

PB-PG-0609-19028 – NIHR Research for Patient Benefit Programme – Final report

Project title: Vascular Augmentation of Late-life Unremitted Depression (VALUeD)

Authors:

Professor Alan Thomas - Newcastle University
Professor Gary Ford - Newcastle University
Professor John O'Brien - Newcastle University
Professor Dame Louise Robinson - Newcastle University
Dr Lynne Corner - Newcastle University
Dr Tom Chadwick - Newcastle University

Plain language summary

Depression has a high prevalence and two-thirds will not improve with routine treatment. About half have a form of depression known as vascular depression. In this study we augmented antidepressant treatment with a vascular treatment (a BP drug called amlodipine) to determine if this is effective in vascular depression. We aimed to find out if giving amlodipine to people with non-responding vascular depression would be acceptable and whether it would be feasible to recruit such patients through their GPs. We also wanted to know whether "augmentation" might have a measurable benefit for patients. Ultimately, we wanted to use the findings from this study to inform the design of a larger study, if this one showed was shown to be feasible and acceptable, and the treatment appeared promising.

72 of 281 general practices in the North East were informed of the study but we do not know whether they were simply notified at GP forums, or approached individually and offered support. Nor could we confirm if 72 was the total for the region. In the South of Tyne area, we learned that of 31 research active sites only 5 were approached. For those practices agreeing to participate it appears that the electronic search strategies used for patient identification were not those we had defined, because practices found it difficult to use the search strategy we had agreed with GP commissioners. This pilot study therefore encountered considerable difficulties in recruitment at both site (general practice) and patient level. Positively, amongst those patients identified and who consented to participate there were very good completion and compliance rates (about 80%), in line with our predictions. We were unable to clarify whether the reason for non-recruitment was because patients with 'vascular depression' do not exist in sufficient numbers or that there are sufficient patients with vascular depression but that the systems we had to work with were unable to identify them. In the latter case a different system for patient identification, such as the Clinical Practice Research Datalink (CPRD), might have been successful

Conclusions

- The study successfully showed that is not feasible to recruit to such a study of vascular depression from primary or secondary care under current circumstances.
- We found that the design of the trial was acceptable to patients as we had good completion and compliance rates
- The low numbers precluded comparative hypothesis testing

Keywords

Summary of research findings

Depression has a high prevalence in all ages and about two-thirds of people don't achieve remission with standard antidepressants. In later-life such failure to remit is strongly associated with vascular disease and people with such disease contributing to the development of their depression are said to have 'vascular depression'. Previous evidence has suggested that augmentation of antidepressant treatment with a class of anti-hypertensive drugs, the calcium channel blockers, can improve remission rates in vascular depression. This was a pilot and feasibility study to assess whether a large scale randomised controlled trial of augmentation treatment with the calcium channel blocker amlodipine would be feasible and acceptable in vascular depression. The main study objective was:

"To demonstrate the ability to identify and recruit sufficient numbers of older people with depression from the primary care setting. This pilot study investigates the effects of amlodipine on mood in older people with depression with data collection designed to determine the size and number of centres required for a definitive study to determine efficacy of amlodipine."

Findings

The areas covered by this study for recruitment were (in their current CCG format); Newcastle North and East; North Tyneside; Northumberland; Newcastle West; Sunderland; Gateshead; South Tyneside. This catchment area has a total of 281 general practices.

Practices

We were informed by NECS (commissioners) that 72 practices were approached about the study. However we were not provided with sufficient information regarding how practices had been approached, or the reasons why they declined to participate, and we are therefore unclear what 'being approached' meant. It appeared to the research team that practices who were approached with full study information participated. Of the 72 practices apparently informed about the study, 51 'did not respond', 5 declined participation (without explanation), and 16 carried out the electronic search of patient records. It also appears that practices experienced some problems in executing the electronic search strategy that we had agreed with commissioners and therefore on some occasions (number unknown) the wrong patient search criteria may have been used.

Patients:

Primary care

236 invitations were sent to patients (an average of 15 in each of the 16 practices)

Of these 10 responded and were screened in our Clinical Ageing Research Unit

Rate = $10/236 = 4.2\%$ (95% CI: 2.1 to 7.7%)

All 10 patients were consented.

Of the 10 consented patients, 8 were recruited into the study.

Rate = $8/10 = 80\%$ (95% CI: 44.4 to 97.5%)

Attempts to Improve Recruitment

During the course of the study, we asked if the research team could approach general practices directly to invite them to participate, but were told that we were not allowed to, and that all contact must be made via PCT/NECS (commissioning services). Previous experience from one of the co-applicants showed that approaching practices directly for another study, led to a significantly higher number of participants being recruited. Practices were a lot more engaged with that study and received direct support from the study team.

Following an amendment suggested by the TSC, screening also took place in secondary care within 5 NHS trusts in the North East (Newcastle upon Tyne Hospitals NHS Foundation Trust; Tees, Esk and Wear Valley NHS Foundation Trust; Northumbria Healthcare NHS Foundation Trust; Northumberland, Tyne and Wear NHS Foundation Trust; and Gateshead Health NHS Foundation Trust).

Secondary care:

15 patients were screened. We were unable to obtain actual numbers of invitations sent from secondary care. 0 were recruited into the study.

Rate = $0/15 = 0.0\%$ (95% CI upper bound 18.1%)

In total, therefore, of the 251 patients invited from primary care and screened from secondary care, 8 were recruited into the study.

Rate = $8/251 = 3.2\%$ (95% CI: 1.4 to 6.2%)

Feasibility Conclusions

The study was successful in demonstrating that is not feasible to recruit to a study with this design under current circumstances. We found we could not identify sufficient patients from primary or secondary care.

