Author's response to reviews

Title: Drug-induced dyskinesia in Parkinson's disease. Should success in clinical management be a function of improvement of motor repertoire rather than amplitude of dyskinesia?

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Version: 5 Date: 10 December 2012

Author's response to reviews: see over
TO: Dr. Alam, Editor, BMC Medicine

December 10th, 2012

Dear Dr. Alam,

I am pleased to resubmit the manuscript entitled "Drug-induced dyskinesia in Parkinson’s disease. Should success in clinical management be a function of improvement of motor repertoire rather than amplitude of dyskinesia?" that we would like to be considered for publication in BMC Medicine as an Opinion paper. We would like to thank the reviewers and editors for their insightful comments. We have made substantial modifications to the manuscript to address the issues brought forward by both the reviewers and editors. We have also focused the paper on the novel aspects related to the treatment of dyskinesias. We believe that those modifications have drastically improved the manuscript. The manuscript is now tailored for both clinicians with and without extensive experience in dealing with dyskinesias and as such, should appeal to the wide breadth of your readers. We believe that it deserves to be considered for publication in your prestigious Journal.

I am looking forward to hearing from you.

Sincerely,

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Response to editor:

We have expanded the “Why is managing dyskinesias as much art as science?”, “What would be the impact of better management of dyskinesias on quality of life?”, “What would be the impact of better management of dyskinesias on the health-care system?”, and “What is the theory behind our proposed approach to the treatment of dyskinesia?” sections of the manuscript as the editor asked.

We have reduced the following sections and focused their content on current and novel aspects related to clinical management as per the editor’s request: “How prominent is the problem of PD?”, “What are the current treatments of PD?”, “What are the main issues with current treatments?”, “How prominent is the problem of dyskinesia and its management?”.

We have also reformatted the abstract so as to conform to the requirements of the journal.
Reviewer's report
Title: Drug-induced dyskinesia in Parkinson’s disease. Should success in clinical management be a function of improvement of motor repertoire rather than amplitude of dyskinesia?
Version: 3 Date: 20 August 2012
Reviewer: Nicola Tambasco

Reviewer’s report:
General comments:
In this manuscript Daneault et al reported a long discussion on the pathogenesis and evaluation of the dyskinesias in Parkinson’s disease. The assessment of drug-induced dyskinesia is always a troublesome dilemma for the clinicians. The authors summarized a very extensive bibliography regarding this interesting topic.

Major Compulsory Revisions:
1) How did the authors conducted their bibliography research, (terms, database…)

ANSWER: The goal of the first section was to provide the reader with an overview of current knowledge related to dyskinesia, in order to put our “opinion” in context. Accordingly, we did not perform a systematic review, but rather an overview of the problem of dyskinesia. In brief, for each section, we searched Pubmed with the appropriate keywords. For example, in the quality of life section, we searched for “Parkinson and Dyskinesia and Cost”. We selected the articles that we felt were the most relevant and to which we had access. We then searched within these articles bibliographies as well as through our own banks of articles to see if we missed any important articles.

Additionally, as Rev.1 can see from the revised manuscript, the review section has been dramatically reduced and refocused, according to the Editor’s demand. Nonetheless, we have modified a sentence in the Introduction section so as to circumscribe the body of literature we have searched:

“However, in order to fully comprehend the complexity of the problem of dyskinesias, we will first provide an overview of the treatments for PD and how they can induce dyskinesias. We will then provide a non-systematic review the impact of dyskinesias on quality of life and health-care costs.”

2) An important point is that the authors have defined the term signal to noise the ratio between voluntary and involuntary movement. This expression is mediated by another term commonly used about the MRI technique and can be confusing.

Consequently, it is good to replace it with another expression.

ANSWER: The term signal-to-noise ratio is a measure that compares the level of a desired signal to the level of background noise. It is defined as the ratio of signal power to the noise power. A ratio higher than 1 to 1 indicates more signal than noise. In this case, the “signal” is the voluntary motor drive and the “noise” is the motor symptoms and side-effects associated with Parkinson’s disease. While signal-to-noise ratio is commonly quoted for
electrical signals, it can be applied to any form of signal. We understand that this term is used in other fields such as in MRI analysis, engineering, etc but the fact is that a signal-to-noise ratio is exactly what we propose to use in our approach. As such, we feel that finding another term would not be appropriate. We will then respectfully keep the signal-to-noise term.

3) The authors utilized an interesting approach to study the impact of the dyskinesias in patients with PD, but important definitions are missed. What the authors mean by motor repertoire? which measurement must be used to assess voluntary movements? How can the observer assess the different distribution of dyskinesias? For example, if a patient had a marked postural instability and want to make a movement with the right hand, how should the observer indicate in the formula “equation 2”?

