannabis?
AUTHORS	Nutt, David; Bazire, Steve; Phillips, Lawrence; Schlag, Anne

VERSION 1 – REVIEW

REVIEWER	Ethan Russo, MD CReDO Science USA
REVIEW RETURNED	28-Mar-2020

GENERAL COMMENTS	The paper is virtually ready for publication. Minor points: 1) page 5, line 27, should be Charlotte's Web 2) page 6, line 3: should be promethazine, not Phenergan 3) page 6: in relation to not knowing what to prescribe or how much, a recent article does describe this (see attached file) 4) page 6: should be delta-9-THC or delta symbol-9 superscript-THC 5) page 6: Sativex, or better, nabiximols is not composed simply of THC and CBD, but rather from whole plant extracts of cannabis chemovars rich in THC and CBD, respectively.

REVIEWER	Melissa Benson The University of Sydney, Australia
REVIEW RETURNED	14-Apr-2020

GENERAL COMMENTS	Overall comment; The authors have brought an important issue to light and have focused on the UK and the issues they are having with prescribing medicinal cannabis products despite it being officially legal. They have done a good job of exploring different aspects of the issue that is causing resistance and the piece is written well overall. There are a few specific points noted below where some further clarification or explanation of the point is required – just to ensure that the point made is not too generalist or vague that it is not useful to a reader with some knowledge of this area or is misrepresentative of what is available (i.e. info from databases etc). Perhaps parallels to Australia could be drawn or commented on by the authors given that the system is very similar to the UK (as is the healthcare system in general) and that Australia is perhaps 12-18months ahead in this same path as the UK and that in the first 12months of official legality the same tiny patient numbers and issues with getting prescribers on board were present – which have now subsided to a degree and are improving continually. Could be an interesting comment to put into perspective where the

	UK sits and where it may(?) in another 12 months time if a similar trajectory were to occur. Specific Comments: “unsatisfactory situation” in the abstract – is this referring to the patient’ view or authors’ - unclear? Strengths and weaknesses; to make it clear – need to say patients self-medicating with illicit CBMs Would also add that they are a class of drugs rather than new medical products? CBPM – why inclusion of the “plant” medicines in acronym explanation? Does this infer that all products are of botanical origin and none are synthetic (i.e. dronabinol, synthetic CBD)? I understood CBPM in UK to stand for cannabis-based products for medicinal use? No mention of plant – therefore this is confusing and not consistent with gov docs etc and how it is referred to. Page 3, line 59: getting children access to treatment; this sentence is a little vague. Need to clarify that this treatment that has proven effective is a cannabinoid medication. Page 3, Line 16: database evidence comment is somewhat misleading. These databases are not comprehensive nor are they easily accessible/available (?) (please provide NY database access reference). Looking for adverse event reporting in a database is not equivalent to being able to scope for PRO changes before and after treatment which it is my understanding that you cannot do from either of these databases. Agreed – patient tracking of prescribing is required and analysis of PROs but this has not been done in a systematic or comprehensive way at all thus far – which is the issue in being able to summarise the patient-reported changes for the thousands thus far. Page 3, Line 22: Perhaps inclusion of a few well known examples here would be good of approved drugs lacking RCTs. Line 26-32: This is agreed however the issue here is being able to access data to complete the evidence base (i.e. large patient observational studies with useful measures). Would suggest that the authors are perhaps overestimating the restrictiveness of RCTs which need to develop to P III and IV to reach market but have interrogated more broad patient groups – language is perhaps too strong that suggests RCTs only cherry pick very select patients (which can definitely be the case and is the case in Phase II or for rare conditions) but we then know that products are prescribed to much more broad classes and follow on RCTs are often conducted to expand the marketing range if appropriate. I agree with the argument that we want products that translate to “real-world” patients – however thus far the quality data we have for PROs with medicinal cannabis products is similar (i.e. poor quality or just missing in formal publications)– again, given the lack of well reported and structured observational reports/trials and n=1 reports. Page 6, line 6; Phenergan RCTs have been conducted for several indications but just showed no significant benefit over placebo/active comparators. Is this what is being referred to? Page 6, line 16. Again, not sure if this is painting a picture that is not accurate – in the sense that accessing the Health Canada (typo in text) database to interrogate efficacy of medicinal cannabis products is not straightforward and is not publicly available to my knowledge. Perhaps clarify very briefly the type of information that

