NETSCC, HTA

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The effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia

1. Objectives

To systematically review non-pharmacological interventions for reducing agitation in older adults with dementia when compared with normal care. We will include:-

i) sensory stimulation,
ii) psychological interventions and
iii) behavioural interventions

We aim to identify, describe, evaluate, summarise and then synthesise all relevant individual studies in order to determine:

1. Their effectiveness at decreasing agitation, and improving functional capacity, and quality of life for patient and carers
2. The cost-effectiveness of the interventions as treatments to reduce agitation.

The findings will be stratified by relevant factors; namely the severity of dementia, setting, whether the intervention is with the patient, the carer or both and whether the effect is immediate or if there are long term beneficial effects.

We will undertake a broad and detailed review of the literature to identify all studies relevant to these objectives. We will rate study validity, using an instrument based on internationally accepted criteria (from the Centre for Evidence Based Medicine (CEBM)). We will conduct meta-analyses to produce appropriate summary statistics of effect size of interventions, and present these in an accessible format. We will summarise the relevant literature, address the implications for clinical practice and identify where future research is needed.

In addition to reviewing cost and cost-effectiveness studies we will also undertake detailed costings of interventions based on their potential implementation in the NHS and undertake economic modelling work to calculate the cost-effectiveness of the interventions identified from NHS/personal social services (PSS) and societal perspectives.

2. Existing research

The frequency of dementia will rise dramatically over the next twenty years due to increased longevity. In the UK, 820,000 people are currently living with dementia (>1% of the entire UK population) and dementia care is currently estimated to cost £23 billion pounds per year[1]. Numbers of people with dementia are projected to reach over a million by 2020 and double again in the subsequent 20 years. Costs are projected to treble in the next 30 years as the number of older people increases[2 3], for comparison, the entire NHS budget was £110 billion in 2009[4]. Dementia affects not only the person with the illness, but also their family and

society. The recent Alzheimer's Society Dementia UK report found that current levels of services and support for people with dementia and families are inadequate[2]. This impacts on patients and families as well as the UK economically, as it can result in breakdown of care at home and therefore in institutionalisation[5;6]. The National Audit Office recently emphasised the need to "spend to save" on dementia care, reducing crises and resultant institutionalisation. The National Dementia Strategy outlines 10 year plans to increase the detection of dementia (currently only 30% of people living with dementia are ever diagnosed) and improve the quality of care for people with dementia and their carers[3]. In a revision to the 2010/11 NHS Operating Framework (published 21/6/10), the secretary of state for health named dementia as one of two priority areas for the NHS, with implementation of the National Dementia Strategy central to these plans[7].

Agitation may be defined as inappropriate verbal, vocal or motor activity which is not judged by an outside observer to be an outcome of need [8]. The term encompasses physical and verbal aggression [9]. Common symptoms are restlessness, pacing, verbal insults, shouting and physical aggression.

Agitation is one of the most common neuropsychiatric symptoms in dementia with nearly half the participants in a representative prevalence study having some symptoms of agitation in the previous month[9;10] .About 80% of those with clinically significant symptoms had symptom persistence at 6 months and this was predicted by initial severity [10]. In one large study, 41% of people with severe dementia were classified as agitated [11]. A recent review reported that 10-52% of people living in 24 hour care, and 19-51% of people with dementia in the community were verbally agitated -one of the most common types of agitation [12].

Three subtypes of agitation have been identified: (a) physically non-aggressive behaviour, such as wandering or trespassing in inappropriate places, (b) physically aggressive behaviour, such as hitting and kicking, and (c) verbally or vocally agitated behaviour, such as repeating words or questions, demanding constant attention, shouting, or verbal aggression [13]. The term agitation may also include wandering [14].

The impact of agitation can be devastating. For the person with dementia, it has been associated with poor quality of life [13;15]. This may result directly from the agitated feelings and resultant behaviour, which often occurs several times per hour, occupying a considerable proportion of their day[16]. It affects relationships within the family and is often associated with feelings of helplessness, anxiety, and anger among carers and others [17].

