PARKINSON'S DISEASE SOCIETY INNOVATION GRANT:
FINAL REPORT

1. Reference number
Ref: K-0613

2. Title of project
Pilot controlled clinical trial of salvia officinalis (sage) for cognitive impairment in Parkinson's

3. Principal Investigator
Professor Elaine K Perry with Professor David burn and the Principal Clinical Investigator

4. Start date
The clinical trial started in March 2008 but preparations including regulatory , training and dispensing issues were initiated up to 12 months before that

5.Completion date

The trial was completed in August 2008 although data analyses and poster preparations continued to the end of October

6. Final Report due
End of December 2008

FULL REPORT

1. Aims of the project

To investigate the effects of sage, a traditional herbal medicine associated with cognitive enhancement, on cognition in a pilot controlled clinical trial of oral sage for six weeks in patients with Parkinson's disease and mild cognitive impairment.

2. Any changes to the original research design which have impeded or accelerated progress

The principal change in design which impeded progress was the rejection by the MHRA of the placebo preparation we had available for the trial. Costs of manufacturing a placebo meeting the regulations would have surpassed the costs of the entire project and were therefore unsustainable. The substitution of vitamin E for placebo the control group was the best available option given it has been tested in people with PD, and found to be safe, passed regulations, and has not been reported to enhance cognition. However we are aware that the results of the trial are less clear as a result of this alteration than they would have been as originally planned

3. **Summary of key findings and achievements in relationship to initial aims (3 A4 pages max.) - this should be written for the scientific community and must contain the key scientific points i.e. background, work undertaken, conclusions, etc.**

Background

Parkinson 's disease (PD) is a common neurodegenerative condition that lists cognitive dysfunction amongst its many non-motor symptoms. Amongst elderly PD patients the cumulative rates of dementia can be as high as 80% . However, there will be many of those requiring treatment who do not tolerate the limited number of conventional anti-cholinesterase based medications well.

Species of salvia (sage) have long maintained their place in the practice of herbal medicine across the world. This naturally occurring cholinesterase inhibitor (ChEI) also has several other bioactivities relevant to attenuating cognitive impairment. These include anti-oxidant, anti-inflammatory and anti-amyloid. As such it has developed a reputation not only amongst herbalist, but also in the scientific community, as a cognitive enhancer. It is also reported anecdotally to benefit those with PD by reducing excess salivation. Recent controlled clinical studies have all reported significant improvement in memory when sage has been administered to healthy volunteers - both young and elderly, as well as to patients with Alzheimer's disease.

Primary objective

This placebo controlled single blind pilot study investigated whether this herbal treatment could be of benefit to PD patients with mild cognitive impairments (MCI).

Methods

DRS II criteria were randomized to twice daily doses of either 600mg encapsulated dried sage leaves or 400iu of the control substance, vitamin E, for 6 weeks. Both supplied by Medic herb UK Ltd (Buckinghamshire).
Assessment of cognition involved completing the computerized Cognitive Drug Research (CDR) battery of tasks at the baseline visit, 4 hours post first dose, 6 weeks and following a two week wash-out period.
Measurements for secondary outcomes were carried out as detailed in the study time table below and comprised of:

Results

Safety
Twice daily doses of 600mg dried sage were well tolerated and can be deemed safe for use in PD patients with MCI.
There were no adverse effects on blood pressure as previously noted in other studies.
There were no Suspected or Unexpected Serious Adverse Reactions reported.

Cognition
The findings show significant improvement from baseline in speed of memory at 6 weeks following administration of sage. However, this significance was eclipsed when compared to the vitamin E control.

The only significant inter group difference was observed in the composite measure of " Quality of working memory". Here there was a significant main effect between groups with the vitamin E group outperforming those assigned sage.

Salivation
Trend for reduction of salivation in both groups that was significantly in favour of the vitamin E group at 6 weeks. The same trend followed after excluding those that did not have symptoms of excess salivation at baseline

Interpretations

Results obtained show there is no superiority of sage over vitamin E.
The possible reasons for this may include:-

The sage used was less active – following further biochemical characterisation of the remaining sage capsules, we found that the capsules used in this study had an IC50 for acetyl-cholinesterase of 0.8mg/mL. This makes it 4.5 times more potent an acetyl-cholinesterase inhibitor than the 0.365mg/mL batch used by Kennedy et al (2006).

Vitamin E is a more potent cognitive enhancer than sage. Although this can not be completely excluded, based on the current literature this is unlikely. Studies looking into the use of vitamin E for cognitive decline are inconclusive and those with positive results attribute this to the antioxidant's neuroprotective role in slowing decline rather than acting as an enhancer.