	could actually be taken and analysed by prescribers from this database? Page 6, line 17; typo – accelerate Page 6, line 49. Think authors need to make a comment here that there are many bad/inaccurate educational programs available and misinformation for medicinal cannabis and therefore finding a reputable and factual/non-biased educational program may also be a challenge for clinicians (further supporting the need for accredited training to be made available or it integrated into University curriculum where appropriate). Page 6, Line 57. Comment that this is a result of recreational and not medicinal use in text – however it can be challenging in the current climate with patients self-medicating using the same recreationally sourced products to differentiate for a clinician and in fact to differentiate from a scientific perspective if the content/dose/frequency/route of use etc are all unknown or in line with recreational use parameters. Perhaps a comment acknowledging this – and therefore this is why it would be much easier for both the patient and doctor if regulated products can be used as dose and quality/content can actually be monitored/known. Page 6, Line 60. Further noting "education is the solution" – completely agree with authors here but think this does require some qualification- that there are still harms associated and we know from several observational/patient report studies/surveys that CUD is present in a (sometimes significant) proportion of self-proclaimed 'medicinal only users' and therefore this still must be a consideration of the prescriber in populations that may be high risk/have a history of substance abuse. Acknowledgement that this is still a concern but can be mitigated if products are controlled/patients are guided/dose and symptoms monitored etc. Perhaps a sentence or two to address this flip side is warranted? Pharmacy perspective: Page 7, Dot point line 23 – 27; these two points are a little confusing/misleading. There is already "generic" substitution given the number of products that have identical THC:CBD content that directly compete and therefore price competition exists on this front already in other legal markets (i.e Australia) where the system is the same as the UK. "giving different actions" is an unclear statement; assuming this is directly relating to different ratios of CBD/THC in a singular product– at this point this is not enough evidence to show that a 10:1 vs a 5:1 CBD:THC product has different actions especially if the CBD concentrations (given they are capped somewhat by the THC ratio) lead to different actions or outcomes – believe this is a common misleading of many manufacturers appealing to patients'/doctors naivety in this arena. Perhaps rephrasing of this to be less absolute as this is not always the case and research is showing this. "many CBPMs do not have sufficient THC to make patients stoned"; this also warrants clarification. For example, a patient may take double the dose prescribed (easily done if forget and take 2ml vs 1ml etc or taking prn but more frequently than suggested given symptoms are present) and we know that in cannabis naïve patients an oral 5-10mg dose of THC can definitely produce intoxicating effects. I would perhaps rephrase to say that there are

	many products with low THC or are absent of THC and that the common routes of ingestion (i.e. oral oil/capsule etc) make it more challenging to have immediate intoxication effects. Perhaps further suggestion calling out to researchers/government to actually conduct health econ analyses from medicinal cannabis – quality cost savings analyses are lacking at present and will be the most convincing thing perhaps to governments to make active changes. Page 7, line 32. Clarify that self medicating with illicit or non-regulated CBPMs (as otherwise there is no distinction between quality products and street weed or backyard artisanal preparations). Still believe need to address industry/research fields and urge them to help fill these gaps and overcome hurdles also so it is not just a burden placed on the prescribers/government. More observational or n=1 trials can be published rather than just anecdotally reported to colleagues – this may assist in adding to evidence base. Better educational programs being produced/disseminated (or those quality ones being promoted) will also help - and then tracking those that have undergone them to see if this does promote a change in prescribing/practice. Perhaps it does not. Finding out from clinicians why they don't prescribe with surveys etc – may find some impediments are not as significant and that is a time-poor issue.

VERSION 1 – AUTHOR RESPONSE

The paper is virtually ready for publication. Minor points:
1) page 5, line 27, should be Charlotte's Web. *Revised*
2) page 6, line 3: should be promethazine, not Phenergan. *We checked and it is the latter, as also highlighted by reviewer 2 below.*
3) page 6: in relation to not knowing what to prescribe or how much, a recent article does describe this (see attached file). *Thank you- we've incorporated this reference.*
4) page 6: should be delta-9-THC or delta symbol-9 superscript- THC. *Revised*
5) page 6: Sativex, or better, nabiximols is not composed simply of THC and CBD, but rather from whole plant extracts of cannabis chemovars rich in THC and CBD, respectively. *We've revised as suggested.*

Reviewer: 2
Reviewer Name
Melissa Benson

Please leave your comments for the authors below
Overall comment;
The authors have brought an important issue to light and have focused on the UK and the issues they are having with prescribing medicinal cannabis products despite it being officially legal. They have done a good job of exploring different aspects of the issue that is causing resistance and the piece is written well overall.
There are a few specific points noted below where some further clarification or explanation of the point is required – just to ensure that the point made is not too generalist or vague that it is not useful to a reader with some knowledge of this area or is misrepresentative of what is available (i.e. info from databases etc).

