PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomized controlled cross-over double blind pilot study protocol on THC:CBD oromucosal spray efficacy as an add-on therapy for post-stroke spasticity
AUTHORS	Marinelli, Lucio ; Balestrino, Maurizio; Mori, Laura; Puce, Luca; Rosa, Gianmarco; Giorello, Laura; Currà, Antonio; Fattapposta, Francesco; Serrati, Carlo; Gandolfo, C; Abbruzzese, Giovanni; Trompetto, Carlo

VERSION 1 – REVIEW

REVIEWER	Raymond L. Rosales, MD, PhFD Department of Neurology and Psychiatry University of Santo Tomas (Professor) and Hospital (Chair) Manila, Philippines
REVIEW RETURNED	13-Apr-2017

GENERAL COMMENTS	This present work (actually a research protocol) caters special interest because of the emerging and perhaps "hyped" therapeutic effects of cannabis for neurological conditions, these hinged on the Endocannabinoid receptors (CB1 and 2) of the brain. The trial design looks good, but this present referee has a number of issues: 1) On the PRIMARY AIM to make the reflex tool as the outcome: Unlike BoNT (botulinum toxin) which is a focal and targeted treatment for spasticity, oral medications (including Sativex spray here) that are not targeted (hence, “random” treatment like Baclofen etc), then more objective and subjective assessments will be desirable. It is anticipated that the yield of this reflex-derived sophisticated assessment tool may potentially not reach their desired outcome, unless one does the measurement on ALL affected joints, rather than choosing certain joints (which makes sense in BoNT because the PMTG-Primary Targeted Group of muscles moving a joint can easily be assessed in a focal kind of Ttherapy). Those said, then it becomes a tedious job to do this reflex tool on all joint movers, OR, that it should be a very strict protocol adherence that those joint muscle movers are the same set of muscles to be assessed overtime. Then again, lumping those data together may not make so much sense anymore. 2) This Referee notes these related statements too (from the argument above) which remains to be clarified in detail: “If spasticity is detectable in more segments, in order to cause less discomfort to patients and examiners and prefer joints with a higher range of motion (allowing more accurate passive movement timing), the segments will be selected in the following order: wrist flexors, elbow flexors, leg estensors, foot plantiflexors (defined “selected segment” and undergoing the stretch reflex procedure)."

	3) Other issues: Better to exclude any patient given BoNT, knowing that there are good studies out there on the BTX-mediated central modulation, whether as direct or indirect effects. 4) This statement needs to be expounded, especially in regard to "return to baseline condition" because then, how about those patients who could potentially worsen in spasticity (say the Placebo cohort; OR those potentially improving in the THC/CBD cohort): "A 2-weeks washout time will allow patients taking THC/CBD oromucosal spray (or placebo) to reach their baseline spasticity condition and then patients will switch arms and perform another month the other treatment. After while the final (T2) assessment will be performed." 5) This present referee wished to be enlightened what was the basis for 10 weeks here: "During the 10 weeks of the study, patients not responding to the treatment and unable to complete the study untreated will undergo a rescue treatment (e.g. BoNT) and exit the study." 6) The role of rehabilitation in Spasticity is critical in regard to outcomes; It is suggested that the authors give fine details as to how this therapeutic modality be figured in the present protocol. 7) Finally, Spasticity treatment is complex (as to phenomenology and course [spontaneous remission or progression}), and for which reason, the GAS (Goal Attainment Scaling) was formulated to address this specific concern, as the tool is person-centered and individualized; Could the authors venture to discuss this matter alongside this present submitted protocol?

