Research Article

International Journal of Psychiatry

Pharmacoeconomic Approach to Dementia: A Review of the Current Pharmacological and Non-Pharmacological Managements – A Cost-Benefit Analysis

Luis Ángel Francisco Sorroza López* **and Laura Martino Roaro**

[1]*General medical practitioner, Master in Clinical Pharmacology, University La Salle Mexico, Mexico*

[2]*Universidad La Salle México, Facultad de Ciencias Químicas, CD de México, Mexico*

***Corresponding author**
Luis Ángel Francisco Sorroza López, General medical practitioner, Master in Clinical Pharmacology, University La Salle Mexico, Mexico, E-mail: sorrozalopezdr@gmail.com.

Submitted: 07 Nov 2016; **Accepted:** 19 Nov 2016; **Published:** 23 Nov 2016

List of Abbreviations

Aβ: Beta amyloid; AD: Alzheimer´s Disease; ADAS-Cog: Alzheimer´s Disease Assessment Scale-Cognition; ANCOVA: Analysis of Covariance; BPSD: Behavioural and Psychological Symptoms of Dementia; CAPE-BRS: Clifton Assessment Procedures for the Elderly – Behaviour Rating Scale; Carer: Caregiver; CI: Confidence Interval; CST: Cognitive Stimulation Therapy; Cornell: Cornell Scale for Depression in Dementia; DLA: daily life activities; DEMQOL: Dementia Quality of Life Measure; EQ-5D: European Quality of Life-5 Dimensions questionnary; FMRI: Functional Magnetic Resonance Imaging; GDP: Gross Domestic Product; HADS-T: Hospital Anxiety and Depression Scale- Total; Holden: Holden Communication Scale; MCI: Mild Cognitive Impairment; MMSE: Mini Mental State Evaluation; NICE: National Institute for Health and Care Excellence; NNT: Numbers needed to treat; PET: Positron Emission Tomography; PWD: Person with Dementia; QALY: Quality-adjusted life-year; QoL: Quality of Life; QoL-AD: Quality of Life – Alzheimer´s Disease; RAID: Rating Anxiety in Dementia; RCT: Randomized Clinical Trials; SD: Standard Deviation; SES: Standardized Effect Size; SHA: Strategic Health Authorities; SPECT: Single-photon Emission Computed Tomography; WHO: World Health Organization.

Introduction

Dementia is a growing world health threatening condition declared as public health care priority by the World Health Organization (WHO); the prevalence of the condition reached 46.8 million people in 2015, affecting mainly population over 65 years old. Yet, due to a longer life expectancy, among other factors, the incidence will raise and is being estimated around 7.7 million new cases per year; therefore, the prevalence is expected to reach 81.1 million by the year 2040 and over 131.5 million in 2050 with an increasing incidence in population under 50 and 40 years of age [1,2].

Dementia represents one of the major burdens to patients, carers, family of people living with the condition, and health care systems globally. Dementia is characterized by a decline in memory, language, problem-solving, and other cognitive skills that affects a person's ability to perform everyday activities [1,3,4]. This decline occurs because nerve cells (neurons) in parts of the brain involved in cognitive function have been damaged or destroyed through accumulation of beta-amyloid peptide (Aβ), hyper-phosphorilation of TAU proteins, and changes in metabolism that stimulate apoptotic pathways [5].

The global costs of dementia have increased from US$ 604 billion in 2010 to US$ 818 billion in 2015, an increase of 115.4%. The current estimate of US$ 818 billion represents 1.09% of global GDP, a slight higher increase from our 2010 estimate of 1.01%. Excluding informal care costs, total direct costs account for 0.65% of global Gross Domestic Product (GDP) [1,2].

The current pharmacological treatments are limited to mitigating the onset and development of the disease and management of the most usual symptoms, which modulate the course of the disease with diverse side effects that range from personal discomfort to sudden death, recent systematic reviews suggest that several classes of medications previously recommended for the treatment of behavioral and psychological symptoms of Dementia (BPSD) have either unacceptable adverse effects and/or uncertain efficacy [3,6-8]. There is strong evidence from clinical studies that participation in mentally and physically stimulating activities in early stages of the disease, mild cognitive impairment (MCI), is associated with decreased incidence and/or prevalence of dementia [9-11].

The term "non-pharmacologic" encompasses a broad range of services delivered to the patient, the caregiver, or the patient-caregiver dyad; the term encompasses essentially all interventions that are not captured in a pharmacopeia [3].

The underlying pathophysiology, which is not fully understood and established, yet, cannot be healed with pharmacological interventions, however, every medical resource, the patients themselves, and their formal and informal caregivers can help the

people with dementia (PWD) to adapt to functional limitations and thereby delay disability, considering the disabling model in accordance to Figure 1.

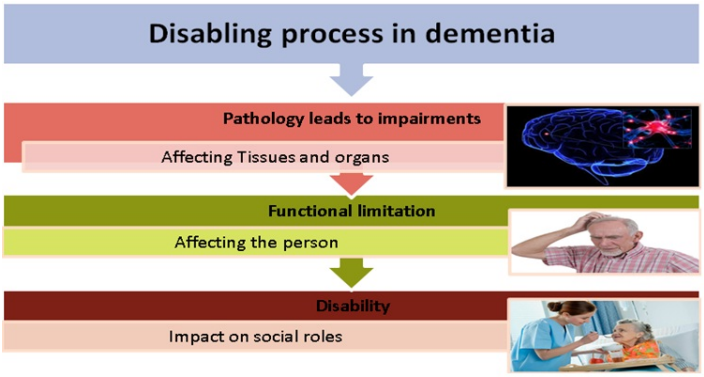

Figure 1: Disabling model of deterioration in Dementia.

Impairments are at the level of tissues and organs while functional limitations impact the whole person. Disability implies a social or environmental context in which the functional limitations must limit social roles (e.g. self-care) before they are regarded as a disability [3].

Delaying the onset and progression of the pathology is considered one of the major commitments of medical research. A delay of five years on the onset of Dementia or its progression might diminish by half the prevalence and would have a meaningful impact on the burden and costs of the disease, and significant improvement in the quality of life (QoL) of patients and their carers [1,12,13].

Definition of concepts

Dementia is considered an umbrella term under which several different pathologies that share certain symptomatology are grouped: it is considered a syndrome characterized by memory impairment, initially referred to short term memory and recent events, and loss of execution function, difficulty to take decisions, and to perform sequential tasks; in more advance stages, increasing cognitive deficit, and changes in personality, with moderate to severe impairment to perform the daily life activities (DLA), and take care of oneself. Speech and motor function might become compromised, affecting the social and occupational skills [14,15]. The pathologies that are included range from MCI [16,17] term issued by Petersen since 1999, to several other diseases such as: Alzheimer Disease (AD), Vascular Dementia (VD), Front temporal Dementia (FTD), Lewy Body Dementia, Parkinson´s Dementia, and Mixed Dementia (MD) [15].