Perhaps parallels to Australia could be drawn or commented on by the authors given that the system is very similar to the UK (as is the healthcare system in general) and that Australia is perhaps 12-18months ahead in this same path as the UK and that in the first 12months of official legality the same tiny patient numbers and issues with getting prescribers on board were present – which have now subsided to a degree and are improving continually. Could be an interesting comment to put into perspective where the UK sits and where it may(?) in another 12 months time if a similar trajectory were to occur. *The authors discussed this comment but felt it not suitable to add a comparison to Australia at this stage as Australia's health system and approach to medical cannabis differ from the UK, and the addition would not add to the main argument of the manuscript.*

Specific Comments:
"unsatisfactory situation" in the abstract – is this referring to the patient' view or authors' - unclear? *We have revised as requested.*

Strengths and weaknesses;
to make it clear – need to say patients self-medicating with illicit CBMs. *Done*
Would also add that they are a class of drugs rather than new medical products? *Done*
CBPM – why inclusion of the "plant" medicines in acronym explanation? Does this infer that all products are of botanical origin and none are synthetic (i.e. dronabinol, synthetic CBD)? I understood CBPM in UK to stand for cannabis-based products for medicinal use? No mention of plant – therefore this is confusing and not consistent with gov docs etc and how it is referred to. *Thank you for pointing out this mistake- we've revised accordingly.*

Page 3, line 59: getting children access to treatment; this sentence is a little vague. Need to clarify that this treatment that has proven effective is a cannabinoid medication. *Done*
Page 3 (4?), Line 16: database evidence comment is somewhat misleading. These databases are not comprehensive nor are they easily accessible/available (?) (please provide NY database access reference). Looking for adverse event reporting in a database is not equivalent to being able to scope for PRO changes before and after treatment which it is my understanding that you cannot do from either of these databases. Agreed – patient tracking of prescribing is required and analysis of PROs but this has not been done in a systematic or comprehensive way at all thus far – which is the issue in being able to summarise the patient-reported changes for the thousands thus far.

We agree that these databases are not easily accessible and need to be further interrogated. We have deleted reference to the NY state database and added further details, as well as the very well organised and fully accessible Minnesota database (including PROs per condition) : https://www.health.state.mn.us/people/cannabis/data/index.html

We also added details about Project TWENTY 21, the recently launched UK medical cannabis registry, as well as audits undertaken on epilepsy children prescribed medical cannabis in the UK.
Page 3, Line 22: Perhaps inclusion of a few well known examples here would be good of approved drugs lacking RCTs. *Examples can be found in ref (6), for the purpose of brevity, we did not include them in the main text.*
Line 26-32: This is agreed however the issue here is being able to access data to complete the evidence base (i.e. large patient observational studies with useful measures). *We have highlighted this point by adding details about Project TWENTY21 as above.*
Would suggest that the authors are perhaps overestimating the restrictiveness of RCTs which need to develop to P III and IV to reach market but have interrogated more broad patient groups – language is perhaps too strong that suggests RCTs only cherry pick very select patients (which can definitely be the case and is the case in Phase II or for rare conditions) but we then know that products are prescribed to much more broad classes and follow on RCTs are often conducted to expand the

marketing range if appropriate. I agree with the argument that we want products that translate to "real-world" patients – however thus far the quality data we have for PROs with medicinal cannabis products is similar (i.e. poor quality or just missing in formal publications)– again, given the lack of well reported and structured observational reports/trials and n=1 reports.

We have revised the page accordingly, however, ll 26-32 is a quotation, hence this text was left as before.