REVIEWER	Dr William Notcutt James Paget University Hospital, Great Yarmouth, UK
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	The N/A answer above reflect that this is a protocol not the final paper

REVIEWER	francesco panza Geriatric Unit and Gerontology-Geriatrics Research Laboratory, Department of Medical Sciences, IRCCS Casa Sollievo della Sofferenza , San Giovanni Rotondo, Foggia , Italy
REVIEW RETURNED	06-Jun-2017

GENERAL COMMENTS	The authors propose a double blind placebo controlled crossover study to assess the effect of THC/CBD oromucosal spray an add-on therapy for post stroke spasticity. The protocol is well written even if I think that it's very important to analyse some aspects: The authors have to insert the ultrasound to identify the status of the muscle of the stroke patients before the enrollment. In fact it has been shown that ultrasound guide is very important to observe the spastic muscle, improving the outcome of the treatment (see. Santamato A, Micello MF, Panza F, Fortunato F, Baricich A, Cisari

	C, Pilotto A, Logroscino G, Fiore P, Ranieri M. Can botulinum toxin type A injection technique influence the clinical outcome of patients with post-stroke upper limb spasticity? A randomized controlled trial comparing manual needle placement and ultrasound-guided injection techniques. J Neurol Sci. 2014 Dec 15;347(1-2):39-43. The authors have to exclude the subjects with Baclofene therapy to avoid confounding effects. The authors have to identify the correct number of puffs/day for each patient to reach an important effect on spasticity reduction. In fact it's known that a limitation of THC/CBD therapy is the presence of important adverse effects for the patients and many times the subjects submitted to this therapy become drop-out. The authors have to insert an adequate follow up to observe the duration of the THC/CBD effect The authors have to correct the scale DSS; probably they refer to Spasm Frequency Scale (see. Penn et al..)

VERSION 1 – AUTHOR RESPONSE

Answer to Reviewer 1

1) On the PRIMARY AIM to make the reflex tool as the outcome: Unlike BoNT (botulinum toxin) which is a focal and targeted treatment for spasticity, oral medications (including Sativex spray here) that are not targeted (hence, "random" treatment like Baclofen etc), then more objective and subjective assessments will be desirable. It is anticipated that the yield of this reflex-derived sophisticated assessment tool may potentially not reach their desired outcome, unless one does the measurement on ALL affected joints, rather than choosing certain joints (which makes sense in BoNT because the PMTG-Primary Targeted Group of muscles moving a joint can easily be assessed in a focal kind of Ttherapy). Those said, then it becomes a tedious job to do this reflex tool on all joint movers, OR, that it should be a very strict protocol adherence that those joint muscle movers are the same set of muscles to be assessed overtime. Then again, lumping those data together may not make so much sense anymore.

Evaluating the efficacy of the treatment on spasticity is the critical point in this study, as well in other studies that have been performed with THC:CBD. Of course a local treatment such as BoNT would obviously require evaluating hypertonia only on the treated muscle, since it would make little sense to evaluate a spastic muscle not treated by BoNT. A systemic drug potentially effective on all spastic segments could allow the examiner to test only one sample segment, using a strictly reproducible technical setup during placebo and active treatment conditions. It must be noted that the majority of other clinical trials assessing the effect of a treatment on spasticity make use of very coarse endpoints, such as NRS for spasticity, which is very subjective, little sensitive e also not much specific (see our previous publication on patients with multiple sclerosis). The use of the stretch reflex shows at least two critically major advantages: it is objective and very sensitive and specific for spasticity. Repeating the stretch reflex procedure on all spastic segments is clearly unfeasible and we believe that the method that we propose in the current protocol is the most appropriate and the best compromise between accuracy and feasibility.

2) This Referee notes these related statements too (from the argument above) which remains to be clarified in detail: "If spasticity is detectable in more segments, in order to cause less discomfort to

patients and examiners and prefer joints with a higher range of motion (allowing more accurate passive movement timing), the segments will be selected in the following order: wrist flexors, elbow flexors, leg estensors, foot plantiflexors (defined "selected segment" and undergoing the stretch reflex procedure)."

In order to improve clarity we provided an example, adding the following sentence in page 7 (Stretch reflex technical setup): "For example, if a patient is affected by spasticity on both wrist flexors (MAS=2) and leg extensors (MAS=3), the stretch reflex procedure will be performed on wrist flexors."