The diagnosis of dementia is a sequential procedure beginning with the observation of certain symptoms referred either by the patient him/herself and/or the family or closest person, that are the main cause of submission to a medical assessment. Figure 2 shows the basic guidelines in the diagnosis proposed by NICE 2016 [18].

Neither Dementias nor MCI, are part of the physiological process of aging; persons with MCI develop up 12% per year to dementia compared with 1-2% of normal cognitive subjects. Otherwise, both of them are always stages of a pathological process with a complex physio-pathology. The average life expectancy for patients with AD, Lewy Body Dementia or FTD is 6 years ranging from 3 to 9 years, and some patients with longer survival periods [4].

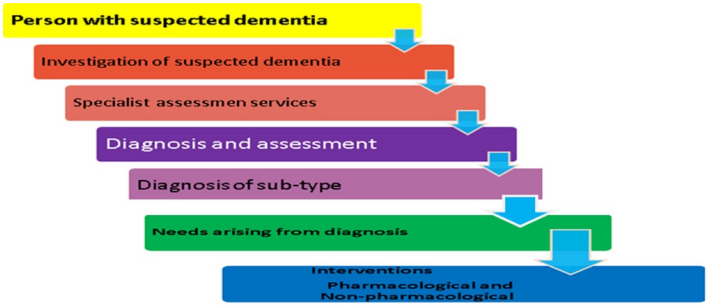

Figure 2: Dementia diagnosis and assessment ©NICE 2016.

Physio-Pathology of Dementias

There are several mechanisms that have already been recognized, suffering certain alterations in brain tissue and cells of patients with Dementia, mostly AD, which provide some evidence to explain de physio-pathology of these conditions (Figure 3) [19].

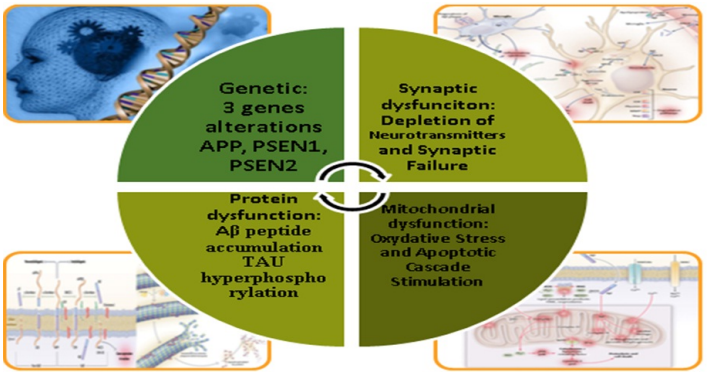

Figure 3: Physiopathology of Dementia [19].

Genetic theory has been particularly researched in dominantly inherited AD [5]. Mutations in one of three genes (APP, PSEN1, and PSEN2) have been identified that cause alterations in Aβ processing, and lead to AD with complete pen trance. The age at clinical onset of autosomal dominant AD is similar between generations and is affected mostly by the mutation type and background family genetics [5].

Alteration of Proteins and peptides are also involved in the pathogenesis of dementia. Cerebral accumulation of plaques laden with Aβ, and hyper-phosphorylation of TAU proteins which cause dystrophic neuritis in neocortical terminal fields as well as prominent neurofibrillary tangles in medial temporal-lobe structures are important pathological hallmarks of AD and most dementias. Loss of neurons and white matter, congophilic (amyloid) angiopathy, inflammation, and oxidative damage are also present [5].

Neurofibrillary tangles, which are filamentous inclusions in

pyramidal neurons, occur in AD and other neurodegenerative disorders termed tauopathies. Normally, an abundant soluble protein in axons, tau promotes assembly and stability of microtubules and vesicle transport. Hyper phosphorylated tau is insoluble, lacks affinity for microtubules, and self-associates into paired helical filament structures [19].

Synaptic failure occurs through the pathological process. Hippocampal synapses begin to decline in patients with MCI, a limited cognitive deficit often preceding dementia; in these patients remaining synaptic profiles show compensatory increases in size. There is a reduction of about 25% in the presynaptic vesicle protein synaptophysin. With advancing disease, synapses are disproportionately lost relative to neurons, and this loss is the best correlation to dementia [19].

Depletion of Neurotrophins and Neurotransmitters is also associated to the pathological process. Neurotrophins promote proliferation, differentiation, and survival of neurons and glia, and they mediate learning, memory, and behavior. The normally high levels of neurotrophins receptors in cholinergic neurons in the basal forebrain are severely reduced in late-stage AD. The deficiency of cholinergic projections in AD disease has been linked to the buildup of Aβ and changes in tau structure. Presynaptic α-7 nicotinic acetylcholine receptors are essential for cognitive processing, and their levels increase in early AD, before decreasing later [5]. Therefore it seems that several compensatory mechanisms operate to protect the injured brain during the development of the pathological events.

Mitochondrial alterations and Oxidative Stress are of relevant importance. Dysfunctional mitochondria release oxidizing free radicals, both in AD and the normal aging brain, and they cause considerable oxidative stress. Experimental models show that markers of oxidative damage precede pathological changes. Aβ, a potent generator of reactive oxygen species and reactive nitrogen species, is a prime initiator of this damage. The receptor for advanced glycation end products mediates Aβ's pro-oxidant effects on neural, microglial, and cerebrovascular cells [19]. The build-up of free radicals stimulates the apoptotic intrinsic pathway.

Another metabolic disturbance of emerging importance in AD and tied into synaptic and energy homeostasis involves insulin signaling in the brain. Levels of insulin receptors, glucose-transport proteins, and other insulin-pathway components in the brain are reduced in some studies of AD [20,21].

The efficacy of the pharmacological treatments has been limited to control the symptoms, and their efficiency to delay the development of the process has been limited; therefore the most precise characterization of pre-clinical stages has been a challenge for researchers in the last ten years, since it is at those stages that preventive strategies show to be more efficient to delay or prevent the cognitive deterioration. The use of cholinesterase inhibitors (AChEI) (donezepil, rivastigmine, galantamine), and N-methyl-D-aspartate (NMDA) glutaminergic receptors blocker (memantine) have been proven to be cost-effective [10] in the management of the early to middle stages of Dementia, with poor efficacy on late stages of the disease,and not exempt of discomforting adverse effects. The use of medication to control or relief the behavioural and psychological symptoms is a more contended field of discussion among the researches; the use of drugs to modulate those symptoms has been a matter of research since it is associated with side effects that vary from discomfort, worsening of the condition, and complications such as falls, strokes, and sudden death. A meta-analysis of seventeen placebo controlled trials of atypical neuroleptics for the treatment of behavioral symptoms in people with dementia conducted by the Food and Drug Administration suggested a significant increase in mortality (OR 1.7) [7,8]. Therefore cognitive and physical interventions should be considering very important therapeutic resources to modulate the onset and development of the disease, and very importantly to manage the behavioral and psychological symptoms, as an alternative management available for the patients.

Pharmacoeconomic foundation of research

Resources are usually not enough to satisfy everyone´s health needs and requirements, and this becomes particularly true regarding efficient care for patients with dementia. Therefore, scarcity of resources means that difficult choices have to be made about how to use them. There are different approaches to pharmacoeconomic studies: cost-effectivenes evidence which provides a way to help decision-makers get "best value" from their resources when choosing between two or more clinical or other interventions. Often one intervention has better outcome(s) than another but also costs more; under these circumstances there is a need for the decision-maker to evaluate whether those better outcomes are worth the higher costs, necessitating difficult trade-offs. If one intervention has lower cost and better outcome(s) than another it is considered dominant, and apparentely it is an easy trade-off, however in Dementia there are other factors to be considered such as fairness, availability, and patient preferences [22,23].

One major problem arises when certain interventions represent a higher cost and better outcome(s). Whilst we would like better outcomes for dementia patients, we must remember that resources are finite, and so commiting extra resources to treating one patient will inevitably mean fewer resources for another patient, therefore the importance of the pharmacoeconomic analysis for acceptability of new or diverse therapeutic resources in the decision making process (Figure 3).

Cost-effectiveness may be reported in terms of many different outcomes measures, ranging from biomedical markers to final health outcomes.

In order to determine if it is worth the extra cost in dementia we might focuse on evaluations regarding longer periods of independence, cognitive preservation, or less burden for carers and the health system; prevention of complications or severe adverse effects from certain medications that are extensibly used in PWD are subject to such economic evaluations [24]. The prefered

outcome measure for many economist and many reimbursment agencies, remains the Quality-adjusted Life-year (QALY), a preference based measure of health outcome that combines length of life and health related quality of life. QALY is often referred as a generic outcome measure. The QALY has the advantage of allowing comparisons between interventions for disparate health conditions, and incorporates individual preferences for health outcomes, thereby moving beyond the narrow biomedical model for evaluating research [22].

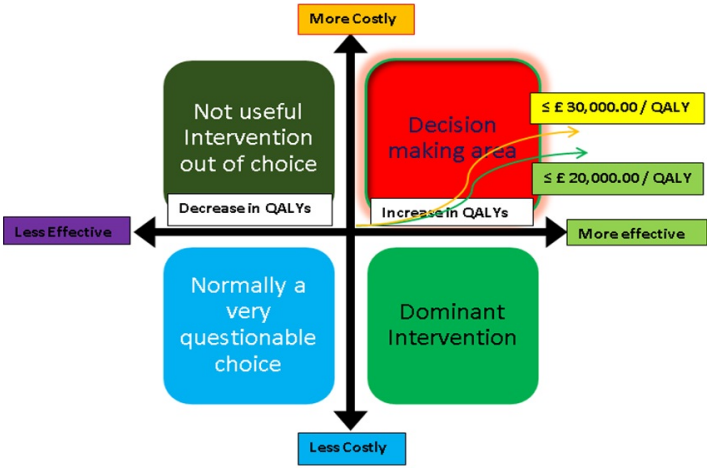

Figure 4: Conceptual model for acceptability of new therapies. Application in the appraisal with incremental cost-effectiveness per QALY.

To evaluate QALY there are validated questionnaires such as European Quality of Life five dimensions questionnaire (EQ-5D), the Health Utilities Index, and Short Form Health Survey six dimensions (SF-6D). A tool that is dementia-specific but nevertheless generates generic QALY measures stems from the Dementia Quality of Life Measure (DEMQOL) [23]. The frequency and timing of assessments should be influenced by disease severity, speed of progression and the questionnaire burden on the patient. When patients are too ill or have lost cognitive competence to complete a questionnaire, proxy measurements may be consider DEMQOL-proxy.

The development of DEMQOL-U and DEMQOL-proxy-U,'U' referring to the utility scores generated in this project,as more precise tools to evaluate QALY in dementia, and to enable a more robust system of assessment to determine more precisely various phases in the development of the disease, and integrate those evaluations in economic studies, reflects the concern of much researchers to improve the precision such economical assessments [25].

For costs, the crucial information is usually the arithmetic mean, average cost, as this allows policy makers to estimate the total cost of implementing a programme, or one, or more intervetions. Often in Dementia cost data are skewed because few patients use very high amount of resources, producing distributions that might violate the assumption of standard statistical tests.

However the fundamental aim of the healthcare system is not to save money, but to save and improve lifes, the best way to achieve this aim is to make best use of the resources that are available which in turn means getting an understanding of cost-effectiveness and highlighting the trade-offs between better outcomes and higher costs that often have to be made [23].

Previous systematic reviews have already explored the benefits of both psychological, cognitive, and other non-pharmacological therapies in PWD [9,26-30].

Although in dementia what enables a good measure of trade-offs is the prevention of complication and the saving in costs that they represent [23,31,32].

Various studies identify the probability that individuals living with dementia experience stroke when receiving antipsychotic drugs more often as in comparison to "no use" of them; or the probability that individuals living with dementia experience a fall, either as a consequence of the motor disabilities that patients often develop, or as an adverse effect of medication [29,33]. Frequently economic evaluations are based either on the cost of delivering behavioural interventions compared to the cost of strokes, or the cost per fall,or QALY gain due to avoid such complications, or preventing the event of death [24].

Objective

The objective of this research was to generate economic evidence of the benefits of non-pharmacological alternatives to drug use for individuals living with dementia, or improvement in benefits with combination therapy.

NICE guidelines recommend that the first line of treatment for behavioral and psychological symptoms among those with dementia should be psychosocial interventions. However, in practice, antipsychotic drugs are used more often as the first line of treatment (Figure 5).

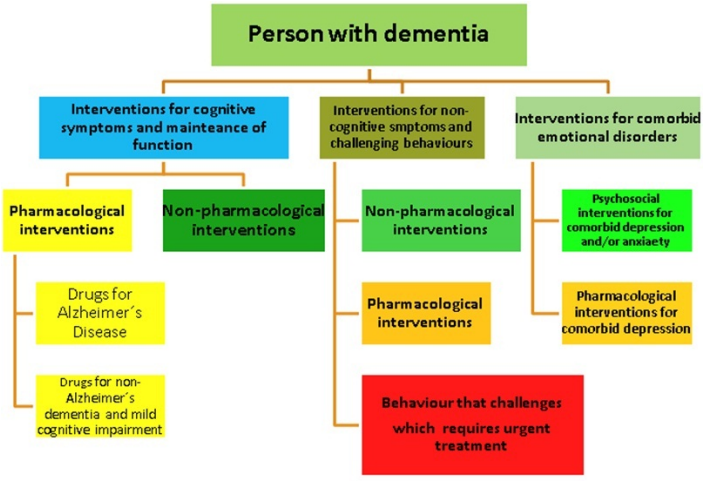

Figure 5: Recommended guidelines for the Management of Dementia © NICE 2016.

In line with NICE guidelines, this report suggests that behavioral interventions are a more efficient use of public money than

antipsychotic drugs, particularly regarding the avoidance of potential complications such as sudden death, stroke, or falls, which have been reported to occur more often with the use of pharmacological interventions, and consequent deterioration of QoL in PWD.

Decision Making Model

An outstanding factor is to evaluate the prevention of complications, which are reported with the use of medication for the control and management of BPSD, which are one of the most threatening circumstances for the management of PWD, and considering the extensive practice of their use, the modeling method for this pharmacoeconomic analysis would be a decision tree presented on figure 6.

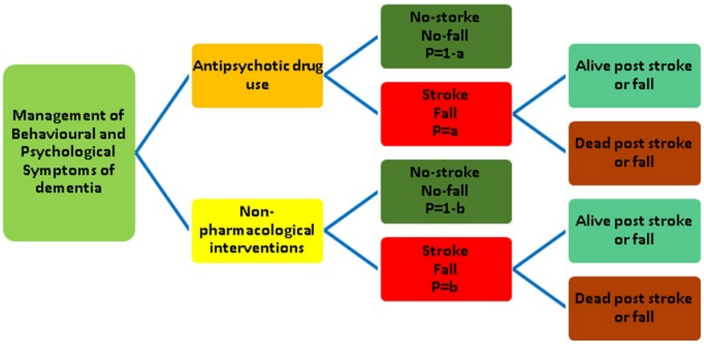

Figure 6: Decision making model for providing non-pharmacological interventions as alternative to antipsychotics versus strokes or falls. P=a: probability of suffering a stroke or a fall with use of antipsychotic drugs. P=b: probability of suffering a stroke or fall with use of non-pharmacological interventions.

Methods

For the purpose of this review we searched in databases of Pub Med, EMBASE, Cochrane Library, PSYCINFO, Alzheimer´s association, ALOIS; focused on systematic reviews and systematic reviews with meta-analysis, and systematic reviews with pharmacoeconomic evaluations reported from 2005 to 2016. The search terms included "dementia" [MeSH] or "cognitive impairment" or "Alzheimer". These were combined with "interventions" [MeSH] and "non-pharmacological" or "occupational therapy" or "psychological interventions" or "cognitive interventions" or "physical therapy" or "cognitive therapy", and "systematic reviews" or "systematic reviews" and "meta-analysis"; "pharmacoeconomic evaluations" or "meta-analysis and pharmacoeconomic evaluation". And "Quality of life", eliminating studies with no human subjects.

Huntington's disease or other progressive neurologic conditions were excluded because these patients are considered to have distinctly different conditions. Studies including subjects with Alzheimer's disease and those with mixed dementia were included in the study.

Any non-pharmacological intervention that had at least one primary outcome measuring any domain of functional limitations or disability was included. We included studies using self-reported measures as well as those using performance-based assessments. Any drug-based interventions were eliminated, but applicable studies including patients with stable medication dosages or studies that included multi-faceted interventions were not eliminated. Several randomized controlled trials with robust data reports and data analysis were also reviewed.

We found 180 references of which 57 duplicates were excluded; 123 studies were considered of which 45 were excluded no being relevant to the subject and 13 not having relevant data reported. Articles were initially reviewed by title. 65 articles were then reviewed by abstract and data analysis. 37 Articles contained important information to the subject, and have been used to integrate the present review. 7 systematic reviews with meta-analysis on the evaluation of non-pharmacological interventions and 2 systematic reviews with pharmacoeconomic evaluation of non-pharmacological interventions fulfill the scope of the review, and are subject of the analysis of this review. Figure 7 illustrates the study selection process.

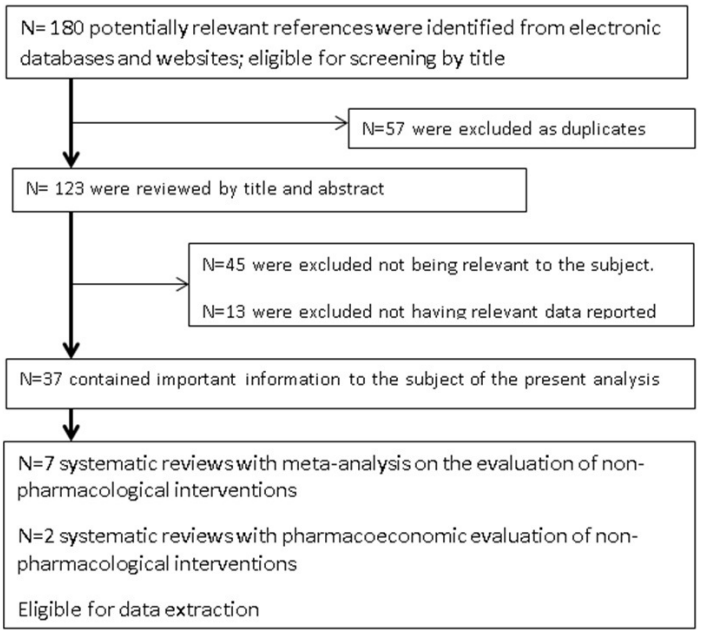

Figure 7: Flow chart of study selection process.

Selection Criteria

Systematic reviews or systematic reviews with meta-analysis of non-pharmacological interventions in PWD formed part of the analysis. Systematic reviews with meta-analysis and pharmacoeconomic evaluations of non-pharmacological interventions for PWD; one study of pharmacological interventions with pharmacoeconomic analysis that encompasses the most important drugs for Dementia, and clinical trials with very robust data were used to integrate the analysis. Several systematic reviews were very weak on the data report and analysis, but contained important literature information, and were consulted

Data Collection and Analysis

The response to non-pharmacological interventions has been

documented all through the medical literature, however the variability of interventions, reporting outcomes, and how fast they might change represents a major challenge to collect and analyze data in Dementia studies. Most studies report favorable results, however different issues, regarding the selection of patients in relationship to the different types of dementia, the blinding of subjects, or interventions; the difficulty to utilize placebo controls, and the standardization of reporting results between the different clinical trials, besides the short term periods of the clinical trials, and the lack of long term follow up, challenge most authors that have performed systematic reviews.

The use of statistical values such as Standardized Effect Size (SES) that evaluates the strength of a phenomenon or correlation between two variable; the regression coefficient estimated, the mean difference; or the risk with which something happens are often integrated in order to have the possibility to compare results.

Reports from individual Randomized Clinical Trials (RCT), single-blind, multi-center, which recruited201 older people with dementia, one hundred and fifteen people were randomized within centers to theinterventiongroupand86to the control group; the results from this study show promising positive effects as seen in table 1.

Efficacy measure [1]	Change from baseline		Group difference		ANCOVA between group difference	ANCOVA other significant differences[2]
	Treatment Mean (SD)	Control Mean (SD)	Mean (SD)	95% CI		
MMSE	+0.9 (3.5)	-0.4 (3.5)	+1.14 (0.09)	0.57 to 2.27	F=4.14, P=0.044	None
ADAS-Cog	+1.9 (6.2)[3]	-0.3 (5.5)[4]	+2.37 (0.87)	0.64 to 4.09	F=6.18 P=0.014	C: P=0.006
QoL-AD	+1.3 (5.1)	-0.8 (5.6)	+1.64 (0.76)	0.09 to 3.18	F=4.95 P=0.028	G: P=0.010
Holden	+0.3 (6.1)	-3.2 (6.3)	+2.3 (0.93)	-0.45 to 4.15	F=2.92 P=0.090	C: P=0.009 G: P=0.001
RAID	-0.5 (10.2)	-0.7 (10.3)	-1.30 (1.10)	-3.48 to 0.87	P=0.200	C: P≤0.001
Cornell	0 (6.2)	-0.5 (7.0)	+0.12 (0.72)	-1.56 to 1.31	P=0.648	C: P≤0.001
1. Primary outcome measure: MMSE; secondary outcome measure: ADAS-Cog and QoL-AD						
2. C: difference s between Centres; G: differences between genders						
3. Zero or more points improvement n=58 (50%); 4 or more points improvement: n=34 (30%)						
4. Zero or more points improvement n=32 (37%); 4 or more points improvement: n=11 (13%)						

Table 1. Change from baseline in measures of efficacy at follow-up: intention-to-treat analysis [9]

The outcomes reported on this table show an improvement in the control tests for the intervention group with non-pharmacological interventions in relationship to the control groups which had care as normal, and the Analysis of Covariance (ANCOVA) show to have statistically significant evaluations for the Mini-mental State Exam (MMSE), Alzheimer´s Disease Assessment Scale-Cognition (ADAS-Cog), and Quality of Life – Alzheimer´s Disease (QoL-AD).

The subsequent mesuarements: RAID Rating Anxiety in Dementia (RAID), Holden Communication Scale (Holden), and Cornell Scale for Depression in Dementia (Cornell), the three of them evaluate diverse areas of response in PWD; all mesuraments show statistical significance comparing evaluations between centres of intervention, and gender of participants, although there are no major differences between the intervetion group with non-pharmacological interventions and controls [9].

In this study the authors include an analysis of numbers to treat to compare the efficacy of non-pharmacological intervention Cognitive Stimulation Treatment (CST) versus the anti-dementia drugs with the conclusions reported on table 2.

Even the results reported show an important variability, and wide range confidence intervals (CI), the figures show certain similarities between CST and the pharmacological intervention with the various anti-dementia drugs.

Treatment	Analysis 1 [1] NNT (95% CI)	Analysis 2 [1] NNT (95% CI)
CST programme	8 (4-144)	6 (4-17)
Rivastigmine, 6-12 mg (Corey-Bloom et al, 1998; Rösler et al, 1999)	4 (3-6)	13 (7-11)
Donezepil, 5mg	5 (4-9)	10 (5-180)
Donezepil, 10mg (Rogers et al, 1998)	5 (3-8)	4 (3-7)
Galantamine, 32mg (Wilcock et al, 2000)	5 (4-8)	6 (4-9)
1. Analysis 1- Alzheimer´s Disease Assessment Scale – Cognition score with no deterioration as improvement; Analysis 2 – same score with increase of 4 or more points as improvement.		

Table 2: Numbers needed to treat: comparison of cognitive stimulation therapy with antidementia drugs [9]

This study found improvements in both the primary (MMSE) and secondary (ADAS– Cog and QoL–AD) outcome; measures for people in the CST group of the Numbers Needed to Treat (NNT) analysis show similarities between the pharmacological interventions and CST, consistent with a good response for the non-pharmacological interventions [9].

Another conclusion from this study is that although there is a body of research on the various psychological interventions for dementia, much of it lacks methodological rigor and might not be considered 'evidence-based'. The previous RCTs were small, with the largest having 56 participants, and could be criticized for weaknesses such as lack of standardization of groups, selection and detection biases, and absence of intention-to treat analyses [9].

From other systematic reviews conducted lately there are less optimistic results on the effect of non-pharmacological treatments in the area of cognitive training, reporting that cognitive training was not associated with positive or negative effects in relation to any reported out comes. The overall quality of the trials was low to moderate. The single RCT of cognitive rehabilitation found promising results in relation to a number of participant and caregiver outcomes, and was generally of high quality.

The conclusions from these systematic reviews is that the available evidence regarding cognitive training remains limited, and the quality of the evidence needs to be improved. However, there is still noindicationofanysignificantbenefitderivedfromcognitivetraining. Trial reports indicate that some gains resulting from intervention may not be captured adequately by available standardized outcome measures. The results of the single RCT of cognitive rehabilitation show promise but are preliminary in nature. Further, well-designed studies of cognitive training and cognitive rehabilitation are required to obtain more definitive evidence. Researchers should describe and classify their interventions appropriately using

available terminology, and including other methods of assessment of results [9,26].

Studies focused on case management approach for PWD found benefits at six months and 18 months but not at 12 and 24 months; these studies examined the benefit in reducing admissions to residential or nursing homes (institutionalization). The benefits in terms of reduced hospital length stay indicated that it was more effective at reducing behavior disturbance at 18 months, reducing carer burden and depression, and improving carer well-being at six months and social support at 12 months, improving patient depression, functional abilities or cognition. Case management increases the use of community services but there was some indication that overall healthcare costs may be reduced in the 1st year [27].

Studies considering interventions directed to the carers to relief tension and prevent their deterioration have demonstrated to be clinically effective and cost-effective in the short and long term. The cost-effectiveness acceptability curve showed a greater than 99% chance of being cost-effectiveness at a £30,000/QALY willingness-to-pay threshold and a high probability of cost-effectiveness based on theHospital Anxiety and Depression Scale-Total score (HADS-T). Carers in the intervention group had less case-level depression [odds ratio (OR) 0.24, 95% CI 0.07 to 0.76], a trend towards reduced case-level anxiety (OR 0.30, 95% CI 0.08 to 1.05), and higher Health Status Questionnaire (HSQ) QoL (mean difference 4.09, 95% CI 0.34 to 7.83) [34].

In care home residents there are studies that reflect benefits of the non-pharmacological interventions to reduce clinically significant agitation; the evaluated interventions were person centered care, communication skills, activities, music therapy, and sensory interventions. The cost of interventions which significantly impacted on agitation was: activities £80-696; music therapy £13-27; sensory interventions £3-257, and training caregivers in person-centered or communication skills with or without behavioral management training £31-339 [35].

The incremental cost per unit reduction of these interventions compared with the health and social costs which ranged from £ 7,000 over 3 months in people without clinical agitation to around £15,000 at the most severe agitation levels shows that a multi component intervention in participants with mild to moderate dementia has positive monetary benefit and 82.2% probability of being cost-effective at a maximum willingness to pay for a quality-adjusted life-year (QALY) of £20,000 and 83.3% probability at a value of £30,000 [35].

Studies with pharmacoeconomic analysis are available mostly from countries that have a solid system of information, therefore, it is estimated that behavioral interventions cost £27.6 million more per year than antipsychotic drugs for the cohort of 133, 713 individuals with dementia requiring antipsychotic drugs in England. However, the additional investment is offset by nearly £70.4 million in health care savings due to reduced incidence of strokes and falls. Specifically, behavioral interventions would avoid nearly 1,348 cases of stroke and 118 falls compared to antipsychotic drugs per year. Of these health care cost savings, £4.7 million were estimated to be realizable as they are due to medication costs [24].

Therefore some of the extra cost of behavioral interventions is paid through financial savings as a result of avoided strokes and falls. The majority of the value of behavioral interventions, however, comes through saving time and other resources that will increase the capacity of the health service.

In addition to the health care cost savings, behavioral interventions generate quality of life improvements. If these quality of life improvements are valued monetarily at the lower end of the NICE threshold, behavioral interventions would generate an additional £12.0 million in benefits per annum [24].

Combining health care cost savings and quality of life improvements, behavioral interventions generate a net benefit of nearly £54.9 million per year as seen in Figure 8.

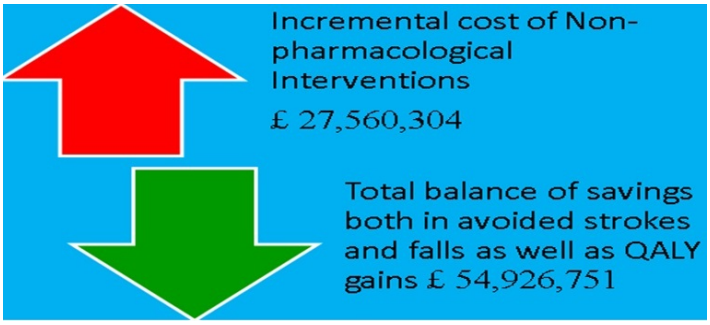

Figure 8: Annual costs and benefits of behavioural interventions for individuals living with dementia in England.

The results of this analysis are expressed below in table 3.

Systematic review and meta-analysis of effect of exercise training on cognitive function in older adults with MCI have overall results which were inconsistent with benefits varying across exercise types and cognitive domains. Analysis of fourteen RCT´s including 1695 participants aged 65-95 years old, met inclusion criteria; 42% SES were potentially clinically relevant Standardized Effect Size analysis (SES) ≥ 0.20) with only 8% of cognitive outcomes statistically significant. Meta-analysis revealed negligible but significant effects on verbal fluency (SES: 0.7 [0.04, 0.30]), and no significant benefit was found for executive measures, memory, or information processing [11].

Conclusions are that large-scale, high quality RCT´s are required to determine exercise benefits on cognition or dementia incidence in those individuals with MCI. A major beneficial effect of the physical interventions is on the domain of improvement of depression, and to prolong independence of PWD [11].

Research with pharmacological intervention has in general more

Parameter	Antipsychotic drug use	Behavioural Interventions		Difference		
Total cost of Interventions			**Units**	**Incremental cost**	**Savings in cost**	**Balance**
Total	£67,000,000	£ 94,560,304	£	£27,560,304		
Strokes						
Total number of Strokes	2,541	1,203				
Total cost of stroke treatment	£ 133,304,032	£ 63,144,015	£		£ 70,160,017	
Falls						
Total number of falls	3,256	3,138				
Total cost of fall treatment	£ 7,373,608	£ 7,105,726			£ 267,780	
Balance of treatment				£ 27,560,304	£ 70,427,797	£ 42,867,493
QALY						
Net QALY gain from strokes			591			
Net QALY gain from falls			12			
Net QALY gain			603			
Total monetary value of QALY gain					£ 12,059,258	£ 12,059,258
Net Benefit						£ 54,926,751
Benefit to cost ratio*			1.99			
Realizable savings						£ 4,656,985

Table 3: Annual costs and benefits of behavioural interventions for individuals living with dementia in England (£ in 2010 prices) [24]. *Values higher than 1 indicate that the benefit exceed the costs, and thus the intervention represents an efficient use of public resources.

robust statistical reports; although the results have been a matter of systematic reviews and cost-effectiveness analysis, there is still debate on the cost-effectiveness evidence on these interventions [36]. Acetyl-cholinesterase inhibitors (Ach-I) for mild to moderate disease and memantine for moderate to severe disease are found to be cost-effective.

Cost-effectiveness analysis undertaken in reviews suggests that donepezil treatment has a cost per quality-adjusted life-year (QALY) in excess of £80,000, with donepezil treatment reducing the mean time spent in full-time care (delays progression of AD) by 1.42–1.59 months (over a 5-year period). Cost-effectiveness analysis undertaken in the review suggests that rivastigmine treatment has a cost per QALY in excess of £57,000, with rivastigmine treatment reducing the mean time spent in full-time care (delays progression) by 1.43–1.63 months (over a 5-year period). Cost-effectiveness analysis undertaken in the review suggests that galantamine treatment has a cost per QALY in excess of £68,000, with galantamine reducing the time spent in full-time care (delays progression) by 1.42–1.73 months (over a 5-year period). Important comments from the authors are that most studies are sponsored by the industry, suggesting that for donepezil, rivastigmine and galantamine, the cost savings associated with reducing the mean time spent in full-time care do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels generally considered acceptable by NHS policy makers. Meaning that even for pharmacological interventions it is still necessary to develop further research.

Future research should include: information on the quality of the outcome measures used; development of quality of life instruments for patients and carers; studies assessing the effects of these interventions of durations longer than 12 months; comparisons of benefits between interventions; and research on the prediction of disease progression [36].

To demonstrate the value of treatments for dementias such as AD, or for MCI some unique issues should be considered, such as hidden cost to society; even it is well known the annual cost worldwide of dementias, there are other important costs associated to not treating the disease: care-givers absenteeism, other health problems associated to stress or depression that have been estimated $60 billion dollars. Costs of ADL, the loss of functional ability is very important to patients and their caregivers, and is also associated with increased healthcare costs in dementia. Under-diagnosis: only 25–50% of patients with dementia received an early diagnosis, and most patients with dementia are diagnosed in the moderate stages, with associated higher costs of management.

Other meaningful associated expenses to dementia are: Hospital costs, which are75% higher for dementia patients than for other geriatric patients. Co-morbidities: 16 co morbidities are present 20% more often in PWD, and represent 60% of the costs of management. Under-coding, only 10% of the patients with dementia have this diagnosis as bill diagnosis. [12].

Results

Most systematic reviews agree that non-pharmacological interventions have a positive effect on physical function, and in cognitive performance in PWD, however the evaluation of

improvements in QoL have been very complex finding that usually the evaluation of improvements on QoL are much higher from the patient´s perspective as from their carers.

There are two main parameters in the value paradigm: cost and effectiveness. One measure of effectiveness is the QALY. This metric is often used in pharmacoeconomic evaluations of health interventions. By convention, cost per QALY in the zero to £50,000 range is sometimes considered good value for money, while cost per QALY over £100,000 is considered too expensive, the barrier for acceptance of interventions to be cost-effective is £30,000, and these values are valid for the United Kingdom. Other countries evaluate the QALY in relation to the GDP accepting a limit of one to two times this value, depending on the economic resources of each country, to rate de cost effectiveness ratio. These values serve as guidelines in the decision-making process for access and reimbursement.

Pharmacoeconomic assessments have been done pointing towards the fact that non-pharmacological interventions are cost-effective worth both having a positive effect lowering the costs of dementia, as well as improving the QoL of PWD.

Due to the complexity of the disease as well as to the process of evaluation certain parameters must be often integrated in the evaluation, such as willingness to pay, to estimate if certain interventions are cost-effective. People may be willing to pay a substantial amount to avoid developing AD or for having a small chance of obtaining benefit from therapy [37].

The standardization of criteria is very important and meaningful. Beginning with the diagnosis, certain diagnostic procedures are fully recognized and NICE and other agencies have already stated the procedures to systematically integrate a diagnosis of the patient, however at present, in many instances the studies include PWD regardless of the type of dementia and often considering only the generic diagnosis of the syndrome without recognizing or establishing major distinctions between the different types of dementia, and it seems that the pathologic process might vary importantly from one case to another, probably influencing also the results of the studies.

It would be of priority importance to standardize the interventions, both by nomenclature, as well as by procedure, content and objectives, in order to be able to compare results from various RTCs, and other studies. A difficulty in the literature lies in characterizing the content of the interventions; authors, which have done systematic reviews, have developed various resources to be able to capture more robust data or to integrate the current results; however there is such a vast diversity of reports, which jeopardizes the integration and analysis of the data reported in order to obtain consistent results, and very often it is major challenge or a limitation for systematic reviews in order to achieve robust statistical information and obtain results to compare the different studies through a meta-analysis, which are often reported by the authors as resulting impossible to be accomplished.

Integration of evaluation strategies such as Positron Emission Tomography (PET), Single-photon Emission Computed Tomography (SPECT), or Functional Magnetic Resonance Imaging (fMRI) in the evaluation of changes in brain plasticity or neuroplasticity would be a very valuable resource in the evaluation of results during RCTs in patients with MCI or PWD; although these resources are very expensive, they could provide a more objective evaluation of effects of interventions, considering in the future the evaluation of risk factors, earlier diagnosis of the pathology, and implementation in very early phases of the pathological process preventive measures with non-pharmacological interventions, which could be proven to be effective in the management of disease. Prevention could be a very resourceful area of pharmacoeconomic evaluation of cost-effectiveness in dementia.

Consistently with NICE recommendations, research is needed to generate robust and relevant data on the effects of treating PWD on both short-term and long-term outcomes, disease progression through relevant health states, and quality of life. Duration of follow up in dementia studies is another major handicap to the moment; certain recommendations have changed, and new studies are planned for periods of at least six months follow up or more. Associated to this problem is also the rapid changes and deterioration that PWD exhibit, which compromises also de evaluations of outcomes in association to evolution of the disease.

The pharmacoeconomic research might supply valuable resources to determine which expenses represent the best value of money in order to optimize the use of resources, and therefore encompasses a diversity of domains that might range from prevention to management of the condition and potential complications. Figure 8 offers us a schematically represented scope of pharmacoeconomic potential research areas of cost-effectiveness evaluation in dementia.

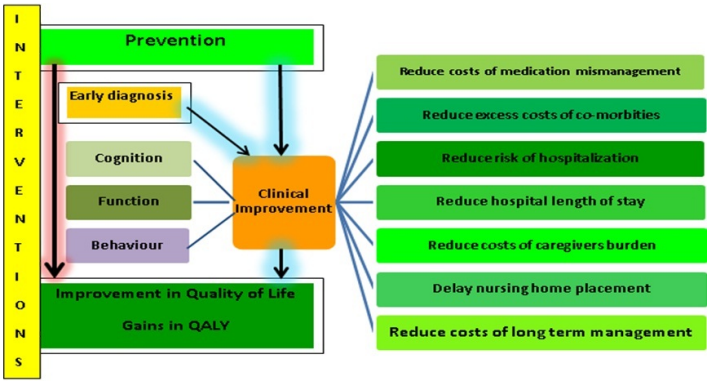

Figure 9: Domains of Pharmacoeconomics in Dementia.

Therefore, pharmacoeconomic in Dementia is a very important and resourceful discipline, and no effort should be spared in order to overcome the present limitations, or reluctance to implement evidence, the poor coordination of health and social provision and financing resources, and promote a major investment in the promotion of every available research method to improve life conditions and present or future expectations of PWD worldwide.

Acknowledgement

This paper is dedicated to the memory of Maria Luisa Lopez Ponce, who died on March 2013, being the inspiration through her strength, and courage in her fight against dementia. Special thanks to Doctor Monico Salvador Vazquez del Castillo for his help in the process of writing this article. This report/article presents independent research. This work received no funding source and all authors declare that they have no competing interests.

References

1. World Health Organization (2012) Dementia: A public health priority. WHO United Kingdom.
2. Prince M, Anders Wimo, Maëlenn Guerchet, Gemma-Claire Ali, Yu-Tzu Wu, et al. (2015) World Alzheimer Report: The Global Impact of Dementia an Analysis of Prevalence, Incidence, Cost and Trends, Alzheimer's disease International (ADI), London.
3. McLaren A, Lamantia MA, Callahan CM (2013) Systematic Review of Non-Pharmacologic Interventions to Delay Functional Decline in Community-Dwelling Patients with Dementia, Aging Mental Health 17: 655-666.
4. Butler R, Radhakrishnan R (2012) Dementia. BMJ Clin Evid 2012.
5. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, et al. (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 367: 795-804.
6. Loveman E, Green C, Kirby J, Takeda A, Picot J, et al. (2006) The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess 10: iii-iv, ix-xi, 1-160.
7. Ballard C, Waite J (2006) The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev : CD003476.
8. Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, et al. (2012) Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry 169: 71-79.
9. Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, et al. (2003) Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. Br J Psychiatry 183: 248-254.
10. Bahar-Fuchs A, Clare L, Woods B (2013) Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev : CD003260.
11. Gates N, Fiatarone Singh MA, Sachdev PS, Valenzuela M (2013) The Effect of Exercise Training on Cognitive Function in Older Adults with Mild Cognitive Impairment: a Meta-analysis of Randomized Clinical Trials. American Journal of Psychiatry 21: 11
12. Alzheimer's Association (2016) 2016 Alzheimer's disease facts and figures. Alzheimers Dement 12: 459-509.
13. Knapp M, Iemmi V, Romeo R (2013) Dementia care costs and outcomes: a systematic review. Int J Geriatr Psychiatry 28: 551-561.
14. Chapman DP, Williams SM, Strine TW, Anda RF, Moore MJ (2006) Dementia and its implications for public health. Prev Chronic Dis 3: A34.
15. www.ninds.nih.gov/disorders/dementias
16. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, et al. (1999) Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56: 303-308.
17. Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, et al. (2009) Mild cognitive impairment: ten years later. Arch Neurol 66: 1447-1455.
18. https://www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/dementia
19. Querfurth HW, LaFerla FM (2010) Alzheimer's disease. N Engl J Med 362: 329-344.
20. De Felice FG, Lourenco MV2, Ferreira ST2 (2014) How does brain insulin resistance develop in Alzheimer's disease? Alzheimers Dement 10: S26-32.
21. de la Monte SM (2012) Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. Curr Alzheimer Res 9: 35-66.
22. Stavros P, Alastair Gray (2011) Economic Evaluations alongside Controlled Trials: Design, Conduct, Analysis, and Reporting. British Medical Journal 342: 1548.
23. Knapp M (2015) The cost-effectiveness challenge: is it worth it? Alzheimers Res Ther 7: 10.
24. Burns A, Chambers N (2011) An economic evaluation of alternatives to antipsychotic drugs for individuals living with dementia. NHS Institute for Innovation and Improvement.
25. Mulhern B, Rowen D, Brazier J, Smith S, Romeo R, et al. (2013) Development of DEMQOL-U and DEMQOL-PROXY-U: generation of preference-based indices from DEMQOL and DEMQOL-PROXY for use in economic evaluation. Health Technol Assess 17: v-xv, 1-140.
26. Carrion C, Aymerich M, Baillés E, López-Bermejo A (2013) Cognitive Psychosocial Intervention in Dementia: A Systematic Review. Dementia Geriatric Cognitive Disorders 36: 363-375.
27. Reilly S, Miranda-Castillo C, Malouf R, Hoe J, Toot S, et al. (2015) Case management approaches to home support for people with dementia. Cochrane Database Syst Rev 1: CD008345.
28. Aguirre E, Hoare Z, Spector A, Woods RT, Orrell M (2014) The effects of a Cognitive Stimulation Therapy [CST] programme for people with dementia on family caregivers' health. BMC Geriatr 14: 31.
29. Olazarán J, Reisberg B, Clare L, Cruz I, Peña-Casanova J, et al. (2010) Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord 30: 161-178.
30. Ojabbemi A, Owolabi M (2016) Do occupational therapy interventions improve quality of life in persons with dementia? A meta-analysis with implications for future directions. Psychogeriatrics Japanese Psychogeriatric Society.
31. Nagayama H, Tomori K, Ohno K, Takahashi K, et al. (2016) Cost-effectiveness of Occupational Therapy in Older People: Systematic Review of Randomized Controlled Trials. Occup Ther Int 23: 103-120.

32. Maud G, Eddy M M Adang, Myrra J M Vernooij-Dassen, Joost Dekker, Marjolein Thijssen et al. (2007) Community occupational therapy for older patients with dementia and their care givers: cost effectiveness study. BMJ.
33. Steinberg M, Lyketsos CG (2012) Atypical antipsychotic use in patients with dementia: managing safety concerns. Am J Psychiatry 169: 900-906.
34. Livingston G, Barber J, Rapaport P, Knapp M, Griffin M, et al. (2014) START (Strategies for Relatives) study: a pragmatic randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of a manual-based coping strategy programme in promoting the mental health of carers of people with dementia. Health Techonolgy Assessment 18: 61
35. Livingston G, Kelly L, Lewis-Holmes E, Baio G, Morris S, et al. (2014) A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia. Health Technol Assess 18: 1-226.
36. Loveman E, Green C, Kirby J, Takeda A, Picot J, et al. (2006) The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technol Assess 10: 1-160.
37. Knapp M, Lene Thorgrimsen, Anita Patel, Aimee Spector, Angela Hallam, et al. (2006) Cognitive stimulation therapy for people with dementia: cost-effectiveness analysis. British Journal of Psychiatry 188: 574-580.