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Snips from the journals

Dementia – care until cure: An update on management

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The endorsement of the Global action plan on the public health response to dementia 2017-2025, by the World Health Organization, marked dementia as a global health burden (1).

This framework provides a comprehensive blueprint for action for policymakers, collaborating with international, regional and national partners in addressing dementia as a public health priority. It embodies an action plan for reducing the risk of dementia and enhancing diagnosis, treatment and care, while strengthening the framework for the support for dementia care givers (1). With more than 50 million people affected by dementia globally, and numbers expected to steadily rise, this overview was written with the aim of updating the clinician with a summary of the latest recommendations in the field of dementia.

Alzheimer's dementia

Nearly 120 years after the seminal first case of Alzheimer's dementia (AD) was published, it remains the largest contributor to dementia (2). The current AD treatment paradigm is to reduce the progression of symptoms and disability. Despite ongoing efforts, a magic cure for AD is unrealistic in the near future. By the time the clinical features become evident, neurodegeneration has already caused devastation in synapses, cells, and networks for a decade or more.

An article by Alireza Atri summaries pharmacological therapies for AD, seeking to minimize the disabling effects of cognitive and functional decline and emergence of behavioral and psychological symptoms, as below (3).

- The FDA-approved anti-AD pharmacotherapies; the cholinesterase inhibitors donepezil, galantamine, and rivastigmine.
- The NMDA antagonist memantine can reduce progression of clinical symptoms and disability.
- The combination of these agents.
  This is in keeping with the NICE guidelines which expand this recommendation by stating that (4).
- The three acetylcholinesterase (AChE) inhibitors as monotherapies are recommended as options for managing mild to moderate AD.
- Memantine monotherapy is recommended as an option for managing AD for people with moderate AD who are intolerant of or have a contraindication to AChE inhibitors, and for those with severe AD (4).

Cummings et al. state that despite the early promise of several new drugs, many have failed larger phase III trials (5). The high failure rate of the therapies stems largely from the complex pathologic causes of the disease. The article also states that research has repeatedly shown that combining cholinesterase inhibitors and memantine has limited success in the treatment of AD, and targeting multiple pathways is likely to be required for successful treatment (5).

Newer research indicates that other NMDA receptor modulators are under extensive investigation with several new drugs entering clinical trials (6). Genome-wide association study has made it feasible to identify associated genes, post-transcriptional modification, single nucleotide polymorphisms, and structural variants as potential biomarkers in multifactorial diseases. Finally, possible interventions through enzymes and metabolites in the kynurenine pathway of tryptophan metabolism in dementia are being currently studied (7). Some of these collaborative efforts are aimed at overcoming the challenge of reliably identifying patients with preclinical AD.

Vascular dementia

Smith et al focused on the pharmacological treatment options in vascular dementia (8). While the authors remind the reader that vascular disease is a common cause of dementia, often presenting along with other neuro-pathology in the aging brain, they also highlight that many of the risk factors for dementia overlap with the risk factors for stroke and cardiovascular disease (8).

The article makes the following recommendations regarding the management of vascular dementia:

- Standardized diagnostic criteria should be used to diagnose vascular cognitive impairment (VCI), aided by neuroimaging.
- Reduction of risk factors for stroke is strongly recommended. The best evidence is for treatment of hypertension.

- Acetylsalicylic acid is suggested for use in patients with vascular dementia and silent brain infarcts on imaging, but evidence is mixed. It's use for patients with white matter lesions only is not recommended.
- Cholinesterase inhibitors may be used in selected patients, and is weakly recommended, based on moderate/low quality evidence.

Lewy body dementia

Lewy body dementia (LBD) is the second most common type of neurodegenerative dementias, comprised of dementia of Lewy bodies (DLB) and Parkinson's disease dementia (PDD) (9). Cognitive symptoms are seen early in LBD, whereas they start at least a year after the appearance of motor symptoms in PDD. Although it is likely there is a pathological and genetic overlap, they are complex and heterogenous conditions with a wide range of other symptoms.

A review on the management of key domains of Lewy body dementia, brings together the evidence base for Lewy body dementia, as well as expert opinion developed via a Delphi consensus process (10). Their key findings are summarized below.

Cognitive symptoms

The following key messages have been given in relation to the management of cognitive symptoms in LBD.

- Donepezil and rivastigmine are similarly effective. These also show positive effects on maintaining activities of daily living and reducing care giver burden (11) (12). Galantamine needs further evaluation.
- Donepezil and rivastigmine are recommended as first line treatments for DLB by the UK National Institute of Health and Care Excellence (NICE), and rivastigmine is licensed for PDD in UK and the USA (4) (11).
- The absence of improvement should not be a reason for discontinuation, as global deterioration is less when prescribed choline esterase inhibitors (11). Sudden withdrawal can be associated with deterioration of cognitive functions and neuropsychiatric symptoms (13).
- Memantine has inconclusive evidence for improving memory but is shown to increase ADCS-Clinical Global Impression (14).

Neuropsychiatric symptoms

Neuropsychiatric symptoms such as hallucinations, delusions, and mood symptoms do not always need interventions. Pharmacotherapy as below is indicated when symptoms are severe and distressing, and not responding to other interventions (4).

