Valproate in dementia: time to move on?

ROUND THE CORNER

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COMMENTARY ON… COCHRANE CORNER[†]

SUMMARY

Baillon *et al*'s Cochrane review included 430 participants with agitation in dementia from five randomised controlled trials. Overall, the reviewers found that valproate was 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 with the controls, although these finding were largely based on low-quality data with incomplete reporting; thus, valproate's safety profile is of concern. This review demonstrates that there is insufficient evidence to change current treatment guidelines.

DECLARATION OF INTEREST

None.

KEYWORDS

Dementia; agitation; valproate; critical appraisal.

Agitation occurs in up to 70% of people with dementia (Ijaopo 2017) and its incidence rises as dementia progresses (Livingston 2017). There is no clear indication of the proportion of patients who require pharmacological interventions for dementia-related agitation.

Valproate, along with other antiepileptics, has been used widely to manage agitation for over 10 years, initially on the basis of findings from case studies (Meyer 2015). A large study carried out in 2007 involving 15 patients with dementia and agitation showed that valproate (either alone or in combination with antipsychotics) resulted in 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 included studies varied significantly in their methodology and outcomes, making it difficult to draw a reliable conclusion.

Guidelines from the UK's National Institute for Health and Care Excellence (NICE) 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: section 1.7). Antipsychotics (e.g. risperidone or haloperidol) should be used at the lowest dose for the shortest possible time, particularly because of the risk of major adverse events, especially strokes (NICE 2018b). The guidelines also advise against the use of valproate to manage agitation in those with dementia, unless it is being used to treat a different illness (NICE 2018a: section 1.7).

Cochrane reviews on the topic

Two previous Cochrane reviews have been conducted on the use of valproate for agitation in dementia (Lonergan 2004, 2009). These included only three trials, because other studies (e.g. Lott 1995) were small and lacked control groups. The 2004 review reported that the trials 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 (Lonergan 2009). Lonergan *et al* argued that most of the side-effects appeared to be mild to moderate in severity and were deemed unrelated to the study drug; however, this finding was based on very low-quality data. They concluded that valproate could not be recommended for controlling agitation in people with dementia, although more methodologically robust research was warranted to support a change in routine clinical practice.

Studies from these two reviews have also been included in the review featured in this

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month's Cochrane Corner: Baillon *et al* (2018). Baillon *et al*'s review included 430 participants with agitation in dementia from five randomised controlled trials.

Methods

The review 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.

Dementia was diagnosed on the basis of international diagnostic criteria or, in the absence of this, on routine medical or psychological evaluation. Importantly, this raises the question as to whether all the included patients truly had dementia. Agitation was loosely defined, as the reviewers accepted definitions provided by individual investigators, and agitation due to delirium was not reliably excluded. Patients were still included if they were on stable treatment with other psychotropic medications.

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

Only randomised placebo-controlled trials were included in the 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 on date, country and language of publication. 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 the five studies (Porsteinsson 2001; Tariot 2001, 2005) were funded by the pharmaceutical company Abbott Laboratories, which has been judged to have promoted the improper use of valproic acid and has paid a £0.9 billion penalty for this in the USA (Roehr 2012).

Two reviewers assessed bias using the Cochrane Collaboration'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 (Box 1). Four out of five studies had an unclear risk of bias in at least two areas; notably, selection bias was generally unclear. Three studies also had insufficient information regarding an aspect of masking (blinding), relating to performance and detection bias. Only one study (Tariot 2005) was deemed of low risk in all areas.

BOX 1 Bias

Bias is a systematic error affecting the validity/accuracy of study results. As such, it is predictable and not reduced by repetition of the study under the same conditions. However, there are several strategies that can be used to minimise or eliminate the various forms of bias, as described below.

Selection bias

This results from the preferential inclusion/exclusion of certain members of the target population in the study's sample, 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 masking (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 how a disease or the effectiveness of a treatment are identified. It can also result from different outcome measures being used. It can be minimised using masking and specific outcome measurements.

Data were pooled into pair-wise meta-analyses using mean differences (MD), odds ratios (OR) and 95% confidence intervals (95% CI) (Box 2) for the calculation of effect sizes.

