

## Review Article

# Pharmacotherapeutic aspects of dementia care in Malta

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## Abstract

Dementia is the most common neurodegenerative disorder of old age affecting one percent of the local general population. It is a major predictor of morbidity and mortality in the elderly, adding a significant burden on health and social care systems across Europe. The financial impact of caring for individuals with dementia is considerable and progressive loss of cognitive function does not only pose challenges to the patients but also adds significant strain on the well-being of caregivers and family members. Although no cure is available, disease progression can be delayed by early intervention and by the use of pharmacotherapeutic agents that interfere with central neurotransmitter systems involved in cognitive processes. This review presents current trends in pharmacotherapeutic intervention in dementia care together with caregiver perceptions on treatment expectations in Malta.

## Keywords

Dementia, Malta, caregivers, pharmacotherapy

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## Introduction

Dementia is a complex clinical syndrome associated with behavioural, cognitive and personality changes. It usually presents itself as impairment in memory, abstract thinking, impaired judgment and other disturbances that are of such severity that they interfere with work and social activities.<sup>1</sup> Several diseases are known to cause dementia. Alzheimer's disease (AD) accounts for 50-70% of cases followed by Vascular dementia, Lewy Body Disease, fronto-temporal dementia and dementia secondary to disease.<sup>2</sup> According to an estimate from World Health Organization (WHO), dementia is responsible for more years lived with disability in people older than 60 years (11.2%) than stroke (9.5%), cardiovascular disease (5%) or all forms of cancer (2.4%).<sup>3</sup> Currently, there are more than 7.3 million people with dementia in Europe, a figure that is expected to double by the next 30 years.<sup>4</sup> This will result in a growing burden on health care resources and family members who, in the majority of cases, provide informal care at home. A recent study estimated that approximately one percent of the general population in Malta has dementia, a figure that is expected to increase significantly by the year 2050 (Table 1).<sup>5</sup>

Over the last two decades, a number of therapeutic strategies have been developed for the symptomatic management of the most common forms of dementia, particularly AD. The latter is characterised by the presence of amyloid plaques and neurofibrillary tangles coupled with significant degeneration of the central cholinergic system resulting in cognitive decline.<sup>6</sup> Indeed, the first pharmacological agents to be approved for symptomatic treatment of AD were the acetylcholinesterase inhibitors which mainly block the enzyme acetylcholinesterase thus increasing the concentrations of the neurotransmitter acetylcholine in the synaptic area (Table 3). Studies showed that the use of these drugs (namely donepezil, galantamine and rivastigmine) significantly improved cognition and activities of daily living.<sup>7</sup> Another drug that is also available in the therapeutic management of AD is the glutamatergic-system modifier memantine which partially blocks glutamate-induced overstimulation of the N-methyl-D-aspartate (NMDA) receptor thus reducing calcium-induced cytotoxicity (Table 3). In randomised clinical trials, this drug demonstrated the ability to delay cognitive and functional decline without any significant incidence of side effects.<sup>8,9</sup> According to the latest guidelines issued by the UK National Institute for Clinical Excellence (NICE), acetylcholinesterase inhibitors should be recommended for use in moderate AD whereas memantine should

**Table 1:** Current and projected number of total dementia cases in the Maltese islands (adapted from Abela et al).<sup>5</sup>

Year	30-59	60-64	65-69	70-74	75+	Total cases	% of total population
2010	203	293	316	629	2947	4388	1.12
2015	204	268	444	749	3227	4892	1.25
2020	201	285	404	1035	3660	5585	1.44
2025	201	253	422	931	4538	6345	1.66
2035	190	257	332	881	5161	6821	1.91
2050	150	268	414	970	4567	6369	2

only be considered for clinical trials.<sup>10</sup> Apart from Malta and Latvia, all EU-member states offer some form of financial reimbursement to any of these classes of anti-dementia drugs.

In recent years, strategies on dementia care have also been developed in parallel with pharmacotherapeutic research since caregivers suffer from high rates of physical and mental disorders including anxiety and depression.<sup>11</sup> Caregivers are also generally excluded in providing their views on the effectiveness of anti-dementia pharmacotherapy in ameliorating the symptoms as most research is focused on the disease model. A recent review study found that not one of the 63 papers (listed in medical databases) reporting on the effectiveness of drug treatments included the carer perspective.<sup>12</sup> Indeed, the carer perspective becomes important in assessing the effectiveness of a particular anti-dementia pharmacotherapeutic regimen in enhancing the quality of life and assessing caregiver burden.<sup>13</sup> The input of carers would also be instrumental in providing qualitative information that should aid medical professionals to adjust therapy ensuring better pharmacotherapeutic outcomes.