Reduction in quality of life may also due to strategies implemented with the intention of managing the agitation. Carers tend to isolate and overmedicate people with agitation[18]. In long-term care facilities, the distress caused to the nursing staff can influence the quality of their care to people with agitation and other residents[16]. Agitation and associated

symptoms predict nursing home admission[19] and can also result in greater use of restraint and psychotropic drugs[20].

The currently accepted approach to good clinical practice begins by considering the underlying cause(s) of the agitation and treating these (for example, pain or delirium or constipation) if possible [21]. After this psychological and social treatment should be considered first. These include avoiding triggers, if possible, reducing environmental complexity and distractors like noise, allowing the person with dementia time to do things, educating carers about communication with someone with dementia, explaining to the person with dementia what is happening during tasks which cause agitation, and occupation to prevent agitation resulting from boredom.

Agitation is however often difficult to manage, and while the use of psychotropic medication is discouraged, professionals often struggle to implement effective alternative treatment plans. The 2006 NICE dementia guidelines recommended a range of non-pharmacological interventions, including aromatherapy, music therapy, dance therapy, animal assisted therapy and multisensory stimulation, but the evidence for many of these therapies is currently unclear[22]. A previous HTA-commissioned systematic review found no conclusive evidence to justify recommending any non-pharmacological interventions for reducing wandering behaviour (which as previously stated may be regarded as a form of agitation) [14].

The potential importance of non-pharmacological approaches has increased because of growing concern regarding the undesirable effects of drug treatments for agitation such as the atypical antipsychotics. In 2004 the Committee on the Safety of Medicines recommended that risperidone and olanzapine should not be used for treatment of non-psychotic symptoms in dementia because of increased risk of cerebrovascular adverse events and death[23]. Recent meta-analyses found modest benefits in the treatment of aggression (best evidence for risperidone, then aripiprazole) but increased risk of cerebrovascular events and death [24-26]. The 2006 NICE Dementia Guidelines, therefore, recommend limiting the use of antipsychotic medication, for treating agitation in people with dementia, to those whose behaviour was causing significant distress[27]. The use of both antipsychotics[28] and benzodiazepines[29] in dementia have been associated with increased cognitive decline. Both classes of drug are currently commonly prescribed to manage agitation. Cholinesterase inhibitors seem to be ineffective, as was no significant difference between groups when 272 patients with Alzheimer's disease and agitation unresponsive to psychological treatment were randomised to either donepezil 5-10mg or placebo[30]. A 2009 UK government-commissioned review found that only 20% of the 180,000 UK dementia patients prescribed anti-psychotics benefited from them, and antipsychotic over prescribing has been linked to 1,800 excess deaths a year[31]. It concluded that it should be an NHS priority to reduce the use of antipsychotics in people with dementia, by two-thirds over the next three years.

Our search of core databases of systematic reviews, namely the Database of Abstracts of Reviews of Effects (DARE), HTA , and the Cochrane

Database of Systematic Reviews (CDSR), identified four reviews focusing on non-pharmacological treatment of agitation in dementia over the past ten years. These were a recent systematic review of non-pharmacological interventions for agitation in dementia, a review of behavioural interventions and two reviews of music therapy[32-35]. The first of these is a well conducted review but only included evidence to 2004 and limited the review to randomised controlled trials (RCTs) and those written in English or Korean[32]. It therefore did not include recent large RCTs of psychological interventions, nor did it consider cost-effectiveness. It concluded that the trials were small but only sensory interventions showed evidence of benefit. The other three papers did not state predefined inclusion criteria in terms of study design nor outcome nor validity measures.