**ANSWER:** We have better defined the term “motor repertoire” in the section “What is the theory behind our proposed approach”:

“This point is important as we should discriminate activities of daily living from the motor repertoire of patients. Activities of daily living are essential for minimal functional independence but the motor repertoire encompasses all movements deemed important for a good quality of life for a specific patient. As such, the motor repertoire will be personalized and will vary greatly depending on the movements patients wish to perform on a regular basis.”

As for the measurement that must be used to assess voluntary movements, it was already stated that both amplitude and velocity were needed to assess each task. Nonetheless, we have but further emphasis on this point in order to avoid any confusion:

“As such, in order to properly assess the complexity of a voluntary movement, both its amplitude and velocity must be examined.”

It is important to note that the formulas are presented, not as a model that can be altered by changing each parameters, but rather as a concept where symptomatology is integrated with voluntary movements. Improving this concept in order to put it into an actual model is currently the focus our laboratory.

4) Moreover, the authors reported that “activities of daily living do not circumscribe the whole motor repertoire deemed necessary by each patient; they merely represent general tasks that provide some functional independence”.

Nevertheless, the Parkinson Disease Dyskinesia Scale (PDYS-26) is an interesting and validated scale for quantifying the impact of dyskinesias on activities of daily living in PD and should be more appropriately discussed. Moreover, the dyskinesias in Parkinson’s disease may widely vary during the day depending on different factors (time of drugs assumption, doses, feeding …), how can the observer assess the time variability of dyskinesias?

**ANSWER:** As the reviewer can see in the manuscript, much of the text has changed. We have also added a discussion about the PDYS-26 as suggested by the reviewer. As for the assessment of time variability, it cannot be better assessed with our approach than with any other method that does not monitor the patients on a continuous manner. We discussed
this issue in a recent paper (Carignan et al 2012, J Parkinson’s disease) and mentioned some methods that are currently under development to assess patients over several hours and potentially days in the near future. But for now, the only method that we are aware of that can accurately assess precisely the time variability of dyskinesias is a self-reported journal.

Minor Essential Revisions:
1) In the second paragraph of the discussion a reference is missing “[15 for comprehensive reviews of current treatment options, see 42 and ..]

ANSWER: Actually, there seems to have been an issue with the reference manager. The references were actually there (15 and 42) but the citation was not properly formatted. Accordingly, we made the modifications in the second paragraph of the discussion section (Line 49):

“[see 15 and, 42 for comprehensive reviews of current treatment options]”

Quality of written English: Not suitable for publication unless extensively edited
ANSWER: As the reviewer can see, extensive modifications were made to the manuscript.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report

Title: Drug-induced dyskinesia in Parkinson's disease. Should success in clinical management be a function of improvement of motor repertoire rather than amplitude of dyskinesia?

Version: 3 Date: 2 October 2012
Reviewer: Fabrizio Gardoni

Reviewer's report:
The review by Daneault and co-workers focuses on a main issue in the field of Parkinson’s Disease, that is the onset and management of drug (L-DOPA) induced dyskinesia. The authors aim to provide a complete review of molecular mechanisms of dyskinesia, as well as to present a possible new way to view its management.

Major Compulsory Revisions:
I think that several points need to be improved.
The authors attempt to cover all main issues in the field ranging from current treatments to molecular mechanisms associated with the onset of dyskinesia, from clinical practice to identification of new algorithms. I think that a review more focused on very few of these items would be more helpful; in particular, the first part on current and future treatments could be dramatically reduced, because already addressed in more details in many other reviews in the last few years.

ANSWER: As the Reviewer will see, we have made extensive modifications to the manuscript and several sections were either focused or expanded according to the suggestion of the editor.

On the other hand, to expand the second part of the review concerning the impact of better management of dyskinesias on the healthcare system and the theory behind the proposed approach would be important.

ANSWER: This was done as per the Reviewer’s comment and the editor’s suggestion.

Minor Essential Revisions
The section about glutamate receptors, A2A is somehow confused, interrupted by other paragraphs, and not fluent. This part of the review really needs extensive revision, or improved or omitted.

ANSWER: This section was extensively modified. It was reduced and focused on certain aspects of these mechanisms.

Moreover, also the section related to new possible treatments is very short and incomplete, maybe it is much better or to remove or to expand it.

ANSWER: We have expanded this section as per the reviewer’s comment and editor’s suggestion.

Quality of written English: Needs some language corrections before being Published

ANSWER: As mentioned above, extensive modifications were made to the manuscript.

Statistical review: No, the manuscript does not need to be seen by a statistician.
Reviewer’s report
Title: Drug-induced dyskinesia in Parkinson’s disease. Should success in clinical management be a function of improvement of motor repertoire rather than amplitude of dyskinesia?
Version: 3 Date: 16 October 2012
Reviewer: Tom Johnston

Reviewer’s report:
The commentary by Daneault and colleagues aims to provide a review of current management of dyskinesia and an opinion as to how this might be optimised. To this end the authors make the argument that dyskinesia might be considered part of ‘signal to noise’ ratio equation and stress the importance of considering not only the amplitude (severity) of dyskinesia but the concomitant level and, moreover, specific phenomenology of accompanying parkinsonism.