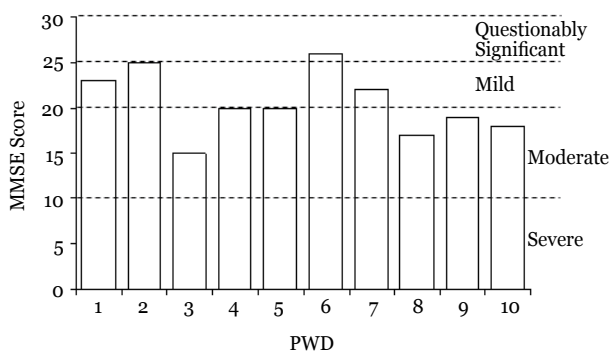
### Hospital-based pharmacotherapeutic management

In Malta, no research has yet been carried out on the use of pharmacotherapeutic agents in treating the various symptoms observed in dementia. In order to have an indication on the use of anti-dementia drugs in a local hospital-based clinic, a small scale exercise involving ten persons with dementia was conducted in October 2008. Also involved were seventeen caregivers, the latter comprising five spouse carers (two husbands and three wives), nine children (eight daughters and one son) and three daughter-in-laws. The sample of potential caregivers was selected from the Zammit Clapp Hospital Memory Clinic and was subsequently interviewed by a member of the research team. All participants had to be caring for a relative who had a formal diagnosis of dementia, who was attending the Memory Clinic, who continued to live in the community and who was over 65 years of age. The medical history of individuals with dementia was analysed for parameters including Mini Mental Scale Examination (MMSE) scores (which classify dementia into mild, moderate and severe), date of first attendance to the Memory Clinic, date of diagnosis, medical conditions

besides dementia and pharmacotherapy. Ethical approval was obtained from three sources prior to conducting the interviews with caregivers. These included the University of Stirling (UK) Ethics Committee, the University of Malta Research Ethics Committee and the Malta Health Department. All relatives participating in the study received a written information sheet prior to consenting to participate and this was also discussed verbally prior to obtaining written consent.

The results showed that more than half of the persons with dementia participating in the exercise had the moderate form of dementia in which there is clear impairment of cognitive function that may require continuous supervision (Figure 1). The rest of the patients had mild or questionably significant deficits in which the person with dementia continues to function normally with support and assistance. No patient had a Mini Mental State Examination score of less than 10 denoting the severe form of the condition which requires continuous supervision and assistance in their Activities of Daily Living (ADL). Table 2 shows the time intervals from when the person with dementia visited the Memory Clinic for the first time until diagnosis of dementia and initiation of treatment was performed. The mean number of days elapsed from first visit to diagnosis was that of 41.3±19.3 (mean±SEM) days. The majority of patients had their diagnosis of dementia during their first visit to the clinic. The mean number of days elapsed from diagnosis till the initiation of treatment was that of 69.4±42.3 (mean±SEM) days with most patients prescribed anti-dementia medication on the day of diagnosis. The mean total number of elapsed days from the patient first visit to the clinic till the initiation of treatment was of 108.3±34.9 (mean±SEM) days. Figure 2 shows the percentage of other pathological disorders in conjunction with dementia (taken as 100% to signify that all patients participating in this exercise had dementia). Most of the patients had depression and a significant number had diabetes, hypertension and hypercholesterolaemia. Other less common comorbidities included gout, anxiety, hearing loss and previous surgical interventions prior to dementia diagnosis. Figure 3a shows the amount of drugs prescribed for every person with dementia. The total number of drugs prescribed was 59 giving an average of 5.9 drugs per patient. The majority of patients were prescribed four or more drugs. All persons with dementia, except one,

**Figure 1:** Minimental State Examination (MMSE) scores for each person with dementia (PWD) participating in the exercise together with interpretation of the scores according to Folstein et al.<sup>29</sup>



Score	Degree of impairment	Day-to-day functioning
25 to 30	Questionably significant	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living
20 to 25	Mild	Significant effect. May require some supervision, support and assistance
10 to 20	Moderate	Clear impairment. May require 24-hour supervision
0 to 10	Severe	Marked impairment. Likely to require 24-hour supervision and assistance with ADL

were prescribed anti-dementia pharmacotherapy which mainly consisted of the acetylcholinesterase inhibitor galantamine and the partial NMDA receptor antagonist memantine. A total of fifty drugs were used to control other coexisting medical conditions with the majority being cardiovascular agents followed by antidiabetics, antidepressants and lipid lowering agents. Supplements and vitamins were prescribed in a number of cases whereas antipsychotics were used in one of the patients (Figure 3b).