3) Other issues: Better to exclude any patient given BoNT, knowing that there are good studies out there on the BTX-mediated central modulation, whether as direct or indirect effects.

It is also true that most studies consider appropriate a BoNT wash-out of 4 months to assess the effect of other treatments. Most importantly, since the majority of the patients that we plan to recruit will come from our outpatient service where we treat patients with BoNT, excluding those patients would render this (monocentric) study unfeasible. To be noted, even if a central effect actually occurred after the 4-months washout, the randomized cross-over design of the study would make this effect balanced between placebo and real treatment arms, without affecting study validity.

4) This statement needs to be expounded, especially in regard to "return to baseline condition" because then, how about those patients who could potentially worsen in spasticity (say the Placebo cohort; OR those potentially improving in the THC/CBD cohort): "A 2-weeks washout time will allow patients taking THC/CBD oromucosal spray (or placebo) to reach their baseline spasticity condition and then patients will switch arms and perform another month the other treatment. After while the final (T2) assessment will be performed."

Stroke is usually an acute and monophasic event possibly leading to chronic spasticity that, differently from progressive conditions such as multiple sclerosis, is not expected to increase over time. It is true that a certain amount of muscle fibrosis could develop over years, but we do not expect any worsening of post-stroke hypertonia over 2-3 months. As reported on Sativex drug monograph, THC:CBD plasmatic half life is 4 hours with a prolonged later half life (related to adipose tissue) lasting 24-36 hours. It is therefore plausible that the effects disappear completely over a 2-weeks time.

5) This present referee wished to be enlightened what was the basis for 10 weeks here: "During the 10 weeks of the study, patients not responding to the treatment and unable to complete the study untreated will undergo a rescue treatment (e.g. BoNT) and exit the study."

The study duration will be 10 weeks resulting from: 4 weeks for the first phase (Period I, between T0 and T1) + 2 weeks washout + 4 weeks for the second phase (Period II, ending at T2, see figure). During these 10 weeks, those patients who will be unable to remain without the effect of BoNT (e.g. because of pain related to spasticity) will exit the study and undergo a rescue treatment (likely BoNT if that was their previous regimen).

6) The role of rehabilitation in Spasticity is critical in regard to outcomes; It is suggested that the authors give fine details as to how this therapeutic modality be figured in the present protocol.

In order to avoid the confounding effect of any physical and rehabilitative treatment on spasticity, patients will not undergo any specific physical and rehabilitative treatment during the study. To be noticed, in our hospital the rehabilitative treatment is limited to the first 2-3 months following stroke, so the patients enrolled in the study are not usually doing rehabilitative treatments. We added the following sentence (page 6): "For the same reason, patients are required not to undergo any physical and rehabilitative treatment during the study."

7) Finally, Spasticity treatment is complex (as to phenomenology and course [spontaneous remission or progression}), and for which reason, the GAS (Goal Attainment Scaling) was formulated to address

this specific concern, as the tool is person-centered and individualized; Could the authors venture to discuss this matter alongside this present submitted protocol?

We are sorry, but we are not sure if the reviewer is suggesting the use of GAS or to avoid its use for the present study. The GAS has been used to subjectively assess improvement or worsening of spasticity following treatments, mostly BoNT; we also used GAS in a recent work in patients with post-stroke spasticity with repeated BoNT injections (Trompetto et al. Med Hypotheses. 2017 May;102:28-32). In this specific study we use NRS for spasticity (to match previous works using THC:CBD) that provides informations about subjective scores that can be easily compared over time to appreciate improvement or worsening. We therefore deem that the use of GAS in this case could be redundant.

