PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review and meta-analysis assessing adverse event profile and tolerability of nicergoline
AUTHORS	Fioravanti, Mario; Nakashima, Taku; Xu, Jun; Garg, Amit

VERSION 1 - REVIEW

REVIEWER	Katie Saunders Cambridge Centre for Health Services Research, UK
REVIEW RETURNED	29-Apr-2014

GENERAL COMMENTS	This is a methodological / statistical review of the paper “A systematic review and meta-analysis assessing safety and tolerability of nicergoline” Given the European Medicines Agency recommendation that the use of nicergoline be restricted for safety reasons this review would appear to be quite timely http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001832.jsp&mid=WC0b01ac058004d5c1b Broadly the paper is OK but there are strong limitations to the methods applied: • There is inadequate recognition that the methods required for a systematic review and meta-analysis of adverse events are not the same as those for main effects. • The selection criteria may need some reconsideration • The critical appraisal of included studies was not appropriate • There is inadequate detail of the statistical methods used for the meta-analysis. • The outcomes (and how they were measured) need to be clearly defined. Sub group analyses need to be specified a priori in the methods sections and then reported systematically in the results. More detail is required for each s **Comments:** There has been recent interest in the correct methods to use for meta-analysis and systematic reviews of adverse events. Consensus for best practice is emerging and three key methodological references can be found here: http://www.bmj.com/content/348/bmj.f7668 http://ctj.sagepub.com/content/10/3/389.full.pdf+html

	http://handbook.cochrane.org/ part 3 section 14 One specific key point is that non RCT sources of adverse event data may well be relevant (they were used in the European regulatory process), but are not included in this review **Search strategy (p7, line29)** Search terms should be listed **Selection criteria (p7, line 46)** If safety is a concern why not include all trials of nicergoline? This would increase the sample size. The outcome is safety rather than efficacy so I think that the argument for disease specific study selection is weak Studies that did not report safety and tolerability were excluded. What about drop-outs? Surely this is a reasonable outcome for "harm" to consider and should be reported for all trials. Could this have increased the scope of the study? **Outcomes assessed** More detail is needed about how the outcomes were measured in each study, and how they were pooled. An extra table would be helpful. **Statistical methods (p8, line 34)** This section is not adequate. There are many standard meta-analytic techniques. Which did you use? **Study selection (section p9, line17)** It is not clear from the PRISMA flow chart why 15 studies (50%) were excluded from the quantitative analysis **Critical appraisal (p9 line 47)** This section was not mentioned in the methods section. The Jadad scale was developed for studies of interventions, rather than studies of adverse events. The Cochrane handbook has a nice section on how to evaluate the quality of adverse event reporting. **Page 10 – reporting of results** The number of adverse events are rare. It would be very helpful to include a table with the number of reported adverse events by study and type. Statistically how did you account for the fact that your outcome measure was rare? (Cochrane handbook 16.9 has a helpful section).

REVIEWER	Yasuhiro Nishiyama at the department of Neurology, Nippon Medical School, Japan
REVIEW RETURNED	10-May-2014

GENERAL COMMENTS	I think statistics are good, but I am not professional statistician. It might be better to check this methodology by them. The study is well performed, the results of systematic review and meta-analysis are clearly presented. They concluded nicergoline is comparable safe and tolerability though it is categorized under ergot derivatives. It is not new drug, but potentially might be effective for patients with cognitive impairment or post-stroke depression. However, there remain some issues which need to be addressed: 1. You didn't show the dairy dose of nicergoline and the number of participant of the studies in Table 1. Please add them into the table. 2. You don't have to show P value of fixed effects in Table 2 and 3 because you already showed 95%CI. 3. I would like to know if dairy dose of nicergoline affect the results. You can show whether the difference between treatment group and placebo group depends on dose of the agent. 4. Ask native language speakers to check the manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Comment 1: There has been recent interest in the correct methods to use for meta-analysis and systematic reviews of adverse events. Consensus for best practice is emerging and three key methodological references can
be found here:
http://www.bmj.com/content/348/bmj.f7668
http://ctj.sagepub.com/content/10/3/389.full.pdf+html
http://handbook.cochrane.org/ part 3 section 14

Response: We completely agree with your response and we can confirm that we have based our methods as per Cochrane handbook. We have followed the recommendations for searches, analysis and reporting as per Cochrane handbook and tried to avoid any bias from our end.