Our systematic review considering psychological approaches to all neuropsychiatric symptoms in dementia, included all other such symptoms as well as agitation[22]. We found that overall psychoeducation for carers and behavioral management techniques for managing neuropsychiatric symptoms were effective treatments whose benefits lasted for months. Music therapy and possibly other sensory stimulation, were useful during the treatment session but had no longer-term effects; and interventions that changed the visual environment looked promising. A more recent very broad review of interventions for agitation, selected 47 trials of pharmacological and non-pharmacological treatment for consideration and concluded that the best evidence for effective non-drug treatment was for aromatherapy although all trials were small and of short duration (<4 weeks).[36]

There is therefore an urgent need for an up to date systematic synthesis of evidence from studies exploring non-pharmacological management of the broader range of related, and often co-morbid, behaviours encompassed by the term 'agitation'. Consistent evidence-based management of agitation could improve the quality of life of people with dementia and their carers and be cost-effective. It might relieve the person's distress, decreasing unnecessary sedation associated with inappropriate use of medication, and enabling people with dementia to engage in more positive relationships and activities. It could also delay institutionalisation. The National Dementia Strategy anticipated at least a 6% decrease in institutionalisation as a result of early detection and diagnosis of dementia when assessing the cost of implementation[3]. Prompt and effective management of agitation may increase this benefit.

3. Research Methods (see flow diagram on page 14)

Design: A systematic review and meta-analysis with economic analysis

Search strategy: We will finalise search terms in email consultation with an advisory group consisting of patient and carer representatives, and clinicians and academics from a range of disciplines. We will search electronic databases, including MEDLINE, Web of Science, EMBASE, PsycINFO, CINAHL, British Nursing Index, the HTA Programme database,

the NHS Economic Evaluation Database, the Health Technology Assessment Database, the Research Papers in Economics database, NHS evidence, NTIS (National Technical Information Service), The Stationery Office Official-documents website, for studies published at any time, reference lists from individual and review articles, and the Cochrane Library (all databases). We will ask experts, including our stakeholder group (see section 12 on study management and consultation for details) about additional studies, including unpublished studies and grey literature. Experts to be contacted will include the corresponding authors of all reviewed studies. We will search grey literature (such as dissertations and theses, and conference proceedings and meeting abstracts), using the SIGLE (System for Information on Grey Literature). Key journals will be hand searched. We will use Reference Manager software to keep a data trail of all studies considered and reasons excluded.

Search terms and a structured search strategy will be finalised in discussions with the research team and our stakeholder group. We will define agitation as a state of chronic restlessness and increased psychomotor activity. Possible search terms are:

Agitation: agitation, restlessness, irritation, aggression, aberrant motor behav$, psychomotor activity, challenging behav$, pacing, sun-downing, wander$

Dementia: dement$, Alzheimer's, vascular, Pick, Huntington, Creutzfeldt, CJD, binswanger, Lewy ([cognit$ or memory] AND [impair$ or declin$ or disorder$ or disturb$ or confus$])

Intervention: Psychol$, sensory, stimulation, behav$, cognit$, management, enhanc$, animal, assisted, mulitsensory, music, dance, aromatherapy, alternative, therapy, validation, reminiscence, educat$, reality orientation, exercise, Snoezelen Simulated presence, Therapeutic activity, Montessori

To identify cost and cost-effectiveness studies we will supplement these with economic search terms: cost$, econ$, pharmacoecon$, value for money, value of life, pric$, expenditure, savings, budget.

We will ensure that our search strategy is not more than 12 months out of date at time of publication, in line with HTA policy. We will keep our searches up to date during the study. This is in line with our customary procedures for undertaking systematic reviews.

Review Strategy:
Study selection: The study selection strategy will be explicit, objective and minimise the potential for errors of judgement. It will be documented clearly to ensure it is reproducible. The reasons for excluding any study will be documented by creating categories in Reference Manager for each reason and moving excluded studies into these categories as decisions are made.

Pilot phase: During the pilot phase of the study, covering approximately the first 20 papers, agreement between assessors (inter-assessor reliability) will be formally assessed using a Kappa statistic. If Kappa is below 90% the selection criteria will be revised refined and clarified as necessary. Alternatively the supervisors will work with the researchers on an improvement of their coding. Disagreements between the raters throughout the study will be discussed and, where possible, resolved by consensus after referring to the protocol. If this does not resolve it the raters will discuss with GL or CC.