Placebo effect had a greater impact on the outcome than expected. The blindness evaluation carried out at the end of the study revealed that three times as many participants in the control group believed they had been allocated sage (n=6, 46.2%) compared with the sage group (n=2, 16.7%). Unlikely explanation as further subgroup analysis did not reveal a difference, although any suspected bearing on the outcome is difficult to assess given the small sample sizes.

Mechanism of cognitive decline in PD is distinct with respect to striatal pathology. Unlike other ChE inhibitors sage is more potent in the striatum than cortex and there is already striatal cholinergic hyperactivity in PD. Given that cognitive impairment in PD occurs despite this hyperactivity it suggests the mechanism of cognitive decline in PD is distinct and different to that in Alzheimer's. If not, and enhancement of striatal cholinergic levels is beneficial to cognition, then why cognition in PD would not be so affected? A possible rationale is that further increase cholinergic activity following sage administration may be detrimental to cognition.

Conclusions
Although small in numbers, this pilot trial has provided valuable evidence to inform on the further use of sage in memory related disorders. The results conclude that:-

- Sage as a cognitive enhancer in normal ageing and Alzheimer's disease may not, on account of regional ChEI effects be appropriate in PD which is associated with striatal cholinergic hyperactivity.
- This controlled trial has not supported anecdotal use of sage by medical herbalist to reduce salivation.
- Herbal agents, such as sage, need to be considered in the context of disease mechanism and that it is important to continually monitor bioactivity of the preparation.

Further work

- Dose optimisation study in PD patients assessing varying doses and preparations from different salvia species.
- Parallel assessment of biological characteristics for each preparation is needed to help identify which is the most important in cognitive enhancement. This evaluation would also determine the degree of clinical relevance differing bioactivities has.
- Another pilot utilizing an inactive placebo with longer recruitment phase to improve participant numbers.
- Addressing the issue of possible striatal ChE hyperactivity, and to better understand cognitive impairment in PD, a rat model for PD could be used. This would help determine what effect altering the level of cholinergic activity in the striatum has on cognition and whether ChE levels follow an inverted "U" dose response.

References

1. Blacker D. (2005) Mild Cognitive Impairment – no benefit from vitamin E and little from Donepezi. *N Engl J Med* **352**(23): 2439-41

2 Kennedy DO, Pace S, Haskell C, et al. (2006) effects of cholinesterase inhibiting sage (salvia officinalis) on mood, anxiety and performance on a psychological stressor battery. *Neuropsychopharmacology* **31**(4):845-52

4. Key findings and achievements

While the results of the trial were disappointing in terms of not supporting our original hypothesis, the trial has highlighted several important key issues concerning the application of herbal agents in the treatment of Parkinson's disease, and also a general principle concerning the use of such herbals in different cognitive conditions. Thus:

Sage as a documented cognitive enhancer in normal ageing and Alzheimer's disease may not, on account of pathology specific to PD (comparative regional cholinergic dysfunctions) be appropriate in PD which unlike AD is associated with striatal cholinergic hyperactivity.

This controlled trial has not supported anecdotal use of sage by medical herbalists to reduce salivation. That this traditional use has not been verified by clinical evidence stands independent of the control agent issue (above).

Herbal agents, such as sage, need to be considered in the context of disease mechanism and that it is important to continually monitor bioactivity of the preparation.

5. **Implications for future research work, and comments as to whether this project will lead to further research either by the grantholders or by others**

Future work in the field of herbals for cognitive impairment in PD would not be likely to include further trials of sage, however strong the arguments are that increased numbers and placebo comparisons are need to test the original hypothesis. However there is scope for investigation of other agents such as ginkgo biloba and lemon balm which have been shown to improve cognition in the normal population and in AD. Nether of these agents has regional ChEI effects as does sage so there would be no expectations of negative PD specific pathology on the clinical effects .In fact lemon balm has nicotinic receptor effects that may be particularly relevant to PD.

6. Summary of results in relation to the initial aims, in lay terms (500 word max). This should be written for non-specialist readers. Where appropriate, this may necessitate some definitions.

7. **The future plans for research staff employed on the grant**

The principle staff member was a medical student carrying out her MRES Project work .She is continuing with her medical education, having gained valuable training experience in the assessment of people with PD and the conduct of RCTs.

8. **List of publications arising from this research grant, including those in press.** Please also list presentations relevant to this grant made by you or members of the research team.

Paper in preparation

Leung R , Burn D, Middleton R, Wesnes, K, Perry E

" Effects of Salvia officinalis (sage) on cognitive function in people with Parkinson's disease and mild cognitive impairment : results of pilot controlled clinical trial

Submission to Journal of complementary and Alternative Medicine in March 2009