The percentage of practices who participated is small (less than 25%) in comparison to the number throughout the region, which contributed to the small number of participants recruited. With a practice participation rate of 22%, an average of 15 patients identified per practice, and a recruitment rate of 3% of those patients identified, then if all 281 practices in the region had been approached using the systems in place during this study we would have recruited about 45 patients.

To achieve our target of 80 participants, using this rate of conversion, 2400 invitations would need to have been sent out; this would have required the participation of 160 practices at the rate of observed patient identification per practice.

Unfortunately, however, we don't have the quality of information to draw these conclusions with confidence. This is an important issue because we remain unclear about whether the target group of patients ('vascular depression') exists in sufficient numbers in primary care, as previous research suggests, and our failure to recruit to target is due to problems with current systems of practice recruitment, patient identification and recruitment. An alternative explanation is that the target group is not large enough to support such a study even if all potential subjects could be identified. Perhaps the use of the Clinical Practice Research Datalink would have enabled us to clarify this important question.

Study Acceptability

8 patients were randomised into the study, 7 completed the study (as defined by compliance with the 16 week follow-up visit (visit 8) for the primary outcome). 1 additional patient attended the screening visit but was not randomised. 6 patients attended the final visit 10 at 20 weeks.

Rate of completion = $7/8 = 87.5\%$ (95% CI: 47.3 to 99.7%)

(Rate for 20 week visit = $6/8 = 75.0\%$ (95% CI: 34.9 to 96.8%))

Study compliance rate:

Compliance was assessed at Visits 4, 6, 8 (weeks 4, 8, 16). Full compliance was defined as compliance at every visit. If a single visit showed non-compliance, full compliance was determined as not possible. Where any available data showed compliance at some visits but there were missing data for other visits, full compliance for that patient was declared as 'missing'.

Data on full compliance was available for 4 patients of the 8 randomised patients; 3 completed the study with full compliance to their allocated intervention.

Rate = $3/4 = 75.0\%$ (95% CI: 19.4 to 99.4%)

Acceptability Conclusions

In summary, therefore, for those patients who consented, there were very good completion and compliance rates, which is in line with our predictions. The study design appeared acceptable to patients.

Analysis

Analysis was by intention to treat following random allocation to study arm in a 1:1 ratio. Randomisation was performed via a web based system using random permuted blocks and was stratified by severity (defined by a dichotomous variable indicating whether baseline HAM-D was less than or greater than/equal to 15). The study was double-blind. Participants were allocated to one of the following groups:

- Amlodipine plus standard antidepressant treatment
- Placebo plus standard antidepressant treatment

Of the 8 recruited and randomised:

- Amlodipine: n=4
- Placebo: n=4

As a result of this small achieved sample size the analysis plan was altered from that described in the protocol. There was no comparative hypothesis testing and instead summary statistics were calculated for pre-specified outcome variables by arm.

Amlodipine group:

4 patients were recruited into this group, 2 achieved remission at some point in the study period up to week 16. Complete HAM-D data was not available for 1 patient for whom it was deemed that remission at any point was not possible as data from all previous visits was available and showed HAM-D \geq 10.

Rate = $2/4 = 50.0\%$ (95% CI: 6.8 to 93.2%)

By week 17 (visit 9 – this only took place if a patient was actually in remission at week 16) remission at any point during the study could be determined for 3 patients; 2 achieved remission at some point.

Rate = $2/3 = 66.7\%$ (95% CI: 9.4 to 99.2%)

By week 20 remissions at any point during the study could be determined for 2 patients; both achieved remission at some point.

Rate = $2/2 = 100.0\%$ (95% CI lower bound: 22.4%)

Placebo group:

4 patients were recruited into this group, 3 failed to achieve remission at any point in the study period up to week 16. Complete HAM-D data was not available for 1 patient for whom it was not possible to determine whether remission was possible.

Rate = $0/3 = 0.0\%$ (95% CI upper bound: 63.2%)

By week 17 remission status could be determined for 3 patients; none achieved remission at any point in the study.

Rate = $0/3 = 0.0\%$ (95% CI upper bound: 63.2%)

By week 20 remission status could be determined for 2 patients; none achieved remission at any point in the study.

Rate = $0/2 = 0.0\%$ (95% CI upper bound: 77.6%)

Interpretation

This analysis is descriptive only. As a result of the achieved sample size no statistical comparison has been made between the trial arms.

Conclusions

- The study successfully showed that it is not feasible to recruit to such a study of vascular depression from primary or secondary care under current circumstances.
- We found that the design of the trial was acceptable to patients as we had good completion and compliance rates
- The low numbers precluded comparative hypothesis testing

Patient and public involvement

This study was developed in consultation with Voice North and Years Ahead: North East Regional Forum. They were involved with the design and management of the research. Voice North was also involved in undertaking the qualitative component of the study. Voice North reviewed the patient information sheets and consent forms for the study.

Two patient representatives were identified to participate in the Trial Steering Committee.

The feedback provided by the lay members during the early stages of study set-up resulted in a significant amendment to the study in order to remove the need to send potential participants the extensive Patient Information Sheet by the addition of a summarised Patient Invite Letter.

Efforts to engage in PPI via MHRN proved unsuccessful.

Data sharing statement

See link

[\[https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253\]](https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253) for the NIHR position of the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

Disclaimer

This project is funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0609-19028). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This final report has not been peer-reviewed. The report was examined by the Programme Director at the time of submission to assess completeness against the stated aims.

This project was carried out between April 2012 and April 2014.