Comment 2: One specific key point is that non RCT sources of adverse event data may well be relevant (they were used in the European regulatory process), but are not included in this review

Response: We are looking at adverse events reported in RCTs and non-RCTs separately. Our focus was evidence from RCTs for we will publish the evidence from our non-RCT SR soon. For the purpose of meta-analysis we refrained from mixing evidence from different study designs.

Comment 3: Search strategy (p7, line29): Search terms should be listed

Response: Key search terms have been added.

Comment 4: Selection criteria (p7, line 46): If safety is a concern why not include all trials of nicergoline? This would increase the sample size.

Response: Our objective for current SR was to look at safety profile of nicergoline reported in RCTs and thus the inclusion criteria are specific to this objective.

Comment 5: The outcome is safety rather than efficacy so I think that the argument for disease specific study selection is weak.

Response: We did not restrict our inclusion to any one indication of nicergoline rather we kept our disease criteria broad by including Alzheimer's disease, dementia or other cognitive disorders.

Comment 6: Studies that did not report safety and tolerability were excluded. What about drop-outs? Surely this is a reasonable outcome for "harm" to consider and should be reported for all trials. Could this have increased the scope of the study?

Response: Yes, we have included all studies that reported study withdrawals as part of safety profile. We haven't excluded any studies which presented only withdrawals and no adverse event data. Study withdrawals were one of the outcomes in meta-analysis as well.

Comment 7: Outcomes assessed: More detail is needed about how the outcomes were measured in each study, and how they were pooled. An extra table would be helpful.

Response: As most of the studies do not specifically report how the outcomes were measured for safety outcomes, we have added a summary of methodology in text and also how we pooled these outcomes in "Outcomes assessed" section.

Comment 8: Statistical methods (p8, line 34): This section is not adequate. There are many standard meta-analytic techniques. Which did you use?

Response: We conducted direct meta-analysis for head-to-head comparisons with various comparators and have reported results individually for all comparisons. This has been updated in the section "Statistical methods"

Comment 9: Study selection (section p9, line17): It is not clear from the PRISMA flow chart why 15 studies (50%) were excluded from the quantitative analysis

Response: These studies were excluded as data from these could not be pooled in meta-analysis. These were the ones reporting standalone adverse events, or for standalone comparators.

Comment 10: Critical appraisal (p9 line 47): This section was not mentioned in the methods section. The Jadad scale was developed for studies of interventions, rather than studies of adverse events. The Cochrane handbook has a nice section on how to evaluate the quality of adverse event reporting.
Response: As we have included only RCTs in our SR, we used Jadad scoring as it is to score the reporting quality of RCTs. We agree with your suggestion that Cochrane provides a scale for rating as well but Jadad is most widely used for RCTs although there is criticism for same.
Comment 11: Page 10 – reporting of results- The number of adverse events are rare. It would be very helpful to include a table with the number of reported adverse events by study and type. Statistically how did you account for the fact that your outcome measure was rare? (Cochrane handbook 16.9 has a helpful section).

Response: We have added a supplementary table for same. We have only concluded that AEs were either similar or lesser in nicergoline group. None of the included studies reported fibrosis or ergotism with nicergoline.

Reviewer 2:

The study is well performed, the results of systematic review and meta-analysis are clearly presented.

They concluded nicergoline is comparable safe and tolerability though it is categorized under ergot derivatives. It is not new drug, but potentially might be effective for patients with cognitive impairment or post-stroke depression. However, there remain some issues which need to be addressed:

Comment 1: You didn't show the dairy dose of nicergoline and the number of participant of the studies in Table 1. Please add them into the table.

Response: Table 1 has been updated to include daily dose of nicergoline

Comment 2: You don't have to show P value of fixed effects in Table 2 and 3 because you already showed 95%CI.

Response: Thanks for your comment, we do agree with you but this is just in line with reporting style of meta-analysis outcomes.

Comment 3: I would like to know if dairy dose of nicergoline affect the results. You can show whether the difference between treatment group and placebo group depends on dose of the agent.

Response: Yes, we found in couple of studies that higher doses (60mg/day) were associated with headache and flushing. Although, this evidence was not significant.

Comment 4. Ask native language speakers to check the manuscript.

Response: Yes, this manuscript has been edited and proof read by professional editor