- Rivastigmine and donepezil are endorsed in treating neuropsychiatric symptoms (4). They are shown to improve composite neuropsychiatric scores, although their role in specific symptoms are not known (12). Galantamine could be an alternative when other AChE inhibitors are not tolerated (11).
- The evidence for memantine is not conclusive.
- If psychotic symptoms persist despite treatment with AChE inhibitors and memantine, an antipsychotic agent could be considered, but evidence for efficacy is scarce (11).
- In LBD, treatment with antipsychotics is associated with increased risk of severe and fatal sensitivity reactions, and long term antipsychotic use is related to increased mortality (15).
- Quetiapine has the least side effects, but efficacy is not proven (16). Clozapine has been shown to be effective in PDD and may help in LBD, but no trials have been done with regards to the use of this medication in patients with LBD only (16).
- Pimavanserin, an antipsychotic drug which shows beneficial effect in psychosis associated with Parkinson's disease is currently being investigated (17).
- There is no clear available evidence as to which antidepressant is best in LBD. Antidepressants can affect sleep and worsen REM behavior disorder.

Sleep disturbances

Sleep disturbances in LBD can be severe and include insomnia, REM sleep behaviour disorder and restless leg syndrome. Education on sleep hygiene and avoiding drugs that affect sleep are preliminary steps in management. The following are the pharmacological interventions that have shown beneficial effects (10).

- Melatonin is well tolerated and improve subjective sleep quality in insomnia associated with neurodegenerative diseases.
- Z drugs: eszopiclone, zopiclone and zolpidem are recommended for short term use for insomnia, while observing with caution for possible side effects such as daytime sleepiness, falls and negative effects on cognition.
- Long-acting levodopa preparations may be useful if insomnia is secondary to nocturnal parkinsonism.
- Dopaminergic agents such as ropinirole, pramipexol, and rotigotine as well as gabapentin and pregabalin which have efficacy in idiopathic restless leg syndrome, but have not been studied for LBD and need to be used with caution.
- Clonazepam, pramipexole, melatonin and memantine may show benefit in REM sleep behaviour disorder associated with LBD.

Taylor et al. stress that symptoms should not be treated in isolation, as the benefit in one domain may be gained at the cost of deterioration in another domain (10).

Frontotemporal dementia

Tsai and Boxer in 2016 reviewed the evidence for currently available therapies in frontotemporal dementia (FTD), as well as the recent advancements in the pathophysiology, treatment development and biomarkers (18).

FTD comprises of 3 main clinical syndromes, behavioural variant of frontotemporal degeneration (bvFTD), non-fluent variant primary progressive aphasia (nfvPPA) and semantic variant primary progressive aphasia (svPPA). The clinical picture overlaps with corticobasal degeneration, progressive supranuclear palsy, and amyotrophic lateral sclerosis. These syndromes are generally recognized under the umbrella term Frontotemporal Lobar Degeneration (FTLD), as they share underlying neuropathology. Impairment in social, behavioural, executive, language and cognitive functions are common in this group of disorders. Currently there are no US Food and Drug Administration (FDA) approved pharmacological treatments for FTD.

Behavioural problems

Behavioural problems are marked and includes disinhibition, apathy, lack of empathy, compulsive behaviours and altered eating habits particularly in bvFTD. Depression is also commonly seen. The following summarises management options for behavioural problems in FTD given in this review.

- Antidepressants may help behavioural symptoms in FTD and are well tolerated, but the evidence for efficacy is limited. Sertraline, citalopram and trazodone have shown to improve mood and neuropsychiatric inventory scores.
- Antipsychotics have less evidence and carry the risk of EPSE for which FTD patients are particularly vulnerable, and are known to increase mortality. Olanzapine, quetiapine, risperidone, and aripiprazole have shown some benefit.
- Mood stabilisers such as valproic acid, topiramate and carbamazepine show limited evidence.
- Early evidence suggests that neuropeptide oxytocin, which is an important mediator of social behavior, has been shown to improve apathy and empathy when administered intra nasally.

Cognitive symptoms

Cognitive symptoms are present in FTD and other related conditions to varying degrees. The following summarises pharmacotherapies for cognitive impairment.

- Cholinesterase inhibitors are not effective in FTD and may in fact worsen the behaviour and motor functions. Memantine was associated with worsening of cognitive functions.

Parkinsonism

A substantial proportion of patients with FTD presents with parkinsonism and related motor difficulties such as tremor, rigidity, and bradykinesia.

- Patients with FTD or other related conditions like PSP or CBD have shown limited benefit from levodopa/carbidopa.

Tsai and Boxer recommend non-pharmacological interventions as an important cornerstone in the management as FTD often cause significant care giver stress (18). Physical therapy for gait, balance training as well as home safety evaluation by an occupational therapist, can be beneficial for patients with movement dysfunction. Exercise has been shown to benefit cognition, mood, and overall health. Speech therapy and interventions delivered by experts with experience in neuro degenerative aphasias may be helpful in primary progressive aphasias.

The authors conclude by stating that the advancement in the knowledge of underlying molecular and genetic basis of FTD have reached sufficient maturity for new drug targets to be identified (18).

Conflicts of interest

None declared.

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