MDS Evidence Based Medicine Committee: Revision of the methodological process for Systematic Reviews: Adoption of the Modified GRADE system

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Since 2002, the MDS Evidence Based Medicine (EBM) Committee has regularly provided Systematic Reviews of the evidence for treatments of Parkinson´s disease motor [1-4] and non-motor symptoms,[1,2,5,6] later followed by the topics essential tremor,[7] restless legs syndrome,[8] and Huntington´s disease (under submission). Regular updates on PD treatments were published on the MDS Website before being incorporated in the subsequent full publications.

The development of MDS EBM Reviews involved a standard method for a literature search of randomized controlled trials. To be included, studies had to fulfil pre-specified eligibility criteria, such as investigating interventions that were commercially available in at least one country or area, and a minimum of 20 patients treated for at least 4 weeks.[1-4] The quality of the evidence was rated using a published Rating Scale for Quality of Evidence.[1-4] Based on the resulting efficacy conclusions and on safety data, the MDS EBM subgroups followed a pre-defined framework to draw consensus-based implications for clinical practice. [3,4] According to the perceived quality of the evidence and the presence or not of a clinical benefit, one of five possible implications for clinical practice was attributed to a given intervention: Clinically useful, Possibly useful, Investigational, Unlikely Useful Not useful ([4] supplemental material).

Over time, the interpretation of the evidence became more complex to summarize in a balanced manner – the number of eligible studies grew, and in several instances results are not consistent or truly divergent. Methodological developments occurred in the field of EBM and the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group has developed a methodological approach to help summarizing and interpreting the evidence in the context of evidence synthesis research.[9]

For the purposes of systematic reviews, the GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest.[10] GRADE has four levels of evidence – also known as certainty in evidence or quality of evidence: very low, low, moderate, and high. For each outcome, a given level of the quality of evidence is obtained after subjective

appraisal of the following domains: risk of bias (using an appropriate tool, such as Cochrane Risk of Bias tool), imprecision, inconsistency, indirectness, and publication bias.[11] Two components should be considered when drawing final conclusions from the results of a systematic review for a specific intervention: the certainty of (or confidence in) the evidence and magnitude of the effect of the intervention.

According to the GRADE approach, moving from the results of systematic reviews to clinical decisions should consider the balance between desirable and undesirable consequences and acknowledge other factors such as the values and preferences underlying the recommendations of clinical guidelines. The MDS recognizes the value of clinical guidelines but its aim continues to be the production of Systematic Reviews, not guidelines, in keeping with its mission as a global society. Nevertheless, MDS EBM reviews aim to provide clear and transparent conclusions for clinical practice following a robust methodological approach.

The MDS EBM committee decided to embrace the GRADE approach but some adaptations were implement at the level of drawing conclusions (implications for clinical practice), for the following reasons:
1) to maintain the well-received terminology on Efficacy and Safety that had been customary in MDS Systematic Reviews (see Tables);
2) to accommodate the limited ability to conduct formal meta-analyses. This is mostly a resource-based limitation but meta-analyses are still planned when possible and necessary to solve a question;
3) Decisions about the size of the effect are not straightforward and the magnitude of the difference estimate is usually determined by meta-analysis.

A collaboration with Cochrane Movement Disorders based in Lisbon, Portugal, was established in 2019. Cochrane Movement Disorders has now trained all MDS EBM contributors in the GRADE system and its application to the MDS Systematic Reviews, and continues to advise to ensure the committee´s work is in line with up-to-date methodological standards.[12]

The **Tables** illustrate the framework to be used for drawing efficacy conclusions (implications for clinical practice) of future MDS Systematic Reviews, based on the described methodological approach. In brief, and similar to the GRADE system, conclusions in MDS EBM reviews will consider two axes: the clinical relevance of the outcome; and the quality of the evidence.
The main differences between the new MDS EBM approach and the original GRADE recommendations for drawing conclusions are:

1) The importance of benefit is based on the clinical relevance of the outcomes and not on the effect size.

2) The information on effect size appears prominently in the text (to make the Table cleaner and more consistent).

3) Low and very low levels of evidence all lead to a classification of “insufficient evidence”.

4) If instances arise where there is a suggestion of a superior effect of the control intervention, these need to be dealt with in separate tables.

The recently conducted HD Review had already used this new approach. The next subgroups expected to complete their new Systematic Reviews are those on motor and non-motor symptoms in PD. These groups are currently applying the GRADE approach to the full time frame, to ensure new studies and those published during the time covered by earlier editions are treated alike. During this transition period, no interim updates will be posted on the MDS Website.

References:

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MDS EBM Modified GRADE – Efficacy Conclusions

Table

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LEVEL OF EVIDENCE IN FAVOUR OF THE INTERVENTION	**IMPORTANT BENEFIT** (CLINICALLY RELEVANT OUTCOME)	**BENEFIT OF INTERMEDIATE IMPORTANCE (**CLINICAL RELEVANCE OF THE OUTCOME UNCERTAIN)	**NO IMPORTANT BENEFIT (**OUTCOMES WITHOUT CLINICAL RELEVANCE**)**
HIGH	Efficacious	Likely Efficacious	Not efficacious
MODERATE	Likely efficacious	Likely efficacious	Unlikely efficacious
LOW OR VERY LOW	Insufficient evidence	Insufficient evidence	Insufficient evidence

LEVEL OF EVIDENCE AGAINST THE INTERVENTION	**IMPORTANT BENEFIT** (CLINICALLY RELEVANT OUTCOME)	**BENEFIT OF INTERMEDIATE IMPORTANCE (**CLINICAL RELEVANCE OF THE OUTCOME UNCERTAIN)	**NO IMPORTANT BENEFIT (**OUTCOMES WITHOUT CLINICAL RELEVANCE**)**
HIGH	NOT Efficacious	NOT Efficacious	Unlikely efficacious
MODERATE	Unlikely efficacious	Unlikely efficacious	Insufficient evidence
LOW OR VERY LOW	Insufficient evidence	Insufficient evidence	Insufficient evidence