Results

The reviewers accounted for clinical heterogeneity (Box 3) between trials using a fixed-effects model (Box 4) for the analysis. However, the studies in fact had significant clinical heterogeneity, particularly relating to the methodology, types of medication, and dosage and length of treatment, thus making direct comparisons difficult and potentially unreliable. The fixed-effects model was used because the reviewers did not regard such heterogeneity as significant. Regarding agitation, the pooled studies were of a low to moderate (11% and 52%) statistical heterogeneity (Box 3). The precision of the data was not commented on; however, 95% CI were used and were of a reasonable size, except those relating to serious adverse events.

The drop-out (attrition) rates of four of the studies were comparable between treatment and control arms; interestingly, one study (Tariot 2001) did have a disproportionately high drop-out rate for valproate compared with placebo (54% for valproate *v.*

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BOX 2 Confidence intervals (CIs)

The confidence interval (CI) is a statistical range of numbers within which 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, the CI is calculated from the standard error of the mean (s.e.m.), 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 precisely this sample mean reflects the whole population mean, as determined by the width of the CI: the narrower the CI, the more precise the finding.

The s.e.m. is not to be confused with the standard deviation (s.d.), which measures how much a participant's data vary from the mean of the study population. The s.e.m. is always lower than the s.d., as the s.d. has to be divided by the square root of the sample size to obtain the s.e.m.

BOX 4 Fixed- and random-effects models

Fixed-effects model

This is a statistical model in which 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, fixed-effects models do not acknowledge differences between studies. Therefore, heterogeneity must be reliably excluded before choosing this model. Additionally, a fixed-effects model makes an assumption that any differences seen among the studies are due solely to random variation.

Random-effects model

A random-effects model is used when studies do not share the same mutual treatment effect. It also assumes that the included studies have different effects and that these are normally distributed. Consequently, it gives smaller studies more power.

29% for placebo), such that the study was terminated early.

Overall, valproate showed little to no effect on agitation, when compared with placebo. However, the results were based on data of moderate to very low quality. Moderate-quality data showed little to no effect over 6 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 (430) is relatively small, thus increasing sampling error, which means that the result may be more likely due to chance than a true treatment effect. Interpretation of the effect size estimates is also limited by the variability in the administration of valproate; for example, there were wide ranges for dosage, treatment duration and number of concomitant psychotropic medications, such as benzodiazepines.

Serious adverse events (OR = 4.77, 95% CI 1.00–22.74; 228 participants, 2 studies) and adverse effects (OR = 2.02, 95% CI 1.30–3.14; 381 participants, 3 studies) were significantly greater with valproate than with placebo. However, it is important to note that most of the studies did not report these in detail and there were significant drop-out rates in one study. Thus, the evidence is of low and very low quality. For example, Sival *et al* (2002) reported a higher mean incidence of adverse effects but did not disclose their number or description. As a result, it is difficult to determine clinical significance because of the weak corroborating evidence.

Of the five studies, only (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, so this important analysis could not be performed.

BOX 3 Heterogeneity

Clinical heterogeneity

This may also be described as clinical diversity and it 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 cannot solely be due to chance. It can be assessed using, for example, the I^2 statistic or *P*-value.

Discussion

This review shows that valproate has little or no effect on agitation in dementia when compared with placebo and is less acceptable/tolerable because of 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 selection and performance/detection bias, therefore there may be systemic differences affecting the results.

The study populations were limited to 'institutionalised' patients (nursing home residents, short-stay psychiatric in-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).

In their methods section the reviewers indicate that they considered studies with loose criteria for diagnosing dementia (e.g. international classifications, or psychiatric, psychological or medical evaluation) and defining agitation (investigators' own definitions), although the five trials included in the review all used standardised measures.

Finally, the acceptability and safety of valproate remains unclear. The adverse effects were poorly reported and perhaps this is due to bias, as three studies were funded by the same pharmaceutical company.

Conclusions

The results do not provide sufficient evidence to change current guidelines and clinical practice. The overall poor methodology of the included trials 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. This is particularly relevant as there is evidence from animal trials (Ichikawa 2005) suggesting that valproate can act synergistically with other sychotropic medication such as antipsychotics.

The safety profile of valproate in these studies does raise serious concerns regarding its acceptability and tolerability. Currently, UK guidelines recommend antipsychotics 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 were no data on the impact of the intervention on carers; since agitation in people with dementia can cause carer burnout, as well as increasing the rates of hospital or care home admission (Livingston 2017), this could be another important area for future research.

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