The qualitative interviews with seventeen caregivers showed a lack of perceived support by carers when caring for a person with dementia. The majority of participants mentioned the lack of professional healthcare services specifically aimed for patients with cognitive difficulties. Most importantly, caregivers reported the significant financial costs involved in the purchase of anti-dementia medication since dementia is not included among the conditions listed in the Fifth Schedule of the Malta Social Security Act. It was also observed that relatives are ambivalent as to the effectiveness of these drugs but they were unwilling to discontinue treatment in case it made caregiving more difficult or that the symptoms will worsen. This is reported in detail elsewhere.<sup>14</sup>

### Discussion

Dementia is an ever-growing condition that is associated with significant social, physical, psychological and psychiatric disability not only in individuals diagnosed with the illness but also in caregivers and family members. Up until recently, there was no effective pharmacotherapeutic intervention to manage the cognitive symptoms associated with dementia.<sup>10</sup> Although the benefits of current treatments are deemed to be modest in that they do not halt the disease progression, they represent a major step forward in the clinical management of these patients.<sup>12</sup> Although the presented small scale exercise

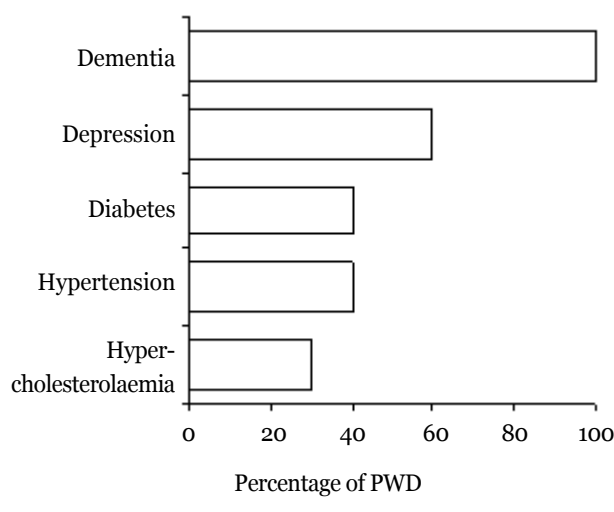
**Table 2:** Time intervals from first visit to initial diagnosis and treatment for each person with dementia (PWD) participating in the exercise (\* signifies diagnosis of dementia during the first visit at the Memory Clinic, \*\* signifies initiation of treatment on the same day of dementia diagnosis).

PWD	Days elapsed from first visit to diagnosis	Days elapsed from diagnosis to initiation of treatment	Total number of days from first visit to initiation of treatment
1	111	0**	111
2	n/a	n/a	n/a
3	0*	306	306
4	90	0**	90
5	26	0**	26
6	0*	77	77
7	0*	103	103
8	0*	n/a	n/a
9	145	0**	145
10	0*	n/a	n/a

has its limitations in terms of the number of subjects involved, the general trend observed indicate that at the Zammit Clapp Hospital Memory Clinic, patients are mostly diagnosed early upon their first clinical appointment, are mostly managed with acetylcholinesterase inhibitors and usually suffer from other comorbidities which may or may not be related to dementia. Furthermore, the overall feeling of caregivers and family members is that they are being left out from decisions on pharmacotherapy prescribed for patients with dementia under their care.

Various studies suggest that pharmacotherapeutic intervention with anti-dementia medication early in the disease process may slow down the disease progression and thus improve the quality of life for both patient and caregivers.<sup>15</sup> Although this exercise did not examine the time lapse prior to seeking clinical advice following the emergence of the first symptoms, it is clear that most of the patients did not seek medical intervention early and thus the majority were in the moderate stages of the disease. Reasons for such delay may include caregiver's lack of knowledge or reluctance to seek help, and patient, family, and physician-related factors.<sup>16</sup> In participating patients, pharmacotherapeutic dementia-related intervention consisted of the use of both acetylcholinesterase inhibitors and glutamatergic-system modifiers. Whether the use of these agents had any significant effect on delaying the disease progression or controlling the behavioural symptoms of our patients is unclear and was beyond the scope of this exercise.