Stage 1: The first decision is made based on titles and, where available, abstracts. These will be assessed against the predetermined inclusion criteria. If it can be determined that an article does not meet the inclusion criteria then it can be rejected straightaway. We will, however, err on the side of over-inclusion during this first stage. Studies that are clearly not relevant i.e. titles are irrelevant to the question will be categorised as such. Others will address the question and be potentially relevant but not meet the inclusion criteria (see below). All potentially relevant abstracts will be read independently by two research assistants to identify those of relevance. The reasons for rejecting any potentially relevant paper will be recorded. Abstracts identified by either researcher will be retrieved.

Stage 2: For studies that appear to meet the inclusion criteria, or in cases when a definite decision cannot be made based on the title and/or abstract alone, the full paper will be obtained for detailed assessment against the inclusion criteria.

Dealing with lack of information

Sometimes the amount of information reported about a study will be insufficient to make a decision about inclusion. The researchers will email the study authors to ask for more details. If the authors are known personally to the supervisors (or any of the other applicants) they will email or telephone them to increase the chance of a response. After one month without a response the researchers will email again. If there is no response or the authors can not clarify then the studies in question will be excluded and listed as 'potentially relevant studies'. The influence on the results of the review can be assessed in a sensitivity analysis.

Multiple reports

When multiple reports of a study are identified e.g. over different follow up periods or considering different endpoints, they will be treated as a single study but reference made to all the publications.

Reporting of study inclusion

A flow chart showing the study selection process with numbers of studies retrieved and decisions about exclusion leading to the final number of included studies will be created and included in publications and reports. A list of excluded studies will be in an appendix to the report to the HTA.

Data extraction: We will design a data extraction tool, and data will be extracted by two research assistants independently to ensure a high level of accuracy.
This tool will be in the form of an excel datasheet to enable data management and construction of tables. This will allow data to be entered as categories, yes/no answers, numerical data and text as required. The form will be piloted on the first 10 included papers to ensure that the relevant data is captured and understandable. Two researchers will independently extract the data. Any disagreements will be noted and resolved by consensus among researchers and if this does not produce consensus then the researchers will discuss with GL or CC. Data extracted will encompass not only allow quality assessment but also the description of the study (see below).

It will include:

i) Methodological characteristics of the study (number of participants in intervention and other group, whether they live in 24 hour care settings or not, severity of dementia, age range and mean age, primary outcome measures, duration of follow-up).
ii) Quality measures (power calculation, power of the study to detect a significant result, blinding of participant, blinding of rater, intention to treat or per protocol analysis, randomised controlled trial or non-randomised study; adequacy of randomisation, if non-randomised whether the intervention and control group are comparable; follow-up rate and number, whether all participants are accounted for, validity and reliability of outcome measures and of the dementia diagnosis, comparability of treatment and comparator groups, and whether intention-to-treat analyses were used).
iii) Descriptors of the intervention (such as who the therapy is administered to (patient or family carer or paid carer), number and duration of sessions how long does a session take, over what time it is delivered, and whether it is an individual or group intervention.
iv) Theoretical basis, any co-intervention; quality control of therapy (fidelity measures) if applicable.
v) Statistical methods used
vi) Details of relevant outcome measures (for each pre-specified outcome: whether reported, definition used in study, measurement tool or method used, unit of measurement (if appropriate),
vii) Length of follow-up, number and/or times of follow-up measurements
viii) Summary outcome data (including mean values, standard deviation and 95% confidence intervals; adverse events; economic data including costs and resource use).

Quality assessment: Two researchers will independently evaluate the studies. 'A validity assessment tool specific for the project will be created by adapting the CEBM randomised controlled trial evaluation criteria and other relevant checklists, including those we have used successfully in previous systematic reviews [22;37-48]. We will contact corresponding authors

where information about quality is missing from study reports. Disagreements will be resolved by consensus between the researchers.