Page 6, line 6; Phenergan RCTs have been conducted for several indications but just showed no significant benefit over placebo/active comparators. Is this what is being referred to? *Yes*
Page 6, line 16. Again, not sure if this is painting a picture that is not accurate – in the sense that accessing the Health Canada (typo in text) database to interrogate efficacy of medicinal cannabis products is not straightforward and is not publicly available to my knowledge. Perhaps clarify very briefly the type of information that could actually be taken and analysed by prescribers from this database? *We have added details and also highlight the importance of publishing these data in peer-reviewed journals.*
Page 6, line 17; typo – accelerate. *done*

Page 6, line 49. Think authors need to make a comment here that there are many bad/inaccurate educational programs available and misinformation for medicinal cannabis and therefore finding a reputable and factual/non-biased educational program may also be a challenge for clinicians (further supporting the need for accredited training to be made available or it integrated into University curriculum where appropriate). *Yes, we now included this addition.*

Page 6, Line 57. Comment that this is a result of recreational and not medicinal use in text – however it can be challenging in the current climate with patients self-medicating using the same recreationally sourced products to differentiate for a clinician and in fact to differentiate from a scientific perspective if the content/dose/frequency/route of use etc are all unknown or in line with recreational use parameters. Perhaps a comment acknowledging this – and therefore this is why it would be much easier for both the patient and doctor if regulated products can be used as dose and quality/content can actually be monitored/known. *Done*
Page 6, Line 60. Further noting "education is the solution" – completely agree with authors here but think this does require some qualification- that there are still harms associated and we know from several observational/patient report studies/surveys that CUD is present in a (sometimes significant) proportion of self-proclaimed 'medicinal only users' and therefore this still must be a consideration of the prescriber in populations that may be high risk/have a history of substance abuse.
Acknowledgement that this is still a concern but can be mitigated if products are controlled/patients are guided/dose and symptoms monitored etc. Perhaps a sentence or two to address this flip side is warranted? *Thank you, we have added this as suggested.*

Pharmacy perspective:
Page 7, Dot point line 23 – 27; these two points are a little confusing/misleading.
There is already "generic" substitution given the number of products that have identical THC:CBD content that directly compete and therefore price competition exists on this front already in other legal markets (i.e Australia) where the system is the same as the UK.
"giving different actions" is an unclear statement; assuming this is directly relating to different ratios of CBD/THC in a singular product– at this point this is not enough evidence to show that a 10:1 vs a 5:1 CBD:THC product has different actions especially if the CBD concentrations (given they are capped somewhat by the THC ratio) lead to different actions or outcomes – believe this is a common misleading of many manufacturers appealing to patients'/doctors naivety in this arena. Perhaps rephrasing of this to be less absolute as this is not always the case and research is showing this. *We have re-phrased as suggested.*
"many CBPMs do not have sufficient THC to make patients stoned"; this also warrants clarification.

For example, a patient may take double the dose prescribed (easily done if forget and take 2ml vs 1ml etc or taking prn but more frequently than suggested given symptoms are present) and we know that in cannabis naïve patients an oral 5-10mg dose of THC can definitely produce intoxicating effects. I would perhaps rephrase to say that there are many products with low THC or are absent of THC and that the common routes of ingestion (i.e. oral oil/capsule etc) make it more challenging to have immediate intoxication effects.
Perhaps further suggestion calling out to researchers/government to actually conduct health econ analyses from medicinal cannabis – quality cost savings analyses are lacking at present and will be the most convincing thing perhaps to governments to make active changes. *We have revised as suggested.*

Page 7, line 32. Clarify that self medicating with illicit or non-regulated CBPMs (as otherwise there is no distinction between quality products and street weed or backyard artisanal preparations). *Done*
Still believe need to address industry/research fields and urge them to help fill these gaps and overcome hurdles also so it is not just a burden placed on the prescribers/government. More observational or n=1 trials can be published rather than just anecdotally reported to colleagues – this may assist in adding to evidence base. Better educational programs being produced/disseminated (or those quality ones being promoted) will also help - and then tracking those that have undergone them to see if this does promote a change in prescribing/practice. Perhaps it does not. Finding out from clinicians why they don't prescribe with surveys etc – may find some impediments are not as significant and that is a time-poor issue. *We have strengthened our paper to include these issues.*

VERSION 2 – REVIEW

REVIEWER	Ethan Russo, MD CReDO Science, USA
REVIEW RETURNED	27-Jun-2020

GENERAL COMMENTS	I am quite satisfied with the revisions.

REVIEWER	Melissa Benson *University of Sydney, Australia * Now left since initial review completed. working within Industry CRO - Applied Cannabis Research
REVIEW RETURNED	07-Jul-2020

GENERAL COMMENTS	I thank the Authors for revisions that have been made to address the queries put forth. This will be an impactful paper that is sorely needed to outline the current status of the UK in terms of medicinal cannabis prescribing.