ROUND THE CORNER

VALPROATE PREPARATIONS FOR AGITATION IN DEMENTIA

Commentary on…Cochrane Corner

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BIOGRAPHY

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What does previous evidence tell us?

Agitation occurs in up to 70% in dementia patients (Ijaopo 2017) and its incidence increases as dementia progresses (Livingston 2017). The incidence of those requiring pharmacological treatment is uncertain.

Valproate, along with other anticonvulsants, has been used widely to manage agitation. These drugs have been in use for over 10 years, initially due to findings from case studies (Meyer 2015). A larger study was carried out in 2007 in 15 patients with dementia and agitation, showing that valproate (either alone or in combination with antipsychotics) caused a marked improvement in irritability and aggression (Forester 2007). A subsequent case series showed that relatively low doses of valproate were beneficial for agitation: 17 out of 20 patients improved, although 4 were on additional psychotropic medication (Dolder 2010). Similar results were obtained in a pooled analysis of 20 non-controlled trials, which concluded that low doses of valproate can be beneficial for agitation in dementia, with or without additional medication (Dolder 2012); however, the studies included varied significantly in their methodology and outcomes, making it difficult to draw a reliable conclusion.

The proposed mechanism of action is that of enhancing GABA (gamma-butyric acid), thus having antimanic and mood-stabilising properties; however, the mechanism is not fully understood (Lon 1995; Rosenberg 2007). It has also been suggested that it can act synergistically with other psychotropic medication such as antipsychotics, as shown in animal trials (Ichikawa 2005).

The UK National Institute for Health and Care Excellence (NICE)'s guidelines recommend that people with dementia experiencing non-cognitive symptoms such as agitation should be offered an antipsychotic only if they are at risk of harm to themselves or others or are under severe personal distress related to agitation or psychotic experiences (NICE 2018a). Antipsychotics (e.g. risperidone or haloperidol) should be used at the lowest dose for the shortest possible time, particularly due to the risk of major adverse events, especially strokes (NICE 2018b). The same guidelines advise against the use of valproate to manage agitation in those with dementia, unless it is being used to treat a different illness.

Contrastingly, two previous systematic reviews had been done on the same topic (Lonergan 2004; 2009); however, they only included a maximum of three trials, because other studies were small and lacked a control group (Lott 1995). The 2004 review showed data that had significant levels of bias, and methodological and statistical flaws (Lonergan 2004). The updated 2009 review still highlighted similar biases and argued that valproate did not improve agitation in patients with dementia; moreover, there was a significant rate of side-effects, notably sedation, infections, and gastrointestinal symptoms. The authors argued that most side-effects appeared mild to moderate in severity and were deemed unrelated to the study drug; however, this finding was based on very low-quality data. Therefore, the authors concluded that valproate could not be recommended for controlling agitation in people with dementia, although more methodologically robust research was warranted to further support a change in routine clinical practice. Importantly, studies from the previous systematic reviews have also been included in this most recent review.

Summary of the study

Baillon et al's Cochrane review (Baillon 2018) included 430 participants with agitation in dementia over 5 randomised controlled trials. Overall, the authors found that valproate was probably no better than placebo for the treatment of agitation in people with dementia; however, the quality of the studies included was very variable. Adverse effects and events were higher in the treatment group compared to controls, although these finding were largely based on low-quality data with inaccurate reporting, thus valproate's safety profile is of concern.

Methods

The study aimed to determine whether valproate preparations are effective in treating agitation in those with dementia, as well as exploring adverse effects and the impact on carers.

The population included 430 individuals diagnosed with dementia on the basis of international diagnostic criteria or, in the absence of this, it relied on routine medical or psychological evaluation. Importantly, the latter does raise the question as to whether all the included patients truly had dementia. Agitation was loosely defined as a subjective description of the clinician, and agitation due to delirium was not reliably excluded. Patients were still included if they were on a stable therapy of other psychotropic medications.

The primary outcome was directly related to the control of agitation, which was assessed using different scales amongst the included studies. Secondary outcomes included adverse effects, impact on carers, measures of cognition and functional performance; however, the latter two outcomes will not be discussed in this commentary.