Data synthesis: We will categorise the papers by treatment modality. We will tabulate details of study type, interventions, numbers of participants, a summary of participant characteristics, outcomes and outcome measures and divide tables into severity of dementia, setting, and whether the effect is immediately or lasts longer term and an indication of study quality. In addition, we will give an initial descriptive summary. Within treatment modality groups, we will subdivide treatments by their active components – for example, psychological therapies may be divided into whether the treatment involves family carers, the person with dementia directly, or both; and whether techniques used are behaviour management, carer coping skills training, cognitive behavioural therapy etc. Results will be collated and tabulated. If fewer than three trials are identified in a particular category, their findings will be evaluated critically but no formal statistical analysis will be performed. If three or more studies are identified, we will undertake a meta-analysis to combine their findings if the studies are homogenous and of high quality. If formal pooling of results is inappropriate, a narrative approach will be used. The approach used will be rigorous and transparent to reduce the bias and will synthesise (as in our previous systematic reviews) rather than solely describe the results. We will develop hypotheses as to how an intervention works, why and for whom from the evidence. This will be based on a preliminary synthesis of findings of included studies, an exploration of relationships within and between studies and an assessment of the robustness of the synthesis.

Review of economic literature and development of cost-effectiveness model

The same procedure described above will be followed for the review of cost-effectiveness papers, except that papers will be reviewed independently by two health economists (SM plus one other to be appointed). In addition to the above, the following data will be extracted, assessed and synthesized:

- Type of economic evaluation
- Analytical approach (perspective of analysis, type of model, time horizon, discount rate, country and date)
- Type and sources of data used to measure effectiveness
- Utility valuations
- Cost components
- Sources of volume of resource use data
- Sources of unit cost data
- Cost, effectiveness and cost-effectiveness outcomes
- Analysis of uncertainty

In addition to the critical review, we will undertake a detailed costing exercise to evaluate the NHS costs incurred by the provision of each of the interventions considered. The cost components will include staff costs,

premises costs and the cost of consumable items. Resource use data will be obtained from the retrieved studies, based *inter alia* on the description of interventions. Unit costs will be obtained from routine sources[49;50]

We will also construct a de novo cost-effectiveness model that can be used to assess the cost-effectiveness of interventions to reduce agitation in dementia. The objectives of this exercise are to: (1) design an appropriate model to characterize health states of agitated patients with dementia, accounting for costs and outcomes incurred by carers; (2) populate this model using the most appropriate data identified systematically from published literature and routine sources; (3) if possible, relate intermediate agitation outcomes to final outcomes, ideally expressed in terms of quality-adjusted life years (QALYs); and, (4) identify which parameters in the model are most uncertain and which of these are important drivers of cost-effectiveness. This analysis is necessary in order to provide decision makers with information on the gain achieved by each intervention relative to its additional cost, in units which permit comparison with other uses of NHS resources. It is helpful to characterise the uncertainty in the data used to populate the model to inform further research.

The model will be developed and populated based on available evidence. The model structure will be informed by existing economic models in this area[51;52]. Following decisions about model structure, a list of parameter estimates required for the model will be developed. The specific details of the data to be used to populate the model will be determined following the development of the structure and the systematic searches of the literature.

At this stage, and based on existing model[51;52], the proposed design is a Markov state-transition model that allows movement between agitation states. The model will have six-month cycles and calculate expected costs and outcomes for a synthetic cohort of patients aged 65 years and older until all patients die from dementia progression or other causes. Model states will include 'physically non-aggressive agitated behaviour', 'physically aggressive agitated behaviour', 'verbally or vocally agitated behaviour', 'non-agitated behaviour' and death. We aim to include costs borne by families and carers in caring for patients.