**Figure 2:** Most common comorbid disorders in PWD participating in the exercise.



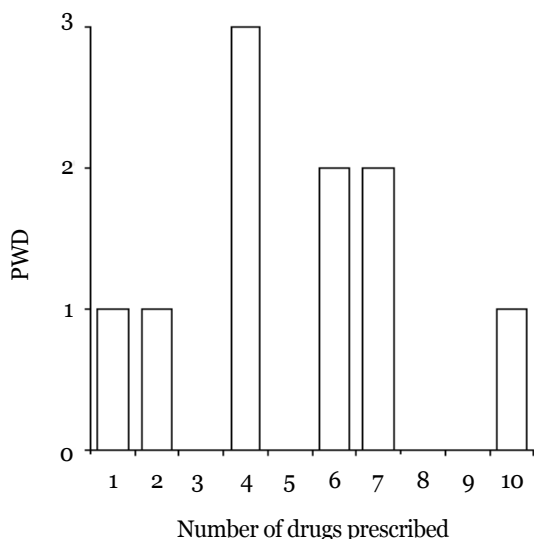
Acetylcholinesterase inhibitors were the first pharmacological treatment approved for symptomatic treatment of AD. These drugs have been found to stabilise the cognitive decline for up to 3-6 months.<sup>17,18</sup> Memantine, the only glutamatergic system modifier approved for the treatment of AD, was also reported to improve dementia symptoms by reducing the rate of clinical deterioration among patients with moderate to severe AD.<sup>9,19</sup> Currently there is a strong debate on the cost effectiveness of the

**Table 3.** Characteristics of pharmacotherapeutic agents used in the management of Alzheimer's disease (AChEI: acetylcholinesterase inhibitor, AD: Alzheimer's disease, nAChRs: nicotinic acetylcholine receptors, NMDA: N-methyl-D-aspartate).<sup>28</sup>

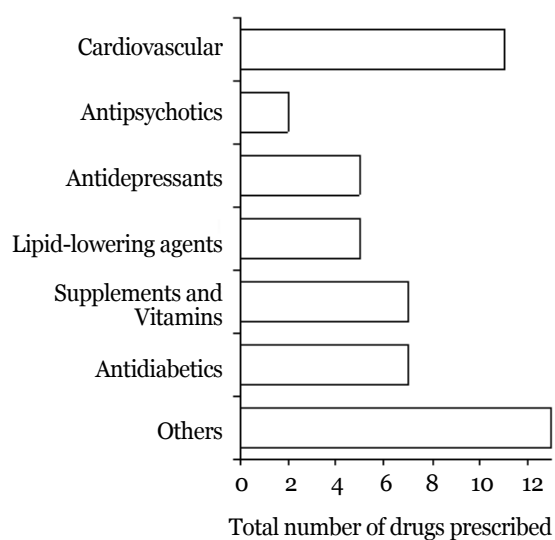
Medication	Pharmacological class	Mode of action	Recommended use	Potential adverse effects
<b>Donepezil hydrochloride (Aricept®)</b>	AChEI	Block acetylcholinesterase enzyme	Mild-to-moderate AD	Anorexia, diarrhoea, dreams, fatigue, insomnia, muscle cramps, nausea, vomiting, weight loss
<b>Rivastigmine tartrate (Exelon®)</b>	AChEI	Block both acetyl- and butyryl-cholinesterase enzymes	Mild-to-moderate AD	Anorexia, diarrhoea, nausea, vomiting, weight loss
<b>Galantamine hydrobromide (Reminyl®)</b>	AChEI	Block acetylcholinesterase enzyme. Allosterically stimulates nAChRs	Mild-to-moderate AD	Anorexia, nausea, vomiting, weight loss
<b>Memantine hydrochloride (Axura®, Ebixa®)</b>	Glutamatergic system modifier	Partial NMDA receptor antagonist	Moderate-to-severe AD	Agitation, constipation, dizziness, hallucinations, headache, insomnia

**Figure 3:** Number of PWD on polypharmacy (a) and total number of drugs prescribed to all patients as per drug mode of action or therapeutic class (b).

