

Efficacy of memantine on behavioural and psychological symptoms related to dement...



Critical Appraisal of the article Efficacy of Memantine on Behavioural and Psychological Symptoms Related to Dementia: A Systematic Meta-Analysis.

The aim of the review conducted was to evaluate the use of Memantine in the treatment of BPSD. Patients who have BPSD are often difficult to manage and end up having negative/adverse patient outcomes.

A systematic meta-analysis is a procedure involving combining data from multiple studies. It can be used to identify a common treatment effect which is consistent from one study to the next. ¹ In this article the researchers quantitatively assessed the results of previous research in order to develop conclusions about that body of research.

Clinical decisions for the management of illnesses should be based on the totality of all the best evidence and not the results of the individual studies. ¹

To ensure all essential elements are included and results are easily reproducible, the recommendation is to use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. ²

Another checklist used to appraise reviews is the Critical Appraisal Skills Programme (CASP). The checklist comprises of questions allowing you to make sense of a systematic review by focussing on what the results of the study are and if they are valid. ³

Did the review address a clearly focussed question?

The review aimed to assess the efficacy of Memantine on BPSD. The researchers established from the data analysed that Memantine had a beneficial effect in patients with BPSD. The analysis was focussed on Memantine combined with cholinesterase inhibitors as well as placebo drugs combined with cholinesterase inhibitors as treatment options rather than other options of pharmacological management of BPSD.

Inclusion criteria for the meta-analysis included studies that were randomised, parallel-group and double blinded. They included patients that had probable Alzheimer's disease according to the Alzheimer's disease and related disorders Association criteria. The final criteria for inclusion in the study also included treatment with Memantine or matched placebo for at least one month. These criteria go against the question that the researchers were attempting to answer because by only including patients with Alzheimer's disease then the findings cannot be applied to other forms of dementia.

Did the authors look for the right type of papers?

The researchers performed a generalised search of databases and search engines like MEDLINE, EMBASE, Pharm-line and PsycINFO for relevant clinical studies using the search terms dementia, clinical trials and Memantine. The search led to 161 articles being identified as being relevant to be included in the analysis but, only 6 articles, after thorough examination, were included in the final meta-analysis. These were identified by 2 of the investigators who solely decided whether the trials or studies should be included in the analysis. The researchers used the Jarad scale to assess the quality of the

methodology of the trial between 0 (very poor) to 5 (rigorous). The Jarad scale has its own limitations in that it demonstrates inconsistency between different researchers using the questionnaire and can place too much emphasis on blinding rather than participant allocation into a specific group, which is vital to avoid researcher bias with data.

By excluding non-randomised controlled trials, open-label studies as well as non-english language studies, researchers straight away had excluded studies which potentially might have been hugely relevant in terms of their contribution to the data examined. By eliminating other review articles, Crossover and open label trials, duplicated publications as well as those in a foreign language, the researchers were able to maximise the details of each study and scrutinise the comparison data. Although the final number of papers examined was very few, they were the most significant and relevant out of the initial 161 papers.

Were all the important, relevant studies included?

The researchers mainly focused on placebo-controlled, double blind randomised controlled trials. RCTs are specially useful when investigating an effect from an intervention.

The studies selected were reviewed independently by 2 of the researchers as to whether they met the inclusion criteria or not. This was quite a subjective selection process and consequently any difference of opinion was resolved through general consensus.

Out of the 6 studies that were identified, 2 compared Memantine in combination with cholinesterase inhibitors against a placebo. One of these studies was mainly focussed on patients who already had a diagnosis of Alzheimer's Disease and had been treated with Donepezil. The other 4 studies were placebo controlled studies where cholinesterase inhibitors were not permitted. These differences can have an effect on the baseline values that had been compared in the statistical analysis. Patients already treated for at least 6 months prior to the start of any study with another pharmacological agent are going to show a certain level of stability in their condition compared to those patients who were treated with a placebo. Having a manipulated baseline before comparing any changes in NPI scores can consequently affect the statistical analysis tests like the level of significance and the confidence interval levels of the data.

Did the review's authors do enough to assess quality of the included studies?