4. Planned inclusion and exclusion criteria

Inclusion criteria:
All participants will have dementia or those with dementia will be reported separately. We will not specify how the dementia diagnosis is made as an inclusion criteria, in order to ensure that our review is inclusive, although we will report on the validity of the diagnostic process when assessing studies.
Age group over 50
Intervention will be sensory, psychological and behavioural
The intervention will be for agitation or the effect on agitation or proxy measure will be measured

The control or comparator arm could comprise: treatment as usual, no intervention, sham therapy or placebo
Outcome will be measured and reported in terms of aggression or using proxy quantitative measures i.e. decreased medication or restraint, functional capacity of patients or quality of life of patient or carer and cost effectiveness.
Primary research
Any language (we will use translators for both abstracts and full papers)

Types of study: We will include randomised and non-randomised controlled trials and observational studies (cohort and case control), economic and costing studies that evaluate a non-pharmacological intervention, whether the intervention is directed at the person with dementia, their family carers or professionals. We will include papers published in all languages.

Types of intervention: We will include all non-pharmacological interventions test. These will include (but are not limited to) psychological therapies, sensory, music, dance therapy, and animal assisted therapies.

Participants: People with dementia of any type and age >50years old. We will exclude trials that also include people without dementia, unless they report, or enable us to calculate, results for people with dementia separately.

Setting: Any (home, hospital, 24 hour care facilities)

Exclusion criteria:

We will exclude trials that do not include a comparator group, either of people who do not receive the intervention or pre and post test comparisons.

We will exclude trials that involve ingestion of a drug or other compound – including homeopathic and herbal remedies.

5. Ethical arrangements

This is a systematic review and we will not be using individual patient data, so do not envisage ethical problems in the carrying out of this research. We will not require research ethics committee permission as the data is in the public domain and we are not engaged in any primary research. We will draw conclusions about which interventions are most effective and cost-effective at decreasing agitation. We will discuss with our stakeholder group and the research team whether any of the interventions included in the review raise ethical dilemmas, and discuss these in the final report.

6. Analysis plan

Results will be organised by type of intervention. For dichotomous data odds ratios with 95% confidence intervals and risk differences will be reported. For continuous data, if means and standard deviations are provided, standardised mean differences with 95% confidence intervals

will be calculated. Ordinal data will be treated as continuous where appropriate. If any data required for analysis are unreported, we will attempt to contact study authors to request the data. Missing data and losses-to-follow-up will be reported. Similar studies of sufficient quality will be combined in a meta-analysis to provide a pooled effect estimate. Heterogeneity will be assessed using forest plots and formal statistical tests. If there is no evidence of heterogeneity, a fixed effects model will be used, but if there is evidence of heterogeneity a random effects model will be used and reasons for heterogeneity will be investigated. If appropriate, results will also be stratified by dementia severity (mild, moderate and severe),settings (whether the person with dementia lives in their own home or in a care home) who the intervention is directed at (patient/carer) and immediate or longer term effect. Publication bias will be explored using funnel plots.

7. Outcomes

Studies will be included if they report outcomes likely to be meaningful to those making decisions about managing agitation in people with dementia. These will include:

Primary outcomes:
Any measure of agitation, as it is broadly defined in this proposal. Change in amount of medication (e.g. antipsychotics) prescribed.

Secondary outcomes:
Functional capacity, quality of life of (i) people with dementia (ii) their family carers , or use of restraints (some studies have used reduction of restraint as an outcome in countries where this is legal).

Economic measures:
Cost of interventions
Impact on NHS/PSS use, especially institutionalisation, as a result of interventions
Costs borne by families and carers
Cost-effectiveness of interventions

8. Timetable and milestones

August 2011: Redeployment of two research assistants- interview and appoint. Recruit stakeholder group. Management group (co-applicants) meet to agree a search strategy and stakeholder email consultation.
October 2011: induct and train research assistants in Reference Manager, essential clinical topics and systematic reviewing.
November 2011- May 2012: Conduct searches. Retrieve articles. Two researchers to independently extract data and rate validity and write tables.
June 2012 – October 2012: Meta-analysis and cost-effectiveness calculations. Write up findings to date

November 2012- January 2013: Write whole draft of review. Submit to high impact journal and funding body. Plan dissemination.