**a.**



**b.**



widespread use of these drugs for the various stages of AD. The National Institute of Clinical Excellence (NICE) recommends the use of acetylcholinesterase inhibitors in the moderate stages of the disease with the use of memantine reserved only for clinical trials.<sup>10</sup> This decision was widely criticised by the Royal College of Psychiatrists, the British Geriatric Society and the Royal College of Nursing as well as by various EU-based dementia societies. In Malta, no such recommendations exist and both classes of drugs can be prescribed by general practitioners and specialists. Interestingly, the trend observed indicated that half of the participating patients were recommended with the use of anti-dementia drugs upon diagnosis during their first visit at the Memory Clinic, irrespective of the severity of the condition.

This prescribing behaviour is in concordance with current recommendations denoting that early initiation of therapy is associated with greater long-term benefits.<sup>20</sup>

A significant number of participating patients were diagnosed with depressive illness possibly indicating a high prevalence rate of depression in patients with dementia. This was also reflected by the significant use of antidepressants as part of the overall prescribed treatment regimen. Epidemiological studies show a possible pathological association between the two conditions, with depression possibly acting as a prodromal sign or early symptom of AD.<sup>21</sup> Due to the limited number of patients participating in this exercise, it was not possible to investigate any link between depression and dementia although this would be an interesting research area for future consideration. The same is also valid with the other main pathologies observed. Although cardiovascular disease, diabetes and hypercholesterolaemia are risk factors in vascular dementia, these conditions are also prevalent in old age.

The use of multiple medication (polypharmacy) in the elderly has always been regarded as a complex issue in pharmaco-geriatric management. Although polypharmacy may be the only choice in some individuals, multiple medication use may increase the risk of non-compliance, medication error and potentially adverse drug interactions.<sup>22</sup> Prescribing for elderly patients with dementia proves to be even more challenging due to the changing needs that accompany cognitive decline and related behavioural symptoms.<sup>23</sup> Furthermore, more medications may be indicated in patients with dementia due to the presence of other pathologies which are common in old age.<sup>24</sup> Our data indicated that, on average, each person with dementia was prescribed with more than five different medications for the management of dementia and other comorbidities. This finding raises important clinical concerns, especially for individuals who still live in the community, in some cases on their own. Furthermore, because the use of polypharmacy increases the risk of falls, prescribing unnecessary medication may further enhance institutionalisation. Polypharmacy is also associated with increased risk of adverse drug-drug interactions which can have potential life-threatening consequences in older adults. This is especially critical in patients with dementia who are cognitively impaired and therefore not be able to explain or self report the symptoms. Interestingly, only one drug (lorazepam) was found to be part of the Beers Criteria,<sup>25</sup> a list of medications that are generally considered to be inappropriate when given to the elderly. No potentially serious drug-drug interactions were observed. In line with guidelines issued by NICE,<sup>10</sup> prescription of antipsychotic drugs was only present in one participating patient attending the Memory Clinic. Recent data shows that the use of these drugs in persons with dementia is associated with an increase in the risk of fatality.<sup>26</sup>

Studies including the views and experiences of caregivers on the effectiveness of anti-dementia drugs are lacking with a major focus directed towards conventional scientific evidence which is mostly relevant to clinicians and research scientists.

This lack of caregiver perspective was apparent in our qualitative assessment of the participating subjects. Caregivers were mostly concerned with the lack of support from the central health authorities in caring for their relatives. The greatest concern is the lack of financial assistance in purchasing anti-dementia medication which, in some cases, can take up a third of the person with dementia pension. Together with Latvia, Malta is the only country where the health authorities do not offer any form of financial support in accessing these drugs.<sup>27</sup> Even though some caregivers interviewed were unsure of the efficacy of anti-dementia medication in slowing the disease progression, they were unwilling to stop treatment.

## Conclusion

Although more research is needed, using a larger sample number, the trends observed highlight the need for a nationwide strategy that includes the various aspects involved in pharmacological and non-pharmacological management of dementia. Such strategy should include the views of policy makers, healthcare professionals as well as patients and their caregivers with the aim of designing and implementing a series of recommendations that that should enhance high-quality dementia care in Malta.

## Acknowledgements

The research work carried out and mentioned in this article was funded by the University of Malta.

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