When assessing the rigour of the studies that were identified by the researchers 3 had achieved a Jarad score of 5 demonstrating extreme rigour in their methodology. The other 3 studies according to the researchers' assessment achieved a score of 2 demonstrating less thoroughness in their research methods.

Also the researchers made no contact personally with experts to obtain extra information. The only extra step taken to ensure good quality evidence was included was to contact the manufacturers for more details of studies such as any missing data.

If the results of the review have been combined, was it reasonable to do so?
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Efficacy in the study was mainly assessed by comparing changes in the mean values of the NPI scores from baseline to endpoint in each of the studies. The results were then compared but in order to make best use of the comparability between each of the studies the researchers did not account for or correct any initial differences at the baseline in NPI values. This subsequently has led to a corrected value obtained of the intended to treat population, leading to a loss of up to 13% of randomized patients who could have been included in the analysis. From the 6 studies reviewed, NPI changes were only able to be identified from 5 of the trials. One study had to be excluded from the final calculations as they had not reported any endpoint NPI values leading to the data being insufficient to be included in the calculation of the overall effect size.

Two of the studies which contributed data but had used combination treatments of a cholinesterase inhibitor treatment 6 months prior to be selected for the trials, should not have been combined with the other 4 studies where cholinesterase inhibitors were not permitted. These 2 meta-analyses are not comparable with the other studies as the patients in these studies already had less severe symptoms of BPSD and so the manipulated baseline NPI values from these 2 studies could show Memantine to be a potentially less or more efficacious as a treatment option if patients had been included in the treatment groups.

How precise are the results?

The NPI is a semi-structured instrument carer rated instrument. The 12 domains cover delusions, hallucinations, agitation/aggression,

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depression/dysphoria, anxiety, elation, apathy, disinhibition, irritability/lability, aberrant motor behaviour and sleep and appetite disturbances. Each item is rated by frequency (score: 0-4) and severity (score: 0-3) and the total is the overall score. Carers have highlighted to clinicians and researchers previously that out of all the symptoms of BPSD listed, agitation and aggression are the most distressing and difficult to manage but, out of the 12 areas covered by the NPI only 1 of the subcategories rates aggression and agitation. This is significant because Memantine's main role has been identified by NICE in particular in helping with agitation linked with dementia. Patients who are already being treated with a cholinesterase inhibitor prior to entering a clinical trial as already mentioned will potentially show a lower severity of symptoms of BPSD.

The meta-analysis included six randomized, parallel group, double-blind studies that included subjects with BPSD. The endpoint outcomes providing improvement data on BPSD were available for five of the six studies. In those five studies, patients taking Memantine had a marginally significant improvement of BPSD as compared to the placebo group.

The confidence interval from the results was shown to be 95%. This value does not reflect the inconsistencies in the unknown parameters and allows the data collected to contain the true 'mean' of the population. If the sample size of the data analysed had been larger, then the confidence interval would be smaller as a larger sample allows for narrower values in the confidence interval due to a greater precision compared to smaller samples analysed.

The authors pointed out that there are a number of limitations with the current data, including the relatively small effect size for Memantine, and concluded that it is unclear at the present time whether Memantine produces any significant clinical benefit. Data from RCTs of Memantine in patients with moderate-to-severe dementia had indicated that Memantine might confer benefit.

Can the results be applied to the local population?

Some critical issues concerning evidence coming from Alzheimer's Disease RCTs can cause concern. Firstly, a question which remains unanswered is how the drug performs in trials involving populations which are more typical than the ones usually included in licensing studies, since the latter are known to be poorly representative of the whole population treated post-marketing. For instance, in a real-world practice study, one-fifth of Memantine-treated patients had at least one clinically relevant comorbidity, and more than

50% were receiving concomitant CNS-acting drugs during the study period, both of which were exclusion criteria in one RCT. Moreover, the proportion of responders to treatment is not always reported in the RCTs, which only illustrate the differences between mean and standard deviation of NPI sub-items between the placebo and the treatment arms.

Finally, data from RCTs do not allow predictions of which patients might have a response. These issues do not invalidate the demonstrated efficacy of Memantine in the placebo-controlled trial, but they do underlie the need to collect more information about the actual effectiveness of the drug in clinical

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practice and to assess whether treatment effectiveness in real life is in line with the efficacy found in clinical trials.