Answer to Reviewer 3

The authors have to insert the ultrasound to identify the status of the muscle of the stroke patients before the enrollment. In fact it has been shown that ultrasound guide is very important to observe the spastic muscle, improving the outcome of the treatment (see. Santamato A, Micello MF, Panza F, Fortunato F, Baricich A, Cisari C, Pilotto A, Logroscino G, Fiore P, Ranieri M. Can botulinum toxin type A injection technique influence the clinical outcome of patients with post-stroke upper limb spasticity? A randomized controlled trial comparing manual needle placement and ultrasound-guided injection techniques. J Neurol Sci. 2014 Dec 15;347(1-2):39-43.

The cited manuscript refers to the use of ultrasound guidance for botulinum toxin injection, concluding that “Ultrasound guidance for botulinum toxin type A injections could improve clinical outcome measures better than manual needle placement in post-stroke patients with spasticity”. Actually we also routinely use ultrasound guidance for botulinum toxin treatment but of course this is not the case for the current study. Maybe the reviewer is suggesting that the degree of muscle fibrosis should be assessed in each patients before the study. We are familiar with semi-quantitative muscle ultrasound evaluation of fibrosis, such as Heckmatt scale, however we believe that such evaluation would not be particularly useful for the present study because THC:CBD effect on spasticity will be measured by picking up the electromyographic signal from active muscle fibers, while fibrotic tissue within the muscle will produce no electric signal nor be affected by the treatment, so we don’t expect any particular influence of muscle fibrosis on our endpoints.

The authors have to exclude the subjects with Baclofene therapy to avoid confounding effects.

Since Sativex had been licensed for use in multiple sclerosis as “add-on therapy” for symptoms associated to spasticity, we were required to perform an “add-on” study also in patients with post-stroke spasticity (as specified in the title). This implies that patients may already be under anti-spastic treatment such as baclofene or BoNT and we are assessing the additional effect of THC:CBD. While we cannot continue BoNT during the study because over the 10-weeks time the relevant effect of the toxin will fluctuate and produce a relevant confounding effect, we see no reasons to exclude patients taking baclofene or other drugs affecting pain or spasticity nor discontinue previous systemic treatments, given that the dosage remain constant, as already stated in the protocol (pages 5-6): “During the whole study, the patients will have to maintain the same therapy apart from the study drug, in order to minimize other conditions that could affect the level of spasticity.”

The authors have to identify the correct number of puffs/day for each patient to reach an important effect on spasticity reduction. In fact it's known that a limitation of THC/CBD therapy is the presence of important adverse effects for the patients and many times the subjects submitted to this therapy become drop-out.

As required for patients with multiple sclerosis, Sativex administration must follow a titration scheme (specified at the end of page 6) until the highest tolerated number of puff/day is reached. Of course this can vary among patients, but, as observed in our previous study on multiple sclerosis, the stretch reflex (and thus spasticity) reduction is probably dose-related and also the number of "responders" to the treatment would be higher if highest dosages were tolerated. So we will invite patients to reach the highest possible number of puffs, but cannot actually identify the correct number of puffs/day "a priori".

The authors have to insert an adequate follow up to observe the duration of the THC/CBD effect

All patients will undergo a neurological clinical follow up after study completion. We now specify it in the manuscript: "All patients will be monitored by a neurological clinical follow-up at least for 1 year upon study termination."

The authors have to correct the scale DSS; probably they refer to Spasm Frequency Scale (see. Penn et al..)

We are grateful to the reviewer for catching this error; we meant the number of spasms per day (as reported in a previous clinical trial by Collin, 2007), a value that can be easily converted to the semi-quantitative score of the Penn spasm frequency scale or Spasm frequency score (see Biering-Sørensen et al. Spinal Cord. 2006;44:708-22). We corrected the definition in the manuscript.

VERSION 2 – REVIEW

REVIEWER	Raymond Rosales University of Santo Tomas, Manila, Philippines
REVIEW RETURNED	16-Jul-2017

GENERAL COMMENTS	Revisions are satisfactory

REVIEWER	Francesco Panza, MD, PhD Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy
REVIEW RETURNED	02-Jul-2017

GENERAL COMMENTS	My previous concerns have been satisfactorily addressed.