Major Compulsory Revisions
As a prelude to the main subject of the manuscript, the authors provide a generally well written account of dyskinesia and cover, briefly, aspects pertaining to mechanism, current and novel treatments and clinical relevance and management. These expansive and complex subtopics have been covered rather superficially with much of the detail and depth regarding mechanisms of dyskinesia, animal models and novel therapies in development instead being summarised and referenced to other publications that cover the material in greater depth. This would not be such an issue were it not for the fact that once these previously well-reviewed topics have been excluded (consider pages 1-14) then the remaining central tenet of the commentary appears to amount to very little.

ANSWER: The goal of the first section was to provide the reader with an overview of current knowledge related to dyskinesia, this in order to put our ‘opinion’ in context. Accordingly, we did not perform a systematic review. This was done by others, rightfully mentioned by Rev 3. Accordingly, we have made extensive modifications to the manuscript as per the Reviewer’s comments and the editor’s suggestion. Some sections were reduced to focus on certain issues whereas other sections were expanded to provide more and better detailed information to the reader.

The authors make reference to the well-established clinical approach that a reduction in levels of dyskinesia, either by a modification of dopaminergic replacement therapy or supplementation with adjunct treatment, is rendered meaningless if a concurrent compromise of the anti-parkinsonian benefit of L-DOPA is also in evidence. Thus far, nothing new. However, the authors then make a well argued and reasonable series of points highlighting that clinical management must be considered in an integrated way and that rigid adherence to rating scales which assess dyskinesia and parkinsonism in isolation or as a ‘total’ disability rating without regard for anatomical localisation or motor repertoire specific for that patient is inappropriate.

If it is the intention of the authors to make this issue known to the broader medical community practising outside of specialist movement disorder centres then such a commentary is deserved. However, any physician operating within such a centre would be well aware of these caveats to successful patient management and as such a further iteration of an often voiced topic would seem unnecessary. As such, while there is nothing fundamentally wrong with this manuscript, its importance is somewhat questionable.
ANSWER: We respectfully disagree with Rev.3 about the importance of the opinion. As mentioned by Rev.3, and ourselves in the manuscript, this paper is not necessarily targeted towards movement disorders specialists (although they may find the schematization of what they are doing intuitively interesting and useful), but rather towards neurologists and general practitioners that do not deal with Parkinson’s patients on a regular basis. The issue of whether a change of medication to avoid dyskinesia is successful or not is currently based on whether dyskinesia was reduced, and whether it generated other unwanted side effects (psychiatric, cognitive, etc.). What is novel about our opinion is that it forces the clinician to put back motor performance (i.e., the breadth of the motor repertoire), back into the equation. Furthermore, the concept of motor repertoire extends further than simply pronation-supination of the hand, or foot tapping; it relates to everyday life activities, something that is not necessarily taken into account when evaluating success of treatment. This is because the most used scales do not provide a good picture of the motor repertoire available to patients in their natural living environment. If the opinion only reinforces this important aspect in movement disorders specialists, our paper will be important. If it introduces to non-specialists the idea that success of treatment should be measured by taking into account symptomatology AND motor repertoire availability, the opinion will be important. Finally, if it lays the foundation for quantitative research aiming at better understanding the signal-to-noise ratio (i.e., the relationship between symptomatology and voluntary movements) in PD, it will be important. Such research could lead to better holistic understanding of the impact of treatment, it could lead to personalization of treatment, and ultimately improvement in the outcome of these interventions. This is why we believe that our paper deserves to be considered for publication in BMC Medicine.

Minor Essential Revisions
There are a few typographical errors in the text. For example;
Page 5, 2nd line from the bottom, “and can only difficulty...”
ANSWER: Actually, what was written was “and can only difficulty...”. Nonetheless we have modified this sentence in order to avoid any further confusion:

“Since dopamine causes severe nausea, and cannot easily cross the blood brain barrier,...”

Page 6, 1st line – missing review reference
ANSWER: As mentioned to Reviewer 1, there seems to have been an issue with the reference manager. The references were actually there (15 and 42) but the citation was not properly formatted. Accordingly, we made the modifications in the second paragraph of the discussion section (Line 49):

“[see 15 and, 42 for comprehensive reviews of current treatment options]”

Page 13, 2nd line – fold, not folds
ANSWER: We have made the modification in the manuscript:

“...expected to grow several fold in upcoming years...”
Page 14, million$ notation incorrect
**ANSWER:** We have made the appropriate corrections.

**Quality of written English:** Needs some language corrections before being Published
**ANSWER:** As mentioned above, the manuscript was extensively modified.

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I have no competing interests to declare