These findings are in line with the evidence from placebo-controlled trials and suggest that the effectiveness of Memantine therapy on behavioural symptoms may be transferred into clinical practice.

An alternative explanation could be that Memantine effects on behavioural symptoms are less pronounced in

real life than in patients observed in the RCT setting.

Were all important outcomes considered?

The data analysed in this paper originated from broader observational studies on Memantine safety and effectiveness in moderately severe-to-severe Alheimers Disease patients, which used not only a behavioural outcome (the NPI total score) but also endpoint outcomes of cognition, global status and function.

The importance of behavioural outcomes for evaluating the effects of drugs in the late stages of dementia has been emphasised in many studies.

Arguably, a behavioural scale could be more sensitive to change than cognitive or functional scales in these stages. However, the NPI total score is not necessarily the only useful parameter to assess behavioural effect as it combines a set of 12 different symptoms, and changes in various areas do not always follow the same direction. Greater attention is being directed at the analysis of individual area scores and clusters of individual symptoms.

Specifically, Alheimers Disease behavioural sub-conditions have been <https://assignbuster.com/efficacy-of-memantine-on-behavioural-and-psychological-symptoms-related-to-dementia/>

identified employing a factor analysis based on the original 12-item NPI scale.

Are the benefits worth the harms and costs?

The analysis demonstrated that Memantine is effective on behavioural outcomes and has a good tolerability profile.

This analysis shows that the standard 20 mg daily Memantine treatment regimen is associated with a modest behavioural improvement. These findings provide evidence that Memantine effectiveness may be transferred into a real life setting where Alzheimers Disease patients receiving treatment are not selected according to strict inclusion criteria.

From a practical point of view, a beneficial effect on behaviour, if any, would generally be observed within 3 months.

Conclusion

The main aim of the analysis was to assess clinical studies which had already been conducted to determine if Memantine is viable as a therapeutic agent for the treatment of BPSD. The results from this meta-analysis highlighted that although Memantine may have a role, as it was well tolerated by most patients, its effectiveness compared to current treatments for BPSD was not evident. More trials are needed with larger patient numbers employing robust assessments before the benefits of Memantine being prescribed can be demonstrated.

There are currently no Memantine trials in clinically significant agitation but, post-hoc analyses in other populations found reduced agitation.

Specific analysis of behavioural symptoms from RCTs indicates that Memantine has a beneficial effect on agitation/ aggression in moderate-to-severe Alzheimers Disease patients. Longer studies of the effect of Memantine on quality and duration of life are needed.

Furthermore, a still unresolved question is how the drug performs in trials in more typical populations than are usual in licensing studies. Post-marketing surveillance studies (PMS) are a useful tool to evaluate a drug's effectiveness in real life. At present, there are no Memantine PMS specifically focused on BPSD.

References

1. M. Moller, P. S. Myles; What makes a good systematic review and meta-analysis?, BJA: British Journal of Anaesthesia, Volume 117, Issue 4, 1 October 2016, Pages 428–430
2. <http://www.prisma-statement.org/documents/PRISMA%202009%20checklist.pdf>
3. https://casp-uk.net/wp-content/uploads/2018/03/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf
4. Ulrich W. Preuss¹, Jessica W. M. Wong², Gabriele Koller³. Treatment of behavioural and psychological symptoms of dementia: a systematic review. Psychiatr. Pol. 2016; 50(4): 679–715
5. Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, et al. (2012) Efficacy of Memantine for Agitation in Alzheimer's Dementia: A

<https://assignbuster.com/efficacy-of-memantine-on-behavioural-and-psychological-symptoms-related-to-dementia/>

Randomised Double-Blind Placebo Controlled Trial. PLoS ONE 7(5): e35185. doi: 10.1371/journal.pone.0035185

6. Gauthier S, Wirth Y, Mobius HJ (2005) Effects of Memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the neuropsychiatric inventory (NPI) data of two randomised, controlled studies. *Int J Geriatr Psychiatry* 20: 459–464
7. Cummings JL, Schneider E, Tariot PN, Graham SM (2006) Behavioural effects of Memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology* 67: 57–63