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Exploring the Recent Trends in Management of Dementia and Frailty: Focus on Diagnosis and Treatment

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Abstract

Dementia and frailty increase health adversities in older adults, which are topics of growing research interest. Frailty is considered to correspond to a biological syndrome associated with age. Frail patients may ultimately develop multiple dysfunctions across several systems, including stroke, transient ischemic attack, vascular dementia, Parkinson's disease, Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, cortico-basal degeneration, multiple system atrophy, amyotrophic lateral sclerosis, and Creutzfeldt-Jakob disease. Patients with dementia and frailty often develop malnutrition and weight loss. Rigorous nutritional, pharmacological, and non-pharmacological interventions generally are required for these patients, which is a challenging issue for healthcare providers. A healthy diet and lifestyle instigated at an early age can reduce the risk of frailty and dementia. For optimal treatment, accurate diagnosis involving clinical evaluation, cognitive screening, essential laboratory evaluation, structural imaging, functional neuroimaging, and neuropsychological testing is necessary. Diagnosis procedures best apply the clinical diagnosis, identifying the cause(s) and the condition(s) appropriate for treatment. The

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CONFLICT OF INTEREST

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patient's history, caregiver's interview, physical examination, cognitive evaluation, laboratory tests, and structural imaging should best be involved in the diagnostic process. Varying types of physical exercise can aid the treatment of these disorders. Nutrition maintenance is a particularly significant factor, such as exceptionally high-calorie dietary supplements and a Mediterranean diet to support weight gain. The core purpose of this article is to investigate trends in the management of dementia and frailty, focusing on improving diagnosis and treatment. Substantial evidence builds the consensus that a combination of balanced nutrition and good physical activity is an integral part of treatment. Notably, more evidence-based medicine knowledge is required.

Keywords

Dementia; frailty; malnutrition; stroke; diagnosis; mediterranean diet

1. INTRODUCTION

An increase in life expectancy by nearly two-fold in the Western world has been one of the most significant accomplishments in public health during the twentieth century. Accompanying this, the associated higher frequency of little-understood geriatric disorders has brought new and urgent problems to this already aging society. The medical and economic cost of caring for dependent elderly adults, restricted by physical and mental impairments, is one of the most intimidating challenges of modern healthcare [1]. After Alzheimer's disease (AD), dementia with Lewy bodies (DLB) is the most frequent form of neurodegenerative dementia. The dementia stage, including AD, is typically preceded by a phase during which cognitive impairment is evident, however, there is still some potential for independence in performing daily tasks. Mild cognitive impairment with Lewy bodies (MCI-LB) is the term given to this condition [2-4]. There is a high risk of severe cognitive deterioration in both types of dementia, accompanied by gradual physical decline and, eventually, complete physical dependence [5]. In 2016, there were 43.8 million dementia cases worldwide, and annual dementia costs (mostly from informal and social care) are predicted to ascend $2 trillion by 2030 [6]. As an example, among many nations, Brazil has one of the world's highest age-standardized prevalences of dementia impacting around 1.7 million people, together with population expansion, aging, and an increase in the frequency of dementia-related risk factors. Whereas the number of dementia-related fatalities has declined in certain Latin American nations during the prior two decades, the mortality rate from this disorder climbed by almost 12% in men and 13% in women in Brazil from 2000 to 2008 [7]. Similarly, in the United Kingdom, more than 850,000 people have dementia [8]. The Fried phenotype and the frailty index, which are identical to those used in other countries, are the most often used frailty evaluation tools in China - where, as yet a further example, frailty impacts 5.9%-17.4% of community-dwelling adults aged 65, which is similar to the rate in developed countries [9].

The most prevalent cause of dementia in older people is AD. Growing data, however, suggest that mixed dementia is the most prominent subtype of aging, particularly in older adults aged 80 years and upwards, varying from 20-25% to 35% of all dementia cases [10, 11]. Furthermore, autopsy of the Alzheimer's Disease Neuroimaging Initiative (ADNI)

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confirmed that, whereas the *in vivo* diagnostic precision of AD was very significant (97%), mixed pathology was observed in several situations in patients who eventually suffered from dementia and died [12]. It has become increasingly appreciated that preventing midlife cardiovascular disease (CVD) is a vital strategy to decrease the risk of dementia in old age [13, 14]. Besides, CVD, including AD, has been reported to play a causative role in the onset of dementia. Indeed, within the oldest subset of the elderly population, coronary comorbidity is a common clinical disorder and supports the well-studied close relation between dementia and CVD [15, 16].

Frailty is a multifaceted ‘reserve depletion syndrome’ that gives rise to weakness (energy, physical capacity, cognitive, wellness). It seems to be a valid construct, but it is uncertain how to describe it precisely [17]. Frailty can be observed across all age groups, but its prevalence is the highest among elder demographics. This is because frailty is recognized for its risk of complications, falls, and hospital stays, which forecast negative results. Furthermore, frailty is considered a transitional stage between stable and disease conditions, which can be improved through effective treatments, in which impairment may be postponed or prevented.In independent practices, such as self-care, elderly adults who have already acquired disabilities demonstrate disadvantages. They may have more significant preferences, which may intensify care pressures, to rely on long-term care policies [17, 18] up to a possible tipping point where it becomes a pre-death period, frailty is theoretically preventable. Practice to avoid and delay the progression of fragility is also paramount. A comprehensive field of study has been dedicated to designing instruments for the scientific calculation of fragility, with endless disputes over the conceptual construct to be assessed to determine which persons will gain from such techniques. In relation to the clinical presentation of frailty in terms of a physical phenotype, the fundamental framework of a measurable biological syndrome was identified in 2001 by Fried and colleagues [19].

2. EPIDEMIOLOGY

Three cross-sectional studies were performed, the first of which reported MAPT (Multidomain Alzheimer Disease Preventive Trial) results on the neuropsychological profile of frail cognitive participants. The second measured the relationship between cognitive frailty and functional independence, and the third was primarily intended to identify the prevalence of cognitive frailty [20-22]. Furthermore, the link between mental frailty and adverse health-related effects (morbidity, hospital stays, the standard of living, and lack of functional independence) and cognitive-related results, such as the development of dementia or neurocognitive diseases, have been investigated in five prospective studies [12, 23, 24].

3. THE CURRENT CHALLENGES IN DEMENTIA AND FRAILTY CARE

Current challenges related to dementia and frailty care raise concerns relevant to an organization’s ability to effectively deal with the associated effects. The healthcare environment has been recognized as the key driving factor which affects a healthcare personnel’s ability to offer personalized care. As personalized care positions the importance of the individual’s interaction over the activities, companies need to encourage clinicians to use a care management approach. Proof, however, shows that systemic variables mitigate

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this occurrence, with health care agencies focused on achieving economic expectations at the cost of personalized care [25]. Finally, a general inadequacy of hospital workers' skills to manage adults who have dementia is a constraining factor, given that many of the associated symptoms are troublesome, difficult to understand, and challenging to tackle appropriately. The delivery of treatment that is personalized is next to impossible in this setting. To gain a comprehensive knowledge of dementia and to become knowledgeable in offering person-centric dementia services and current health care, training updates for providers are required [26-28]. A novel cognitive biomarker technology can provide information relating to the pathology of the brain. It should be made available at the healthcare level, facilitating slower cognitive decline and preserving cognitive reserve. Such combination with intervention may increase our ability to tackle the challenges of dementia [29]. Population-based fragility screening may be costly, although resource-intensive, and there is currently no firm indication of possible gain, cost-effectiveness, or improved performance.

Nevertheless, it was concluded at the 2012 Frailty Consensus Conference that screening for frailty should be recommended for persons with particular disabilities or living in some specific environments [30]. The UK Fragility Practice Recommendations released in 2014 by the British Geriatrics Association, Age UK, and Royal College of General Practitioners recommend performing a fragility evaluation using all the experiences gathered by health and social care professionals, aged people community, and outpatient environments. A policy commitment to older adults with early (pre-) frailty should not be deficient in research and development programs to identify and disseminate best practices in which frailty misses an opportunity to resolve some health and social care service demands [31, 32]. A physical disability may be first recognized, increasing the likelihood of potential falls and representing some of the earliest signs of frail older adult patients. Hence, in such a case, a falls clinic may screen such frail patients to improve their well-being and provide an adequate management approach early [33]. Among the existing challenges in frailty science, one of the most critical concerns is the shortage of an international normative description of frailty [34].

4. INTERVENTION

An estimated 35 million people live with dementia worldwide, with half of them experiencing recurring pain. Despite this, present methods for assessing and treating pain in this patient population are insufficient. In addition to causing discomfort and suffering, pain is frequently the underlying cause of behavioural problems, often leading to improper antipsychotic prescription use. Pain might also lead to more issues during therapy and care. This study examines four main viewpoints on dementia pain treatment and offers practice and research recommendations. The first point raised is the literature's lack of consensus on the impact of dementia neuropathology on pain perception and processing in AD and other dementias, where white matter lesions and brain atrophy appear to influence pain neurobiology. The second viewpoint discusses how to assess pain in dementia patients. This is difficult, especially given these poor self-reports, which implies that assessment is heavily reliant on observational approaches. There are several tools available, but their psychometric validity and clinical value are mainly unknown. With few statistically well-powered trials, the evidence for effective treatment (the third perspective) with analgesics is, likewise,

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limited. The best evidence supports graded therapy approaches and shows that pain and behavioural therapies can help with these acute symptoms. The fourth viewpoint discusses additional challenges in pain treatment due to a lack of adequate training and education for health care providers at all levels, where evidence-based guidance is desperately needed. A comprehensive approach is required to address the existing insufficient management of pain in dementia. This would include a reliable, validated evaluation tool that is sensitive to diverse types of pain and therapeutic effects, as well as improved training and support for care providers in all settings [35].

On the other hand, no adequate and appropriate interventions are available in case of frailty, and highquality and cost-effective health care approaches are required [36]. Multi-dimensional intervention is suggested [37, 38], many of which involve exercise, potentially having more significant beneficial effects than unidimensional interventions [39]. The multicomponent exercise approach seems to be effective in frailty intervention [40, 41]. Frailty can be improved through physical activity, training, nutrition, and a combination of treatment plans. Frailty can best be considered as a set of signs and symptoms rather than a disease. This is why a practical intervention approach can potentially prevent frailty or slow its development [42].

5. THE CORE OF CLINICAL CRITERIA

The term ‘dementia’ does not explicitly indicate any particular neuropsychiatric symptom but, rather, a loss of creative abilities, such as memory loss or problem-solving sense or language. Standard dementia criteria sometimes overlook psychological evaluation, such as a change of behaviour caused by dementia at the time of cognitive decline, which may also occur a few years after the diagnosis of dementia [43]. In particular, a new case of misery/misfortune in the aged could indicate a potential dementing process, specifically in highly educated patients [44]. These aspects should best be included as part of the diagnostic criteria. Any potential patients already taking anti-dementia drugs should not be excluded if any other standard signs of dementia arise.

Moreover, the Cardiovascular Health Study (CHS) has reported the neuropsychiatric symptoms in the course of dementia to be about 75%. Previously elucidated, some proposals have been written that include aged patients who have not reached the current level of dementia following the standard criteria such as Age-associated memory impairment (AAMI) [45], Cognitive impairment, no dementia (CIND) [46], