GENERAL PRACTITIONER’S APPROACH TO
DIAGNOSIS, DISCLOSURE AND
MANAGEMENT OF DEMENTIA IN THE
MALTESE ISLANDS
Dedicated to my dear family…
Statement of authenticity

To whom it may concern

I hereby declare that the thesis entitled ‘The General Practitioner’s approach to diagnosis, disclosure and management of Dementia in the Maltese islands’ which I am submitting in partial fulfilment of the Degree of Master of Science in Pharmacology, is not one for which another degree has been or will be conferred by this or any other University.

I also confirm that the work of the thesis and its composition are my own.

Finally, I certify that the work of the thesis has not been presented to any other institution.

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OANA CARUANA PULPAN
GENERAL PRACTITIONER’S APPROACH TO
DIAGNOSIS, DISCLOSURE AND
MANAGEMENT OF DEMENTIA IN THE
MALTESE ISLANDS

A dissertation submitted
to the Faculty of Medicine and Surgery
University of Malta
in partial fulfilment of the requirements
for the degree of Master of Science in Pharmacology

Oana Caruana Pulpan
2010
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<td>AA</td>
<td>Atypical antipsychotics</td>
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<td>AAT</td>
<td>Animal-assisted therapy</td>
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<td>ACh</td>
<td>Acetylcholine</td>
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<td>AChE I</td>
<td>Acetylcholinesterase Inhibitor</td>
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<td>AD</td>
<td>Alzheimer's disease</td>
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<td>ADCS-ADLs</td>
<td>Alzheimer’s Disease Cooperative Study Activities of Daily Living Inventory</td>
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<td>ADEAR</td>
<td>Alzheimer’s Disease Education and Referral</td>
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<td>ADI</td>
<td>Alzheimer's Disease International</td>
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<td>ADL</td>
<td>Activities of Daily Living</td>
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<td>APA</td>
<td>American Psychiatric Association</td>
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<td>ApoE</td>
<td>Apolipoprotein E</td>
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<td>APP</td>
<td>Amyloid Precursor Protein</td>
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<td>Aβ</td>
<td>beta-amyloid</td>
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<tr>
<td>b.d.</td>
<td>Twice daily</td>
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<td>Benzo</td>
<td>Benzodiazepine</td>
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<td>BGP</td>
<td>Behavioral Rating Scale for Geriatric Patients</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>BNF</td>
<td>British National Formulary</td>
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<td>BPSD</td>
<td>Behavioral and Psychiatric Symptoms of Dementia</td>
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<td>BuChE</td>
<td>Butyrylcholinesterase</td>
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<td>CBC</td>
<td>Complete Blood Cell Count</td>
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<td>CGI-C</td>
<td>Clinical Global Impression of Change</td>
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<td>CIBIC-Plus</td>
<td>the Clinician’s Interview-Based Impression of Change plus Caregiver Input</td>
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<td>CJD</td>
<td>Creutzfeldt-Jakob disease</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>DSM-IV</td>
<td>The fourth edition of Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>EEG</td>
<td>Electroencephalography</td>
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<td>EFNS</td>
<td>European Federation of Neurological Societies</td>
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<td>EGB</td>
<td>Extract of Ginkgo biloba</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EURODEM</td>
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<td>FAD</td>
<td>Familial AD</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>Acronym</td>
<td>Full Form</td>
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<td>FTD</td>
<td>Fronto-Temporal Disease</td>
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<td>GBD</td>
<td>Global Burden of Disease</td>
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<td>Global Deterioration Scale</td>
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<td>General practitioner</td>
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<td>GPCOG</td>
<td>General Practitioner Assessment of Cognition</td>
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<td>HBSC</td>
<td>Health Behaviour in School-aged Children</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>ICAD</td>
<td>Alzheimer’s Association International Conference on Alzheimer's Disease</td>
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<td>IDDM</td>
<td>Insulin-Dependent Diabetes Mellitus</td>
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<td>LDL</td>
<td>Low Density Lipoprotein</td>
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<td>LTD</td>
<td>Long-Term Depression</td>
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<td>LTP</td>
<td>Long-Term Potentiation</td>
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<td>MA</td>
<td>Market Authorization</td>
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<td>MCFD</td>
<td>Malta College of Family Doctors</td>
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<td>MCI</td>
<td>Mild Cognitive Impairment</td>
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<td>MHS</td>
<td>Maltese Health System</td>
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<td>MIMS</td>
<td>Monthly Index of Medical Specialties</td>
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<td>Mini-Cog</td>
<td>Mini-Cognitive Assessment Instrument</td>
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<td>Memory Impairment Screen</td>
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<td>MMDNA</td>
<td>Malta Memorial District Nursing Association</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>Multisensory Stimulation Environments</td>
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<td>N</td>
<td>Northern</td>
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<td>N/A</td>
<td>No Response</td>
</tr>
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<td>NA</td>
<td>Not Applicable</td>
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<td>nAChR</td>
<td>nicotinic Acetylcholine Receptor</td>
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<td>NDSP</td>
<td>National Dementia Strategy Plan</td>
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<td>NFT</td>
<td>Neurofibrillary Tangles</td>
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<td>Nutriceutical Formulation</td>
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<td>Northern Harbour</td>
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<td>NHS</td>
<td>National Health System</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>NIDDM</td>
<td>Non Insulin-Dependent Diabetes Mellitus</td>
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<td>NINCDS-</td>
<td>National Institute of Neurological and Communicative Disorders and Stroke</td>
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<td>ADRDA</td>
<td>and the Alzheimer’s disease and Related Disorders Association</td>
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<td>N-methyl-D-aspartic acid Receptor</td>
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<td>NMDA-receptor antagonist</td>
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<td>Nootr</td>
<td>Nootropics</td>
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<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>NSAIDs</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<td>Positron Emission Tomography</td>
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<td>PPARγ</td>
<td>Peroxisome Proliferator-Activated Receptor-gamma</td>
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<td>PWD</td>
<td>People with Dementia</td>
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<td>RSNA</td>
<td>Radiology Society of North America</td>
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<td>sAPPα</td>
<td>Soluble Amyloid Precursor Protein alpha</td>
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<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitors</td>
</tr>
<tr>
<td>SVPR</td>
<td>Saint Vincent de Paul Residence</td>
</tr>
<tr>
<td>SYST-EUR</td>
<td>Systolic Hypertention in Europe trial</td>
</tr>
<tr>
<td>TA</td>
<td>Typical antipsychotics</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic Antidepressants</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>Vit E</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>W</td>
<td>Western</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WONCA</td>
<td>World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians</td>
</tr>
</tbody>
</table>
Abstract

National Dementia Strategies abroad suggest that early detection of Alzheimer’s disease (AD) and other dementias in the community depends on an improved knowledge of the condition among general practitioners (GPs). There is no data on clinical diagnosis and management of dementia in the community in the Maltese islands. The aim of the study was to assess if further training is required for local GPs to approach better diagnosis and management of dementia, with particular interest on AD. A total of 346 questionnaires were mailed to members of the Malta College of Family Doctors (MCFD), of which 131 were valid. Questions were sectioned in four main data groups: demographic, diagnosis, disclosure and treatment. The majority of GPs (76.0%) called for a national protocol for diagnosis of dementia and AD and felt they need more training (56%). Loss of memory (90%) and behavioral symptoms (77%) were the symptoms which made GPs most likely to suspect dementia. On suspicion of cognitive impairment, a general physical examination and interview with the family were the first two actions taken in the majority of cases. One in ten GPs adopted a wait and observe approach, with close follow-up every two to four months and referral to specialist was overall considered late. The majority of GPs (89%) agreed that early diagnosis of AD may postpone or preclude costly institutionalization. Psychometric tests were considered to be useful for assessing the severity of dementia (55%) with few (27%) commenting that they are not readily available in community practice. Most GPs preferred to exclude a number of other conditions which may cause cognitive impairment in their work-up although only 39% correctly excluded all other possible differentials listed. Moreover, local GPs took a cautious approach towards disclosure and communicated diagnosis only if sure of it. Those who were routinely disclosing amounted to just below a third with only a fifth believing this was of any benefit. The results also showed that disclosure consultation generally focused onto medical issues like prognosis and progression of the condition (86%) but also included caregivers’ health issues. On pharmacotherapeutic management, half of the GPs would consider acetylcholinesterase inhibitors (AChEIs) in mild cognitive impairment. Psychotropic drug use was found to be low. Aims of treatment were delay in
institutionalization (67%) and maintenance of functional ability (60%). Only a third believed that AChEIs should be prescribed only by relevant specialists and 65% had a tendency to prescribe them in the community. Follow-up is close to every two to four months (69%) with the rest opting for a six to eight monthly period. Domiciliary home help (85%) and Telecare services (81%) were mostly recommended by GPs to aid their patients and caregivers even though these are of no particular benefit for disease management. Non-pharmacological approaches to managing people with AD were met by the highest rate of absenteeism. Of these, multisensory stimulation was the one which was mostly recommended (53%). The data from this study indicated that there is not enough knowledge on the diagnosis, disclosure, management and treatment of dementia, particularly AD, among the Maltese and Gozitan GPs. Furthermore, such data would be of benefit in the development of an on-going educational training programme on dementia involving GPs that would invariably lead to an enhancement of high quality dementia care within the community.

**Key words:** Alzheimer's disease, dementia, general practitioner, diagnosis, disclosure, management, Malta
Chapter 1

Introduction and aims
1.1. Definition of dementia

Dementia is a term used to describe a group of brain diseases which result in progressive impairment of brain function with symptoms involving multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment (WHO 10th revision of the International Classification of Diseases, 2007). According to the American Psychiatric Association Practice Guidelines of 2006, the essential features of a dementia are acquired multiple cognitive deficits that usually include memory impairment and at least one of the following phenomena in the absence of a delirium that might explain the deficit: aphasia, apraxia, agnosia, or a disturbance in executive functioning (the ability to think abstractly and to plan, initiate, sequence, monitor and stop complex behavior). The order of onset and relative prominence of the cognitive disturbances and associated symptoms vary with the specific type of dementia.

These definitions emphasize that this clinical syndrome is progressive, irrevocable and affects several higher cortical functions of the brain, reflected in the patient as different grades of cognitive impairment. An individual falling within the above criteria is referred to as a 'person with dementia' (PWD). Any other individuals involved in the supportive care of people with dementia are termed 'Caregivers' or 'Carers' for people with dementia.

The family physician who is in charge of the continuing and comprehensive health care of an individual and his family or carer within the community is termed a 'general practitioner' (WONCA Europe, 2005). Most general practitioners in Malta are members of the Malta College of Family Doctors (MCFD), an autonomous academic institution founded in 1989 whose objective is to encourage, foster and maintain the highest possible standards in family medicine in Malta, and to sustain and improve the professional qualifications of members of the medical profession in Malta who are engaged in family medicine (MCFD statute, 1996).
1.2. Classification of Dementia and Mild Cognitive Impairment (WHO, 2007)

1.2.1. Dementia in Alzheimer's disease (AD)

Alzheimer's disease is a primary degenerative cerebral disease of unknown etiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years (WHO, 2007). The two main sub-types are listed in Table 1.1.

| Early onset AD | Dementia in AD with onset before the age of 65, with a relatively rapid deteriorating course and with marked multiple disorders of the higher cortical functions. |
| Late onset AD | Dementia in AD with onset after the age of 65, usually in the late 70s or thereafter, with a slow progression, and with memory impairment as the principal feature. |

Table 1.1. The two main types of AD presentations according to timing of onset (WHO, 2007).
1.2.2. Vascular Dementia

Vascular dementia is the result of infarction of the brain due to vascular disease, including hypertensive cerebrovascular disease. The infarcts are usually small but cumulative in their effect. Onset is usually in later life. Sub-types are listed in Table 1.2.

<table>
<thead>
<tr>
<th>Vascular dementia of acute onset</th>
<th>Usually develops rapidly after a succession of strokes from cerebrovascular thrombosis, embolism or haemorrhage. In rare cases, a single large infarction may be the cause.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-infarct dementia</td>
<td>Gradual in onset, following a number of transient ischaemic episodes which produce an accumulation of infarcts in the cerebral parenchyma.</td>
</tr>
<tr>
<td>Subcortical vascular dementia</td>
<td>Includes cases with a history of hypertension and foci of ischaemic destruction in the deep white matter of the cerebral hemispheres. The cerebral cortex is usually preserved and this contrasts with the clinical picture which may closely resemble that of dementia in Alzheimer's disease.</td>
</tr>
</tbody>
</table>

**Table 1.2.** Description of the three main sub-types of vascular dementia (WHO, 2007).
1.2.3. Other dementias

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal dementia (FTD) or Pick's disease</td>
<td>A progressive dementia, commencing in middle age, characterized by early, slowly progressing changes of character and social deterioration, followed by impairment of intellect, memory, and language functions, with apathy, euphoria and, occasionally, extrapyramidal phenomena.</td>
</tr>
<tr>
<td>Dementia in Creutzfeldt-Jakob (CJD) disease</td>
<td>A progressive dementia with extensive neurological signs, due to specific neuropathological changes that are presumed to be caused by a transmissible agent. Onset is usually in middle or later life, but may be at any adult age. The course is subacute, leading to death within one to two years.</td>
</tr>
<tr>
<td>Dementia in Huntington's disease</td>
<td>A dementia occurring as part of a widespread degeneration of the brain. The disorder is transmitted by a single autosomal dominant gene. Symptoms typically emerge in the third and fourth decade. Progression is slow, leading to death usually within 10 to 15 years.</td>
</tr>
<tr>
<td>Dementia in Parkinson's disease</td>
<td>A dementia developing in the course of established Parkinson's disease. No particular distinguishing clinical features have yet been demonstrated.</td>
</tr>
<tr>
<td>Dementia in human immunodeficiency virus (HIV) disease</td>
<td>Dementia developing in the course of HIV disease, in the absence of a concurrent illness</td>
</tr>
</tbody>
</table>
or condition other than HIV infection that could explain the clinical features.

| Dementia in other specified diseases classified elsewhere | - cerebral lipidosis  
| - epilepsy  
| - hepatolenticular degeneration  
| - hypercalcaemia  
| - hypothyroidism, acquired  
| - intoxications  
| - multiple sclerosis  
| - neurosyphilis  
| - niacin deficiency (pellagra)  
| - polyarteritis nodosa  
| - systemic lupus erythematosus  
| - trypanosomiasis  
| - vitamin B₁₂ deficiency |

Table 1.3. Other types of dementia associated with known medical conditions (WHO, 2007).

1.2.4. Mild Cognitive Impairment (MCI)

MCI is a disorder characterized by impairment of memory, learning difficulties, and reduced ability to concentrate on a task for more than brief periods of time. There is often a marked feeling of mental fatigue when mental tasks are attempted, and new learning is found to be subjectively difficult even when objectively successful. None of these symptoms is so severe that a diagnosis of either dementia or delirium can be made. This diagnosis should be made only in association with a specified physical disorder, and should not be made in the presence
of any of the mental or behavioural disorders classified elsewhere. The disorder may precede, accompany, or follow a wide variety of infections and physical disorders, both cerebral and systemic, but direct evidence of cerebral involvement is not necessarily present. It can be differentiated from post-encephalitic syndrome and post-concussional syndrome by its different etiology, more restricted range of generally milder symptoms, and usually shorter duration (WHO, 2007).

1.3. Epidemiology of AD

1.3.1. Historical background of AD

Just about hundered years have passed since Alois Alzheimer presented the clinico-pathological features of pre-senile dementia after intent study and observation of the case of Mrs. Auguste Deter in a Frankfurt asylum (Maurer and Maurer, 2003).

Indeed Alzheimer, who was a German psychiatrist and neuropathologist, was the first scientist to link the clinical presentation of cognitive impairment to the presence of amyloid plaques and neurofibrillary tangles using silver staining techniques (Graeber, 2003).

Of interest is the fact that since Mrs. Deter was 51 years old when she manifested the symptoms observed by Alzheimer; the term Alzheimer’s disease was being used as a substitute for presenile dementia. The term was first coined by Alois’s director Emil Kraepelin and the diagnosis of Alzheimer’s dementia was being done in patients aging between 45 and 65 years of age (Boller and Forbes, 1998).
It was only in the 1970's that research recognised that the clinical and histopathological presentation of the majority of cases of both presenile and senile dementia were very similar, and by consensus, they were grouped together under the name of Dementia of the Alzheimer type (Katzman, 2004). This was enabled partly by the fact that advances in other fields of medicine and surgery improved survival of these individuals from other co-morbidities with the incidence of Alzheimer’s disease in the over 65 age group being increasingly recognised.

1.3.2. The demographics of aging

The last century has seen unprecedented advances in medicine which are resulted in lower mortality rates and longer longevity. The percentage of elderly in the population is rising in all world regions and is expected to increase further over the next 50 years (Figure 1.1).

![Figure 1.1. Percentage of population aged 60 and over in the year 2000 and a projection in 2050 (adapted from Global Demographic Ageing [UNIDES], 2000-2050).](image)

Although the Western World has as yet the current highest percentage of elderly in the population aged 60 and over and is predicted to remain so till 2050, Latin America, China and India are experiencing unprecedentedly rapid demographic ageing as indicated in Figure 1.2.
Growth in Latin America is expected to exceed that of any other world region while overall, increases to 2050 will be much sharper in developing (300%) than developed regions (100%) (Chaves et al., 2009).

![Comparison of ageing demographics between the U.K. and China from the 10/66 Dementia Research Group (Prince et al., 2007).](image)

**Figure 1.2.** Comparison of ageing demographics between the U.K. and China from the 10/66 Dementia Research Group (Prince et al., 2007).

The 10/66 Dementia Research Group's title refers to the 66 percent of people with dementia that live in developing countries and the less than one tenth of population-based research carried out in those settings. The aim of this group was to address shortcomings in research in dementia coming from these countries after recognising that poor data contribution from this part of the world would seriously undermine worldwide demographics and epidemiology (Prince et al., 2007).
1.3.3. Incidence

Many individuals find that they become more forgetful as they become older. Yet, dementia is not a normal part of aging. It is also different to the ‘Age associated memory impairment’ that is common in older people (EFNS, 2007).

Between 10% and 20% of individuals aged 65 and older have mild cognitive impairment (MCI). Among those whose MCI symptoms cause them enough concern to visit a physician, as many as 15% per year go on to develop dementia. From this estimate, nearly half of all people who have visited a physician regarding MCI symptoms will develop dementia in three or four years. Individuals with MCI are at higher risk of progressing more rapidly to Alzheimer’s disease (Alzheimer’s Association, 2009).

The main risk factor for most forms of dementia is advanced age, with prevalence roughly doubling every five years over the age of 65. Onset before this age is relatively uncommon and in the case of AD, often suggests a genetic cause (ADI World Report, 2009). This phenomenon is replicated in all worldwide data comparing incidence and ageing making it the most important non-modifiable risk factor for disease development (Table 1.4).
<table>
<thead>
<tr>
<th>Age group</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-59</td>
<td>0.16 %</td>
<td>0.09 %</td>
</tr>
<tr>
<td>60-64</td>
<td>1.58 %</td>
<td>0.47 %</td>
</tr>
<tr>
<td>65-69</td>
<td>2.17 %</td>
<td>1.10 %</td>
</tr>
<tr>
<td>70-74</td>
<td>4.61 %</td>
<td>3.86 %</td>
</tr>
<tr>
<td>75-79</td>
<td>5.04 %</td>
<td>6.67 %</td>
</tr>
<tr>
<td>80-84</td>
<td>12.12 %</td>
<td>13.50 %</td>
</tr>
<tr>
<td>85-89</td>
<td>18.45 %</td>
<td>22.76 %</td>
</tr>
<tr>
<td>90-94</td>
<td>32.10 %</td>
<td>32.25 %</td>
</tr>
<tr>
<td>95-99</td>
<td>31.58 %</td>
<td>36.00 %</td>
</tr>
</tbody>
</table>

Table 1.4. EURODEM estimates of prevalence rates of moderate to severe dementia in men and women according to nine different age groups in each European country (EURODEM, 2005).

Europe’s demographic situation is characterized by low fertility, an increasing life expectancy, and a projected shrinking of native populations in the decades to come. During the period 2005-2050, the median age of the European Union’s population is projected to rise by 10 years (from 38 to 48 years). This reversal in the population pyramid will bring change in several social issues spanning from ethno-religious to cultural and undoutedly economical (Muenz, 2007).
1.3.4. Prevalence

It is estimated that currently 35.6 million people have dementia worldwide. Up to 70 percent of these have Alzheimer’s disease. The number increases with mixed dementia of the Alzheimer and vascular type which is increasingly being diagnosed (World Alzheimer Report, 2009). These figures are expected to triplicate by 2050 (Figure 1.3).

![Graph showing increase in dementia cases from 2000 to 2050](image)

**Figure 1.3.** Total number of cases as a function of calendar year, based on data from the Delphi consensus study (Ferri et al., 2005).

The more recent statistics published in Alzheimer Disease International’s (ADI) World report of 2009 are yet the most accurate worldwide data available and based on 147 studies conducted in 21 Global Burden of Disease (GBD) world regions, with a substantial amount of information coming from middle and low income countries. Previous estimates published in 2005 were based on expert consensus and were found to be 10% short of the current data.
Since middle and low income countries are major contributors to the figures mentioned, for which data was mostly missing in 2005, this report is being considered as delivering more robust statistics.

In the UK alone, it is estimated that 820,000 people have dementia (Matthews et al., 2005), with up to 570,000 living in England (UK National Dementia Strategy, 2009). EU-27 estimates in 2006 were approximately 7 million people according to EuroCoDe data and circa 6.5 million according to EuroDem data (Alzheimer Europe, 2006).

In the United States of America (US), it was estimated that about 3.5 million people have dementia, of which 2.4 million were of the Alzheimer’s type (Plassman et al., 2007). The latter rose sharply to 5.3 million people according to Alzheimer’s disease facts and figures published by the Alzheimer’s Association in 2009. The trend continues to increase with figures expected to reach 13.5 million by 2050.

In Malta, data relies on EURODEM estimates between 2001 and 2005 which saw a rise of 16.5 percent in a period of 5 years from 3,495 to 4,072. Using this data, 2010 estimates were projected to be round 4,388 (1.12% of the total Maltese population) rising to 6,369 by 2050 (2% of the total population) (Abela et al., 2007).

The data presented is mostly centred on figures from the Western World, where evidence based data is becoming quickly outdated. The situation elsewhere, especially third world and developing countries, is more approximate. Studies from these regions were criticised for being of poor quality and for misapplying research designs, yet this data cannot be ignored as it is the only available. It is clear that proportionate increases in incidence over the near future will be in undeveloped countries (Table 1.5).
<table>
<thead>
<tr>
<th>Region</th>
<th>Increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>40</td>
</tr>
<tr>
<td>North America</td>
<td>63</td>
</tr>
<tr>
<td>Southern Latin America</td>
<td>77</td>
</tr>
<tr>
<td>Developed Asia Pacific countries</td>
<td>89</td>
</tr>
<tr>
<td>East Asia</td>
<td>117</td>
</tr>
<tr>
<td>South Asia</td>
<td>107</td>
</tr>
<tr>
<td>Rest of Latin America</td>
<td>146</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>125</td>
</tr>
</tbody>
</table>

Table 1.5. Proportionate increase over the next twenty years in the number of people with dementia (ADI World Report, 2009)

The rate of increase is exponential with the UK reporting 163,000 new cases every year; one new case every 3.2 minutes (Matthews et al., 2005). Even worse in the US, with a rate of a new case every 70 seconds. This is just for the regions which are expected to raise their prevalence by less than 70 percent over the next twenty years.

1.3.5. Costs

The monetary figures accompanying this disease are astronomical, surpassing those of stroke, heart and cancer diseases put together (Ferri et al., 2005; Abela et al., 2007). These costs, rather than the burden of the disease *per se*, are the strongest tool of lobbying when it comes to alluring governments in investing in more research, with the hope that a new discovery would avert the currently grim financial outlook for AD.
rather than the burden of the disease *per se*, are the strongest tool of lobbying when it comes to alluring governments in investing in more research, with the hope that a new discovery would avert the currently grim financial outlook for AD.

Dementia costs in relation to other chronic diseases are overwhelmingly high in all of Europe (Figure 1.4). In the UK, the results of an economic analysis commissioned by the Alzheimer’s Society indicated a total annual cost of £17 billion. The breakdown of this total cost is illustrated in Figure 1.5. The single largest cost driver is the cost of institutional care in care homes (contributing 41% of the total costs) (Figures 1.4 and 1.5).

![Figure 1.4.](image)

*Figure 1.4.* The comparative societal costs (in £ billions) of cancer, ischaemic heart disease, stroke and dementia in the UK. (The Alzheimer’s Society, 2007).
Figure 1.5. The breakdown of the total annual cost of dementia (£17 billion) in the UK (The Alzheimer’s Society, 2007).

Figure 1.6. Five yearly projections of cost rise for AD from 2010 till 2050 in the US alone (Alzheimer’s Association, 2010).
A model of the current trajectory in the US shows that in 2050, almost half of all AD patients will be in its severe, most dependent, more costly form. (Figure 1.7)

![Disease severity in 2050 using the current trajectory](Alzheimer's Association, 2010).

The total worldwide societal cost of dementia, based on a dementia population of 34.4 million individuals with dementia, was estimated to $422 billion in 2009, including $142 billion for informal care (34%). This means that the worldwide cost of dementia has increased by 34% (18% in fixed prices) between 2005 and 2009 (Wimo et al., 2010).

1.4. Modifiable risk factors of AD

There is an increasing body evidence which links AD with cardiovascular risk factors. An unhealthy diet rich in fats and cholesterol combined with a sedentary lifestyle with a high Body Mass Index (BMI) and smoking were shown to be strongly related to earlier onset of sporadic AD (ADI World Report, 2009). Adding hypertension and diabetes mellitus, altogether known as the metabolic syndrome, the risk is even higher.
1.4.1. Smoking

Smoking is the single most modifiable risk factor in any disease. In both short (Juan et al., 2004) and longer latency (Whitmer et al., 2005) incidence studies, smoking was shown to increase the risk for AD. In the Rotterdam study, this trend was not observed in individuals carrying the apolipoprotein E (ApoE)-4, as smokers with this gene were not found to show an increased risk compared to non-smokers. It was only current smoking at the time of study which was positively correlated with increased risk of AD vis-à-vis past smoking which was found not to be correlated. Furthermore, smoking was related with an increased risk of dementia of the Alzheimer’s type but surprisingly not with the vascular type (Ott et al., 2004; Reitz et al., 2007).

1.4.2. Alcohol consumption

Controversy has surrounded a direct correlation between alcohol consumption and AD risk. Chronic alcoholism has many complications of its own, leading to reduced life expectancy and mortality prior to reaching senility, causing a skew in the end results of subjects studied in this area. In addition, chronic alcohol abuse causes brain atrophy, leading to alcohol-related dementia which resembles AD in clinical manifestation. Both alcohol and AD substantially affect the cholinergic system, and thus it is possible that alcohol use could be linked to AD through their common effects on this system. Chronic alcohol use causes degeneration of cholinergic neurons (Arendt, 1993), decreases acetylcholine levels and reduces its synthesis and release, thus further aggravating reductions already present in AD. However unlike AD, improvement of cognitive function is possible in alcoholics after abstention from alcohol. This suggests that the cognitive deficits may reflect neurochemical alterations rather than neuronal loss (Kril and Halliday, 1999); a pathology which is altogether different from the irreversible nature of plaque and neurofibrillary tangles formation observed in AD. No study has to date given convincing causal evidence that alcohol abuse leads to AD and most of the studies were observational. Furthermore, a peer review of 44 studies published since 1990 showed that moderate alcohol consumption; defined as not more than 1 unit of alcohol per day for women and not more than 2 units of alcohol per day for men, decreased
the incidence of MCI and Alzheimer's dementia (Collins, 2008). Further evidence was obtained from one of the longest and largest studies looking at alcohol consumption in older people, whereby a 37% drop in incidence of dementia was associated with moderate alcohol intake. Yet the same moderate consumption accelerated cognitive decline in those with established MCI, suggesting that any level of alcohol is toxic once the disease process has began (Fauber, 2009).

1.4.3. Diet and obesity

With a focus onto the Western type of life-style, mostly sedentary with a diet containing high amounts of carbohydrate and fat, research was conducted to investigate the relationship between unhealthy diet, obesity and increased risk of developing AD.

It was proposed that a high-fat diet could promote the development of AD. In order to try to prove this, a team from Quebec have fed two sets of transgenic mice a diet different in fat content. The mice whose diet was poor in omega-3 fatty acids and rich in fat (60% of consumed calories) showed changes in three protein markers (β-amyloid, tau protein and drebrin) which are strongly associated with the development of AD (Julien et al., 2008).

Several epidemiological studies suggest that higher midlife serum total cholesterol levels are associated with an increased risk of AD. Using positron emission tomography (PET) scans, researchers concluded that higher midlife serum total cholesterol levels accelerate brain processes associated with normal aging (Reiman et al., 2010). The hypothesis is further strengthened in individuals who are genetically predisposed to high levels of low density lipoprotein (LDL) cholesterol due to an inherited LDL receptor dysfunction (heterozygous familial hypercholesterolaemia). Persons with familial hypercholesterolemia were found to have a high incidence of mild cognitive impairment compared to controls (Zambon et al., 2010).
This data is of great relevance considering the exponential increase in the incidence of obesity, associated with high triglyceridaemia and hypercholesterolaemia. Population based studies show that people who were obese in mid-life were 74% more likely to have dementia, while overweight people were 35% more likely to have dementia compared with those with normal weight (Whitmer, 2005). The last Health Behaviour in School-aged Children (HBSC) study carried out by the World Health Organisation (WHO) listed Malta as the country with the highest number of obese children at 15 years of age. If the trend is not reversed, this will lead to a high prevalence of mid-life cardiovascular risk factors like pre-hypertension, established hypertension, insulin resistance and diabetes which in turn are independent risk factors for the development of AD (Kivipelto et al., 2001).

A healthy lifestyle with a diet rich in unsaturated fatty acids, vitamins and antioxidants together with regular exercise do help in suppressing the onset of neurodegeneration. However, in considering the worldwide distribution of AD, it can easily be observed that AD is not a sole problem of Westernised countries and is not a disease limited to the obese. The disappointing results from preventive intervention trials to date indicate that, despite much research, little is known about the environmental and lifestyle factors linked to dementia and Alzheimer’s disease. It may be that the focus upon research in the developed West has limited possibilities to identify risk factors. In low and middle income countries dietary deficiencies, particularly of micronutrients, are widespread and strongly linked to poverty. Deficiencies of folate and vitamin B12 are of particular interest given their consequences: anaemia, raised homocysteine levels (Selhub et al., 1993), increased risk of stroke and ischaemic heart disease (Robinson et al., 1998). Vitamin B12 deficiency is very common (more than 40%) across Latin America (Allen, 2004; Garcia-Casal et al., 2005). The same studies also show that folate deficiency is endemic in those living in poverty, and following economic crisis. Micronutrient deficiency is probably even more common in older people but there is few data on this particular age group. Research on micronutrients and neuronutrition in developed countries has focused upon antioxidants and polyphenols (Luchsinger and Mayeux, 2004; Ramesh et al., 2010) with less attention towards deficiencies in vitamin B12 and folate. Available studies are small in size and provide inconsistent findings (Ravaglia et al., 2005).
1.4.4. Diabetes and insulin resistance

Several large epidemiological surveys reported an increased incidence of dementia among diabetes mellitus patients, apparently both of the Alzheimer's and Vascular type. Yet it is difficult to determine whether there is a direct causative effect of diabetes in cognitive impairment. Patients studied do generally have other co-morbidities, including hypertension and dyslipidaemia, altogether forming part of the metabolic syndrome. Since a number of these factors have been identified as independent predictors of cerebrovascular disease, ischaemic stroke and accelerated dementia, it may be difficult to determine which factor is the prime culprit in the development of cognitive dysfunction (Biessels and Kappelle, 2005).

There are two main types of diabetes; insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). Mild to moderate impairments of cognitive functioning has been reported in both IDDM (Brands et al., 2005) and NIDDM (Awad et al., 2004) but clinically relevant deficits mainly occurred in elderly patients with NIDDM (Biessels and Kappelle, 2005). Even though hyperglycaemia is reported to be toxic to neurons (Gispen and Biessels, 2000) causing oxidative stress and a pro-inflammatory state, on its own it is not enough to explain why only NIDDM gives significant deficits in cognitive function. An increasing amount of evidence links insulin itself to cognitive decline and dementia in NIDDM (De la Monte, 2005). Firstly, alterations in cerebral insulin receptor signaling may be involved, as already shown in mouse models, with a particular focus on the glycogen synthase-kinase-3 (GSK3). Secondly, insulin may affect the metabolism of β-amyloid and tau, two proteins that represent the building blocks of amyloid plaques and neurofibrillary tangles, the neuropathological hallmarks of Alzheimer's disease (Jolivalt et al., 2009).

The two main insulin actions in the brain are control of food intake and an effect on cognitive functions (Laron, 2009). This is achieved via a ‘neuromodulator’ action, influencing the release and reuptake of neurotransmitters (Zhao et al., 2004). Brain insulin decreases with aging and disturbances in the remaining cerebral insulin signalling pathways may be involved in AD. Furthermore, postmortem analyses of brains from patients with AD revealed a
markedly downregulated expression of insulin receptor and this progresses with severity of neurodegeneration (Freude et al., 2009).

Restoring normal insulin activity may exert a beneficial effect on neurodegenerative processes. Rosiglitazone, a peroxisome proliferator-activated receptor-gamma (PPARγ) agonists used as an insulin sensitizing agents in NIDDM patients, was found to facilitate memory in patients with AD via modulation of neuronal cell survival, inflammatory responses, mitochondrial functioning, and possibly beta-amyloid processing and deposition (Lin et al., 2005). An alternative way of supplementing insulin directly to the brain is via the intranasal route. Studies to date suggest that this procedure can facilitate memory and modulate plasma beta-amyloid levels in memory-impaired adults. Interestingly, the adverse effects of insulin abnormalities and the beneficial effects of improving insulin sensitivity may differ by ApoE genotype (Stennis Watson and Craft, 2008).

1.4.5. Hypertension

A microangiopathic remodelling model was proposed as a link between hypertension and AD. The Systolic Hypertension in Europe (SYST-EUR) trial, a double-blind randomised control trial assessing the effects of hypertension onto cardiovascular events, showed a clear reduction of about 50% in incidence of dementia in the treatment group, suggesting that adequate hypertensive control may prevent development of AD, vascular dementia and mixed dementias (Fagard, 2003).

Further evidence to support this is seen radiologically. A report at the 93rd Scientific Assembly of the Radiology Society of North America (RSNA) concluded that hypertensive patients with AD have lower cerebral blood flow than AD patients without hypertension. Hypertensive patients evaluated had decreased blood flow in the hippocampus, one of the earliest structures affected by AD. Furthermore, hypertensive patients categorised as having MCI showed more blood flow than AD hypertensives yet lower blood flows when compared to hypertensives alone suggesting a continuum of pathology with a more prolonged state of hypertension accompanying closely the progression from MCI to AD. Subjects with systolic blood pressure
greater than 160 mmHg or arterial fibrillation progressed through the stages of AD quicker. After excluding vascular dementia, the relationship between hypertension and AD seems thus to be two fold: increase in incidence and worsening of prevalence and severity (Mielke et al., 2007).

The hypothesis that primary prevention of hypertension should lead to secondary prevention of AD is a plausible one. Valsartan, a leading angiotensin-receptor blocking agent, was shown to lower brain β-amyloid protein levels and improved spatial learning in a mouse model of AD (Wang et al., 2007). This preclinical study suggested that certain antihypertensive drugs may have AD-modifying activity and may protect against progressive β-amyloid related memory deficits in subjects with AD or in those at high risk of developing the disease. Similar results were observed also with other antihypertensives like propranolol and carvedilol (Wang et al., 2007).

The objective of a 2006 Cochrane systematic review was to assess specifically the effects of blood pressure lowering treatments for the prevention of dementia and cognitive decline in patients with hypertension but no history of cerebrovascular disease. It was concluded that there was no convincing evidence from the trials identified to accept the hypothesis of a positive effect as true. This conclusion however did point out that there was bias created from a large number of patients who were lost to follow-up and a good number of placebo patients who were given active treatment. An update of the same review in 2009 arrived to the same conclusion (McGuinness et al., 2009).

1.5. Genetics of AD

AD is classified as early-onset and late-onset (ADEAR, 2008). The degree of genetic contribution to the development of the disease is different in the two types. Late-onset AD,
also referred to as sporadic AD, is assumed to be multifactorial, whereas the early-onset form appears to be closely linked to genetic causes (Bird, 2008)

1.5.1. Early-onset AD

Early-onset AD is a rare form of AD, affecting less than 1 percent of all people with the disease (Ertekin-Taner, 2010) and which develops in individuals aged 30 to 60. Some cases of early-onset AD, called familial AD (FAD), are inherited. FAD is caused by a number of different gene mutations on chromosomes 1, 14, and 21, and each of these mutations causes abnormal proteins to be formed (Table 1.6).

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene Defect</th>
<th>β-amyloid Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Amyloid Precursor Protein (APP) mutations</td>
<td>Increases production of total β-amyloid peptides</td>
</tr>
<tr>
<td>14</td>
<td>Presenilin 1 mutations</td>
<td>Increases production of β-amyloid peptides</td>
</tr>
<tr>
<td>1</td>
<td>Presenilin 2 mutations</td>
<td>Increases production of β-amyloid peptides</td>
</tr>
</tbody>
</table>

Table 1.6. Types of genetic alterations found in FAD (Ertekin-Taner, 2010).

All mutations affect β-amyloid physiology in the brain leading to a build up of this protein. This can occur through enhanced production, increased aggregation, and/or decreased clearance of β-amyloid peptides. The gradual cerebral build up of β-amyloid, first in soluble and then in particulate forms, activates local inflammation-like tissue responses. These alterations, along with direct β-amyloid neurotoxicity, result in synaptic loss and multiple neurotransmitter deficits culminating in cell death and underlying clinical dementia (Ertekin-Taner, 2010).
Even if only one of these mutated genes is inherited from a parent, the person will almost always develop early-onset AD. This inheritance pattern is referred to as "autosomal dominant" inheritance meaning that an offspring in the same generation has a 50 percent chance of developing FAD if one of the parents has the mutated gene which results in an increase in the synthesis of β-amyloid, a major component of AD plaques. These early-onset findings were critical because they showed that genetics were involved in AD, and they helped identify key players in the AD cellular metabolism. These studies also helped explain some of the variation in the age at which AD develops (ADEAR, 2008).

### 1.5.2. Late-onset AD

Most cases of Alzheimer’s disease are of the late-onset form, developing after the age of 60 years. Scientists studying the genetics of AD have found that the mutations seen in early-onset AD are not involved in this form of the disease.

Although a specific gene has not been identified as the cause of late-onset AD, one predisposing genetic risk factor that appears to contribute to the development of the disease is related to the allele combination for the apolipoprotein E (ApoE) gene found on chromosome 19. ApoE contains the instructions needed to make a protein that helps carry cholesterol in the bloodstream. ApoE comes in several different forms, or alleles. ApoE ε2, ApoE ε3 and ApoE ε4 are the three alleles which occur most frequently (ADEAR, 2008).

ApoE ε2 is relatively rare and may provide some protection against the disease. An ε2/ε2 genotype provides the highest protective effect and a person with this allele combination will develop AD later in life than it would in someone with the ApoE ε4 gene. It is also considered that having an ε2 allele can to a certain extent buffer the presence of an ε4 allele. Thus an ε2/ε4 is better than a ε3/ ε4 genotype (Chan and Shea, 2010).

ApoE ε3 is the most common allele. Researchers have till recently thought that it plays a neutral role in AD; neither decreasing nor increasing risk (ADEAR, 2008). However new theories are emerging regarding the presence of this allele and its relation to AD risk. The
observation that the e3 allele is approximately half as effective compared to e2 at buffering the impact of a single e4 allele and the trend of a linear increase in risk of AD for the genotypes e2/e2, e2/e3 and e3/e3 have lead scientists to categorise e3 as a genetic risk factor of AD especially in the presence of another environmental risk like nutritional imbalance (Chan and Shea, 2010).

ApoE e4 occurs in about 40 percent of all people who develop late-onset AD and is present in about 25 to 30 percent of the population. People with AD are more likely to have an ApoE e4 allele than people who do not develop AD. Many studies have confirmed that the ApoE e4 allele increases the risk of developing AD (Rippon et al., 2006; Zintl et al., 2009). The risk increases further with the number of ApoE e4 alleles (Martins et al., 2005); calculated at 1.7 for heterozygotes and 2.3 for homozygotes (Zintl et al., 2009). There is also a strong hypothesis that the presence of ApoE e4 exerts its maximal effect before the age of 70 years (Luciano et al., 2009). These studies have helped explain some of the variation in the age at which AD develops, as people who inherit one or two ApoE e4 alleles tend to develop AD at an earlier age than those who do not have any.

However, many people with AD do not have an ApoE e4 allele and inheriting an ApoE e4 allele does not necessarily signify that a person will definitely develop AD. Some people with one or two ApoE e4 alleles never get the disease, and others who develop AD do not have any ApoE e4 alleles. The role of ApoE e4 in the pathogenesis of AD is yet to be clarified. Prevailing evidence suggests that the differential effects of ApoE isoforms on β-amyloid aggregation and clearance play the major role in AD pathogenesis. Other potential mechanisms, such as the differential modulation of neurotoxicity and tau phosphorylation by ApoE isoforms as well as its role in synaptic plasticity and neuroinflammation, have not been ruled out (Kim et al., 2009).

The genetic risk for late-onset AD is apparently dependent on a number of genes, each contributing in a small way to the development of the disease. Identifying genes that are associated with a smaller dementia risk could aid in developing AD risk profiles that include
genetics and other potential risk factors. Yet to date, inconsistent replication of original association findings has been the rule rather than the exception in AD. With an exception for APOE, even candidate genes with convincing functional data and thorough genetic assessment with positive association results in the initial study have been difficult to replicate. Initial false-positive results, false negative follow-up results, heterogeneity in phenotype and genotype, or environment, genotyping errors, and initial small sample size are all potential reasons for failure of replication (Luciano, 2009).

Further research can eventually lead to the ability of combining baseline genetic tendencies, possible biomarkers, and perhaps even a cognitive profile to determine an individual's risk of developing AD, and help effectively allocate disease-modifying therapies. Discoveries in the sequence and structure of the human genome, technical advances in high-throughput genotyping, and development of novel analytical approaches led to an unlimited extent of genetic studies in common, complex diseases such as late-onset AD (Khoury et al., 2009; Manolio et al., 2009).

1.6. Pathophysiology – the amyloid hypothesis

The neurodegenerative process in AD is characterised by the progressive and irreversible deafferentiation of the limbic system, association neocortex, and basal forebrain, accompanied by the formation of neuritic amyloid plaques, amyloid angiopathy, neurofibrillary tangles, and neurophil threads (Crews et al., 2010). This neurodegenerative process is followed by reactive astrogliosis and microglial cell proliferation. Axonal and synaptic damage secondary to the above processes leads to neurodegeneration and subsequent clinical cognitive impairment. The unique patterns of cognitive impairment that characterize AD, in turn, depend on the neural circuitry specifically affected, the extent of the synapto-dendritic damage and the speed with which the injury propagates.
1.6.1. Neuritic amyloid plaques

Plaques are mainly composed of small peptides called β-amyloid (Aβ), 42 amino acids in length. It is a proteolytic product of a larger protein called amyloid precursor protein (APP), a transmembrane protein, which is acted upon by secretase enzymes to release Aβ oligomers. APP is critical to neuron growth, survival and post-injury repair (Priller et al., 2006) and depending on the secretase enzyme that is upregulated, the balance for or against neuron survival is affected. Beta (β) and gamma (γ) secretase enzymes cleave amyloid precursor protein (APP) to release toxic 40 and 42 toxic Aβ oligomers which will proceed to form part of the Aβ plague. On the other hand, alpha (α) secretase enzymes cleave within the fragments that give rise to the toxic Aβ oligomers. The product, soluble amyloid precursor protein alpha (sAPPα) is released extracellularly and was shown to have neurotrophic effects that counteract apoptotic signaling and promote synapse formation (Tian et al., 2010). Thus the balance between these two pathways highly affects amyloidogenesis (Figures 1.8 and 1.9).

![Diagram of Aβ plaque formation](image)

**Figure 1.8.** Formation of Aβ toxic oligomers from APP cleavage by beta (β) and gamma (γ) secretases (APP: Amyloid Precursor Protein; sAPPβ: soluble beta Amyloid Precursor Protein; Aβ: beta-amyloid; ApoE: Apolipoprotein E; PS1: Presenilin-1) (Crews et al., 2010).
In AD, Aβ accumulates in the neuronal endoplasmic reticulum (ER) and extracellularly (Cuello, 2005; Trojanowski and Lee, 2000). Recent studies suggest that nerve damage might result from the conversion of normally non-toxic monomers to toxic oligomers (Walsh and Selkoe, 2004), whereas larger polymers and fibers that often constitute the plaques might not be as toxic (Walsh et al., 2002). Neprilysin, a Aβ degrading enzyme, can hydrolyse monomeric and oligomeric forms of Aβ, however abnormal forms that result from the Flemish, Dutch, Italian and Arctic mutations in the APP gene are not cleaved leading to toxic accumulation (Tsubuki et al., 2003). Oxidative stress, signaling alterations, mitochondrial dysfunction, lysosomal pathology and cholesterol metabolism then act onto these oligomers to create neurosynaptic damage (Revesz et al., 2009) (Figure 1.10).
Figure 1.10. Schematic diagram showing (i) accumulation of toxic Aβ oligomers from dimerasation and tetramisation of Aβ monomers and (ii) how several pathological mechanisms act on these oligomers to lead to neurogenetic and synaptic damage and ultimately cognitive dysfunction (Crews et al., 2010).

Studies performed using transgenic murine models for AD showed that the locus of mutations in the APP gene also does affect the type of pathogenesis created. While mutations in the N-
terminal flanking regions of Aβ are characterized by increased Aβ production with plaque formation, mutations in the mid-segment of Aβ result in increased formation of oligomers, and mutations toward the C-terminus segment results in amyloid angiopathy (Crews et al., 2010). It does follow that specifically targeting these toxic oligomeric species of Aβ; for example with β and γ secretase inhibitors, immunization, and neurogenesis-stimulating therapies may provide individual or combination treatments that ameliorate multiple features of AD pathology.

1.6.2. Neurofibrillary tangles (NFT) and neuropil threads

In addition to extracellular accumulation of the Aβ peptide in senile plaques, the pathogenesis of AD is also marked by the intracellular accumulation of the abnormally hyperphosphorylated tau forming neurofibrillary tangles in the brain (Ertekin-Taner, 2010). This makes of AD both a proteopathy and a tauopathy (Hernández and Avila, 2007). The tau gene is located on chromosome 17 which encodes for the microtubule-associated protein tau whose primary function is to promote the assembly and stabilization of microtubules (Gabelle et al., 2010). When hyperphosphorylated tau accumulates in neurons it forms neurofibrillary tangles while its accumulation inside neuronal processes leads to the formation of neuropil threads. Recent studies suggested that failure of elimination of tau from the extracellular spaces of the brain may play a role in the intracellular accumulation of tau (Clavaguera et al., 2009). In AD, tau inclusions first appear in neurons in the transentorhinal cortex and then spread to the hippocampal formation and neocortex. NFT’s are found in cognitively intact elderly persons and are encountered in viable neurons until the late stages of the disease (Gabelle et al., 2010). Cognitive impairment ensues as tau inclusions reach the hippocampus, and neocortical tau inclusions are a hallmark of the later and more severe stages of AD (Braak et al., 2006).
1.6.3. Reactive astrogliosis

Astrocytes are the most abundant cells in the brain, forming the microarchitecture of the brain through neuronal-glial-vascular units, regulating the blood–brain barrier, controlling the microenvironment of the central nervous system and defending the nervous system against multitude of insults (Pekny and Nilsson, 2005). However there is a pathological potential of astroglia in various forms of dementias and some studies hypothesise that both atrophy of astroglia and reactive hypertrophic astrogliosis may develop in parallel during neurodegenerative processes resulting in dementia (Pekny et al., 2007). Thus the reaction of astrocytes to the AD progression is spatially distinct: astroglial cells surrounding the plaques undergo gliosis, whereas astrocytes distant from the amyloid deposits develop atrophy. Thus astroglial atrophy may account for early changes in synaptic plasticity and cognitive impairments, which develop before gross neurodegenerative alterations (Rodriguez, 2009).

1.6.4. Inflammation and AD

The inflammation hypothesis in relation to AD pathology has emerged relatively recently even though evidence for the involvement of inflammatory processes in the pathogenesis of AD has been documented for a long time (Zotova et al., 2010).

Neuroinflammation is still considered to be a downstream consequence in the amyloid hypothesis, with Aβ within the CNS bringing about activation of microglia, initiating a pro-inflammatory cascade that results in the release of potentially neurotoxic substances, including cytokines, chemokines, reactive oxygen and nitrogen species, and various proteolytic enzymes, leading to degenerative changes in neurons (Eikelenboom et al., 2006; Griffin, 2006). The inflammation hypothesis is also supported by epidemiological retrospective observations that patients with rheumatoid disease who are on long-term anti-inflammatory therapy have a lower prevalence of AD (Breitner et al., 1994). Furthermore, transgenic animal studies and human trials have demonstrated that treatment with nitric oxide releasing non-
steroidal anti-inflammatory drugs (NSAIDs) can reduce and/or prevent the AD pathology (McGeer and McGeer, 2007). It has also been shown that a certain drug with anti-inflammatory properties suppresses amyloid pathology and improves memory performance in transgenic mice (Bacher et al., 2008). Although these effects did not reach significant levels in large human cohorts, interest in the inflammatory processes of AD pathology has persisted. One particularly interesting aspect of these studies was that (at least in animal models) the observed beneficial action of anti-inflammatory drugs was not necessarily attributed to down-regulation of inflammatory processes. Instead, activation of microglia via a route that enhances its phagocytic activity against Aβ was suggested (Zotova et al., 2010).

1.7. Diagnosis of dementia and AD

1.7.1. Differential diagnosis and work-up

According to the fourth edition of the Diagnostic and Statistical manual of Mental disorders (DSM-IV), dementia is a disorder characterized by disturbances of

- memory
- at least one additional cognitive function (e.g., language, praxis, gnosis, or executive function) (APA, 2004).

Dementias are distinguished from pure amnestic disorders by the presence of these additional impairments. The cognitive deficits present in dementia must represent a significant decline from premorbid functioning and must result in significant declines in activities of daily living (ADLs). Furthermore, the deficits must occur in the absence of delirium. Subtypes of dementia are differentiated by additional features, including course of illness, characteristic symptoms, and presumed etiology (Twamley and Bondi, 2006).
Various dementias are associated with a wide range of neuropathological features, and it is generally acknowledged that patients with different types of dementias present with varied cognitive, behavioral, and affective disturbances. Furthermore, most differential diagnosis of demented patients do not consistently exhibit global cognitive impairments, but instead possess areas of relative cognitive preservation (Twamley and Bondi, 2006). Patterns of cognitive strengths and weaknesses, along with affective and behavioral features, are important considerations in the differential diagnosis of dementia.

One of the main distinctions drawn in the classification of dementing disorders has been captured by the categories of "cortical" and "subcortical" dementia.

Subcortical dementias such as those due to Huntington's disease or Parkinson's disease are characterized by:

(1) moderate memory retrieval deficits (i.e. recognition better than free recall abilities);
(2) slowed cognitive processing;
(3) impairment in attention and working memory;
(4) problem solving or executive deficits;
(5) personality or mood changes.

Deficits in motor functions may also be present.

Cortical dementias, including AD, are characterized by:

(1) prominent memory dysfunction, with poor recognition and recall, or rapid forgetting;
(2) aphasic/dysphasic, apraxic, and/or and agnostic disturbances;
(3) the relative absence of sensory and motor deficits

(Hubert et al., 1986; Cummings and Victoroff, 1990).
However this type of dichotomy, which emerged in the mid-1970's and was for long time considered useful in the clinical setting, has been put under severe criticism by the increasing advance in neuroimaging, neurophysiology and neuroanatomy (Turner, 2002). Distinctive and reliable biomarkers of AD are now available through structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analyses to the extent that re-evaluation of the defining criteria is being called for (Dubois et al., 2007). The differential diagnosis of dementia is vast but since dementia syndromes have distinctive natural histories, precise diagnosis leads to a better prognosis. The main aetiologies of dementia are presented in Table 1.6.
<table>
<thead>
<tr>
<th>Type</th>
<th>Common</th>
<th>Unusual</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative/inherited</td>
<td>Alzheimer’s disease</td>
<td>Dementia with Lewy Bodies, Frontotemporal dementia, Parkinson’s disease, Huntington’s disease. Others (e.g. cortico-basal degeneration, progressive supranuclear palsy, argyrophilic grain disease)</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>Diffuse small-vessel disease</td>
<td>Amyloid angiopathy, Multiple emboli, Diffuse hypoxic/ischemic injury</td>
<td>Cerebral vasculitis</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Metastatic Disease</td>
<td>Primary Central Nervous System (CNS) tumor</td>
<td>Paraneoplastic syndrome (limbic encephalitis)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Chronic subdural hematoma</td>
<td>Post-head injury (diffuse axonal injury)</td>
<td>Dementia pugilistica</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td></td>
<td>Communicating / non-communicating ‘Normal Pressure’ hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Toxic/nutritional</td>
<td>Alcohol, Medications</td>
<td>Thiamine deficiency (Wernicke-Korsakoff), B12 deficiency, Niacin deficiency (Pellagra), Vitamin E deficiency</td>
<td>Anoxia / carbon monoxide poisoning, Heavy metal poisoning (Lead, arsenic)</td>
</tr>
<tr>
<td>Metabolic/Endocrine</td>
<td>Uremia/dialysis dementia, Chronic hepatic encephalopathy</td>
<td>Hypo/hyperthyroid, Cushings/ Addison’s, Hyperparathyroid</td>
<td>Post-encephalitic</td>
</tr>
<tr>
<td>Infectious/Inflammatory</td>
<td></td>
<td>Herpes Simplex Virus, Lyme, Human Immunodeficiency Virus, Tuberculosis/Fungal meningitis</td>
<td>Syphilis CNS, Whipple’s Behcet’s, Lupus Neurosarcoid</td>
</tr>
<tr>
<td>Demyelinating</td>
<td>Multiple Sclerosis</td>
<td></td>
<td>Leukodystrophy</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Depression</td>
<td></td>
<td>Decompression sickness</td>
</tr>
<tr>
<td>Secondary Medical</td>
<td></td>
<td>Sleep apnea, Chronic hypercapnea/hypoxaemia, Chronic sleep deprivation</td>
<td>Gerstmann-Sträussler-Scheinker disease</td>
</tr>
<tr>
<td>Prion diseases</td>
<td>Creutzfeldt-Jakob disease (CJD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epileptic</td>
<td>Medically</td>
<td></td>
<td>Complex partial status</td>
</tr>
<tr>
<td></td>
<td>refractory</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.6. Aetiologies of dementia in adults by mechanism and relative prevalence (adapted from Moo, 2009).
AD is the most common pathologic cause of dementia in elderly persons. AD with no other associated pathology accounting for up to 60% of most unbiased autopsy samples and up to 80% if it occurs in conjunction with other pathologic lesions (Knopman et al., 2003).

Although autopsy is still considered the gold standard for diagnosis, experience over the past 20 years has shown that the clinical diagnosis of AD is accurate. With the current diagnostic criteria, AD diagnosis is based solely upon clinical symptoms (Mattsson and Zetterberg, 2009). Pervasive forgetfulness is the most common manifestation of typical AD and can go undetected for years. Repeating questions and statements is probably the most common initial observation of family members. Forgetting to pay bills, taking medications incorrectly, and having problems with time orientation are other common observations in early AD. Some patients may experience notable geographic disorientation, word-finding and name finding difficulties, and lapses in judgment and problem solving abilities, in addition to the excessive forgetfulness.

Because of concerns about the specificity of behavioral and personality changes for AD, they are not included in the core definition of AD. Nonetheless, the behavioral symptoms of AD are common and clinically relevant (Mega et al., 1996). Personality changes may antedate the more obvious memory changes but may be evident only in retrospect. Apathy, loss of interest in previous pastimes and activities, and loss of initiative are all part of the insidious changes in a person who is developing AD. Insight is usually lost early in the process (Tabert et al., 2002). However, insight is not invariably absent, and preserved insight should not be considered against a diagnosis of AD. Some patients with AD can have prominent depression either spontaneously or as a result of their sense of declining functions. Patients with AD vary considerably in the extent of language deficits and visuospatial deficits. Sometimes, anomia or visual agnosia can be nearly as prominent as the anterograde amnesia in AD (Knopman et al., 2003).
<table>
<thead>
<tr>
<th>Test</th>
<th>Intended diagnosis</th>
<th>Use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychometric</td>
<td>All dementias, especially MCI, FTD</td>
<td>In appropriate clinical context</td>
<td>Virtually required for MCI, mild AD, FTD; may be essential if medicolegal complications are possible</td>
</tr>
<tr>
<td>CBC, electrolytes, calcium, creatinine, glucose</td>
<td>Common metabolic disorders</td>
<td>Routinely</td>
<td>Not intended to be dementia-specific, but part of routine screening for any elderly person</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Vitamin B12 deficiency</td>
<td>Routinely</td>
<td>Common disorder in elderly persons; may be associated with cognitive impairment</td>
</tr>
<tr>
<td>Thyroid function test</td>
<td>Hypothyroidism</td>
<td>Routinely</td>
<td>Common disorder in elderly persons; may be associated with cognitive impairment</td>
</tr>
<tr>
<td>MRI or CT</td>
<td>Brain structural lesions; CJD</td>
<td>Routinely</td>
<td>Needed only at initial diagnosis or after a rapid clinical change; perfusion MRI for CJD</td>
</tr>
<tr>
<td>PET or SPECT</td>
<td>AD, FTD</td>
<td>For added diagnostic certainty in selected instances</td>
<td>Marginal additive value over clinical diagnosis for AD, perhaps more helpful in FTD</td>
</tr>
<tr>
<td>EEG</td>
<td>CJD</td>
<td>When CJD is suspected</td>
<td>Not useful routinely, but required as part of diagnosis of CJD</td>
</tr>
<tr>
<td>Routine CSF examination</td>
<td>Meningitis, encephalitis, meningeal cancer, other infections</td>
<td>In rapidly progressive dementias</td>
<td>None</td>
</tr>
<tr>
<td>CSF examination for 14-3-3 protein or neuron-specific Enolase</td>
<td>CJD</td>
<td>When CJD is suspected</td>
<td>Highly sensitive and specific, if acute infections, stroke, and neoplastic diseases are excluded by other means</td>
</tr>
<tr>
<td>CSF examination for β-amyloid and tau</td>
<td>AD</td>
<td>Rarely</td>
<td>Marginal additive value over clinical diagnoses</td>
</tr>
<tr>
<td>ApoE genotyping</td>
<td>AD</td>
<td>Rarely</td>
<td>Marginal additive value over clinical diagnoses</td>
</tr>
</tbody>
</table>

Table 1.7 Laboratory Diagnostic Evaluation of Dementia in the Elderly Population (CBC: complete blood cell count; CJD: Creutzfeldt-Jakob disease; CSF: cerebrospinal fluid; CT: computed tomography; EEG: electroencephalography; FTD: frontotemporal dementia; MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: single-photon emission CT) (adapted from Knopman et al., 2003).
Several biomarkers for AD have been tested, but none have reached the threshold of accuracy and utility to be recommended for routine use. The critical issue is whether a diagnostic test provides genuine additive value to diagnostic accuracy beyond what is provided by the clinical diagnosis. Computed tomography (CT) and Magnetic resonance imaging (MRI) are required for diagnostic purposes to eliminate brain structural lesions, but only MRI is being considered for diagnosing AD specifically. MRI for detecting hippocampal atrophy differentiates patients with AD from healthy patients. The sensitivity of hippocampal atrophy for diagnosing AD has been in the 80% to 90% range, but the specificity is generally lower (Frisoni et al., 2010). Single-photon emission computed tomography (SPECT) also can differentiate patients with AD from healthy patients or patients with other dementias. However, available studies show that SPECT is not much better than the clinical diagnosis alone (Jagust et al., 2001). In the future, amyloid imaging using SPECT is likely to supplement clinical evaluation in selecting patients for anti-amyloid therapies, while MRI and other modalities of PET may be more appropriate markers of clinical progression (Rabinovici and Jagust, 2009).

Biochemical biomarkers are increasingly becoming more prominent as the effort to diagnose AD at its earliest stage. CSF biomarkers are reported to be able to identify AD with high precision, with optimal diagnostic accuracy being achieved when different biomarkers are used in combination. In a recent study, a combination of Aβ42, T-tau and P-tau CSF biomarkers managed to correctly identify 83% of MCI patients with incepient AD and 72% of patients without AD (Mattson et al., 2009). A key challenge for the broad usage of CSF biomarkers is the general implementation of CSF analyses in dementia investigation. Their current usage is varied, being less common in the USA to being used routinely in specialised centres in Europe. Resistance might be due to both physicians and patient fear from an effectively invasive procedure compared to less invasive ones like MRI (Mattson and Zetterberg, 2009). Despite the additional value of blood biomarkers published reports to date on CSF and blood biomarkers in AD indicate that although biomarkers in body fluids may be utilized in the clinical diagnosis of AD, there are no specific markers that permit accurate and reliable diagnosis of early-stage AD or the monitoring of disease progression (Thambisetty and Lovestone, 2010; Zheng et al., 2010).
1.7.2. Psychometric tests

The clinical evaluation of a medical professional is yet so far the highest predictor of AD diagnosis. After a thorough history taking and clinical examination, psychometric tests are the next step in the patient's cognitive evaluation. The number of neuropsychological tests available for the clinician to use in assessing dementia is truly immense. Screening measures, such as the Mini-Mental State Examination (MMSE) and the Dementia Rating Scale are helpful as global cognitive screening instruments and can be used to track progression of dementia (Folstein et al., 1975; Mattis, 1988). Yet these measures need to be supplemented with other neuropsychological tests for the purpose of differential diagnosis of dementia.

The MMSE is arguably the best-known cognitive screen in the world (Nieuwenhuis, 2010). It is the test preferred locally by both family physicians and specialists. Originally designed to assess cognitive impairment in elderly populations, it has become one of the first steps toward a dementia diagnosis. Routinely used in the clinic and in research internationally, the MMSE, despite its flaws, has managed to retain its popularity for more than 30 years. The advantages of the MMSE include that it is well known, easy to administer in about five to ten minutes, that it samples a number of cognitive functions, and has test-retest and inter-rater reliability. A limitation is that it varies with the patient's age and education (Dimech et al., 2009). Also, only three words are to be remembered on the recall test, making the MMSE insensitive for patients with mild but clinically relevant memory problems. Another limitation is that the interval between registration and recall is not standard. Instead, it is dependent upon the time it takes for the patient to perform the attention and calculation section. Thus, patients who take a long time to complete the attention and calculation section will end up with a more difficult memory test compared with those who complete the attention and calculation section more quickly (Budson and Price, 2005).

Although the MMSE is widely used, a recent study in the UK about screening in the primary care setting identified the General Practitioner Assessment of Cognition (GPCOG), the Memory Impairment Screen (MIS), and the Mini-Cognitive Assessment Instrument (Mini-Cog) as brief, easy to administer, clinically acceptable, effective, and minimally affected by
education, gender, and ethnicity when compared to the MMSE. They were considered to be overall robust and more appropriate for routine use in primary care (Milne et al., 2008).

1.7.3. The future

Draft reports from Alzheimer's Association International Conference on Alzheimer's Disease (ICAD) 2010 have been proposed as the basis for new diagnostic criteria for MCI and AD, the first update of the current criteria in 25 years, as well as outline a new category of preclinical AD (Jeffrey, 2010).

1.8. Treatment and management of AD

There is currently no cure for AD (Alzheimer Disease International, 2009). It is a progressive disease and patients will continue to decline in function whether they are treated or not. Neuronal loss starts much earlier than the appearance of the first symptoms and this is irreversible. Current treatment is symptomatic and aimed at preserving and facilitating remaining synaptic function allowing a constant cognitive function for a longer period of time. When therapy is discontinued, it can be expected that decline will occur at the same rate as untreated dementia, as the rate of neuronal death is not affected (Downey, 2008).

1.8.1. Pharmacological management

The main aim of the pharmacological treatment currently available is the preservation of the patients' quality of life (NICE, 2006). This is reflected in terms of:

- improvement and/or the preservation of cognitive function
- delay in development of behavioural deterioration and their control once they develop
- delay in loss of performance at activities of daily living (ADL)
- delay in institutionalisation
• reduced burden upon caregivers
(Geldmacher, 2003; Fisher Center for Alzheimer's Research Foundation, 2010).

There are two main classes of drugs that have been approved for achievement of the above aims; acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists.

1.8.1.1. Acetylcholinesterase inhibitors (AChEIs)

The biochemical rationale for treating AD with AChEIs lies on the 'cholinergic hypothesis' and the Acetylcholine (ACh) mediated pathways. If loss of ACh is the primary neurotransmitter defect, then increasing production, inhibiting destruction or activating its receptors all should translate into effective therapy and thus slowing in functional decline. ACh is broken down in the synaptic junction by acetylcholinesterase and butyrylcholinesterase. By inhibiting these enzymes, breakdown of ACh will be slowed down, allowing higher concentration of this neurotransmitter to be achieved within the synaptic cleft for longer periods of time (Delagarza, 2003). During the years, it has been realised that cholinergic dysfunction is secondary to Aβ and tau accumulation leading to the 'amyloid hypothesis'. It was therefore suggested that AChEIs provide additional protection against oxidative stress and Aβ toxicity (Seltzer, 2010). If so, they might potentially modify the course of AD (Melo et al., 2009) in addition to improving clinical symptoms. This however needs yet to be solidly proven.

In clinical trials for the AChEIs, the cognitive portion of the Alzheimer Disease Assessment Scale (ADAS-Cog) was used to assess cognitive function. The results of 13 randomized, double blind, placebo controlled trials demonstrate that treatment for periods of 6 months and one year, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease produced improvements in cognitive function (Birks, 2006). Cochrane reviews concluded that the three cholinesterase inhibitors available are efficacious for mild to moderate Alzheimer's disease. It is not possible to identify those who will respond to treatment prior to actual treatment. There is no evidence that treatment with a AChEI is not cost effective. Despite the slight variations in the mode of
action of the three cholinesterase inhibitors, there is no evidence of any differences between them with respect to efficacy (Birks, 2006). There appears to be less adverse effects associated with donepezil compared with rivastigmine. It may be that galantamine and rivastigmine match donepezil in tolerability if a careful and gradual titration routine over more than three months is used. Titration with donepezil is more straightforward and the lower dose may be worth consideration (Birks, 2006). The use of AChEIs in MCI was not associated with any delay in the onset of AD or dementia and the risk benefit ratio for these drugs was high (Raschetti et al., 2007).

The rate of nonadherence to prescribed AChEIs treatment regimens in elderly patients is high. This appears to occur for a variety of reasons, such as forgetfulness, interference with daily life, lack of understanding of instructions, or complex dosing regimens (Ryan, 1999). Two main reasons in particular for patients with AD discontinuing treatment are a perceived lack of clinical benefit and the occurrence of adverse events (Small and Dubois, 2007). Adverse effects of these drugs are related to their cholinergic properties including nausea, gastrointestinal upset, diarrhoea, weight loss, bradycardia, syncope, and insomnia. Some patients complain of vivid dreams or nightmares; these symptoms improve with a decrease in dose (Downey, 2008). There are three approved AChEIs on the market. A summary of their pharmacological properties is provided in (Table 1.8).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacologic actions</th>
<th>Dosage dosage</th>
<th>Target dosage*</th>
<th>Minimum therapeutic dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Acetylcholinesterase Inhibitor</td>
<td>Start at 5 mg once daily, taken at bedtime; after 6 weeks, increase to 10 mg once daily.</td>
<td>10 mg once daily</td>
<td>5 mg daily</td>
</tr>
<tr>
<td></td>
<td>Butyrylcholinesterase inhibitor (BuChE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Acetylcholinesterase inhibitor</td>
<td>Start at 1.5 mg twice daily taken with food; at 2-week intervals, increase each dose by 1.5 mg, up to a dosage of 6 mg twice daily.</td>
<td>6 mg twice daily</td>
<td>3 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Butyrylcholinesterase inhibitor (BuChE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>Acetylcholinesterase inhibitor</td>
<td>Start at 4 mg twice daily with food; at 4-week intervals, increase each dose by 4 mg, up to a dosage of 12 mg twice daily.</td>
<td>12 mg twice daily</td>
<td>8 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Nicotinic receptor actions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.8.** Summary of pharmacological characteristics of the three mainly used AChEIs (* signifies manufacturer’s recommendation on the dosage that produces the best results (Delagarza, 2003).

**1.8.1.1.1. Donepezil (Aricept®)**

A study which pooled data from 3 randomized, double-blind, placebo-controlled studies, assessing the efficacy of donepezil in preventing clinical worsening in patients with mild-to-moderate AD (MMSE 10-27), concluded that donepezil treatment was associated with reduced odds of clinical worsening of AD symptoms. Moreover, patients worsening on donepezil were likely to experience less cognitive decline than expected if left untreated (Wilkinson *et al.*, 2009).

Data from the Cochrane database also concluded that people with mild, moderate or severe AD treated for periods of 12, 24 or 52 weeks with donepezil experienced benefits in cognitive function, activities of daily living and behaviour. Benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose. Taking into consideration the better tolerability
of the 5 mg/day donepezil compared with the 10 mg/day dose, together with the lower cost, the lower dose may be the better option (Birks and Harvey, 2006). Studies for Donepezil in MCI concluded that the putative benefits are minor, short lived and associated with significant side effects (Birks and Flicker, 2006) and useful only in cases who demonstrated additional depressive symptoms (Lu et al., 2009).

The once-daily dosing is advantageous for patients who live alone or who have difficulty managing medications. This drug is metabolized within a minor substrate of the CYP2D6 and 3A4 metabolic system; competing drugs make the drug less available for its therapeutic effect. Donepezil is available in tablet and an orally dispersable form (Downey, 2008).

1.8.1.1.2. Galantamine (Reminyl®)

The pivotal trials, published in 2000 (Raskind et al., 2000; Tariot et al., 2000; Wilcock et al., 2000) and 2001 (Rockwood et al., 2001; Wilkinson et al., 2001), compared total daily doses of an immediate release form of galantamine (16 to 32 mg) to placebo for periods of 12 to 24 weeks in subjects with mild to moderate AD (baseline mini mental state examination [MMSE] score range, 10 to 24). Main outcomes were cognitive performance measured by the Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog) and global change, measured by the Clinician Interview-Based Impression of Change incorporating Caregiver Information (CIBIC-plus). Meta-analyses of the results coming from these and other trials have concluded that galantamine, in doses within the above mentioned range, significantly improves cognitive performance and global rating scores for 3 to 6 months. However, no statistically significant dose-response effect was found. A recent expert opinion review reconfirmed that galantamine can improve and stabilize cognitive performance, activities of daily living and behavioral symptoms over the course of 6 months (Prvulovic et al., 2010). The clinical results obtained with galantamine were generally comparable to those of similarly constructed pivotal trials of donepezil and rivastigmine in the same population (Prvulovic et al., 2010).
There are not enough, properly designed, “head to head” trials for a meaningful, direct comparison of galantamine with the other two AChEIs (Seltzer, 2010). Subsequent, long term, non-placebo controlled extension trials showed continuing cognitive and functional benefit from galantamine for periods of up to 36 months (Raskind et al., 2004; Pirttilä et al; 2004). Significant improvement in some, but not all, domains was demonstrated in subjects with severe AD (MMSE score range, 5-12) (Burns et al., 2009) as well as vascular dementia (Auchus et al., 2007). However, galantamine failed to reduce conversion to dementia in subjects with mild cognitive impairment (Winblad et al., 2008).

In addition to being AChEI, galantamine is also believed to enhance central neurotransmission by allosteric modulation of pre- and post-synaptic nicotinic receptors (Maelicke, 2000). Galantamine is also available as a once-daily sustained-release form. This extended release form was found to be sufficiently similar to galantamine-immediate release to be approved by the FDA and agencies in other countries for use in mild to moderate AD (Seltzer, 2010). This drug also is metabolized within a minor substrate of the CYP2D6 and 3A4 systems. It is available in tablet and liquid form (Downey, 2008).

1.8.1.1.3. Rivastigmine (Exelon®)

Apart from blocking acetylcholinesterase, rivastigmine is active also against another cholinesterase enzyme, butyrylcholinesterase (BuChE), which increases considerably in the brain in individuals with AD changing from a ratio of 99:1 to 2:1. This may have a favourable effect on sustained cholinesterase inhibition and subsequent disease stabilization (Scerri, 2006). A Cochrane review assessed nine trials, involving 4775 participants, done with rivastigmine in patients with mild to moderate dementia. Use of high-dose rivastigmine (6 to 12 mg daily) was associated with a two-point improvement in cognitive function on the ADAS-Cog score compared with placebo and a 2.2 point improvement in activities of daily living assessed on the Progressive Deterioration Scale (weighted mean difference -2.15, 95% confidence interval -3.16 to -1.13, on an intention-to-treat basis) at 26 weeks. At lower doses (4 mg daily or lower) differences were in the same direction but were statistically significant.
only for cognitive function (Birks et al., 2009). There were statistically significantly higher numbers of events of nausea, vomiting, diarrhoea, anorexia, headache, syncope, abdominal pain and dizziness among patients taking high-dose rivastigmine than among those taking placebo. There was some evidence that adverse events might be less common with more frequent, smaller doses of rivastigmine (Darreh-Shori and Jelic, 2010).

The 2008 Cochrane update includes a new study testing two types of rivastigmine transdermal patch, one delivering a higher dose than previously tested (17.4 mg/day) and a smaller patch delivering 9.6 mg/day. The efficacy of the smaller patch was not significantly different compared with the capsules of similar daily dose, but was associated with significantly fewer adverse events of nausea, vomiting, dizziness and asthenia. The efficacy of the larger patch was not significantly different compared with the smaller patch, but the smaller patch was associated with significantly fewer adverse events of nausea, vomiting, weight loss and dizziness. There appears to be advantages associated with the smaller patch compared with both the higher dose patch and the 6-12 mg/day capsules (Birks et al., 2009).

Rivastigmine oral capsule dosing starts at 1.5 mg b.d. and is increased to 3 mg b.d., then 4.5 mg b.d., and then 6 mg b.d. at 4-week intervals. Unlike donepezil and galantamine, rivastigmine has a nonhepatic metabolism. Since there have been case reports of eosphageal rupture when rivastigmine was stopped and then restarted at the highest tolerated dose, all anticholinesterase drugs which are stopped for any reason must be restarted at the lowest dose and titrated up again as in the original taper schedules. For this reason, rivastigmine should also be used with caution in patients with peptic ulcer disease or those using nonsteroidal anti-inflammatory drugs. As is the case with the other drugs in this class, cholinergic drugs may potentiate the drug effect, while anticholinergic drugs may inhibit effectiveness. Rivastigmine is available in tablet, liquid and transdermal formulations (Downey, 2008).
1.8.1.2. NMDA-Receptor Antagonist

1.8.1.2.1. Memantine (Axura®)

The non-competitive N-methyl-D-aspartate receptor antagonist, memantine interferes with glutaminergic overstimulation which leads to excitotoxicity due to intracellular calcium ion overload. It was shown that Aβ plaques increase a neuron’s vulnerability to excitotoxicity (Koh et al., 1990) inducing astrogliosis and leading to extracellular accumulation of glutamate and intracellular calcium ions (Harkany et al., 2000). Thus by interfering with excitotoxicity, memantine affects the NMDA receptors implicated in memory processing and the core pathology of AD (Reisberg et al., 2003). In several studies, memantine was found to prevent neuronal death induced via excitotoxic mechanisms (Pellegrini et al., 1993; Vorwerk et al., 1996).

In 2003, memantine was approved for the treatment of moderate to severe AD in the US and in Europe. Three randomized, double-blind, placebo-controlled trials were submitted to the Food and drug administration (FDA) in the New Drug Application (Winbald and Poritis, 1999; Reisberg et al., 2003; Tariot et al., 2004). The first of the studies submitted to the FDA evaluated memantine as a therapy for AD in a long-term care setting (Winbald and Poritis, 1999). In a placebo-controlled trial, patients were selected according to DSM-III criteria, a Mini-Mental State Examination (MMSE) of less than 10, and a Global Deterioration Scale (GDS) score of 5–7. The primary efficacy measures were the patient’s response to therapy, functionally and globally using the Behavioral Rating Scale for Geriatric Patients (BGP) and the Clinical Global Impression of Change (CGI-C). Administering 10 mg/day (half the current recommended dosage) of memantine for 12 weeks, a statistically significant improvement in global and functional parameters was noted. The measurements for behavior were not statistically significant. They also used Ferm’s D-test as a secondary variable to determine efficacy and found that the treated patients needed less time for nursing care due to improved functionality. While no behavioral improvement was observed, the global and functional improvement demonstrated its value as a potential therapy for patients with moderate to severe AD.
Reisberg et al. (2003) conducted a similar study in an outpatient setting. They used similar selection criteria with the addition of satisfying the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA). Memantine 10 mg twice daily was administered for 28 weeks at 32 US centers. The study used the Severe Impairment Battery (SIB), the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus) as primary efficacy variables for cognition and global measurements, respectively. Secondary efficacy measures included the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev) and the Neuropsychiatric Inventory (NPI) to measure impact on behavior. Patients receiving memantine showed statistically significant benefits when compared to placebo in both of the primary efficacy measures, the SIB and the CIBIC-Plus, over the 28-week trial. The patients receiving memantine also showed statistically significant improvement over placebo in the ADCS-ADLsev but not in the NPI. These results confirmed the results of the previous study with the addition of better cognitive outcomes for patients receiving memantine.

The third and final study submitted to the FDA was for a combination therapy of memantine and donepezil. Tariot et al. (2000) conducted a RDBPC trial using 404 outpatients already on donepezil, from 37 US centers for 24 weeks with 322 patients completing the trial. Patients were selected according to the NINCDS-ADRDA diagnostic criteria for AD. They were also selected for MMSE scores between 5 and 14, age of at least 50 years and CT scans consistent with AD. Primary efficacy variables included cognition, using the SIB, and global measures, using the CIBIC-Plus. Secondary outcome measures were behavioral and functional and were measured using the NPI and BGP, respectively. All patients remained on donepezil with half randomized to the addition of memantine and half to the addition of placebo. At the conclusion of the study, statistically significant benefits were found in all primary and secondary endpoint measures in favor of donepezil/memantine vs donepezil/placebo. This confirmed previous studies with the addition of improvement in behavioral outcomes. Similar findings were replicated in another study by van Dyck et al. (2006).
Not withstanding that all studies agreed on the benefit of memantine in moderate to severe dementia for cognition and global function, there were conflicting outcomes on behavioral measurements. While Tariot et al. (2000) demonstrated a positive outcome, Reisberg et al. (2003) and Winblad et al. (2008) had no statistically significant outcomes in measures of behavioral outcomes. Since behavioral disturbances are common in patients with AD and are the cause of great distress to care-givers (Thomas and Grossberg, 2009), great interest lies in determining if memantine truly improves behavioral outcomes. Wilcock et al. (2008) conducted a pooled analysis of three large 6-month studies of memantine using the NPI as an efficacy variable. The authors found a statistically significant improvement in behavioral outcomes, especially in measurements of agitation and aggression (Wilcock et al., 2008). In the same year, Gauthier et al. (2008) published a study with a shorter time period and a larger study group. This study used the NPI as well and also yielded statistically significant improvement in patients receiving memantine over those receiving placebo (Gauthier et al., 2008). These studies suggest that memantine may be a reliable treatment option for patients with AD with behavioral symptoms (Thomas and Grossberg, 2009).

Finally, a recent study compiled memantine data from all clinical trials and from pivotal studies between 1992 and 2008 for a post-hoc analysis (Grossberg et al., 2009). The study, which excluded patients in nursing homes or assisted living facilities, found that a meta-analysis of all the study groups showed statistically significant improvement in both the NPI and BGP for patients receiving memantine over placebo. However, the behaviors with statistically significant improvement were agitation/aggression, irritability/lability, and delusions. Perhaps more importantly, this study found a delay in the emergence of behavioral symptoms with memantine compared to placebo. Improvement in these measurements and prevention of emergence would ease the burden for care givers and increase the time to institutionalization.

FDA approval for memantine permitted it to be prescribed alone or in combination with AChEI (Thomas and Grossberg, 2009). Combination therapy is a promising choice of therapy for patients with moderate to severe AD. Since it is not currently approved by the FDA to treat mild AD with memantine, AChEI are the principal choice for treatment in mild cases. As the
disease progresses, it has been shown that transition from a AChEI to memantine is well tolerated (Waldemar et al., 2008), but better primary and secondary outcomes may be achieved in patients receiving combination memantine/AChEI (Tariot et al., 2004). Thus clinicians should add memantine to the patient’s treatment plan without discontinuing the use of AChEIs. No studies have been published regarding memantine use in MCI (Mc Clendon et al., 2009).

The dosing schedule is 5 mg once daily for one week, 5 mg b.d. for one week, 10 mg in the morning and 5 mg in the evening for one week, and then 10 mg b.d. Adverse effects include dizziness, headache, GI upset, and hypertension. There have been case reports of worsening behavioral status and agitation, which have cleared when stopping the drug. Memantine undergoes nonhepatic metabolism and is excreted by the kidney, so caution should be taken by patients with renal insufficiency or when other renally excreted drugs are used. Dosages may need to be adjusted or lowered if creatinine rises; sometimes the drug will need to be stopped altogether. Memantine can be taken without regard to meals (Downey, 2008).

1.8.1.3. Other pharmacological therapy

A large number of patients with AD are also prescribed antipsychotics, antidepressants, anxiolytics or neuroleptics (Grossberg et al., 2009). These treatments are common due to the prevalence of behavioral symptoms in patients with AD. One of the most prevalent behavioral symptoms is agitation and aggression (Thomas and Grossberg, 2009). Vocal behaviour is a common form of agitation displayed by people with dementia. It refers to excessive screaming, abusive language, moaning, perseveration, and repetitive and inappropriate requests (Magri et al., 2007). Other non-cognitive symptoms are mood disorders, psychosis, sexual disinhibition and feeding difficulties. These have been grouped together under the umbrella term “behavioural and psychological symptoms of dementia” (BPSD) by the International Psychogeriatric Association.
1.8.1.3.1. Antidepressants

There is a high prevalence rate (30-50%) of AD and depression comorbidity (Lee and Lyketsos, 2003). Depression can be a risk factor for the development of AD in MCI patients (Ownby et al., 2006) or it can develop secondary to a neurodegenerative process (Zubenko et al., 2003). Diagnosis of depression itself is challenging due to the absence of objective diagnostic tests. Diagnosing depression associated with neurological disorders poses further challenges (Aboukhatwa et al., 2010). The etiology of AD and depression depends on reductions in levels of neurotransmitters which are common to both, such as serotonin and noradrenaline (Meltzer et al., 1998). For this reason, an urgent need for standardized protocols for the diagnosis of depression associated with AD is required (Lee and Lyketsos, 2003).

The monoamine hypothesis postulates that depletion in the levels of serotonin, noradrenaline, and dopamine in the central nervous system are the pathophysiologic basis of depression (Aboukhatwa et al., 2010). Antidepressants aim at counteracting these depletions as outlined in each section. Yet this is not the only way antidepressants can benefit the AD patient. Based on neurophysiological studies, and accepted theories of AD, antidepressants were found to have other modulatory properties which make their use useful.

Depression and stress may decrease neurogenesis (formation of new neurons in specific brain areas) and chronic treatment with antidepressants can antagonize this effect and increase neurogenesis in the hippocampus (Warner-Schmidt and Duman, 2006). Interestingly, the effects of antidepressants on neurogenesis are evident across different classes. This neurogenic effect requires chronic administration between 14-21 days, and includes an increase in the proliferation rate and new neuron survival (Nakagawa et al., 2002). Although based only on animal studies, antidepressants were shown to stimulate the proliferation and survival of new neurons, particularly if the treatment is started early when depressive symptoms appear as a risk factor (Aboukhatwa et al., 2010).

There are major changes in the hippocampus associated with the aging process, one of which is difficulty in encoding and retaining information measured in terms of reduction in long-term
potentiation (LTP) and elevation in long-term depression (LTD) (Lister and Barnes, 2009). Preclinical studies have proven that different classes of antidepressants affect differently the balance between LTP and LTD, some favouring LTP and vice-versa. This raises awareness about the proper selection of antidepressant for AD patients. Some antidepressants can cause memory impairment and close attention should be paid to these medications if prescribed in AD (Majlessi and Naghdi, 2002).

Mounting evidence supports the hypothesis that inadequate stimulation of NMDA receptors is a pathophysiological component of both depression and AD. A number of studies report that chronic antidepressant treatment can modulate the expression of specific NMDA receptors subunits and ultimately reduce NMDA receptor function (Nowak et al., 1993; Nowak et al., 1996; Boyer et al., 1998). Additionally, NMDA receptor antagonists such as memantine, have antidepressant-like effects (Skolnick, 1999). This creates a common site of action for the treatment of depression and AD.

The effect of antidepressants on amyloid peptide has gained particular importance only recently (Aboukhatwa et al., 2010). The high prevalence rate of co-morbidity between depression and AD warrants the investigation of the possible dual role of action antidepressants could have or be made to achieve in order to modulate both diseases. Proof that antidepressants could have a direct role on the main pathology of AD could mean that their spectrum of action is increased.
Antidepressants

- Increase monoamine levels in the synapse
- Increase BDNF, pCREB
- Increase neurogenesis
- Improve learning and memory
- Antagonism and modulation of NMDA receptors
- Reduce amyloid peptide

Figure 1.11. A summary of the different actions of antidepressants that can modulate the pathological features of AD (Aboukhatwa et al., 2010).

1.8.1.3.1.1. Tricyclic antidepressants (TCAs)

Tricyclic antidepressants inhibit the reuptake of both serotonin and noradrenaline. It has also anticholinergic properties. Commonly used in this class are imipramine, clomipramine and amitriptyline. A strong placebo effect was recorded with the TCAs clomipramine (Pacher and Kecskemeti, 2004) and imipramine (Reifler et al., 1989) making it challenging to decide the real benefit obtained by these medications.

Although amitriptyline treatment does not seem to increase neurogenesis, it reduces the decline in synaptic density as a result of olfactory bulbectomy, a well established animal model for depression (Norrholm and Ouimet, 2001). More importantly, tricyclic antidepressants were shown to reduce LTP in pyramidal cells (Von Frijtag et al., 2001). The reduction of LTP can be attributed to the anticholenergic effects of TCA that counteract their effects on neuroplasticity (Pittenger and Duman, 2008). Clinical trials have also shown that TCAs impair cognitive function (Reifler et al., 1989; Petracca et al., 1996).
An *in vitro* study addressed the effect of TCAs on Amyloid precursor protein (APP) processing in rat primary basal forebrain cultures (Pakaski *et al*., 2005). Imipramine significantly reduced intracellular levels of APP after two hours of treatment and citalopram increased levels of secreted APP in the medium of the treated primary cultures. It is anticipated that the increase in APP secretion is accompanied by a decrease in intracellular APP levels. Presumably, the secreted APP will not be available for processing by β and γ secretases. Interestingly, serotonin and muscarinic agonists also increase APP secretion (Nitsch *et al*., 1992; Arjona *et al*., 2002).

Tricyclic antidepressants inhibit the NMDA receptor directly (Semagor *et al*., 1989; Cai and McCaslin, 1992) with the potential benefits in AD as discussed above.

The number of unwanted side effects including antihistaminic, cardiotoxic and anticholinergic effects are due to the widespread action of TCAs on a large number of different receptors. The prescription of TCAs has declined due to these unwanted side effects and the advantage of new antidepressants with a better tolerability profile (Pacher *et al*., 1999).

### 1.8.1.3.1.2. Selective Serotonin Reuptake Inhibitors (SSRIs)

Serotonin signaling pathways are implicated in the pathology of AD since the death of neurons and the dysfunction of synapses can result in reduction in the activation of serotonin coupled signaling pathways (Mattson *et al*., 2004). Accumulating evidence emphasizes the positive role that serotonin plays in cognitive function (Schmitt *et al*., 2006). Post-mortem AD brains show reductions in the levels of serotonin and its metabolites (Gottfries, 1990; Nazarali and Reynolds, 1992) which highlights the potential advantage of prescribing SSRIs to AD patients versus other antidepressants.

The selective serotonin reuptake inhibitor class includes antidepressants that selectively inhibit the reuptake of serotonin and subsequently increase the amount of serotonin available to bind
to the postsynaptic receptor. SSRIs are the most commonly prescribed class of antidepressants. Examples of this class include citalopram, sertraline, fluvoxamine, fluoxetine and paroxetine (Berton and Nestler, 2006). The major advantage of the introduction of SSRIs in the 1980s was their good safety and tolerability profiles. These favorable profiles are attributed to the low affinity of SSRIs to histamine, muscarinic and α adrenergic receptors (Aboukhatwa et al., 2010).

Fluoxetine treatment for as short as 5 days was shown to increase synaptic density in the hippocampus as determined by electron microscope (Hajszan et al., 2005) proving that neurogenesis takes place following SSRI treatment.

SSRIs have less anticholinergic properties in comparison to TCAs and were found to increase LTP and prevent stress induced reduction in LTP (Vouimba et al., 2006; Holderbach et al., 2007). There are conflicting reports on how SSRI treatment affects performance in the Morris water maze, a typical animal model used to assess spatial learning and memory.

A number of studies have reported that chronic SSRI antidepressant treatment can modulate the expression of specific NMDA receptors subunits and ultimately NMDA receptor function (Nowak et al., 1993; Nowak et al., 1996; Boyer et al., 1998), as is the case of citalopram (Boyer et al., 1998). Like TCA’s, the SSRI fluoxetine inhibits the NMDA receptor directly (Szasz et al., 2007).

Fluoxetine and paroxetine were both shown to significantly decrease β-amyloid oligomers, but do not to affect the levels of extracellular amyloid peptide. Based on these results, fluoxetine and paroxetine are likely to be beneficial to AD patients due to their role in modulating β-amyloid metabolism (Aboukhatwa et al., 2010). Transgenic mice treated with paroxetine for three months had reduced levels of β-amyloid and APP levels in brain homogenate (Tucker et al., 2006). Citalopram significantly increased the levels of secreted APP (Pakaski et al., 2005) as is done also by serotonin and muscarinic agonists directly (Nitsch et al., 1992; Arjona et al., 2002).
In clinical studies, citalopram has been shown to significantly improve the score of depressed patients in the Hamilton Rating Score (HAM-D), the Clinical Global Impression Scale, and the Montgomery Asberg Depression Scale (MADRS) (Nyth et al., 1992).

Citalopram also significantly improves emotional and cognitive function in a subgroup of patients with from dementia based on the Gottfries-Brane-Steen Dementia Rating Scale (Nyth et al., 1992). The SSRI sertraline was tested in an eight-week trial in thirty-one female patients diagnosed with late stage AD to determine its efficacy. Using objective rating scales, including the Cornell Scale for Depression in Dementia and others, sertraline and placebo improve ratings similarly but sertraline treatment showed a better improvement in “knit brow” facial behavior (Magai et al., 2000). “Knit brow” is facial behavior where the brows are somewhat lowered and pulled together. It is a robust index of dysphoria in advanced stage dementia (Magai et al., 2000). Another clinical study with sertraline treatment that lasted twelve weeks involving twenty-two patients who suffer from major depression and AD showed that sertraline reduced depressive symptoms significantly in comparison to placebo. Interestingly, sertraline-treated patients do not show any significant change in daily living activities according to the Psychogeriatric Dependency Rating Scale in comparison to the placebo group where there was a significant decline in daily activities at weeks nine and twelve (Lyketsos et al., 2000).

A meta analysis study for the safety and efficacy of antidepressants in treatment of depression in AD found that antidepressants, especially SSRI’s, are efficacious in treatment of depression in AD patients (Thompson et al., 2007).

1.8.1.3.1.3. Selective noradrenaline reuptake inhibitors (SNRI)

The selective norepinephrine reuptake inhibitor (SNRI) class of antidepressants selectively inhibits the reuptake of noradrenaline. Examples of this class are maprotiline, reboxetine and venlafaxine. Maprotiline causes side effects similar to those of TCAs including dry mouth,
fatigue and weight gain. As was true for fluoxetine, venlafaxine was demonstrated to improve the Morris water maze performance after chronic treatment (Nowakowska et al., 2006) while maprotiline was not found to significantly alter Aβ metabolism (Aboukhatwa et al., 2010).

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Neurogenesis</th>
<th>Aβ</th>
<th>Learning and memory</th>
<th>NMDA Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA in general</td>
<td></td>
<td></td>
<td>Reduce LTP in CA1 pyramidal cells.</td>
<td>Inhibit NMDA receptor directly.</td>
</tr>
<tr>
<td>Amitriptyline (TCA)</td>
<td>Does not increase synapse number but reduce decline in synaptic density.</td>
<td>Increase secreted APP, reduces intracellular APP in culture.</td>
<td>Blocks age -induced deterioration of learning and memory.</td>
<td></td>
</tr>
<tr>
<td>Imipramine (TCA)</td>
<td>Increase synaptic density in hippocampus.</td>
<td>No effect on animal performance in Morris water maze and even worsen spatial working memory in radial arm maze test.</td>
<td>Changes in binding to NMDAR and expression of NMDAR in brain.</td>
<td></td>
</tr>
<tr>
<td>Clomipramine (TCA)</td>
<td>Increase synaptic density in hippocampus.</td>
<td>Increase the levels of secreted APP in the medium of the treated neurons.</td>
<td>Inhibit NMDA receptor directly.</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (SSRI)</td>
<td>Does not interact with Ab fibrils.</td>
<td>Protects hippocampal LTP. Performance improvement in Morris water maze after chronic treatment.</td>
<td>Adaptation of NMDAR complex. Changes in expression of NMDAR.</td>
<td></td>
</tr>
<tr>
<td>Citalopram (SSRI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine (SSRI)</td>
<td>Reduces levels of Ab and tau in Tg mice and cells.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (SNRI)</td>
<td></td>
<td>Performance improvement in Morris water maze after chronic treatment.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.9. Summary of potential targets of antidepressant drugs in relate to AD pathology (Aboukhatwa et al., 2010).
1.8.1.3.1.4. Natural antidepressants - Extract of Ginkgo biloba (EGB)

Ginkgo biloba leaves are a common herbal remedy in traditional Chinese medicine. Extract of Ginkgo biloba leaves demonstrated antidepressant action in animal models of depression (Sakakibara et al., 2006). Another study demonstrated antidepressant activity of Ginkgo biloba lipophylic extract in learned helplessness and behavioral despair animal models (Kalkunte et al., 2007). Ginkgo biloba leaves exhibits a number of beneficial effects for AD patients such as cognition and mood improvements and resolution of mild-to-moderate dementia symptoms (Le Bars et al., 1997). Although a recent Ginkgo trial failed to demonstrate prevention of memory impairment, the authors discuss the possibility that the extract was given too late to see a preventive effect (DeKosky et al., 2008). In preclinical studies, Ginkgo biloba extract (EGB 761) blocked the production of amyloid beta peptide and amyloid precursor protein in aged rodents (Yao et al., 2004).

EGB 761 also inhibits the aggregation of amyloid peptide and apoptosis by blocking the activation of caspase-3 in a neuroblastoma cell line (Luo et al., 2002) and found to inhibit amyloid peptide induced hippocampal cell death (Bastianetto et al., 2000).

Flavonoids are class of compounds that are derived from different plants such as tea, Ginkgo biloba and citrus (Benavente-Garcia and Castillo, 2008). Accumulating evidence supports the antidepressant activity of flavonoids in depression animal models (Aboukhatwa et al., 2010). Ginkgo flavonols also reduced amyloid peptide burden in double AD transgenic (TgAPPswe/PSe9) mouse hippocampal neurons (Hou et al., 2009).

Up till 2010, the largest randomised controlled study performed with Ginko failed to show a positive effect on on global cognitive change or on specific cognitive domains of memory, language, attention, visuospatial abilities and executive functions. It also failed to prevent or delay progression from MCI to AD (Beth et al., 2009).
1.8.1.3.2. Antipsychotics

BPSD develop in approximately 60% of people with dementia living in the community and in more than 80% in similar patients living in nursing homes (Bugeja, 2010). The presence of these and other neuropsychiatric symptoms in dementia is known to decrease the quality of life of both patients and caregivers. No medication has been approved for the treatment of BPSD but antipsychotics are the best studied and most commonly used (Bugeja, 2010). These drugs are sought after for their general tranquillizing effect and their efficacy in controlling the psychiatric symptoms of BPSD. Antipsychotic use in 1322 patients on 59 dementia special units in 25 Dutch nursing homes was positively associated with psychosis, agitation and disruptive night-time behaviour and negatively associated with apathy (Nijk et al., 2009).

Antipsychotic use is associated with unwanted effects, especially if used long-term and at high doses. Extrapyramidal side-effects are well known to antipsychotic medications leading to Parkinsonism and dyskinesias. In 2004, the US Food and Drug Administration (FDA) issued a warning on the increase in the mortality rate in elderly patients on antipsychotics. In the following year, the FDA issued a black box warning regarding the risks of atypical antipsychotic use in elderly with dementia in relation to a significantly increased risk of cerebrovascular co-morbidity and even increased risk in mortality (Bugeja, 2010). This has left a dilemma on whether, when or how to use these medications in dementia and AD.

A descriptive weighted analysis on data released from the 2004 US National Nursing Home Survey (NNHS) revealed the widespread use of antipsychotics in patients with dementia (32.9%) with a large discrepancy in the use of atypicals (31.6%) vis-a-vis typical agents (1.8%) respectively (Kamble et al., 2009). This was however before the FDA’s black box warning. In 2007 similar, results were reported by Alldred et al. (2007) with a 20% of the
study population being on antipsychotics and a clear preference for atypical antipsychotics rather than typical ones (70% versus 40% respectively). A small study performed locally at Saint Vincent de Paule Residence (SVPR) showed similar general trends in the use of antipsychotics in general (20%) yet more interesting is the fact that a clear preference for typical (60%) rather than atypical (40%) agents was seen in this Maltese study (Bugeja, 2010).

Higher rates of antipsychotic use were seen in Alzheimer special care units. Out of 349 patients in 35 such units, 60% were taking at least one antipsychotic. Risperidone and promazine were the most frequently prescribed antipsychotics and 40.7% had additional psychotropic medication like benzodiazepines and/or antidepressants. The higher the cognitive impairment as measured using psychometric scales, the higher the prevalence of psychotropic drugs (Nobili et al., 2009).

The preferential use of atypical antipsychotics (risperidone, olanzapine, quetiapine) laid on the perceived idea that they do cause less extrapyramidal side-effects (Bugeja, 2010). Although atypical antipsychotics were found to improve the aggression and the psychosis of BPSD, risperidone and olanzapine treated patients had a significantly higher incidence of serious adverse events like cerebrovascular events and including extrapyramidal symptoms leading to a significant drop-out rate when compared to placebo (Ballard et al., 2006). The same authors, who performed a Cochrane review in the use of antipsychotics in dementia patients, concluded that despite the modest efficacy, the significant increase in adverse events suggested that neither risperidone nor olanzapine should be used routinely to treat dementia patients with BPSD unless there is severe distress or risk of physical harm to those living and working with the patient (Bugeja, 2010). The newest anti-psychotic in the UK, aripiprazole, has also been trialed with some success in demented patients with behavioural problems but again has shown an increase in cerebrovascular events (Magri et al., 2007).

A systematic literature review of randomized, double-blind, placebo controlled trials done on the use of typical and atypical antipsychotics in patients with dementia spanning between the

61
1986 and 2007 concluded that both types of antipsychotics are beneficial in the control of BPSD. Extrapyramidal symptoms are more frequent when typical antipsychotics were used while risk of cerebrovascular events and death were more frequent with the atypical ones (Forlenza et al., 2008). The results of large randomized controlled trials are clear in indicating the higher incidence of mortality in patients on atypical antipsychotics with an overall risk difference between 1% and 2% over a period of 8 to 12 weeks (Jeste et al., 2007). Further studies showed that typical antipsychotics are no safer. Loperoti et al. (2009) performed a retrospective cohort study in 2009 to compare risk of death associated with atypical and typical antipsychotics in a large population of nursing home residents with dementia. After adjusting for possible confounding factors, the rate of death was increased for users of typical antipsychotics. Relative to risperidone, a higher rate of death was documented for haloperidol. Thus typical antipsychotics are not a safer substitute for atypical antipsychotics in individuals with dementia or BPSD (Loperoti et al., 2009).

A report commissioned by the UK Health department about the use of antipsychotics in persons with dementia concluded that the current level of use of antipsychotics in this population presents a significant issue in terms of quality of care, with negative impacts in patient safety and clinical effectiveness (Banjee, 2009).

It was remarked that antipsychotic drugs appear to be used too frequently in dementia and that the potential benefits are likely to be outweighed by the risks. Based on the latest evidence available, it was estimated that each year

- 180,000 people with dementia receive antipsychotics in England.
- Up to 36,000 of these people benefit to some degree from the treatment.
- Around 1,620 additional cerebrovascular adverse events (such as stroke) will result from the treatment. About half of these will be severe.
- Each year, about 1,800 additional deaths will be caused by the treatment in this frail population i.e. 1% of the total population treated.
The report made eleven recommendations that aim to reduce the use of antipsychotics to a level where the benefits outweigh the risks. Professor Banerjee estimated that antipsychotic use could be reduced to a third of its current level, and that this could be done safely over 36 months.

Broadly, the report recommended that:

- People with dementia should receive antipsychotics only when they really need them.
- Reducing the use of antipsychotics in people with dementia should be a priority.
- Care home staff are given a curriculum to develop skills in non-pharmacological treatment of behavioural disorder in dementia.
- Care homes could be assessed based on their use of antipsychotic medications and the availability of staff who are skilled in non-pharmacological management of behavioural and psychological symptoms in dementia.
- Psychological therapy resources should be made available for people with dementia and their carers.
- Further research should be carried out, including studies of non-pharmacological methods of treating behavioural problems in dementia and of alternative pharmacological treatments.

The best evidence for alternative pharmacological medication use in BPSD is for the AChEIs, NMDA inhibitors and SSRIs (Passmore et al., 2008). Fossey et al. (2006) have however shown a significant reduction in the proportion of patients taking antipsychotics in residential homes where staff was trained in the delivery of person-centred care and skills development in training and supervision. No significant differences were found in the levels of agitated or disruptive behaviour between homes with specifically trained staff and control homes, thus showing that promotion of person-centred care and good practice in the management of patients with dementia with behavioural symptoms may provide an effective alternative to antipsychotics (Magri et al., 2007).
1.8.1.3.3. Benzodiazepines

Anxiety is a frequent symptom of AD, affecting over half of the patients in some cohorts (Devier et al., 2009). It has also been suggested that the occurrence of neuropsychiatric symptoms, including anxiety, was associated with continued cognitive decline in community-dwelling elders without cognitive impairment (Sinoff et al., 2003). Another study in a sample of 47 MCI patients found that the presence of anxiety increased the risk of MCI conversion to AD, and endorsement of each additional symptom of anxiety doubled the risk of conversion (Palmer et al., 2007). Other studies have shown no significant association (Devier et al., 2009).

Benzodiazepines such as lorazepam appear efficacious at treating anxiety and insomnia when patients' symptomatology lacks psychotic features but their efficacy has not been comprehensively studied (Hogan et al., 2008). Fastbom et al. (1998) observed that benzodiazepines may have protective effects against the disease yet this finding was never validated and was poorly followed-up in literature and if anything contradicted (Lagnaouia et al., 2002). Unfortunately, a paradoxical effect has been noted in Alzheimer's patients, in which the administration of benzodiazepines leads to increased confusion, disorientation, and ultimately, even greater agitation and anxiety. These agents are generally safe when used in low doses, but with increasing doses, common side effects include over-sedation, ataxia, confusion, and agitation. In addition, with long-term use, tolerance and dependence is likely. These risks would outweigh any benefit obtained from treating the symptom alone (Shah and Reichman, 2006).

When it comes to BPSD, Bugeja (2010) reported that in Malta up to 60% of institutionalised people with dementia were on one or more types of anxiolytics. Insomnia is common among patients with dementia. Individuals with dementia should be carefully assessed for factors that might be contributing to this problem and non-pharmacologic approaches (i.e. sleep hygiene, daily walking and increased exposure to daytime light with the use of a light box) can be
effective and should be considered first (McCurry et al., 2005). If medications, especially
benzodiazepines are used, the lowest effective dose of the selected agent should be used for
the shortest time possible (Hogan et al., 2008). In cases of vocal behaviour, even though no
research-based evidence exists to support the supposition, it is possible to justify a trial of an
anxiolytic in terms of interpreting the symptoms as an anxiety equivalent, and even potential
dependence may be an acceptable risk in chronic severe cases (Magri et al., 2007).

1.8.1.3.4. Nootropics – Piracetam

Piracetam was one of the first drugs used for dementia and forms part of a class of drugs
referred to as nootropics, whose putative actions are still poorly defined (Flicker and Grimley
Evans, 2001). Long-term use at high doses was suggested to have a potential benefit with
observed improvement in recall of picture series, recent incident and remote memory, yet not
reaching statistical significance (Croisile et al., 1993). A cochrane review in the clinical
efficacy of piracetam for features of dementia concluded that published evidence does not
support the use of piracetam in the treatment of people with dementia or cognitive impairment
and that evidence indicates a need for further evaluation and studies (Flicker and Grimley
Evans, 2001).

1.8.1.3.5. Vitamin E

A growing body of research indicates that nutritional deficiencies contribute to AD onset and
progression (Ramesh et al., 2010). Key genetic and/or environmental factors may remain
latent pending age-related decline in nutrition. This suggests the potential importance of early
nutritional intervention, including preventative approaches prior to definitive diagnosis.
Oxidative stress is a pivotal factor in AD, and it is evident prior to cyto-pathological hallmarks
of the disorder. Antioxidants may therefore represent a potential preventative approach.
Vitamin E is a dietary compound that functions as an antioxidant scavenging toxic free
radicals (Chan et al., 2009).
To date, two unconfounded, double blind, randomized trials were conducted in which treatment with Vitamin E at any dose was compared with placebo for patients with AD or MCI. Results showed that there is no evidence of efficacy of Vitamin E in the prevention or treatment of people with AD or MCI (Isaac et al., 2008). A possible contributor to this could be that vitamin E provides some, but not complete, neuroprotection due to its lipophilic nature and resultant inability to quench cytosolic oxidative species, including those resulting from antecedent membrane oxidation (Dhitavat et al., 2001). Chan et al. (2009) examined the efficacy of a combination of the compounds (folic acid, vitamin B12, vitamin E and other substances) grouped together as nutriceutical formulation (NF) in early-stage AD. NF was shown to improve performance in several domains of the Neuropsychiatric Inventory including nighttime behaviour, irritability, disinhibition, agitation and aggression.

The apparent efficacy of NF for early-stage AD coupled with the demonstration that NF improves cognitive response in non-demented adults suggests that NF may also be useful in efforts to delay progression of MCI to AD (Chan et al., 2009). Furthermore, NF showed similar improvements in NPI scores to Donepezil at 3 and 6 months of therapy from baseline compared to placebo.

The findings of this study should be interpreted with caution pending completion of larger, placebo-controlled studies (Chan et al., 2009). Nonetheless the findings support the idea that nutritional intervention can have a positive effect on progression of early-stage AD. They further suggest that a combinatorial approach can provide superior neuroprotection than individual supplements and suggest that NF may potentiate pharmacological approaches, as was also shown in the severe stage of the disease (Remington et al., 2009).
1.8.2. Non-pharmacological management

Non-cognitive symptoms and behavioural and psychiatric symptoms of dementia (BPSD) develop progressively in the moderate-to-severe stages of the disease and may pose a challenge in achieving symptom control and avoidance of side-effects. This is why interventions for the non-cognitive symptoms and behaviour in patients with dementia were developed (NICE, 2006).

Early assessment to identify factors that may cause the altered behaviour in individuals with dementia should be performed in order to exclude biological pathology, depression, undisclosed pain, side-effect of medication, psychosocial upset, environmental changes and unhealthy relationship with carers. If agitation and anxiety are the main symptoms, interventions should be tailored to the person’s preference, skills and abilities. Depending on availability, NICE (2006) guidance suggests consideration of the following:

- aromatherapy
- multisensory stimulation
- therapeutic use of music and/or dancing
- animal-assisted therapy
- massage.

This further suggested that medication should be considered for non-cognitive symptoms and challenges in behaviour only if there is severe distress or an immediate risk of harm to the person with dementia or others. For less severe distress and/or agitation, a non-drug option should initially be used (NICE, 2006).
1.8.2.1. Aromatherapy

In a consensus statement published by the British Association for Psychopharmacology, the use of aromatherapy as an adjunct to the pharmacological treatment of dementia is supported by evidence from randomised controlled trials (Burns and O'Brien, 2006).

A number of controlled studies have shown that aromatherapy (the therapeutic use of pure plant essential oils) can be useful in the management of patients with dementia. Lavender and lemon balm are two essential oils of particular interest in this area (Holmes and Ballard, 2004). Benefit was attributed to the direct effect of the essential oils rather than the placebo effect of a pleasant-smelling fragrance as most people with severe dementia would have lost any meaningful sense of smell because of the early loss of olfactory neurons (Vance, 1999).

A large number of small, uncontrolled case studies have demonstrated the efficacy of inhaled and/or topical lavender oil in this setting. In summary, these studies have shown lavender oil to improve sleep patterns (Hardy et al., 1995; Wolfe and Herzberg, 1996) and to improve behavior (Smallwood et al., 2001).

A single-blind, case-controlled study showed that lavender essential oil significantly reduced the frequency of excessive motor behaviour in patients with severe dementia (Smallwood et al., 2001). In a small double-blind, placebo-controlled, crossover trial in patients with severe dementia on an NHS care ward, lavender oil reduced agitated behaviour in patients with severe dementia compared with placebo (Burns et al., 2002).

Recent studies on the use of aromatherapy were mainly conducted in China and Japan. In a cross-over randomised trial, lavender oil was shown to be an effective adjunctive therapy in alleviating agitated behaviours in Chinese patients with dementia and an alternative option in patients who are particularly vulnerable to side-effects of psychotropic medications (Lin et al., 2007). Jimbo et al. (2009) reported that aromatherapy is an efficacious non-pharmacological therapy for dementia with some potential for improving cognitive function, especially in AD patients.
The last updated Cochrane review analysing aromatherapy use in dementia could use only one trial that had results that could be analysed (Ballard et al., 2002), dismissing the rest. It concluded that more well designed large-scale randomised controlled trials are needed before clear conclusions can be drawn on the effectiveness of aroma therapy. Additionally, several issues need to be addressed, such as whether different aromatherapy interventions are comparable and the possibility that outcomes may vary for different types of dementia (Holt et al., 2009).

1.8.2.2. Multisensory stimulation (MSS), Music therapy and Massage

The empirical data supporting the use of multisensory stimulation environments (MSE) are limited, and there is only anecdotal evidence indicating effectiveness in psychiatric and geriatric neuropsychiatry populations (Knight et al., 2010). Multisensory stimulation was mostly available in specialised units where specific investment was done to create environments which enhanced stimulation of touch, vision, sound, smell, taste and movement. In geriatric institutions catering for persons with dementia, MSE was demonstrated to decrease the number of incidences of disruptive or problematic behavior but not the number of symptoms. The use of these interventions was suggested to be considered prior to the use of pharmacological methods (Ward-Smith et al., 2009).

In 2009, a pilot study in the use of domiciliary MSE evaluated the positive and negative effects of this non-pharmacological intervention on the behaviors of the person with dementia, caregiver burden, and family interpersonal relationships. Overall, MSS was discovered to promote a relaxing and calm environment in the home, which helped the person with dementia attend more to their immediate surroundings, and to improve family interactions. Although the majority of caregivers reported that they enjoyed MSS, they acknowledged their disappointment in the MSE as not providing more caregiver respite (Riley-Doucet, 2009).
Music therapy is a form of MSS whereby auditory stimulation is aimed at controlling the challenging behaviour and enhance response. A study conducted to investigate the effects of musical therapy, painting inanimate-animate object pictures, and orientation to time-place-person interventions on the cognitive state, depression, and anxiety levels of mildly-affected Alzheimer's patients revealed that this type of MSS had a positive effect on cognitive state (Ozdemir and Akdemir, 2009).

Cochrane review about the use of music therapy in dementia concluded that there is no substantial evidence to support nor discourage its use (Vink et al., 2006). Also, a Cochrane review about the use of light therapy concluded that there is insufficient evidence to determine whether light therapy is effective in the management of cognition, sleep, functional or BPSD (Forbes et al., 2009).

1.8.2.3. Animal-assisted therapy (AAT)

Various studies suggested that the presence of pets reduced aggression and agitation, as well as promoted social behavior in people with dementia. One study has shown that aquaria in dining rooms of dementia care units stimulate residents to eat more of their meals and to gain weight (Filan and Llewellyn-Jones, 2006).

A prospective study performed in France concluded that pet therapy could prove to be effective in reducing BPSD in severe dementia. Animal-assisted therapy had a calming effect on the patients, increasing the self-esteem of the patient and contributing to a more secure environment. Social isolation due to the condition was counteracted by the increased interactions with a pet. In spite of the lack of normal verbal use of language, nonverbal communication continued including touching and posture (Tribet et al., 2008). More recent data further consolidated the efficacy of AAT in patients who have the physical ability to
interact with a pet, specifically a dog, with nursing homes being urged to invest in this type of non-pharmacological intervention (Dimitrijević, 2009; Marx et al., 2010). Further interest is being developed in technology-assisted therapy based on robots (Shibata and Wada, 2010).

1.9. Dementia and the general practice

1.9.1. Diagnosis

Although potentially more demanding to achieve, early diagnosis by the GP can be envisaged to maximize the person with dementia’s capacity to utilize the diagnosis more effectively. A considerable number of individuals with dementia are recognized to be aware of their experienced cognitive decline, regardless of whether a diagnosis has been given (Maguire et al., 1996; Down et al., 2002). Ensuring the timely availability of potentially effective anti-dementia drug treatments requires access to early detection in primary care for people with dementia, followed by specialist assessment.

1.9.1.1. Informal caregivers

In the majority of cases, patients with AD are cared for in the home by unpaid and untrained family members. In addition to the progressive deterioration in memory, cognition and functional ability seen in such patients, the disease also impacts on the caregiver and other relatives of the patient. The burden of caring is significantly increased by the need to take over, or supervise, the patient’s activities of daily living. In the early stages of AD, patients may no longer be able to prepare meals or use the telephone, and in the later stages may even be unable to wash, dress or toilet themselves. Behavioural disturbances, such as wandering, agitation and aggression, are also common and are often difficult to manage. This ‘caregiver burden’ is an important factor for physicians to consider when managing patients with AD (Wilkinson et al., 2004).
1.9.1.2. Caregiver burden

In a multinational study conducted in UK, Spain, Italy, France and Australia by Wilkinson et al. (2004) caring for an individual with dementia has been described as being tiring, demanding, depressing and frustrating. Half the caregivers said that they sometimes suffer depression and only a small portion of respondents used the words rewarding or fulfilling. Overall, the respondents to this study felt there was a burden placed on them as a caregiver (Figure 1.12).

![Figure 1.12. Caregivers' perceptions of the burden imposed by caring for a patient with Alzheimer's disease (Wilkinson et al., 2004).](#)

Not being able to have a social life or enjoying holidays, have also been associated by caregivers as patient care burdens along with not spending as much time with children or other dependents, financial considerations and giving up or reducing work (Wilkinson et al., 2004).

1.9.1.3. Caregiver sources of information on AD

In addition to information received from their doctor, most caregivers use Alzheimer’s associations to obtain information and advice about AD. Other popular sources of information
include magazine or newspaper articles and educational leaflets or booklets provided by their doctor. Carers also use Alzheimer’s associations for emotional support and counselling, in addition to disease education and information on new treatments and respite care (Wilkinson et al., 2004).

1.9.1.4. Caregiver feedback on medical AD care-system

In the same multinational study, a third of caregivers were dissatisfied with the time taken from first seeking help to diagnosis. However, the majority of caregivers were satisfied with the medication the patient was receiving, with the doctor currently treating the patient, and with the overall treatment the patient had received. When respondents were asked how confident they were concerning the skill of their GP in diagnosing and treating AD, around half responded positively, and around three-quarters agreed that GPs understand the impact AD has on both the patient and caregiver. Overall, caregivers perceived the specialists positively (Wilkinson et al., 2004).

1.9.1.5. Most commonly reported symptoms

Wilkinson et al. (2004) further reported that in most cases, the patient’s symptoms were first noticed by the caregiver being interviewed, with only 4% being noticed by the general practitioner. The symptoms most commonly reported to have first prompted caregivers to make the initial doctor’s appointment for the patient were forgetfulness or memory problems, difficulty performing everyday tasks (49%) and a change or decline in the patient’s behaviour.

In a separate study conducted in Greece, it was reported that the first individual to observe the symptoms of AD was the caregiver. The first symptoms reported were memory problems, followed by changes in personality, and deteriorating behavior. The behavioral problems (55%) and the depression (46%) which were observed led to seek the advice of a specialist (Tsolaki et al., 2009).
1.9.1.6. Time to first doctor’s appointment

One interesting finding was that a large percentage of Greek neurologists admitted that they would experience difficulties if they were asked to distinguish between normal symptoms of ageing and AD (Tsolaki et al., 2009). Renshaw et al. (2001) identified the need for more training in the early diagnosis of dementia among English GPs. An Irish study investigating screening diagnosing and disclosing dementia in the community indicated that most GPs had never undergone any dementia specific training and most of these expressed a desire for undergoing training. The study concluded that GPs experience difficulty diagnosing and disclosing dementia to patients (Cahill et al., 2006)

According to Wilkinson et al. (2004) only a small percentage of patients saw a doctor immediately. The average time from when symptoms were first noticed by the caregiver to making the first doctor’s appointment was 4 months. A quarter of caregivers waited more than one year before consulting a doctor, considerably delaying early diagnosis. On average, there was a six months delay from when symptoms were first noticed by the caregiver to the first appointment (Figure 1.13).
Figure 1.13. Average time from when the symptoms of AD were first noticed by the caregiver to the first doctor’s appointment (adapted from Wilkinson et al., 2004).

The Greek physicians also noticed that there is a delay in diagnosing, partly due to the patients’ hesitancy to seek help (Tsolaki et al., 2009).

In most cases, the GP is the first contact with the patient (Table 1.10.)

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>France</th>
<th>Italy</th>
<th>Spain</th>
<th>UK</th>
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</tr>
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<tr>
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<td>200</td>
<td>150</td>
<td>150</td>
<td>91</td>
<td>741</td>
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<td>14</td>
<td>28</td>
<td>26</td>
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<td>15</td>
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<tr>
<td>Number Geriatricians</td>
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<td>5</td>
<td>14</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
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<td>7</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1.10. Percentage of patients with Alzheimer’s disease, in different countries, who first presented to doctors from the listed specialties (GP: General practitioner) (Wilkinson et al., 2004).
1.9.1.7. Primary care knowledge about AD

Since most individuals with Alzheimer’s disease and their families are cared for in primary care clinics, there is increasing awareness on the role that primary care physicians have in the management of this condition. Studies assessing primary care physicians’ knowledge about AD have revealed important gaps, especially in symptom recognition and epidemiological and legal issues. Special attention has been devoted to the difficulties confronting primary care physicians in the diagnosis of the disease and its disclosure to patients and caregivers. Studies assessing the rate of recognition of dementia by primary care clinicians found that the disease is often not recognized, with the percentage of cases of undetected mild-to-moderate dementia ranging between 50% and 95%. However, the involvement of primary care physicians in the management of AD should not be restricted to diagnosis only but should also include treatment. Yet there is a dearth of evidence available regarding primary care physicians’ treatment preferences. Findings of a European survey regarding treatment patterns for AD found that although most physicians initiated pharmacological treatment soon after the diagnosis, general practitioners recommended less medication than did specialists (Werner, 2007).

In the majority of cases, the doctor with whom the patient first discussed their symptoms was not the doctor who eventually diagnosed AD. Patients initially presenting to a specialist were four times more likely to be diagnosed by the same doctor compared with patients first presenting to their GP (Table 1.11)

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>France</th>
<th>Italy</th>
<th>Spain</th>
<th>UK</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total n</strong></td>
<td>150</td>
<td>200</td>
<td>150</td>
<td>150</td>
<td>91</td>
<td>741</td>
</tr>
<tr>
<td><strong>Number GPs</strong></td>
<td>30</td>
<td>11</td>
<td>-</td>
<td>3</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td><strong>Number Neurologist</strong></td>
<td>19</td>
<td>63</td>
<td>73</td>
<td>76</td>
<td>9</td>
<td>52</td>
</tr>
<tr>
<td><strong>Number Geriatrician</strong></td>
<td>31</td>
<td>20</td>
<td>19</td>
<td>6</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td><strong>Number Psychiatrist</strong></td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>32</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 1.11.** Percentage of patients with Alzheimer’s disease who were diagnosed by doctors from the listed specialties: neurology, geriatrics and psychiatry (GP: General practitioner) (adapted from Wilkinson et al., 2004).
According to Wilkinson et al. (2004), the average time taken from when symptoms were first noticed to the diagnosis of AD was 12 months (Figure 1.14). Yet, a European study conducted in France, Germany, Italy, Spain, UK and Poland, by the same author, indicated a wide disparity between each country ranging from 10 months in Germany to up to 32 months in the UK (Wilkinson et al., 2005).

![Histogram showing average length of time taken from when symptoms were first noticed to diagnosis of Alzheimer's disease](image)

**Figure 1.14.** Average length of time taken from when symptoms were first noticed by the caregiver to diagnosis of Alzheimer's disease (adapted from Wilkinson et al., 2004).

### 1.9.1.8. Reluctance to diagnose AD

According to van Crevel and Van Gool (1997) physicians in the community are reluctant in diagnosing AD. The reasons can be various and include that there are no studies at levels of clinical efficacy relating to therapeutic (or counselling) impact or to patients' and caregivers' outcomes. Another important reason may be that once they made the diagnosis, physicians felt helpless and there was little more they could do. Further more, it has been suggested that not
only that AD can be diagnosed accurately but many diagnostic modalities themselves point
directly and usefully to AD course and treatment as well as the diagnosis. This can clearly
make a difference in patient care and the caregiver's understands of the patient's care needs
(Reisberg and Burns, 1997).

Views on dementia diagnosis were sought from over 1000 GPs across 12 health authorities in
England and Wales (Renshaw et al., 2001), with approximately half of respondents identifying
they did not believe early diagnosis was beneficial. Furthermore, in this survey most
respondents identified a need for more training in this area. A study in Scotland found that
GPs who reported that an early diagnosis of dementia was important were significantly more
likely to tell the diagnosis (Down et al., 2002).

1.9.2. Disclosure

1.9.2.1. Ethical concerns

Disclosure of Alzheimer's disease is a complex clinical and practical issue. There is a growing
discussion in the studies about the merits of disclosing the diagnosis to the person with
dementia. Some have attributed this growth to the fact that more and more people with
dementia are being identified at earlier stages, a trend that will only continue with advances in
drug treatments (Down et al., 2002).

1.9.2.2. Reversal of attitude in disclosure cancer diagnosis

A change of attitude toward disclosure of the diagnosis of medical conditions has become
apparent in the past few decades, from an attitude of medical paternalism to one that takes into
account patient autonomy. The best example of this shift comes from studies of cancer
patients. More than 45 years ago, Oken (1961) used a questionnaire to survey the attitudes of physicians regarding diagnosis disclosure of cancer and reported that 90% of doctors adopted the practice of not disclosing the diagnosis. The same questionnaire was administered 18 years later by Novack et al. (1979) to doctors working in a university hospital, and 97% indicated a preference for telling a cancer patient their diagnosis. This indicates an absolute reversal of attitude such that disclosure of cancer diagnosis by physicians has become the ethical norm.

The best practice in disclosure can be obtained from diagnostic disclosure practices with other groups (e.g. people with cancer). For example, the main features of breaking bad news in palliative care have been identified by Cheston and Bender (1999) as of value in the assessment of dementia. These include:

- providing sufficient time for individuals to explore the meaning and implications of the diagnosis,
- if desired, having a relative or caregiver present during the initial discussions of the diagnosis,
- providing sufficient information at the right time in ways that are easy for the patient and his or her family to access,
- encouraging the acceptance of emotional distress while allowing the possibility of hope to exist (Downs et al., 2002).

There is a compelling need to establish best practice in diagnosis disclosure to people with dementia and their families (Downs et al., 2002). The American Medical Association (AMA) guidelines for the diagnosis and treatment of dementia states that diagnosis should be given directly to the patient “if at all possible” (Guttman and Seleski, 1999). However, it has been suggested that these guidelines are inadequate to address the clinical complexities of this issue,
or to cater for the cultural diversity between countries or even within the same country, especially in view of the flow of migrants with distinct social and cultural backgrounds from developing to developed countries (Raicher et al., 2008). The British National Service Framework (NSF, 2001) for Older People identified:

- The importance of early diagnosis in enabling people and their family to respond effectively to the prognosis of dementia.
- That many people with dementia will be diagnosed and cared for within primary care, with the support of social services.
- That early diagnosis gives access to ‘treatment, planning of future care and helps individuals and their families come to terms with the prognosis’.
- That caregivers can become demoralized if early diagnosis is not offered and recognizes that the provision of support to caregivers is challenging, as the impact of the condition both upon the person with dementia and their family presents each with considerable adjustment challenges.

Moreover, the NSF clearly indicates that the treatment of dementia ‘always involves explaining the diagnosis to the older person and any caregivers and where possible giving relevant information about sources of help and support’.

1.9.2.3. Rate of disclosure among specialists

The issue of diagnosis sharing has appeared to split opinion equally amongst specialists. In the UK a total of 44% of respondents confirmed that it was their normal practice to inform patients with Alzheimer’s disease of their diagnosis (Clafferty et al., 1998). The authors identify the issue of informing such patients of their diagnosis as being difficult and plagued by ethical issues (Down et al., 2002).
A study in Nottingham, UK (Johnson et al., 2000) investigated current practice and attitudes among geriatricians and old age psychiatrists. The authors found that only 40% of these specialists regularly tell patients the diagnosis. However, 72.5% of the respondents stated that they would wish to know the diagnosis if they were suffering from the illness. Other studies in the UK examining the attitudes of general practitioners, geriatricians and psychiatrists have shown similar findings (Rice and Warner, 1994; Gilliard and Gwilliam, 1996; Rice et al., 1997; Vassilas and Donaldson, 1998; Pinner and Bouman, 2003).

In Brazil disclosure of AD diagnosis is not common among specialists. A recent study found that there were no significant differences between the three specialties: geriatricians, neurologists and psychiatrists, regarding the frequency with which they informed patients of their AD diagnosis. The trending revealed that only 44.8% of the physicians would regularly inform the patient of the diagnosis and almost all of them believe that patients wanted to know their diagnosis. Despite their usual practice, the majority of specialists would want to know their diagnosis if they themselves were affected by early AD, however, only 47.5% of them think that the patient would like to know. Within the group of those who rarely or never tell patients the diagnosis, 52.2% would like to know their diagnosis if they had early AD (Raicher et al., 2008).

1.9.2.4. Rate of disclosure in general practice

There is growing empirical evidence that general practitioners are reluctant to share the diagnosis with people with dementia. In Britain, a postal survey of 261 GPs in Cambridgeshire, found that 39% of those responding reported telling the diagnosis always or often. A similar percentage reported that they provided information about the prognosis always or often (Vassilas and Donaldson, 1998).
A study conducted in France (Cantegreil-Kallen et al., 2005) examined whether and how diagnosis of AD is disclosed by French general practitioners and found that a quarter of the physicians reported having disclosed diagnosis to their patient and one in ten reported not having communicated a diagnosis at all.

1.9.2.5. Disclosure to caregiver versus person with dementia

Most practitioners find disclosing AD to the patient very difficult. Consequently, diagnosis seems to be more often disclosed to caregivers than to patients, especially in general practice. In the French study, general practitioners were found to be less reluctant towards disclosing consequences of AD and its symptoms with caregivers rather than with patients (Cantegreil-Kallen et al., 2005).

A study in Scotland revealed a disparity between what general practitioners tell the family and the person with dementia. People with dementia tend to be given information about the symptoms and the cause is described predominantly as part of ageing. Almost all of the GPs reported that when they were sure that the person had a dementing illness they told the caregiver the diagnosis, while only slightly more than half of these told the person with dementia. The New England survey suggests that while just over half of GPs would tell the person their diagnosis, 90% of the same group would share this diagnosis with family members (Fortinsky et al., 1995). Alternatively, while 80% of GPs practicing in Australia see benefits in telling the person their diagnosis, the researchers gathered no information about such practices (Down et al., 2002).
1.9.2.6. Physicians’ age

Down et al. (2002) found that Scottish GPs who reported that they told the patient the diagnosis tended to be younger than GPs who withheld the diagnosis. Gender was found not to be associated with disclosure of diagnosis. Raicher et al. (2008) reported that in Brazil physicians’ age was correlated significantly to AD disclosure. When comparing younger (20 to 39 years) with older (40 to 79 years) specialized doctors, 32 of the former group and 49 of the latter responded that they always or usually tell the diagnosis, while 10 physicians of the younger and 36 of the older groups rarely or never tell.

1.9.2.7. Factors affecting disclosure decision

Difficulty in finding the right time for disclosure may arise if diagnosis is not obtained in time while the affected individuals can still understand the given information (Pinner, 2000). Raicher et al. (2008) summarized the following factors affecting doctors’ decision to disclosure: patient age, degree of certainty of the diagnosis of dementia, degree of certainty of diagnosis of type of dementia, state of patient’s finances, university degree, severity of dementia, patient’s express wish to be told or not, relative’s views about telling the patient, comorbidity or patient’s personality.

1.9.2.8. Caregiver’s views about telling the person with dementia

A Brazilian study revealed that disclosure of AD diagnosis to patients was approved by more than half of 40 family caregivers. Among Brazilians geriatricians the relatives’ views about telling the patient constituted the main deciding factor (Vilela and Caramelli, 2006).

The disclosure rates of the AD diagnosis to patients were not correlated to socioeconomic level. Indeed, few Brazilian specialists were influenced by the patients’ financial state (Raicher et al., 2008).
1.9.2.9. Patient’s opinion on disclosure

Professional opinion is increasingly in favor of the patient deciding whether to know about the diagnosis of dementia. General agreement favors giving people with mild dementia sufficient information to understand the diagnosis and prognosis unless providing such information would cause harm (Meyers, 1997; Rice et al. 1997; Post, 2000). Patient’s expressing their wish to be told was the main factor influencing disclosure among Brazilians specialits (Raicher et al., 2008). There is also evidence from healthy adults that they would like to know if they were diagnosed with AD (Erde et al., 1988).

1.9.2.10. Severity of dementia

The risks and benefits of being given diagnostic information vary according to the severity of dementia. Patients’ lack of insight and understanding represents an argument against disclosure of diagnosis. This idea supposes that disclosure makes sense only if the person with dementia still has the ability to understand the importance and consequences of the illness. The capacity of understanding seems to depend on severity of the disease. Studies results demonstrated that 30 to 61 percent of patients were still able to understand their condition (Cantegreil-Kallen et al., 2005) and individuals with mild dementia seem to want to know the diagnosis (Piner et al., 2003). Surveying geriatricians and psychiatrists Rice et al. (1997), found a relationship between disclosure of diagnosis and dementia severity: patients with mild and moderate dementia were told their diagnosis more frequently than patients with severe dementia. The severity of dementia was a factor that was taken into account more frequently by geriatricians and psychiatrists than by neurologists (Raicher et al., 2008).
Insight is varying from patient to patient without a clear relationship to the degree of experienced cognitive deterioration (Maguire et al., 1996). The study conducted by Ahujn and Williams (2000) has previously identified that the level of insight a person has regarding their progressive cognitive decline is an important determinant of the person’s reaction to disclosure.

Down et al. (2002) reported that Scottish GPs would tailor their responses to the person with dementia depending on factors such as their level of perceived awareness or insight.

Professionals including general practitioners might risk underestimating the patients’ understanding of the condition. Additional research is required to provide doctors with enough knowledge to effectively manage disclosure to individuals with dementia and their caregivers.

1.9.2.11. Concerns for Disclosure

To date, not enough research has been undertaken on how to decide whether dementia patient is competent to understand a diagnosis, or on how much information to convey. Pinner (2000) observed that doctors withhold diagnosis for fear of causing distress by telling the truth about dementia diagnosis. Ahujn and Williams (2000) highlighted the possible risk of depressive reactions and suicide in relation to disclosing a dementia diagnosis (Figure 1.15).
Figure 1.15. General concerns of physicians regarding disclosure of AD diagnosis (CDP: causing psychological distress; PRC: precipitating a catastrophic reaction; PDP: precipitating a depressive illness; SP: suicide of the patient; DEMP: destroying the patient’s hope or motivation) (Raicher et al., 2008).

Although physicians are aware of many benefits in disclosing, there were concerns regarding the certainty of diagnosis, the patients’ insight, and the possibility of causing distress and destroying hope or motivation (Raicher et al., 2008).

1.9.2.12. AD’s nomenclature employed to caregivers versus people with dementia

Despite the central importance of information for people with dementia and their families, relatively little research has examined what is told about the condition and even more little research has examined what GPs tell their patients and their families.

As indicated in Table 1.12, GPs in Scotland were more likely to assign the condition a medical label and to discuss its prognosis with families than with the diagnosed relative.
GPs knowingly avoid using medical terminology with people with dementia, tending instead to ‘normalize’ their experience. This is quite different from the more medical explanations given to the family or caregiver. These explanations by the GPs used more medical terminology, including words such as senile dementia or Alzheimer’s, or as precise a diagnosis as possible. Discussions with caregivers also indicated the likely progression of the disease and available support services were also mentioned as well as care issues. Thus GPs provide different explanations for the condition to people with dementia than to their families (Down et al., 2002).

In a French study, the expressions: “Alzheimer’s disease” was significantly more pronounced in the presence of caregivers, whereas the terms “memory problems” were used in disclosing the diagnosis to the patient. (Cantegreil- Kallen et al., 2005).

<table>
<thead>
<tr>
<th>Term</th>
<th>Person with dementia</th>
<th>Caregiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>Any medical term</td>
<td>44</td>
<td>96</td>
</tr>
<tr>
<td>Dementia</td>
<td>28</td>
<td>84</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>25</td>
<td>59</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Multi-infarct dementia</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Euphemistic terms</td>
<td>89</td>
<td>78</td>
</tr>
<tr>
<td>Memory problems</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td>Confusion</td>
<td>47</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 1.12. Employed nomenclature by Scottish general practitioners to caregivers versus people with dementia (Down et al., 2002).
In Scotland, general practitioners used euphemistic terminology in disclosing the diagnosis of dementia (Table 1.13) (Down et al., 2002).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Percentage (Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical terms</td>
<td>61.0 (36)</td>
</tr>
<tr>
<td>Dementia</td>
<td>37.3 (22)</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>37.3 (22)</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>11.9 (7)</td>
</tr>
<tr>
<td>Multi-infarct dementia</td>
<td>37.3 (22)</td>
</tr>
<tr>
<td>Euphemistic terms</td>
<td>94.9 (56)</td>
</tr>
<tr>
<td>Memory problems</td>
<td>93.2 (55)</td>
</tr>
<tr>
<td>Confusion</td>
<td>50.8 (30)</td>
</tr>
</tbody>
</table>

Table 1.13. Nomenclature employed by Scottish general practitioners who reported telling the diagnosis to people with dementia (Down et al., 2002).

In their survey of diagnostic disclosure policy in memory clinics in the UK, Gilliard and Gwilliam (1996) found that while most clinics have a policy of diagnosis disclosure to patients, few used medical terms such as Alzheimer's disease on disclosure.

The Brazil study revealed that majority of geriatricians, neurologists and psychiatrists would use clear terminology such as AD or dementia, with the rest using a variety of terms including “memory impairment,” “forgetfulness,” “senility” or “sclerosis” (Raicher et al., 2008). This contrasts with the findings from the UK study in which only a third of the physicians reported
this practice (Johnson et al., 2000). On analyzing the data Raicher et al. (2008) observed that the Brazilian study had a higher rate of academic affiliated doctors and that this difference might explain the divergence in the nomenclature employed. The fact that many of specialists have academic positions and teaching activities is important because their opinions and practices might influence a substantial number of other colleagues. Furthermore, the Brazilian study was conducted more recently, when terms like AD and dementia were more familiar to lay people may also have contributed to this discrepancy.

1.9.2.13. Disclosure of prognosis

There is evidence that a number of the GPs were aware of their need to offer reassurance to recently diagnosed individuals with dementia. The need for doctors to address the distress and be there for the patient, even if the diagnosis is not taken well, is an important aspect of the disclosure process (Pinner, 2000). The prospect of the person with dementia becoming dependent on others was identified in a number of responses including:

- this will require support and understanding of your family and caregivers,
- perhaps they will need a little input of health for their own safety,
- they may need help and support at home (Down et al., 2002).

The Scotish study (2002) revealed that the GPs’ descriptions of the effect of the condition on both persons with dementia and their families include a range of negative predictions for the future such as progressive and irreversible loss of mental abilities, personality and reasoning, thus help from outside will be required, or else, having dementia means no cure and it will only get worse.
There is also a body of literature (Kitwood, 1997; Snyder, 1999; Sabat, 2001) which explored the positive side to living with dementia and their active coping and resilience evident in both people with dementia and their families. However in 2002, a specific positive focus with the person was identified only by one Scottish respondent who stressed on the need to discuss the nature of condition, emphasizing the positive things that can be done to help rather than pointing to the negative aspect of the condition (e.g. the fact that no cure is available). The potential for positive adaptation was also identified by another respondent in talking to the person, explaining the need to reassure and discuss ways of helping to adapt to short-term memory loss.

1.9.2.14. Topics discussed during disclosure

Most doctors withheld a considerable amount of information from people with dementia, relying on symptom description and euphemisms rather than on factual medical knowledge (Down et al., 2002).

A study found that only a quarter of French GPs explained the nature of the illness, prognosis, and risk factors to the patient, while 90% explained these to the family. Respondents reported having addressed the issue of behavioral problems with 23% of the patients and 83% of patient caregivers.

Depression was discussed with approximately half of the patients and 85% of the caregivers. Stress was discussed with 79% of the caregivers. The possibilities of psychosocial care and support had been explained to patients (6%) and relatives (48%) by 65% of GPs (Cantegreil-Kallen et al., 2005).
In describing the information given to families, none of the Scottish GPs identified the specific issue of caregiver’s stress. The focus of responses appeared to centre on how caregivers may be supported in the practical elements of caring rather than identifying the possible emotional impact on the families themselves. Respondents did not appear to identify the need to protect family members through ‘normalizing’ statements or using softer language as an alternative to diagnostic terms (Down et al., 2002).

Caregivers complained about lack of information on prognosis and lack of consideration of the emotional aspects by the physician. The type of information relatives want to be told varies with time, but at time of disclosure, caregivers prefer information on the nature of the illness, behavioral symptoms, and prognosis (Connell et al., 2004).

1.9.2.15. Impact on Patients

Not enough research has been conducted on the impact of disclosing a diagnosis of dementia. Indeed, the need for additional information is crucial since it is still unknown the attitudes of patients and the actual emotional consequences of receiving diagnostic information (Raicher et al., 2008).

Positive reactions to disclosure have also been reported. These included: experiences of relief following the understanding of the problem and hence dissipation of doubt and uncertainty (Cantegreil-Kallen et al., 2005). In fact, the limited research evidence present suggests that people with dementia who get to know their diagnosis appear less troubled by the symptoms. Interviews with people with dementia who knew the diagnosis provide useful insights into the effects of sharing the diagnosis. Providing the diagnosis helps people with dementia making sense of what is happening to them. Not telling them the truth, or telling it in a vague way, seemed to produce anxiety and confusion (Down et al., 2002).
There is also evidence of negative consequences following disclosure to the patient with dementia. These included: denial or minimization of deficits, low self-esteem, self-stigmatization, fear of others finding out and associated social embarrassment, fear of not being listened to, fear of long-term dependency needs, somatic problems, depressive mood, and social withdrawal. No long-term damage has been found, and risks of major depression and suicide have been overestimated (Cantegreil-Kallen et al., 2005).

1.9.3. Pharmacotherapeutic management

Since guidelines (NICE, 2006) recommend referral to a specialist for initiation of treatment and specify that such treatment should only be started by a specialist in the field of dementia, general practitioners are reluctant to initiate treatment. It does follow that few studies about pharmacotherapeutic management by GPs in the primary setting were found in the literature.

1.9.3.1. The Role of General Practitioners in the Diagnosis and Treatment of Alzheimer’s disease (multinational study)

1.9.3.1.2. Medication recommended at diagnosis

In the multinational study conducted in France, Italy and Spain, Australia and UK, medication was recommended to the patient around the time of diagnosis. Specialists were more likely to recommend medication for AD than GPs (Figure 1.14) (Wilkinson et al., 2004).
This same study also indicated that when AD was diagnosed, medication was recommended to a higher proportion of patients in France, Italy and Spain compared to in Australia and UK. Almost one-third of the patients were not receiving any AD medication at the time of the study. According to the respondents, the main reasons given by doctors for not recommending medication at the time of diagnosis were that there was no cure currently available and that the disease was too advanced to warrant treatment. At the time of diagnosis, the majority of the patients were recommended AChEI. Patients with AD diagnosed by a specialist were more likely to be prescribed AChEI than those diagnosed by a GP. Persons with dementia younger than 80 years old were much more likely to be recommended AChEI at the time of diagnosis than older patients. The data also indicated that caregivers of individuals with dementia who were prescribed AChEI were less likely to have given up their jobs to care for the patient than those currently receiving another type of medication or those receiving no medication at all (Wilkinson et al., 2004).
1.9.3.2. Drug prescription in mild cognitive impairment: the physician’s perspective in Italy

Italian specialists prescribed cholinesterase inhibitors to almost all patients with AD but, interestingly, only to about one in four patients with MCI. Gingko and nootropics were prescribed infrequently, but in MCI two to three times more often than in AD. About one in four and one in ten MCI patients were prescribed SSRIs and benzodiazepines, a proportion similar to that observed in AD, while atypical and traditional neuroleptics are virtually never used in MCI patients. Vitamin E was prescribed to more than half of MCI and in about half as many AD patients. At the time when this study was carried out memantine was not approved for use and its prescription was not assessed (Table 1.14) (Frisoni et al., 2006).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>AChEI</th>
<th>Nootr</th>
<th>Gingko</th>
<th>SSRI</th>
<th>Benzos</th>
<th>Vit E</th>
<th>TA</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>27%</td>
<td>12%</td>
<td>9%</td>
<td>27%</td>
<td>9%</td>
<td>57%</td>
<td>Never</td>
<td>never</td>
</tr>
<tr>
<td>AD</td>
<td>90%</td>
<td>6%</td>
<td>3%</td>
<td>28%</td>
<td>10%</td>
<td>27%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.14. Drug prescription in mild cognitive impairment (MCI) by physicians in Italy (MCI: mild cognitive impairment, AD: Alzheimer’s disease, AChEI: acetylcholinesterase inhibitors, Benzos: benzodiazepines, Ginko: gingko containing drugs, TA: typical antipsychotics, AA: atypical antipsychotics, Vit E: Vitamin E) (adapted from Frisoni et al., 2006).

These results suggested that lacking approved or clearly effective drugs for cognitive symptoms, physicians respond with “analogy treatments” and by increasing the prescription of “accessory drugs”. Non-cognitive symptoms in MCI are managed virtually exclusively with SSRIs and benzodiazepines (Frisoni et al., 2006).

1.9.3.3. Specialists’ attitudes and perceptions regarding AD in Greece

In a recent study on the dementia management in Greece involving specialists (pathologists, neurologists and psychiatrists), primary caregivers, and the general public.
It was reported that the goals of a therapeutic regimen of the Greek specialists were to maintain functioning, to slow down the progress of AD overall, and to slow down memory loss (Tsolaki et al., 2009). An important issue that was emphasized by all Greek specialties was that although prescription of medication usually begins at first visit, most of the people with dementia visit a physician when they are already in the middle or the final stages of the disease, a trend that makes treatment more challenging. Usually medications relevant to AD are prescribed. However, most of psychiatrists also prescribe antidepressant medications and vitamins. Most medications are rather expensive and because most individuals visit their physician at middle-to-late stages of AD the cost/benefit ratio is very low. Considering these factors, there is a trend to under-prescribe AD modifications because they are expensive and there are reimbursement issues from insurance companies in Greece (Tsolaki et al., 2009).

1.9.3.4. Pharmacological Treatment Strategies of Residential Primary Care Providers in Dementia Diseases (Western Austria study)

The vast majority of primary care providers prescribe nootropic drugs where approximately two thirds of the primary care providers prescribe acetylcholinesterase inhibitors. The dementia subtype influences the prescription frequency of acetylcholinesterase inhibitors, but not the specific choice of nootropic compound. Half of the primary care providers combined anti-dementia drugs (Gurka et al., 2002).

Nearly two-thirds of all primary care providers frequently prescribed antidepressants, most of which are specific serotonin reuptake inhibitors, applied by the majority of primary care providers. The remaining one-third preferred tricyclic antidepressants (Gurka et al., 2002).

Antipsychotics are applied frequently by around a quarter of all Austrian physicians. More than half of primary care providers and internists treat patients with typical antipsychotics. Psychiatrists and neurologists are significantly more reluctant to prescribe tricyclic antidepressants and typical antipsychotics. Despite the lack of scientific evidence, residential primary care providers combine anti-dementia drugs very frequently. In contrast to
neurologists and psychiatrists, primary care providers and internists frequently prescribe tricyclic antidepressants and typical antipsychotics. (Gurka et al., 2002)

1.9.3.5. Prescribing patterns for AD (Survey of Canadian family physicians)

An interesting discordance in prescription of AChEIs for individuals with AD was noticed in a Canadian study. About 27% of GPs reported that AChEIs were prescribed for less than 10% of AD individuals while 12.5% reported that AChEIs were prescribed for more than 90% people with AD. The formulary coverage was making such a difference. GPs prescribed more AChEIs in the two regions with provincial formulary coverage than in the two regions without coverage. Factors that significantly predicted lower prescribing rates included female sex, perception of AChEIs’ effectiveness, and self-reported knowledge of AChEIs (Hilmer et al., 2006).

The most important factors Canadian GPs reported as being very or extremely important in their decisions to prescribe AChEIs were the expected effect on cognitive status, persons with dementia or caregivers ability to comply with medical regimens, the severity of the dementia, the severity of behavioural symptoms, and the availability of insurance coverage for the drug (Hilmer et al., 2006).

1.9.4. Non pharmacological management

1.9.4.1. Family Physicians’ Recommendations for the Treatment of Alzheimer’s Disease (Israeli study)

Engagement in social activities and participation in a support group were the treatment approaches most often recommended, while the use of physical restraints and isolation were the least recommended. The Israeli study indicated that GPs recommended more group activities and vitamins than restraint, pharmacological, or relaxation interventions. The results
of the Israeli study show that in the treatment of dementia, non-pharmacological or lifestyle interventions are also highly recommended by professionals. Studies assessing their knowledge and practice in the management of AD have shown that primary care physicians are knowledgeable about anti-dementia drugs but are limited in their awareness of available social and support services. Male physicians recommended more vitamins and natural herbs and more meditation and relaxation techniques than did female physicians. It is not clear why male physicians were found to recommend more these non-pharmacological interventions but it is possible that the difference between the genders stems from the fact that the male physicians were older than the female physicians. Additional research should throw more light on the role of physicians’ gender in their recommendations for AD treatments. Regarding the use of relaxation and meditation techniques, it was found that only a small percentage of the physicians in the study recommended these for the management of dementia. This finding is given that sensory enhancement and relaxation interventions (such as massage and touch, white noise, and individualized music) are reported to be effective interventions in the management of dementia, even in its advanced stages (Table 1.15) (Werner, 2007).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Not recommended (%)</th>
<th>Recommended (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engagement in support group</td>
<td>12.5</td>
<td>76.2</td>
</tr>
<tr>
<td>Engagement in social activity</td>
<td>4.1</td>
<td>83.9</td>
</tr>
<tr>
<td>Vitamins</td>
<td>31.1</td>
<td>42.0</td>
</tr>
<tr>
<td>Natural/herbal medications</td>
<td>57.9</td>
<td>18.6</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>59.5</td>
<td>24.0</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td>37.4</td>
<td>37.9</td>
</tr>
<tr>
<td>Relaxation</td>
<td>59.9</td>
<td>18.9</td>
</tr>
<tr>
<td>Sleeping pills</td>
<td>42.3</td>
<td>25.8</td>
</tr>
<tr>
<td>Yoga or meditation</td>
<td>77.7</td>
<td>8.9</td>
</tr>
<tr>
<td>Physical restraints</td>
<td>96.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Isolation</td>
<td>96.7</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 1.15. Israeli general practitioners’ recommendations for treatment of AD (adapted from Werner, 2007).
1.9.4.2. Family physicians' perspectives on care of dementia patients and family caregivers (Canadian study)

On the use of community resources, Canadian GPs were aware of organizations such as Alzheimer societies but they were less knowledgeable of what these societies do, and rarely referred patients or families directly to them. Those in need were referred to a recognized caregiver support centre. The doctors' offices did not maintain any lists of community resources, handouts, or pamphlets for people with dementia or families. The doctors felt strongly that community information in "e-format" would not be helpful, though the younger generation of physicians will use it more frequently (Yaffe et al., 2008).

In a separate study in the US on GPs attitudes towards community resources, it was reported that few American GPs referred people with dementia to social workers or community agencies (Cody et al., 2002).

1.9.4.3. Respite care (Malta)

St. Vincent de Paul Residence is a Maltese residential complex for elderly providing a range of services, including respite and long-term care. Elderly respite users are a mixed group with multiple and diverse needs. Of the study group more than half of respite users were found to be suffering from moderate to severe dementia (MMSE 0-20). High dependency on the Barthel Index (0-7/20) was found in more than half of cases whilst 45% had low dependency.
<table>
<thead>
<tr>
<th>MMSE Score</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-30 (cognitively preserved)</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>21-23 (mild dementia)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>10-20 (moderate dementia)</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>0-09 (severe dementia)</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Not graded</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The Barthel Index of the Study Group (n=91) on admission

<table>
<thead>
<tr>
<th>Barthel Score</th>
<th>Total</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (independent)</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>13-19 (low dependency)</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>8-12 (medium dependency)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4-7 (high dependency)</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>0-3 (very high dependency)</td>
<td>26</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 1.16. Assessment for dementia based on MMSE scores in the Respite Study Group on admission (Dimech et al., 2009)

In their own homes, these care needs are principally met by informal helpers who are frequently under physical and psychological stress. Caregiver’ strain was reported in the majority of cases. The expansion of in-patient respite services will reinforce the informal community care network and will help avoid or postpone long-term institutionalisation. This gives caregivers time to recuperate physically, mentally and psychologically, hence enabling them to continue coping with the care of their dependent elderly. The main reasons behind requests for respite were included in Table 1.17.
<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Break in care</td>
<td>117</td>
<td>57</td>
</tr>
<tr>
<td>To go on holiday</td>
<td>49</td>
<td>24</td>
</tr>
<tr>
<td>Poor carer health</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Care conflict</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>To admit permanently</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Rehabilitation of the elderly dependent</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Convalescence after illness of dependent elderly</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>To have a trial in a Home</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1.17. Reasons given by caregivers for applying for respite care (Dimech et al., 2009).

Respite care not only provides relief to caregivers, but it also presents an excellent opportunity to expose dependent elderly to a multi-dimensional assessment (Dimech et al., 2009).

1.10. The aim of the study

The main task of the study was to evaluate the local general practitioners’ perspective on diagnosis, disclosure and treatment of people with dementia giving particular importance on Alzheimer’s disease and to provide a comprehensive picture of the management of dementia in the Maltese islands. To the best of my knowledge, no local study to date has undertaken a similar assessment.
Chapter 2.

Methodology
2. Methodology

A postal questionnaire was sent to 346 General practitioners (GPs), all members of Malta College of Family Doctors (MCFD).

The general practitioner was chosen as test subject due to various advantages including the long-term knowledge of the patients, the ability to employ the primary health-care team in the investigation of the patient, and availability to visit the patients in their home (Fossan, 2000).

The GPs and the primary care team are uniquely situated to play a central role both in the diagnosis and ongoing management of dementia. GPs face several challenges in fulfilling this role and they should be supported to maximize their role in dementia diagnosis and management (Downs et al., 2002).

This study was based on a questionnaire since it is an inexpensive way to gather data from a potentially large number of respondents. Often it is the only feasible way to reach a number of reviewers large enough to allow effective analysis of the results. The questionnaire is a multi-stage process, beginning with the definition of the points to be examined and ending with interpretation of the results. It is a means of quick data collection, yet time consuming both in design and interpretation. Every step was designed carefully aware of the fact that the validity of the final results is dependent upon a questionnaire which is consistent throughout. The questionnaire was sent by normal mail and included a cover letter explaining the aim of this project and a self-addressed envelope.
2.1. Designing the questionnaire

A population of 346 general practitioners, 324 in Malta and 22 in Gozo, all members of the Malta College of Family Doctors participated in this study. This association was the officially recognised organization for general practitioners in Malta. The GP’s addresses were provided by Malta College of Family Doctors. The newly designed questionnaire was structured upon recognised guidelines (Joseph and Haire, 2003) and was designed along similar studies conducted elsewhere. In order to quantify the responses (either forced choice or multiple-choice format) the questions were in closed-ended format. A pilot study involving five questionnaires was conducted with the result that the questionnaire was shortened so to enhance response rate. The questionnaire was in English language due to the ambiguity of Maltese terminology with most of the text. Some of the terminology used does not have a counterpart in the Maltese language. The ethics committee recognised this and approved the non-use of a Maltese version.

The covering letter and the questionnaire provided instructions on how to answer and return the questions. Similar studies carried out elsewhere focused on specific themes relating to the clinicians’ approach to dementia (such as diagnosis, disclosure and treatment) rather than treating the theme together. Some studies concentrate on primary care management while others focus specifically on tertiary care centres. The questionnaire was anonymous in that respondents could not be tracked thus protecting both physician and the patients. Questions were not formatted in a way to examine knowledge but to summarise conclusions regarding dementia management. The contents of the questionnaire were approved by the University of Malta Research Ethics Committee (see Appendix II).

To enhance the response rate, follow-up reminders were sent via e-mail to all the members of Malta College of Family Doctors with the support of MCFD President. A note in the Synapse Magazine was posted with the support of the editor who had also sent reminders via e-mail to all members of The Synapse Magazine and to other members of this publication and to other members of the Association of Private Family Doctors.
Out of a total of 346 questionnaires, 145 were returned (response rate 42%). From these, 14 were invalid, either due to change of address or retirement (Table 2.1). Therefore, the remaining questionnaires (n=131) were considered to be valid and thus analyzed. Return of the questionnaire was a voluntary way to opt-in the study.

<table>
<thead>
<tr>
<th>Reasons</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>The post office returned 9 undelivered envelopes for the reasons stated below:</td>
<td></td>
</tr>
<tr>
<td>8 envelopes – ‘Gone away’;</td>
<td>9</td>
</tr>
<tr>
<td>1 envelope - ‘Gone away’, plus ‘Letter box full up’;</td>
<td></td>
</tr>
<tr>
<td>4 doctors reported that they were retired</td>
<td>4</td>
</tr>
<tr>
<td>1 doctor reported being no longer GP but working in Public Health</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2.1. Number and reasons of disqualified questionnaires

2.2. Analyses of the questionnaire

Descriptive analyses were carried out by computing frequencies and proportions. The means of continuous variables were estimated with 95% confidence level. The confidence level it is expressed as a percentage and represents how often the true percentage of the population would pick an answer within the confidence interval. The Confidence interval is the margin of error reported in opinion poll results. The three factors that determine it: the sample size, percentage and population size are represented in the Table 2.2. This proves that the sample collected was representative over the whole population.

<table>
<thead>
<tr>
<th>Confidence level</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>131 GPs</td>
</tr>
<tr>
<td>Population</td>
<td>346 GPs</td>
</tr>
<tr>
<td>Percentage</td>
<td>50%</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>6.76</td>
</tr>
</tbody>
</table>

Table 2.2. Study's confidence interval

Data was double inputted in Excel 2007 and also in SPSS 15, ensuring data reliability. Frequency distribution was used to describe the responses to a particular variable by
Data was double inputted in Excel 2007 and also in SPSS 15, ensuring data reliability. Frequency distribution was used to describe the responses to a particular variable by displaying the counts and percentages after adjustment for no responses. Pie charts displayed relative proportions of the responses and vertically bar charts showed absolute and relative magnitudes.

2.2.1. Data preparation

Data was analyzed using iterative thematic analysis. Prior to data analysis, the data has been examined to ensure its validity. Blank responses were referred to as missing data and inputted into the data base as “no response”. The respondents were number coded from 1 to 131. To ensure correct coding and data entry the questionnaires actual database was doubled checked for possible errors. Coding was also used for general practitioners’ area of practice (Table 2.3).

<table>
<thead>
<tr>
<th>Code</th>
<th>The locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No response</td>
</tr>
<tr>
<td>1</td>
<td>Northern Harbour – Ta’ Xbiex, Swieqi, Sliema, Santa Venera, San Ġwann, St.Julians, Qormi, Pieta’, Pembroke, Msida, Ilamrun, Gżira, Birkirkara.</td>
</tr>
<tr>
<td>2</td>
<td>Northern – St. Paul’s Bay, Naxxar, Mosta, Mgarr, Mellieha, Gharghur.</td>
</tr>
<tr>
<td>4</td>
<td>South Eastern – Żurrieq, Ħejtun, Safi, Qrendi, Mqabba, Marsaxlokk, Marsascala, K稠kop, Gudja, Ghaxaq, Birżebbuġia.</td>
</tr>
<tr>
<td>5</td>
<td>Western – Żebbug, Siggiewi, Rabat, Mtarfa, Mdina, Lija, Iklīn, Dingli, Balzan, Attard.</td>
</tr>
<tr>
<td>6</td>
<td>Gozo and Comino</td>
</tr>
<tr>
<td>7</td>
<td>More than 2 regions (The category “more than two regions” grouped all the GPs who had provided the following information about their region of practice: south, north or central of Malta.)</td>
</tr>
</tbody>
</table>

Table 2.3. General practitioners’ area of practice.
2.2.2. Questionnaire structure and content

The questionnaire containing a total of 30 questions was divided in four sections (see Appendix IV).

2.3. Demographic data

This was the first section and had three closed format questions with forced choice responses and one open format question. This data was collected at the beginning of the questionnaire in order to stratify the sample into groups which could later help in correlation of responses to demographic subsets. Questions included gender, age group and GPs’ experience in medicine. The town/ village/ region of practice was also determined via an open format question.

2.4. Diagnosis

The diagnosis section had eight closed format questions with single choice or multiple-choice format responses. This section was important to identify the role of local general practitioners in the diagnosis of dementia, especially Alzheimer’s disease. Questions included a list of symptoms associated with dementia which GPs were prompted to select actions they would take into furthering their quest for a definite diagnosis and initial management of the case and examination techniques required in assessing the GPs’ perception of the disease.

Considering there is no current definite test which can conclusively confirm Alzheimer’s disease, the GPs were invited to prompt out which other pathologies they would need to exclude before clinical diagnosis of a dementia. Furthermore, the cardinal clinical symptoms of Alzheimer’ disease were listed differentiating AD per se from cognitive impairment in general.

In view of the detrimental progression of Alzheimer’s disease with severe limitations at its
end-stages, the opinion of the GPs about the early diagnosis was sought. Early diagnosis can have both advantages and hazards, enlisted statements seek to provoke the response of the GP. Advantages proposed included: early initiation of treatment, postponement and precluding costly institutionalization. Most licensed anti-dementia drugs are known to be effective in the early stages of the condition and early diagnosis will enhance the pharmacotherapeutic outcome. Other questions tackled the issues of an altered doctor-patient relationship, further investigation of other pathologies, fear of the consequences of misdiagnosing dementia and the current role of the GP in the community care of the AD’s patient.

2.5. Disclosure

This section had nine closed format questions and the responses are either forced choice or multiple-choice format.

The GPs were asked if they think it was ethical to inform the patients about their diagnosis. This part of the questionnaire was intended to identify if in the Maltese islands the diagnosis of Alzheimer’s disease is routinely disclosed or whether the health care professionals should seek to understand their patients' preferences and act appropriately according to their choice. The terminology usually used in disclosing Alzheimer’s dementia was also addressed. GPs were asked if they believe that giving the true diagnostic and prognostic information can influence the patients’ cooperation in therapeutic management and if they were more likely to disclose upon correct diagnosis of dementia. The GPs were also asked if they noticed any improvement in the care of AD’s patients and their carers following diagnosis disclosure.
2.6. Non-pharmacological and pharmacological management

This part of the questionnaire tried to assess general practitioners' attitude towards non-pharmacological and pharmacological interventions in the management of dementia. A total of nine closed-format questions with forced-choice or multiple-choice format responses included. Several international guidelines are available which establish different timelines of follow-up depending on the stage of disease management and course of treatment. No such local guidelines are present, and it was interesting to assess whether the local GPs are following any of the recognized guidelines available or whether follow-up is random or self-imposed. Once treatment is initiated, the NICE guidelines suggest follow-up every two to four months till maintenance dosage is achieved and then every six months. Part of this section involved the non-pharmacological management of AD. Questions related to services present in Malta and Gozo, referral trends within the community and their opinion regarding the efficiency of available services were included.

While no drug has been shown to cure AD, pharmacological agents that inhibit the degradation of acetylcholine within the synapse or block glutamate-induced cytotoxicity are the mainstay of treatment of Alzheimer's disease (Delagarza et al., 2003). This statement introduced the set of questions regarding pharmacological management. Based on extensive review of recent research, the GPs were presented with a list of drugs that are used in the pharmaco-therapeutic management of dementia, with proven and unproven benefits.

Questions related to prescription trends should assess:

- Whether treatment of MCI and mild-to-moderate AD considered to be the same
- The preferred initial treatment of AD at different stages in the community vis-à-vis specialised treatment
- The use of pharmacological agents proven agents like acetylcholinesterase inhibitor and NMDA receptor antagonists in the community
- The use of agents like nootropics and gingko and Vitamin E
Other agents used in controlling the behavioural symptoms such as benzodiazepines and antidepressants

Questions were also asked to determine the rationale of treatment. Some GPs would look for symptomatic amelioration; others aim specifically at cognition while others seek to keep the patient in the community as much as possible. Acetylcholinesterase inhibitors and NMDA receptor antagonists are available in the community as an out of pocket expense. Although these drugs can be prescribed by any doctor, the NICE guidelines specifically suggest that these should be only indicated by relevant specialists. The opinion of GPs was sought in this regard as well as the reasons on selecting a particular pharmacological agent over another. Schedule V coverage of anti-dementia drugs has been on many occasions requested by the Malta Dementia Society yet to date these drugs have still to be purchased. Due to the cost, most guidelines suggest discontinuation of therapy when dementia is severe, when deterioration persists despite of treatment or when overall MMSE scoring is below 12 (NICE) or 10 (Alzheimer’s Disease Managed Care Advisory Council, 2006). Physicians’ judgment is also crucial.

The last part of this was intended to assess alternative ways of cognitive and functional therapies available and whether the local GPs consider these to be of any relevance with or without conjoint pharmacological therapy.
Chapter 3.
Results
3. Results

3.1. Demographic data

One hundred thirty one questionnaires were valid and this was considered to be the total number of respondents of which 73.3% were male (Figure 3.1).

![Figure 3.1. Gender of respondents to valid questionnaires (n=131).](image)

According to respondents' medical experience, 74% of GPs had 15 years or more medical experience and 26% were practicing medicine for 6-14 years. The category 1-5 years experience in general medical practice did not show any respondents. This is because the questionnaire was only distributed to members of Malta College of Family Doctors, who were qualified specialists in family medicine. The doctors in the subgroup 1-5 years experience were not in this list as they were all still trainees (Figure 3.2).
Approximately 92% of GPs area of practice was located in Malta with the remaining 8% located in Gozo (Figure 3.3).
The majority of participants indicated their area of practice as being located in the northern (35.9%) and southern (27.8%) regions of Malta and 7.6% indicated that they practice medicine in more than one region (Table 3.1).

<table>
<thead>
<tr>
<th>NSO regions</th>
<th>Locations</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH</td>
<td>Ta’ Xbiex, Swieqi, Sliema, Santa Venera, San Ġwann, St.Julians, Qormi, Pieta’, Pembroke, Msida, Hamrun, Gżira, Birkirkara</td>
<td>25.2</td>
</tr>
<tr>
<td>N</td>
<td>St. Paul's Bay, Naxxar, Mosta, Mġarr, Mellieħa, Gharghur</td>
<td>10.7</td>
</tr>
<tr>
<td>SH</td>
<td>Zabbar, Xgħajra, Valletta, Tarxien, Santa Luċija, Paola, Marsa, Luqa, Kalkara, Senglea, Floriana, Fgura, Cospicua, Vittoriosa</td>
<td>17.6</td>
</tr>
<tr>
<td>SE</td>
<td>Żurrieq, Zejtun, Safi, Qrendi, Mqabba, Marsaxlokk, Marsascala, Kirkop, Gudja, Ghaxaq, Birżebbugia</td>
<td>9.9</td>
</tr>
<tr>
<td>W</td>
<td>Zebbug, Siggiewi, Rabat, Mtarfa, Mdina, Lija, Iklin, Dingli, Balzan, Attard</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>Gozo and Comino</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>More than 2 regions</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Table 3.1. General practitioners’ location of practice, according to National Statistics Office (NSO) regions data (2009) (NH: Northern Harbour, N: Northern, SH: Southern Harbour, SE: South Eastern, W: Western). More than 2 regions is the category which grouped all the GPs who stated that their region of practice was north, south or center of Malta.

3.2. Diagnosis

Approximately 56% of GPs indicated that they need more training in diagnosing dementia. A further 14% of participants were not sure if they need more training. The remaining 29% of GPs believed that they have enough training in diagnosing dementia (Figure 3.5).
The symptoms associated with dementia which elicited the suspicion of cognitive impairment by GPs include: loss of memory (90.1%), followed by behavioural difficulties (77.1%), apraxia and agnosia (24.4%), and dysphasia (19.8%). Loss of memory and behavioural difficulties together, suggested the possibility of cognitive impairment only by 44.3% GPs (Figure 3.6).
Figure 3.6. Percentage of General practitioners (GPs) indicating various symptoms combinations observed in dementia. Only combinations that showed a response are indicated (A: Loss of memory, B: Behavioural difficulties, C: Dysphasia, D: Apraxia and Agnosia, N/A: No response).

However, on its own or in combination, loss of memory option was chosen by 90% of GPs and behavioural difficulties by 77% of GPs, denoting a belief that these two symptoms are of particular importance in the diagnosis of dementia (Figure 3.7).
GPs initial course of action in the management of dementia indicated a preference towards general physical examination (62.6%) followed by interview with family as second option (36.1%). The third and fourth options taken were shared between bio-chemical investigations (32.7% and 31.7% respectively) and psychometric tests (24.8% and 25.7% respectively). The fifth and sixth options taken were shared between referring to specialist (34.8% and 32.1% respectively) and waiting and observing (22.7% and 27.3% respectively). These results may indicate a tendency by the respondents to diagnose within the community instead of referring the individual to a specialist in the dementia field. Of particular interest is that 13.6% of GPs indicated that they would wait and observe the progress of the symptoms as their first choice (Figure 3.8).
Figure 3.8. Percentage of general practitioners (GPs) indicating different options in the management of dementia (1st: first action taken, 2nd: second action take, 3rd: third action taken, 4th: fourth action taken, 5th: fifth action taken, 6th: sixth action taken, N/A: No response).

More than half of GPs (55%) considered that psychometric testing helps in assessing severity of dementia. Approximately 41.2% considered it essential for follow-up, as well as essential for confirming diagnosis (34.4%). The remaining GPs considered psychometric testing not readily available (27.5%), time-consuming (13.7%) and inefficient and non-specific (3.1%) (Figure 3.9).
Figure 3.9. General practitioners’ (GPs) opinion about the psychometric testing (A: Not readily available, B: Inefficient and non-specific, C: Time-consuming, D: Helps assessing severity of dementia, E: Essential for follow-up, F: Essential for confirming diagnosis, N/A: No response). Only the first option as selected is included.

Interestingly, 19.1% of GPs who considered psychometric testing essential for follow-up and for confirming diagnosis also considered it time-consuming (Figure 3.10).

Figure 3.10. General practitioners’ (GPs) multiple opinion of psychometric testing (A: Not readily available, B: Inefficient and non-specific, C: Time-consuming, D: Helps assessing severity of dementia, E: Essential for follow-up, F: Essential for confirming diagnosis, N/A: No response). Only combinations that showed a response are indicated.
Pathologies excluded prior to clinical diagnosis of dementia included: intracranial lesions (87.8%), depression and psychosis (84.7%), hypothyroidism (76.3%), side effects of medication (71.8%), Parkinson’s disease (64.1%) and vitamin B₁₂ deficiency (58.8%) (Figure 3.11).

![Figure 3.11. Pathologies excluded as first choice to diagnosing dementia (A: Vitamin B₁₂ deficiency, B: Hypothyroidism, C: Depression and psychosis, D: Side effects of medication, E: Intracranial lesions, F: Parkinson’s disease).](image)

Only 39% of GPs excluded all the conditions listed in the questionnaire. Figure 3.12 shows all the combination of pathologies excluded by the local GPs before reaching the diagnosis of dementia.
Figure 3.12. Combination of pathologies excluded before reaching the diagnosis of dementia. (A: Vitamin B₁₂ deficiency, B: Hypothyroidism, C: Depression and psychosis, D: Side effects of medication, E: Intracranial lesions, F: Parkinson’s disease, N/A: No response, Others: a group of 16 other options). Only combinations that showed a response are indicated.

Figure 3.13 shows the GPs response to the clinical symptoms that are observed in AD. The majority of respondents (93.1%) indicated loss of short-term memory to be an important clinical sign in dementia. This was followed by difficulty in concentration (70.2%), inability to acquire new information (64.9%) and apraxia and agnosia (45.0%).
Only 27% of GPs have selected all the clinical deficits normally associated with Alzheimer’s disease (Figure 3.14).

The GPs opinion about early diagnosis of AD was that it: may postpone or preclude costly
institutionalization (88.5%), may lead to under diagnosis of other pathologies (26%), may lead to labeling and alteration of the doctor-patient relationship (9.9%) and AD is untreatable so no need to diagnose (3.1%) (Figure 3.15).

Figure 3.15. General practitioners’ (GPs) perception about early diagnosis of AD (A: AD is untreatable so no need to diagnose, B: It may lead to under diagnosis of other pathologies, C: Early treatment may postpone or preclude costly institutionalization, D: It may lead to labelling and alteration of the doctor-patient relationship, N/A: No response). Only combinations that showed a response are indicated.

In response to what factors were most helpful in looking after patients with AD, 75.6% of GPs indicated that a protocol for assessment and diagnosis of AD would be helpful. This was followed by the need of having information about community-based care and social services (69.5%), having a specialized nurse in mental health (53.4%) and the availability of a central register of residential and nursing home facilities (39.7%). All the above were found most helpful by 30% of respondents (Figure 3.16).
Figure 3.16. General practitioners’ (GPs) views regarding added services in AD’s community management. (A: Information about community-based care and social services, B: Central register of residential and nursing home facilities, C: Specialised nurse in mental health, D: Protocol for assessment and diagnosis of AD, N/A: No response). Only combinations that showed a response are indicated.

3.3. Disclosure

This section of the questionnaire sought to provide information about dementia disclosure patterns by GPs in the Maltese Islands. More than half of the respondents (59.5%) indicated that disclosure depends on the merits of each case. This was followed by ethical reasons (35.9%), an agreement between doctor and relatives (25.2%) and personal judgment (8.4%), (Figure 3.17).
Only 29% of GPs indicated that they are routinely disclosing the diagnosis of Alzheimer’s dementia, while 40.5% of GPs seek to understand the patients' preferences and act appropriately according to their choice, followed by 20.6% who believed that providing disclosure information depends on the level of impairment. A small percent (8.4%) were not sure if they should routinely disclose the diagnosis of AD or any other form of dementia (Figure 3.18).
Figure 3.18. General practitioners’ (GPs) first choice on disclosure practice (A: Yes, B: No, I'm seeking to understand patients' preferences, C: No, depends on the level of impairment, D: Not sure, N/A: No response).

The terminology that is routinely used by the respondents in disclosing dementia include: dementia (53.4%), memory problems (41.2%), slowing down due to aging (23.7%), Alzheimer’s disease (22.1%) and cognitive problems (13.7%) (Figure 3.19).
Figure 3.19. General practitioners’ (GPs) first preference on terminology used in disclosing Alzheimer’s dementia (A: Others, B: Slowing down due to aging, C: Cognitive problems, D: Memory problems, E: Dementia, F: Alzheimer’s disease).

Only 6% of GPs are using both dementia and Alzheimer’s disease as terminology in their disclosure (Figure 3.20).
Figure 3.20. General practitioners' (GPs) terminology used in disclosing Alzheimer’s dementia (A: Others, B: Slowing down due to aging, C: Cognitive problems, D: Memory problems, E: Dementia F: Alzheimer’s disease, N/A: No response). Only combinations that showed a response are indicated.

More than half (52.7%) of GPs considered that giving the true diagnostic and prognostic information to the patients depends on the level of impairment. Increased patients’ cooperation in therapeutic management resulting from true disclosure information was perceived to be true by only 20.6% of GPs. Fewer (13.7%) were not sure whether this information helped. A similar number of GPs (13.0%) did not believe that such information was beneficial (Figure 3.21).
Figure 3.21. General practitioners' (GPs) perception of benefit of full disclosure

The GPs were more likely to disclose the diagnosis of dementia if they were sure the patient had AD or other form of dementia (60.3%) then if they suspecting it (27.5%), where 6.9% of GPs reported that would rather not disclose (Figure 3.22).

Figure 3.22. Disclosure of Alzheimer’s dementia by GPs based on diagnosis

The majority of GPs (64.9%) indicated that they would prefer disclosing information on diagnosis and prognosis of AD to the patient and caregivers, whereas 31.3% of GPs would
prefer disclosing diagnosis to the caregivers and only 3.1% of GPs reported disclosing to the patient (Figure 3.23).

![Pie chart showing subject preference of AD disclosure by GPs](image)

**Figure 3.23.** Subject preference of AD disclosure by GPs

Approximately 38% of GPs noticed improvement in care of AD patients and their carers from diagnosis disclosure, while 16.8% did not. The majority of GPs (43.5%) were unsure about the outcome of disclosure (Figure 3.24).
Topics that were mostly discussed by GPs with caregivers on dementia disclosure included: progress of dementia (86.3%), caregiver health issues (70.2%), using reminder aids (65.6%) and financial planning (48.1%) (Figure 3.25).

Figure 3.24. Disclosure by GPs as a tool in AD’s management

Figure 3.25. General practitioners’ (GPs) first choice on management issues discussed with the caregivers (A: Caregiver health issues, B: Progression of dementia, C: Financial planning, D: Using reminder aids).
All above mentioned management issues were discussed by only 37% of GPs (Figure 3.26).

Figure 3.26. Issues discussed with the caregivers. (A: Caregiver health issues, B: Progression of dementia, C: Financial planning, D: Using reminder aids, N/A: No response). Only combinations that showed a response are indicated.

The majority of the GPs believed that disclosure of Alzheimer's disease may help the patient and caregivers in future planning and treatment decisions (94.7%). This was followed by 23.7% of GPs who believed that disclosure may evoke anxiety and/or depression altering patient's direct relationships. A lower number of GPs (13.0%) believed that disclosure should be withheld if relatives request so, whereas another 12.2% believed that disclosure may lead to social stigma. None of the respondents believed that because AD is untreatable it shouldn't be disclosed.
Figure 3.27. Alzheimer’s disease disclosure concerns by General practitioners (GPs). (A: It may evoke anxiety and/or depression altering patient’s direct relationships, B: It may help patient and caregivers in future planning and treatment decisions, C: It may lead to social stigma D: Should be withheld if relatives request so, E: AD is untreatable so why disclose, N/A: No response). Only combinations that showed a response are indicated.

3.4. Pharmacological and non-pharmacological management

This last section of the questionnaire tried to produce information on patterns and trends relating to pharmacological and non-pharmacological intervention in the management of AD.

3.4.1. Pharmacological management

In this study, GPs were presented with a list of drugs that are used in the pharmacotherapeutic management of dementia. Results indicated that 49.6% of GPs preferred AChEI as first choice in the management of mild dementia. Nootropics were selected by 26%. Only 3.1% of GPs
indicated a first preference for memantine. Interestingly, 68.7% of GPs indicated AChEIs for MCI as either their first, second and third choice. This was followed by nootropics (45.1%), Ginko (20.6%), SSRIs (19.1%), memantine (15.3%), benzodiazepines (9.9%) and vitamin E (7.6%) (Figure 3.28).

In mild to moderate AD, 64.9% of GPs indicated AChEI as their first choice of pharmacotherapy. Only 1 in 10 GPs indicated a preference for memantine whereas, nootropics were selected by 6.1%. Interestingly, 76.3% of GPs indicated AChEIs for mild-to-moderate AD as either their first, second and third choice, followed by memantine (35.9%) and nootropics (29%). SSRIs were preferred as one of the choices by 18.3% of GPs (Figure 3.29).
AChEI were indicated as first choice in the management of severe dementia by 39.7% of GPs. Only 30.5% of GPs indicated a preference for memantine. Nootropics were selected by 3.8% of GPs. Interestingly, 57.3% of GPs indicated AChEIs for severe dementia as either their first, second and third choice. This was followed by memantine (44.3%), nootropics (18.3%), SSRIs (17.6%), typical antipsychotics (9.9%), atypical antipsychotics (9.9%), tricyclic antidepressants (3.8%), vitamin E (3.1%) and Gingko drugs (2.3%) (Figure 3.30).
The majority of GPs (67.2%) indicated that their main aim of treatment in AD was: to keep the patient in the community as much as possible. This was followed by patient’s functional ability improvement (59.5%), patient’s cognition improvement (38.2%) and improvement in behavior (38.2%). All the above options were considered by 25% of GPs (Figure 3.31).
Figure 3.31. General practitioners’ (GPs) main aim of pharmacotherapeutic intervention in AD. (A: Delay in institutionalisation, B: Functional ability improvement, C: Improvement in behaviour, D: Improvement of cognition, N/A: No response). Only combinations that showed a response are indicated.

With regards to AChEIs in AD patients, more than half of the GPs tend to prescribe them relying on evidence-based data (68.5%). Other trends included cost-effectiveness (38.2%) and formulation (5.4%). A significant number of GPs (27.2%) indicated that they would always prescribe if the condition is recognized in the Schedule V list. Only 40 GPs (31.0%) considered that the drugs should be prescribed only by relevant specialists (Figure 3.32).
Figure 3.32. General practitioners’ (GPs) perception on AChEIs in AD patients. (A: They should be initiated only by relevant specialists, B: I would always prescribe if they were recognised Schedule V items, C: I tend to prescribe according to variety of formulation, D: I tend to prescribe along cost-effectiveness, E: I tend to prescribe along evidence-based data, N/A: No response). Only combinations that showed a response are indicated.

The majority of GPs (39.7%) indicated that stopping the treatment depends solely on physician’s judgment. This was closely followed by GPs (38.2%) who indicated that they would stop treatment when the MMSE score keeps on deteriorating. A fewer number of GPs considered that treatment should be stopped when MMSE score remains the same and does not improve after 6 months of treatment (16.0%). Only 13% would consider stopping treatment when the overall MMSE score is below 12 (Figure 3.33).
3.4.2. Non-pharmacological management

Prior to initiating treatment the majority of GPs (80.9%) were following-up the patient every two to four months. A smaller percent of GPs (15.3%) followed-up the patient at every six to eight months interval (Figure 3.34).
Following initiation of treatment, almost 70% of the GPs reported that the patients were continued to be followed-up at every two to four months time interval. A smaller percent of GPs were following-up the patients at every six to eight months time interval (19.1%) and only 1% of GPs reported a follow-up once a year after initiation of treatment. This indicated an increased interest on the effect of pharmacological management of the condition following drug intervention (Figure 3.35).
Most commonly recommended community-based services that were indicated by GPs included: domiciliary home-help (84.7%), telecare services (80.9%), rehabilitation-respite referral (58.8%), day centres (54.2%), social workers referral (40.5%) and MMDNA services (37.4%). Together, the following four services: telecare, social workers, rehabilitation-respite and day centres would be recommended by almost 23% of GPs (Figure 3.36).

Figure 3.36. Dementia community-based services recommended by General practitioners (GPs) (A: Telecare services, B: Social workers referral, C: Rehabilitation / respite referral, D: Day centres, E:
The majority of GPs reported that there are no adequate community services for dementia (76.3%). This was followed by a good percent of GPs who were not sure if the dementia services in the community are adequate. Only a small number of GPs agreed that these services are adequate (5.3%), (Figure 3.37).

![Pie chart showing the responses of GPs about competence of dementia community services.]

- **Yes**: 5.3%
- **No**: 17.6%
- **Not sure**: 0.8%
- **No response**: 76.3%

**Figure 3.37.** General practitioners' opinion about competence of dementia community services

The majority of the GPs indicated that there is not enough communication between the different disciplinary members making up the community team around the AD patient (75.6%). This was followed by fewer GPs who were unsure (16.0%). Only a very small percent of GPs considered that there is adequate communication in the community team around AD (7.6%) (Figure 3.38).
Figure 3.38. General practitioners’ (GPs) opinion about communication between the members of the community team around the AD’s patient.

Alternative ways of cognitive and functional therapies met the highest rate of absenteeism (26% to 33%, respectively). GPs that replied to this question mostly suggested multisensory stimulation (52.7%), music/dancing therapy (31.3%), animal-assisted therapy (22.9%), massage (10.7%) and aromatherapy (7.6%). All the above mentioned alternative methods were recommended by only 6% of GPs (Figure 3.39).

Figure 3.39. Alternative methods suggested by General practitioners (GPs). (A: Animal-assisted therapy, B: Music/dancing therapy, C: Massage, D: Multisensory stimulation, E: Aromatherapy, N/A: No response). Only combinations that showed a response are indicated.
Interestingly, the majority of GPs (51.9%) suggested that these alternative methods should be used together with pharmacological treatment. Only a small number of GPs indicated that these should be used on their own prior to initiation of pharmacological treatment (13.7%) or after failure of pharmacological treatment (8.4%) (Table 3.2).

<table>
<thead>
<tr>
<th>Choice of alternative method/s</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>7.6</td>
</tr>
<tr>
<td>B</td>
<td>45.8</td>
</tr>
<tr>
<td>C</td>
<td>7.6</td>
</tr>
<tr>
<td>A+B</td>
<td>1.5</td>
</tr>
<tr>
<td>B+C</td>
<td>4.6</td>
</tr>
<tr>
<td>N/A</td>
<td>32.8</td>
</tr>
</tbody>
</table>

Table 3.2. Alternative methods with or without conjoint pharmacological therapy (A: Only after failure of pharmacological treatment, B: Always along with pharmacological treatment C: On their own before initiation of pharmacological treatment, N/A: No response). Only combinations that showed a response are indicated.
Chapter 4.
Discussion and conclusion
4. Discussion and conclusion

4.1. Demographic data

The majority (70%) of the 364 GPs contacted, all members of the Malta College of Family Doctors (MCFD), were male. This was reflected in the sample’s gender distribution. Most of the respondents had more than 15 years of experience and thus the results should thus give an indication of how dementia has been managed in the Maltese islands for at least the past 15 years.

Participation rate from the north part of Malta was higher than the south. This was expected because according to the last National Statistics Office (NSO) survey (2005), the Northen Harbour area had the highest population per km$^2$ in Malta. It would follow that there is a higher concentration of GP practices in this region. Male and female GPs showed the same interest in completing the questionnaire both in Malta and in Gozo. Most male respondents had their practice in the Northern and Northern Harbour regions.

4.1.1. Diagnosis

More than half of the GPs believed that they need more training in diagnosing dementia. Out of the total respondents, the majority of females answered that they need more training compared to males. A number of studies suggest that female physicians possess superior communication skills, attach more importance to psychosocial aspects of care and better integrate patients in the decision-making process (Kaduszkiewicz et al., 2008). Female doctors in Malta may be more sensitive to the necessity of providing a more thorough approach and might have reflected on the higher request for training in this cohort. It is also true that in
Ireland, female doctors were shown to diagnose significantly less cases annually than males (Cahill et al., 2006).

Regarding clinical experience, out of the total GPs who had been practicing for 6-14 years, just more than 70% indicated that they need more training compared to half of GPs who had been practicing for more than 15 years. In a study in Germany, half of the GPs reported an interest in a training program on how to deal and speak with people with dementia and their relatives yet only 30% of the specialists who enrolled in the study showed similar interest (Kaduszkiewicz et al., 2008). A higher level of experience and longer exposure to management of dementia might give GPs more confidence in diagnosing dementia.

Most doctors have chosen loss of memory and behavioural difficulties as the symptoms which are mostly associated with dementia and which mostly elicited their suspicion of cognitive impairment. Although behavioural and personality changes are not included in the core definition of AD because of their lack of specificity, they are still very common and clinically relevant (Mega et al., 1996). Personality changes may antedate the more obvious memory changes and provide a marker for early suspicion and screening. Dementia is difficult to recognize in its early stage in general practice (Rondeau et al., 2008) and GPs may be biased by what is reported by relatives or caregivers who first noticed an abnormality in the index person. Symptoms which are most commonly reported by caregivers include forgetfulness or memory problems and decline in patient’s behaviour (Wilkinson et al., 2004).

Prominent memory dysfunction, with poor recognition, recall or rapid forgetting with or without aphasic, dysphasic, apraxic or agnostic disturbances are defining features of a cortical dementia (Hubert et al., 1986; Cummings and Victoroff, 1990). Loss of short-term memory was in fact considered to be a clinical feature of AD by almost all of the respondents. However, inability to acquire new information was selected by only 65% of respondents. Loss of short-term memory and inability to acquire new information are interchangeable terms and is therefore interesting to inquire what led to a discrepancy between the two options. Possibly, the GPs considered the terms differently on considering other parameters such as lack of attention and concentration which may also lead to a lack in acquiring new information.
Difficulty in concentration was also selected by the majority of respondents, showing that Maltese and Gozitan GPs would be able to suspect MCI due to early AD. The highest choice favoured the amnestic type of symptoms with apraxia and agnosia being chosen only by 45% of GPs. Even though the amnestic type of presentation is by far the most common, AD can present otherwise (Jeffrey, 2010). Rondeau et al. (2008) reported that new cases of dementia in general practice in France were often diagnosed at the moderate stage of dementia, with MMSE scores being lower than 20 at the time of diagnosis. Waiting for the amnestic symptoms to be evident might lead to a delay in the diagnosis of dementia. Emphasis on different types of presentations including the non-amnestic types might need to be set if training in diagnosing dementia in the community is eventually developed.

When suspecting cognitive impairment, GPs initial action in the management of dementia indicated positive preferences towards general physical examination followed by interview of family. The latter is essential as most of the time it is relatives or carers who notice the first symptoms (Wilkinson et al., 2004). A small yet significant percentage of local GPs preferred to adopt a wait and observe approach with a consequent delay in early management options. This was not considered to be positive as early diagnosis is instrumental in delaying institutionalization. Multinational studies across six countries in Europe revealed that the average time from symptom recognition by carers to their consultation with a doctor was 47 weeks (Bond et al., 2005). This means that the effective time from first symptom to diagnosis is much more than what the GP might be aware of. All these GPs do however follow-up the patient every 2 to 4 months. It thus follows that although concerned, these GPs keep on following up yet not referring. There is a widespread belief in general practice that AD is so complex that it cannot easily be recognized during a short consultation (Bond et al., 2005).

Psychometric tests were poorly considered (6.9%) as first option in the management of AD. Regarding their use in the community, only two of the total number of respondents failed to give any opinion about their use. Although the majority of GPs expressed an opinion about the use of psychometric tests, this does not necessarily denote that these tests are being used in the community. More than half of the respondents however did consider psychometric tests as helpful in assessing the severity of dementia. Despite of their perceived use in the community,
GPs (of which most had less than 15 years of clinical experience) still complained that these tests are not readily available. Evidence of cognitive testing in primary care in the UK was found in 20% of GP referrals (Fisher and Larner, 2007). Depending on referrals in this assessment introduces a bias yet does give a good indication of the percentage of GPs who regularly use psychometric tests.

The MMSE has been around for about 30 years (Nieuwenhuis, 2010). Yet this test’s availability could have remained a query as it was never formalized as a public document available for use by family doctors. It must be pointed out that even less of the same group (<15 years experience) believed that the MMSE can contribute to follow-up, assessment of severity or diagnosis of dementia. This probably explains the view in the lack of a local protocol in determining the levels of impairment in dementia, the classification of AD in the community in its mild, moderate or severe forms without the use of MMSE would be entirely up to GPs interpretation. The classification between mild AD and MCI might be even more difficult with obvious management and treatment implications. GPs in the Netherlands highlighted diagnostic uncertainty during the early stages of the disease with many claiming they felt embarrassed to conduct psychometric examination (van Hout et al., 2000). This could be an issue for local GPs too. Some questions in the MMSE test, unless explained prior to initiation of the test, may provoke anxiety in some patients, making them think that they are being belittled or assessed for a psychiatric condition. A cluster randomized control trial conducted in France concluded that more information on dementia and not necessarily a protocol, together with application of simple psychometric tests could improve the precision of a GP's diagnosis without changing the efficacy of detection of dementia (Rondeau et al., 2008). One would need to test whether the recently initiated course leading to specialist accreditation in family medicine including rotations in geriatric hospitals and wards would achieve this purpose with the current formation of new generation GPs.

An English version of the MMSE has been distributed by a local pharmaceutical distributor for use in the community, thus promoting the idea that dementia should be diagnosed and possibly treated by GPs. Geriatricians have both a Maltese and English version available at the Memory clinic in Karen Grech Hospital. Since a good percentage of the population is elderly,
the language barrier is more relevant in this group and might reflect the request for a Maltese version to be more readily available in the community.

Bio-chemical investigations were poorly considered as first-line management of dementia yet considered by most GPs prior to referral to a specialist. Although NICE (2006) states that general population screening for dementia should not be undertaken, it does advice that a basic dementia screen should be performed at the time of presentation, usually within primary care which should include blood investigations like routine haematology, biochemistry tests (including electrolytes, calcium, glucose, and renal and liver function), thyroid function tests and serum vitamin B₁₂ and folate levels. These tests are all available for ordering by GPs through the national health services. Despite of this, 1 in 5 GPs abstained from performing blood investigations throughout their management, only few of which referred immediately to a specialist. This reveals a serious omission in the approach to the work-up of dementia. A study performed in Denmark tried to correlate adherence to dementia diagnosis guidelines in the community with whether relevant blood tests were ordered or not by GPs. GPs who specifically read the guidelines and stated that it was applicable in primary care failed to significantly change their practice and order more frequently the indicated battery of blood tests (Boch Waldorff et al., 2003). This infers that accustomed practices in general practice may be difficult to change across geographical borders. Some GPs may have the attitude to depend more on clinical history and examination in their approach to any diagnosis, relying less on biochemical markers. If this is the case, these GPs should refer to a specialist, as clinical history and clinical examination alone are not enough to diagnose dementia and differentiate between its subtypes.

Referral to a specialist as first option was considered in a very small number of respondents. Of more interest is the observation that more than half of the GPs would consider specialist referral in the later stages of management. This does suggest a tendency of the GPs in Malta and Gozo to investigate and manage prior to referral. It does contrast with the fact that many GPs agreed that they need more training in diagnosing and managing dementia in the community. This may reflect challenges that GPs are facing in their attempt at managing people with dementia prior to referral. Although Scottish guidelines for the primary care
management of dementia exist, an Audit Commission study in 2002 reported that less than half of GPs felt they had sufficient basic and post-qualification training in dementia. Analysis of referrals by Scottish GPs to memory clinics showed that less than half of the cases referred were confirmed to be dementia, in contrast to a 75% catchment rate by neurologists (Fisher and Larner, 2007). It does follow that people with dementia should come in contact with a relevant specialist at some time or another of the management, the earlier the better, and it does depend on the GPs’ knowledge, discretion and clinical acumen when this happens.

GPs in Malta and Gozo showed that they did investigate other causes of cognitive impairment prior to arriving to a diagnosis of dementia. All pathologies listed in the related question need to be excluded in a formal work-up of dementia (Moo, 2009). As high as 39% of GPs selected all options and more encouragingly both depression and side-effects of medications were both chosen with high frequencies (85% and 72% respectively) as these two options were the ones which could present more subtly or as a double diagnosis and easily not considered (Aboukhatwa et al., 2010). Depression and MCI can co-exist and the risk for the development of AD in persons with MCI increases if depression sets in (Ownby et al., 2006). Exclusion of depression by a GP, psychiatrist or geriatrician is essential prior to further progress in the work-up of dementia.

The majority of GPs participating in this study believed that early treatment could postpone or preclude institutionalisation. This was regarded to be a positive response considering the limited resources and bed-space with respect to dementia management in Malta. Only early diagnosis and management of AD could avert an exponential rise in the level dependency onto the long-term services in local institutions (Zammit and Ferry, 2006). Conversely, 1 in 10 GPs, most of whom were Maltese and with over 15 years of experience, believed that early diagnosis may lead to labelling and alteration of the doctor-patient relationship. A possible reason for this is the lack of formal training in management and disclosure of AD which keeps back a number of GPs from attaining an early diagnosis. A very small percentage (3%), believed that since AD is untreatable, there is no need to formally diagnose. Albeit small, this group of Maltese doctors with over 15 years of experience in general practice, is providing a niche where individuals with AD are going undiagnosed and unmanaged up until the time
when they become fully dependent on state funds. Tolman (2008) reported findings by Alzheimer’s Association in the UK that a sense of therapeutic nihilism was more common in older GPs who mostly lacked formal training in diagnosing dementia. Training in the diagnosis and management of dementia in the community might serve the purpose of removing such attitudes.

The absolute majority of GPs in Malta and Gozo believed that the availability of a standardized protocol for assessment and diagnosis of AD would be beneficial in their practice. Considering that the international medical community in the field of dementia is considering new criteria for the diagnosis and management of AD (Jeffrey, 2010), if approved and applied, the near future might be presenting the Maltese authorities with the perfect chance to promote these new guidelines locally in an effort to improve the current management of AD in the community. A similarly high percentage of GPs have asked for more information regarding community-based and social services in relation to domiciliary care of people with AD. This reflects either the lack of these services per se or the lack of knowledge of GPs in this regard. This information can be gathered by the Department of Health and presented to all GPs in Malta and Gozo in order to maximise community care and decrease dependency on institutions.

4.1.2. Disclosure

GPs in Malta and Gozo that routinely disclosed amounted to 29% of respondents. Of these, family physicians were more likely to disclose dementia if they were certain of the diagnosis rather than if they were only suspecting it. Males tended to disclose twice as much as females and Gozitans tended to disclose more than Maltese. A small number of GPs decided to opt not to disclose yet this was not because AD is untreatable. This group contained only GPs from Malta, mostly of more than 15 years of experience and with equal gender ratios. In Germany, GPs with a higher number of working years in ambulatory care expressed more reservation
towards diagnosis disclosure (Kaduszkiewicz et al., 2008). Physicians’ age was found to be associated with disclosure of diagnosis (Down et al., 2002; Raicher et al., 2008).

More than half of GPs base disclosure of AD on the merits of each case, in favour of other options like a straight yes due to ethical reasons, only on agreement with relatives or depending only on doctor’s personal judgement. The highest probability is that these GPs adopt all these options depending on the case. Of interest is the fact that 1 in 4 GPs do base their disclosure on previous agreement with the relatives, yet only 1 in 10 would withhold the disclosure had the relatives specifically asked so. One might consider this ratio high, yet in a close community like that found in the Maltese islands, where relatives are generally always close to the affected person and are the carers themselves, it can be expected. Furthermore, in comparison with other larger countries, Maltese results showed that GPs locally have managed to overcome to a certain extent the ethical question of assuming a relatives-based approach. In Brazil, a minimum of 67% of specialists claimed that they did base their decision to disclose on a previous agreement with the relatives (Vilela and Caramelli, 2006; Raicher et al., 2008).

Even though local GPs are not routinely disclosing a diagnosis of AD, this does not necessarily preclude the affected individual. Encouragingly, over 60% of respondents felt more comfortable disclosing to both patient and caregivers, with less opting for caregivers alone and only four doctors opting for the patient alone. Since some people with AD would not want to be informed, 40% of GPs claimed that they were seeking to understand the individual’s preferences and act accordingly. Only 29% opted for a straight disclosure and none claimed that they are undecided on the issue. In France it was reported that GPs were preferred to disclose to caregivers rather than affected individuals (Cantegreil-Kallen et al., 2005). A different approach exists in Sweden where more than half of the GPs would always, or often, discuss the diagnosis and consequences of the diagnosis with the patient at the first visit and the relative at the second visit (Tolman, 2008). Thus overall, Maltese and Gozitan GPs appear to take a very cautious approach towards disclosure. They do seek to involve the affected individuals and the carers, understand their preferences and decide case by case. This
may be warranted in a close community where many people know each other and stigma can be a problem. The size of the country makes it also possible for information to be given slowly in multiple sittings with the GP.

Insight is usually lost early in the condition (Tabert et al., 2002). GPs in Malta and Gozo might be in the search for the individual’s ability to understand the information given prior to disclosing. In fact, more than half of respondents claimed that giving the true diagnostic and prognostic information depended on level of impairment. This approach pointed towards an insufficient trust in the affected individual’s level of comprehension. To substantiate this, a fear exists that diagnosing and further disclosing dementia might affect the doctor-patient relationship. The issue of insight is in line with existing literature. Although physicians are aware of many benefits in disclosing, they had concerns regarding the certainty of diagnosis, the patients’ insight and the possibility of distress and destroying hope or motivation (Raicher et al., 2008).

An effort at using nomenclature which is correct and yet understandable was clearly preferred by more than half of the respondents who use ‘dementia’ as the ideal term in their disclosure, avoiding medical terminology like Alzheimer’s disease. Most of the GPs who are routinely disclosing are using the correct terminology. Raicher et al. (2008) reported that almost half of physicians (of which most were young) disclosed regularly with the majority using clear terminology. Also similar to results published abroad (Down et al., 2002), more than a third of the respondents used euphemistic terms to describe the illness like ‘memory’ or ‘cognitive’ problems. Up to 24% of GPs who are disclosing downplayed the diagnosis as ‘slowing down due to aging’. Even though aging is the highest risk factor for the development of dementia, the two do not go invariably hand in hand and the term is incorrect as dementia is not part of normal aging (EFNS, 2007). The usage of this term only incorrectly attempts to normalise dementia, passing on the idea that since it is part of aging, nothing can be done about it.

GPs that routinely disclosed, used the correct terminology of dementia, claimed that giving the true diagnostic and prognostic information aided their therapeutic management and noticed
improvement in the care of people with AD totalled 12.2%. Presumably one can argue that the use of correct terminology and the disclosure of true information related to the condition leads in most cases to improved care. A significant number of GPs (43.5%) did admit that they were not sure whether disclosure did effectively lead to any improvement in care. Sub-analysis of this group showed that even though they believed that disclosure may help both patient and caregivers in future planning and treatment decisions, in general they did fear more than others that the same disclosure could evoke anxiety, depression or social stigma. Importantly, these fears were held in absolute more by Maltese GPs in contrast to their Gozitan counterparts who had only a positive attitude towards disclosure. This may stem from a closer doctor-patient relationship which may develop in a smaller community like Gozo.

In the process of disclosure, GPs tend to focus on explaining the progression of the condition and caregiver health issues over financial planning and use of reminder aids. As expected, GPs felt more comfortable focusing onto medical issues in their consultation. Interestingly, up to 70% of GPs considered carers' health issues, with studies abroad stating that the carers are frequently side-lined (Brodaty and Green, 2002). This difference is probably due to the close relationship that exits between the GP and the family of the individual with dementia in the Maltese islands. Nonetheless, reminder aids and financial planning were both considered by more than half of the respondents, showing a generally holistic approach taken by GPs.

4.1.3. Pharmacological Management

More than half of the GPs sought improvement in functional ability and delay in institutionalisation after initiation of treatment in dementia. These aims were also cited by the NICE guidelines (2006) along with improvement or preservation of cognitive function and delay in development of behavioural deterioration. These latter two options were also offered for choice but only selected by the 38% of doctors. From a primary care physician's point of view, this choice might make sense because the main aim within the community could be to
keep the person with dementia functional in activities of daily living and away from institutions. Improvement in cognition is relative and control of behavioural problems could be referred to the relevant specialists whilst keeping the individual in the community.

4.1.3.1. Mild cognitive impairment (MCI)

In MCI, 1 in 2 GPs would prescribe acetylcholinesterase inhibitors (AChEIs) as a first-line treatment, with a higher tendency shown in the 6-14 years experience group. NICE (2006) recommended the use of AChEIs in the management of people with AD of moderate severity only, that is, those with a Mini Mental State Examination (MMSE) score of between 10 and 20 points. Even though studies have shown the benefit of AChEIs in mild AD (Wilkinson et al., 2009), studies performed specifically in MCI showed a high rate of side-effects compared to little objective benefit (Raschetti et al., 2007) unless there are co-existing depressive symptoms (Lu et al., 2009). Multiple clinical trials have attempted to demonstrate the utility of these medications in milder AD and non-AD dementias, and extend their use to MCI yet although successful for the former, were not convincing for the latter (Mc Clendon et al., 2009).

This result may reflect that younger community doctors in the Maltese islands were aware of the increasing shift in the use of AChEIs from the moderate to the mild stages of AD, yet the rate of use of AChEIs in MCI is inadvertently high considering that evidence based data available to date has not proven their benefit at this stage.

Only a quarter of GPs from all categories of medical experience showed a high interest in the use of nootropics in MCI with no significant difference reported between Malta and Gozo. A Cochrane review in the clinical efficacy of piracetam, the nootropic most frequently used locally, concluded that there is not enough support for the use of this compound in the treatment of people with dementia or MCI (Flicker & Grimley Evans, 2001). To date, no study has changed this version of facts. The relatively high use of nootropics in the Maltese community may reflect a persuasive marketing strategy from the relevant pharmaceutical companies.
About 1 in 10 GPs equally considered selective serotonin reuptake inhibitors (SSRIs) or ginko-containing drugs or NMDA receptor antagonists as second-line therapy. Depression at this stage needs to be excluded and treated as discussed earlier. On the other hand, ginko was not shown to be beneficial in MCI (Beth et al., 2009) and trends in its prescribing may again depend onto marketing strategies. Memantine is not advised for the use in MCI (NICE, 2006) and no studies have been published regarding memantine use in MCI (Mc Clendon et al., 2009).

Benzodiazepines, Tricyclic antidepressants (TCAs), antipsychotics, NMDA receptor antagonists and Vitamin E were generally not considered as first line therapy for MCI.

4.1.3.2. Mild-to-Moderate AD

Treatment in the community of mild-to-moderate AD relies significantly on AChEIs and to a lesser extent on memantine as first-line agents. Memantine choice rose as second-line agents. No other drug class was opted for with frequencies worth mentioning. No gender difference was noted in prescriptions for AChEIs, with the same interest being shown in Malta and Gozo, however nearly double the use was noted in the South (South harbour and South Eastern) of Malta when compared to the North (North harbour and Northern). Use of AChEIs did not vary with level of medical experience.

The higher use of AChEIs in the South of Malta could not be explained by a higher percentage of people aged 65 years and over in this region compared to the North as in 2005, each of these regions shared a 25% elderly population (NSO, 2005). The reason behind such a discrepancy may lie in education. Limited education is associated with development of AD (ADI, 2009). The last national census of 2005 exposed that the literacy divide still existed between the North and the South of Malta. The South carries the highest rate of illiteracy and the lowest number of graduates per capita. There may be various reasons for such a discrepancy and further studies should throw more light on the use of anti-dementia
medication in various parts of the Maltese Islands focusing on socio-economic and educational criteria.

Although NICE (2006) does not mention AChEIs for treatment of mild AD, while limiting use of memantine for clinical trials, empirical studies overseas have shown widespread clinical usage of both these classes of drugs in the mild form of the condition (Mc Clendon et al., 2009). It appears that at such an early stage, local GPs would consider either a switch to memantine or in the minority of cases combination therapy. Combination therapy is a promising choice of therapy for patients with moderate to severe AD (Thomas and Grossberg, 2009). Thus even though the use of AChEIs in the mild to moderate stages of AD in Malta and Gozo is evidence based, the use of memantine is not.

4.1.3.3. Severe

Despite choice for AChEIs as first line options in severe AD dropped when compared to their use in the mild to moderate stage, their prescription remained significantly high compared to other drug classes, even higher than memantine. According to published guidelines, results should have revealed a transition from the use of AChEIs to memantine (NICE, 2006). Subanalysis of this group revealed that in severe AD, doctors with more than 15 years of experience opted more for AChEIs. Memantine was chosen at double the frequency by doctors with less than 15 years experience. Thus the transition from AChEIs to memantine in severe AD is being done mostly by doctors who qualified more recently. From the design of the questionnaire, it could not be concluded whether there is an actual transition from AChEIs to memantine or combination therapy. Although recent evidence points towards the addition of memantine without discontinuation of AChEIs, this option is highly improbable in the community due to its financial burden.

The use of psychotropic drugs in severe AD increased when compared to the other stages of the disease, albeit overall frequencies were still low. Benzodiazepines were prescribed as first-
line agents in 3% of cases, presumably as an anxiolytic in BPSD. If deemed necessary, the lowest effective dose should be used for the shortest time possible (Hogan et al., 2008) after attempt at non-pharmacological approaches (McCurry et al., 2005). Overall, the use of benzodiazepines in people with severe AD in the community highly contrasts with their usage in St. Vincent de Paule Residence (SVPR) for the elderly, where 60% of the elderly there are on one or more types of benzodiazepines (Bugeja, 2010). This shows that local GPs do overall limit the use of benzodiazepines in AD within the community.

Antipsychotics were considered by 4% of primary care physicians as first line treatment with a 3:1 preference for typical antipsychotics. This ratio however reverses if second-line treatment with antipsychotics is considered with more GPs preferring the atypical rather than the typical ones. This data indicates that, overall, GPs in the community do not prescribe antipsychotics in AD probably because they are aware of the risks involved in their use. In those who use them however, one cannot determine whether there is a preference for a typical or an atypical antipsychotic, possibly exposing a lack of knowledge in risks associated with AD. An effort to limit the use of antipsychotics in AD as first-line agents should be one of the main aims in a targeted informative campaign towards local health professionals, promoting other possible measures as an initial approach.

Surprisingly nootropics still found their way in the management of severe AD in 4% as first-line agent increasing to 8% as third-liners, in contrast with ginko and vitamin E, which were not considered as a treatment option in severe AD. Here again marketing strategies may influence these options rather than evidence based knowledge. Overall, GPs avoid the use of nootropics and do not use ginko or vitamin E in severe AD.

The use of SSRIs in severe AD rose from 2% as first-line agent to 11% as third-line agent. Tricyclic antidepressants were in general not considered. Depression is not usually associated with the severe stage of AD, yet the quality of life of individuals with severe AD depends on
earlier exclusion of this condition (Volicer, 2001). Thus the rise in the use of SSRI as secondary or tertiary agents in severe AD may reflect the GPs’ need of reassurance that such a diagnosis was not missed in an individual who at this stage cannot objectively be evaluated for disorders of affect. Overall, the use of SSRIs in all stages of AD was low. With the emerging evidence that antidepressants, especially SSRIs, can potentially modulate the pathological features of AD, GPs in Malta and Gozo should in the future be kept updated about the additional benefit of these drugs in the early rather than the later stages of the condition (Aboukhatwa et al., 2010).

Interestingly, 16.8% of GPs abstained from prescribing any medication in severe AD. The majority of this group had more than 15 years of experience and practiced in the Northern part of Malta. More than half agreed that AChEIs should be started only by the relevant specialists and showed interest in the use of non-pharmacological approaches to AD.

Of those who prescribed AChEIs in general, 52% claimed that they orient their choice of pharmacotherapeutic management on evidence-based data. The high use of AChEIs in MCI and severe AD is not evidence based (NICE, 2006). Tendency to prescribe along cost-effectiveness was opted by 29% of the respondents. There is no evidence that treatment with AChEIs is not cost effective. Despite the slight variations in the mode of action of the three cholinesterase inhibitors, there is no evidence of any differences between them with respect to efficacy (Birks, 2006).

A total of 65% of respondents specifically agreed that they prescribe AChEIs for one or more of the reasons discussed above. The rest pointed out that these drugs should be initiated only by specialists. In this regard, NICE (2006) recommends that AChEIs should be started only by relevant specialists. In the UK, family doctors are allowed to take over prescribing the drugs where there is shared-care protocols setting out how this will work within a Trust (Taylor et al., 2001). This setting does not exist in Malta. There is no shared-care protocols available with most GPs (75.6%) admitting that they were not satisfied with the type of communication between the different disciplinary teams working round the individual with AD within the community. A systematic interdisciplinary collaboration between GPs, medical specialists and
professionals in the field of social and psychological dementia care will be a key issue in the future (Holle et al., 2009).

There is no hindrance that limits the GP from prescribing AChEIs or memantine. No specialist signature is required for the issuing of such drugs from a community pharmacy as they are not part of the Government’s formulary list of medications. Marketing of AChEIs in Malta and Gozo has targeted both specialists and GPs and considered both to have the same prescription power.

Cost is an issue with these medications yet only 21% agreed that they would always prescribe AChEIs had they been available under a free medicine scheme like the government’s Social Security Act Schedule V. Such a low adherence could be explained by the fact that if such a scheme had to be put in practice, then AChEIs would become prescription only medications requiring initial clearance by a specialist. This suggests that most GPs are satisfied with the current system where they are free to fully manage the individual with dementia if they decide so, notwithstanding the financial burden these medications carry. Malta is one of two countries in the European Union which does not yet offer AChEIs for free.

Once treatment is initiated, the majority would follow-up their patients every 2 to 4 months (69%) with the absolute majority falling within the 6 month range (88%). This goes along advice given by published guidelines. With regards to cessation of therapy, the results were spread. Only 38% opted to stop medication if the MMSE keeps deteriorating while 40% opted for sole dependence on physician’s judgement. A total of 29% opted to stop treatment if MMSE remained the same or did not improve and if the overall MMSE dropped below 12. NICE (2006) recommends continuation of treatment only if MMSE is at 10 or above. Improvement in cognition is not a requisite on which continuation of treatment is based. In fact the major therapeutic effect of AChEIs is reported to be their ability to maintain cognitive function compared with placebo and not necessarily improve it (Scerri, 2006). The indications for stopping AChEIs need to be clarified with professionals prescribing them within the community.
4.1.4. Non-pharmacological management

While observing the course of AD prior to initiation of treatment, the majority of the GPs (81.0%) followed their patients, at an interval of 2 to 4 months. The rest of the GPs were following the patients within the 6 months period. It is reassuring to observe that local GPs are aware of the need to follow-up closely the course of the condition especially in its earlier stages where a decision to investigate and treat needs to be taken. Overall, GPs in Malta and Gozo provide a close follow-up program both before and after initiation of treatment.

Management within the community focused onto referral for domiciliary home-help and the telecare service. GPs here tackled an issue of safety with regards to their patients. The increasing limitation of the person with dementia to basic ADLs brings up the need for a carer at home that can perform the busy errands and daily needs safely. This however does not actively cater in any form to disease improvement, control or progression. The relevance of the telecare services fades with disease progression as the individual would not recognize anymore the function of the device.

Up to 59% of respondents considered rehabilitation or respite facilities thus creating a link with specialists in the geriatric field whilst accommodating caregivers family, health and time issues. More than half of the GPs considered referring people with AD to community day centres. The only dementia-specific day centre unit in Malta is found at SVPR. While another 17 were present in Malta, these cater for the elderly in general with staff not specifically trained to deal with people with dementia. It could be that the lack of awareness of such service or else the expectation of trained services to be available within their region that drove most GPs (76%) to state that the current services for dementia within the community in general were not adequate. Only 5% responded in the affirmative while the rest (18%) were not sure. Social workers and MMDNA services were not considered by most. Overall, GPs are dissatisfied with the current community services available for individuals with dementia, and most GPs lack knowledge about the few that are currently available. Multisensory stimulation (MSS) was the non-pharmacological management of choice of most respondents (53%) followed by music therapy which in itself is a type of MSS. However further questioning on
their use revealed that more than half of the GPs would use these alternative methods always along pharmacological intervention. Many less considered these methods before initiation of pharmacotherapy and even less after. MSS, music therapy, ATT, massage and aromatherapy are alternative methods which are indicated in challenging behaviour and for the control of non-cognitive symptoms. Unless the distress is severe or potentially of immediate harm, NICE (2006) suggests that these approaches should be initially used as a drug-sparing approach. The use along with pharmacological therapy reveals lack of trust in the results which could be achieved by these methods alone.

For these methods to be successful, a backing framework of dedicated volunteers is necessary and does not require simply a prescription from a doctor. Two centres offering MSS and ATT in Malta are the specialised unit at SVPR in Luqa and Inspire in Marsascala. Gender or level of experience did not influence the consideration of alternative methods and although both services are in the South, interest in MSS was not higher for GPs in this region. The perceived idea that community services are not adequate to cater for persons with dementia explains the highest rate of absenteeism in response about the topic.

4.1.5. Study strengths and limitations

Among the strengths in this study were the detailed information gathered on the GPs' diagnostic, disclosing and therapeutic considerations, which are unique in the local field. For a postal survey, response was adequate and comparable to that of similar studies done abroad. The sample can be considered representative.

A limitation is that participation was restricted to full members of The Malta College of Family Doctors (MCFD). Although this is the main professional body which gathers together general practitioners (GPs) in Malta and Gozo, there are other GP associations and this could have created bias. GP trainees had to be also excluded even though these are fully practicing doctors both in health centers and private clinics. Since there are no local studies on this topic,
the findings of this study could not be put forward for comparison. Thus the robustness of the results presented will have to be challenged and confirmed. It is hoped that this work will inspire local researchers to conduct more studies in this area. It would have been interesting if this study was compared to other neurological disorders in the Maltese Islands. However, no such studies are available to date. Of particular interest would be the study of disclosure trends of other neural illnesses so as to determine whether a general trend exists between different neurological conditions. It might have been interesting to have asked GPs what tools and criteria use to distinguish between mild cognitive, mild Alzheimer etc. Unfortunately no protocol exists on the assessment of the severity of dementia in the community. With respect to the clinical practice in a hospital setup, the MMSE scores are utilized although the interpretation of results lies with the practitioner. It would also have been interesting to see what GPs think about evidence-based medicine in general for all conditions. Most of the evidence within the community comes from the pharmaceutical industry through their medical representatives.

4.1.6. Conclusion

The results presented in this study highlight the important role that the general practitioner plays in the diagnosis and management of AD and related dementia in the Maltese islands. Important findings included that:

i. a significant number of GPs believed that they need more training in the diagnosis and management of dementia

ii. local GPs tended to investigate and attempt management of dementia in the community prior to referral to specialists or Memory Clinic

iii. local GPs appear to take a very cautious approach towards disclosure and do so only if sure of diagnosis, using a variety of terminologies some of which are euphemistic
iv. disclosure consultation generally focuses onto medical issues including those of the caregiver

v. GPs would want to see an increase in the community services available for people with dementia coupled with a better interdisciplinary approach

vi. the rate of interest in AChEIs use in MCI was inadvertently high and not evidence based

vii. AChEIs are the mainstay of therapy used for all stages of AD in the community, as are nootropics though at a lower frequency. Only the use of AChEIs in mild to moderate AD is evidence based

viii. transition from AChEIs to memantine in severe AD is carried out more by GPs who qualified more recently

ix. the use of psychotropic drugs in people with AD in the community is very limited

x. prescription of SSRIs was found to be low

xi. interest in the use of non-pharmacological approaches was high yet trust in their effectiveness was low

The outcome of this study will also complement the recommendation for the National Dementia Strategy Plan which were recently presented to the Maltese Health authorities of which primary care forms an integral part. The implementation of this plan will be of benefit not only to individuals with dementia and their caregivers but also to the general public and the medical profession. It is hoped that the results presented in this study will form a base for the future drafting of specific guidelines intended to enhance high quality clinical care and management of dementia in the Maltese islands.
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Appendix
Appendix I
Letter of approval
Ref No: 19/2009

12th June 2009

Ms Oana Caruana Pulpan
186 ELOI
Parilja Street
Sta Venera SVR1937

Dear Ms Caruana Pulpan

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

THE GENERAL PRACTITIONERS' APPROACH TO THE DIAGNOSIS, DISCLOSURE AND MANAGEMENT OF DEMENTIA IN THE MALTESE ISLANDS

The University Research Ethics Committee at its meeting of 5th June 2009 approved the above-mentioned Protocol.

Yours sincerely

Dr M Vassallo
Chairman
Research Ethics Committee
Appendix II

The questionnaire covering letter
The General Practitioners’ approach to the diagnosis, disclosure and management of dementia in the Maltese islands

Dear Doctor;

My name is Oana Caruana Pulpan. I am currently reading for a M.Sc. in Clinical Pharmacology at the University of Malta. As the title implies, my thesis will assess the current trends in the management of dementia in the community.

Attached please find a questionnaire which should be kindly completed and sent back in the provided postage-paid envelope by not later than OCTOBER 2009. This exercise should not take more than 10 minutes.

More than one answer can be selected for each question except when instructed otherwise.

The conclusions of this study will be published in peer-reviewed medical journals. If you are interested in receiving further information, please do not hesitate to contact me.

Thanking you

Best Regards;

Ms. Oana Caruana Pulpan

186, Eloi, Parilja Street, Santa Venera SVR1937

Mob: 99229496 Email: ocar0003@um.edu.mt
Appendix III
The reminder
Dear General Practitioner;

My name is Oana Caruana Pulpan and I am currently reading for an MSc in Clinical Pharmacology at the University of Malta.

As you might recall, a questionnaire was posted to you in July entitled ‘The General Practitioners’ approach to the diagnosis, disclosure and management of dementia in the Maltese islands’.

If you have already answered this questionnaire please ignore this notice.

If not, I would really appreciate if you could fill it in as soon as possible and post it in the provided postage-paid envelope.

More than one answer can be selected except when requested otherwise. Data from this study will be partly used for the development of the National Dementia Strategy Plan, which should enhance high quality dementia care in Malta. The results will also be made public and published in relevant peer reviewed medical journals.

Best Regards;

Ms. Oana Caruana Pulpan
186, Eloi, Parilja Street, St.Venera SVR1937
Mob: 99229496, Email: ocar0003@um.edu.mt

Dr. Charles Scerri PhD (Dundee)
Chairperson, National Dementia Strategy Group
Appendix IV

The questionnaire
Section 1 - Demographic data

1. Are you:  
   - Female  
   - Male

2. How long have you been practising medicine?  
   - 1-5 years  
   - 6-14 years  
   - 15 years or more

3. Select your area of practice:  
   - Malta  
   - Gozo

4. Town/village/city of practice:

Section 2 - Diagnosis

5. Do you consider that you need more training in diagnosing dementia?  
   - Yes  
   - No  
   - Not sure

6. Which symptoms make you mostly suspect the possibility of cognitive impairment?  
   - Loss of memory  
   - Dysphasia  
   - Behavioural difficulties  
   - Apraxia and agnosia

7. If, on interviewing the patient, you suspect cognitive impairment, what would be your initial course of actions?  
   *Kindly number in order of action taken. (1= first action taken)*  
   - Wait and observe  
   - General physical examination  
   - Psychometric tests  
   - Bio-chemical investigations  
   - Interview of family  
   - Refer to specialist

8. What is your opinion of psychometric testing (e.g. Wechsler scale, MMSE, AMTS)?  
   - Essential for confirming diagnosis  
   - Helps assessing severity of dementia  
   - Essential for follow-up  
   - Inefficient and non-specific  
   - Time-consuming  
   - Not readily available

9. If you suspect cognitive impairment, what other pathologies would you consider to exclude before reaching a diagnosis of dementia?  
   - Parkinson’s disease  
   - Intracranial lesions  
   - Depression and psychosis  
   - Vitamin B12 deficiency  
   - Hypothyroidism  
   - Side effects of medication

10. From the below, tick the clinical features of Alzheimer’s disease (AD).  
    - Loss of short term memory  
    - Difficulty in concentration  
    - Inability to acquire new info  
    - Apraxia and agnosia

11. Which statements concerning early diagnosis of Alzheimer disease do you consider to be true?  
    - Early treatment may postpone or preclude costly institutionalization  
    - It may lead to labelling and alteration of the doctor-patient relationship  
    - It may lead to under diagnosis of other pathologies  
    - AD is untreatable so no need to diagnose
12. Would any of the following help you in looking after patients with AD?
- Protocol for assessment and diagnosis of AD
- Specialised nurse in mental health
- Central register of residential and nursing home facilities
- Information about community-based care and social services

Section 3 - Disclosure

13. Do you think it is right to inform the patients about their diagnosis?
- Depends solely on doctors’ personal judgment
- Depends on an agreement between doctor and relatives
- Yes, for ethical reasons
- Depends on the merits of each case
- Not sure

14. Are you routinely disclosing the diagnosis of Alzheimer’s dementia?
- Yes
- No, I am seeking to understand patients’ preferences and act accordingly
- No, providing information depends on the level of impairment
- Not sure

15. What terminology would you usually use in disclosing Alzheimer’s dementia?
- Alzheimer’s disease
- Dementia
- Memory problems
- Cognitive problems
- Slowing down due to aging
- Others

16. Do you believe that giving the true diagnostic and prognostic information can be useful to favour the patients’ cooperation in therapeutic management?
- Yes
- Depends on impairment level
- No
- Not sure

17. Would you rather disclose if you are?
- Suspecting AD
- Sure of AD
- Not disclose

18. To whom would you prefer disclosing information on diagnosis and prognosis of AD?
- the patient
- the patient and caregivers
- the caregivers

19. Did you notice improvement in care of AD patients and their carers from diagnosis disclosure?
- Yes
- No
- Not sure

20. Do you discuss the following with the caregivers?
- Using reminder aids
- Financial planning
- Progression of dementia
- Caregiver health issues
Which of the following statements concerning disclosure of Alzheimer’s disease do you consider to be true?
- It may help patient and caregivers in future planning and treatment decisions
- Should be withheld if relatives request so
- It may evoke anxiety and/or depression altering patient’s direct relationships
- It may lead to social stigma
- AD is untreatable so why disclose

Section 4 - Non-pharmacological and pharmacological management

While observing the course of Alzheimer’s disease, at what time interval do you follow up the patient:
- Prior to initiating treatment
  - 2-4 months
  - 6-8 months
  - Once a year
- After initiation of treatment
  - 2-4 months
  - 6-8 months
  - Once a year

What community-based services do you recommend?
- Domiciliary home-help
- MMDNA services
- Day centres
- Telecare services
- Social workers referral
- Rehabilitation / respite referral

Do you believe that community services for dementia are adequate?
- Yes
- No
- Not sure

Do you feel that there is adequate communication between the different disciplinary members making up the community team around the AD patient?
- Yes
- No
- Not sure

What pharmacological treatment would you consider in the following clinical situations?
Kindly NUMBER in order of prescription your first three preferences. (1= first preference)

A. Mild cognitive impairment.
- Acetyl cholinesterase inhibitors
- Benzodiazepines
- SSRI/ SNRIs
- Tricyclic antidepressants
- Gingko containing drugs
- Typical antipsychotics
- Atypical antipsychotics
- NMDA-receptor antagonist
- Nootropics
- Vitamin E
B. Mild to moderate AD
- ☐ Acetyl cholinesterase inhibitors
- ☐ Benzodiazepines
- ☐ SSRI/ SNRIs
- ☐ Tricyclic antidepressants
- ☐ Gingko containing drugs
- ☐ Typical antipsychotics
- ☐ Atypical antipsychotics
- ☐ NMDA-receptor antagonist
- ☐ Nootropics
- ☐ Vitamin E

C. Severe AD
- ☐ Acetyl cholinesterase inhibitors
- ☐ Benzodiazepines
- ☐ SSRI/ SNRIs
- ☐ Tricyclic antidepressants
- ☐ Typical antipsychotics
- ☐ Atypical antipsychotics
- ☐ NMDA-receptor antagonist
- ☐ Nootropics
- ☐ Gingko containing drugs
- ☐ Vitamin E

27. What is your main aim of treatment in AD?
- ☐ Improvement of cognition
- ☐ Improvement in behaviour
- ☐ Functional ability improvement
- ☐ Delay in institutionalisation

28. With regards to acetyl cholinesterase inhibitors in AD patients, tick below if you agree
- ☐ I tend to prescribe along evidence-based data
- ☐ I tend to prescribe along cost-effectiveness
- ☐ I tend to prescribe according to variety of formulation
- ☐ I would always prescribe if they were recognised Schedule V items
- ☐ They should be initiated only by relevant specialists

29. When would you consider stopping treatment?
- ☐ MMSE score remains the same and does not improve after 6 months of treatment
- ☐ The MMSE score keeps on deteriorating
- ☐ The overall MMSE score is < 12
- ☐ Depends solely on physician’s judgement

30. Which of the following alternative methods would you suggest?
- ☐ Aromatherapy
- ☐ Multisensory stimulation
- ☐ Music /dancing therapy
- ☐ Animal-assisted therapy
- ☐ Massage

And if any...
- ☐ On their own before initiation of pharmacological treatment
- ☐ Always along with pharmacological treatment
- ☐ Only after failure of pharmacological treatment