Only randomised, placebo-controlled trials were included in this review, which is in accordance with best practice. The identification of eligible studies was done through validated databases that included trial registers and grey literature. There were no restrictions to date, and studies from other countries and languages were also included. The eligibility criteria were clearly reflected in the search strategy.

The study selection process included a flow diagram and table explaining the reasons for exclusion. Three out of five studies were funded by Abbott laboratories (Porsteinsson 2001;

Tariot 2001; Tariot 2005), which have been judged to have promoted the improper use of valproic acid and have paid a £0.9 billion penalty for this in America (Roehr 2012).

Two authors assessed bias using the Cochrane's tool for assessing methodological quality and risk of bias (Higgins 2011). Trials' authors were contacted if there was inadequate information to determine the risk of bias. Four out of five studies had an unclear risk of bias in at least two areas; notably, the selection bias was generally unclear. Three studies also had insufficient information regarding an aspect of blinding; relating to performance and detection bias. Only one study was deemed of low risk in all areas (Tariot 2005).

Data were pooled into pair-wise meta-analyses using mean differences (MD), odds ratios (OR), and 95% confidence intervals (CI) for the calculation of effect sizes.

Results

The authors accounted for clinical heterogeneity between trials using a fixed effects model for the analysis. However, the studies themselves had significant clinical heterogeneity, particularly relating to the methodology, types of medication, and dosage and length of treatment, thus, making direct comparisons was difficult and potentially unreliable. The fixed effects model was used because the authors did not such heterogeneity as significant. Regarding agitation, the pooled studies were of a low to moderate statistical heterogeneity (11% and 52%). The precision of the data was not commented upon; however, 95% confidence intervals were used and were of a reasonable size, except those relating to serious adverse events.

The dropout rates of four studies were comparable between treatment and control arms; interestingly, one study did have a disproportionately high number of dropouts for valproate compared to the placebo group (54% valproate vs 29% placebo), such that the study was terminated early.

Overall, valproate showed little to no effect on agitation, when compared to placebo; however, the results were based on moderate to very low-quality data. Moderate quality data showed little to no effect over six weeks (MD -0.67, 95% CI- 1.49 to 0.15; 202 participants, 2 studies) and very low-quality data showed no effect (MD -1.84, 95% CI -6.02 to 2.34; 217 participants, 3 studies).

Together, the clinical significance of these findings remains doubtful. This is because the total number of participants is relatively small (total of 430), thus increasing sampling error, which means that the result may be more likely due to chance than a true treatment effect. The interpretation of the effect size estimates is also limited by the variability in the administration of valproate; for example, there was a large range in the dosage of valproate used, the treatment duration, and the concomitant use of other psychotropic medications such as benzodiazepines.

Serious adverse events (OR 4.77, 95% CI 1.00 to 22.74; 228 participants, 2 studies) and adverse effects (OR 2.02, 95% CI 1.30 to 3.14; 381 participants, 3 studies) were significantly greater than placebo. However, it is important to note that most of the studies did not report these accurately and there were significant dropout rates in one study, thus the evidence is of a low and very low-quality. For example, Sival et al (2002) reported a higher mean incidence

of adverse effects but did not disclose any number or description of these. As a result, the clinical significance is difficult to determine due to the weak corroborating evidence.

Amongst all studies, only one (Tariot 2005) had a low risk of bias in all categories; this study showed no significant clinical benefit of valproate and reported an increase in adverse effects.

Finally, none of the included trials assessed the impact on carers' outcome, thus this important analysis could not be performed.

Discussion

This review shows that valproate has little or no effect on agitation in dementia when compared to placebo and is less acceptable/tolerable due to side effects; however, the generalisability of these results is subject to certain limitations. For instance, the study population included different types of dementia; as these have different aetiologies and clinical presentations, their response to medication could vary accordingly.

Moreover, the review did not attempt to identify potential confounding factors (e.g. delirium as a cause of agitation, other comorbidities), which may affect its external validity. Importantly, for studies to be externally valid they must have internal validity (Dekkers 2010); the majority of the studies had unclear bias in selection and performance/detection bias, therefore there may be systemic differences affecting the results.

The study populations were limited to institutionalised patients. Since the environment is a known contributing factor to agitation in dementia, it is difficult to extrapolate these findings to other settings (Müller-Spahn 2003).

The methods' section of this review states that loose criteria could have been used for diagnosing dementia and agitation; however, the trials included all used standardised measures.

Finally, the acceptability and safety of valproate remains unclear. The adverse effects were poorly reported and perhaps this can be due to bias as three studies had the same source of funding.

Conclusion

In conclusion, the results do not provide sufficient evidence to change current guidelines and clinical practice. The overall poor methodology of the trials involved argues that it is difficult to draw firm conclusions on the efficacy of valproate for agitation in dementia. A more robust methodology including similar dosages and the exclusion of other psychotropic medications would help to elicit the true result. Additionally, the safety profile of valproate in these studies does raise serious concerns regarding its acceptability and tolerability. Currently, antipsychotics are recommended in UK guidelines for the treatment of agitation in dementia (NICE 2018b), but these pose significant risks to patients; however, the current evidence for valproate does not reassure that this could be a safer treatment option. Therefore, further research should evaluate alternative medications such as gabapentin and citalopram or identify novel drugs, many of which are currently in clinical trials (Panza 2015). Finally, there was no data on the impact on carers; since agitation in those with

dementia can cause carer's burnout, as well as increasing the rates of institutionalisation (Livingston 2017), this could be another important area for future research.

BOXES (underlined in the manuscript)

(Box 1)
Bias: This is a systematic error affecting the validity/accuracy of the study results. As such, it is predictable and not reduced by the repetition of the study under the same conditions; however, there are several strategies that can be used to minimise or eliminate bias (see below).
Selection bias: This results from the preferential inclusion/exclusion of certain subjects of the target population within the study's population, which may restrict the generalisability of the findings. It can be reduced through randomisation.
Performance bias: This occurs when the participants or researchers know what intervention is being given, thus resulting in a particular group receiving preferential attention from the researchers or participants modifying their behaviour. It can be reduced through blinding.
Detection bias: This refers to differences in how the outcomes are identified and assessed. It may be due to certain characteristics of a participant that could affect a disease or effectiveness of a treatment from being identified. It can also result from different outcome measures being used. This can be minimised using blinding and specific outcome measurements.

(Box 2)
Confidence interval (CI): This represents a statistical range of numbers where we can expect, to a certain degree, the true effect of a study to lie. For example, a 95% CI means that there is a 95% chance of the result being true if it lies within the range. Importantly, it is calculated from the Standard Error of the Mean (SEM), which is a random error resulting from the fact that a sample as opposed to the whole population has been used. This allows for an interpretation of how precise this sample mean reflects the whole population mean, as determined by the width of the CI; the narrower being more precise. This is not to be confused with standard deviation (SD), which measures how much the subject data varies from the mean of the study population. SEM is always lower than SD; the SD has to be divided by the square root of the sample in order to obtain the SEM.

(Box 3)
Fixed effects model: This is a statistical model where random variables are managed as fixed variables and it relies on the studies sharing a mutual treatment effect. It assumes that these variables do not change or are constant over time. Notably, these models don't acknowledge differences between studies; therefore heterogeneity must be reliably excluded before using this model. Additionally, it makes an assumption that any differences seen amongst the studies are due solely to random variation.

Random effects model: These models are used when studies do not share the same mutual treatment effect. It also assumes that the included studies have different effects, which are normally distributed. Consequentially, it gives smaller studies more power.

(Box 4)
Clinical heterogeneity: This may also be described as clinical diversity and relates to differences in treatments, study participants and outcomes.

Statistical heterogeneity: This occurs as a result of clinical and methodological heterogeneity. It relates to the variation in treatment effects and is significant when the difference of effect is cannot solely be due to chance. For instance, this can be assessed using the I^2 statistic or P value.

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DECLARATION OF INTERESTS
None declared

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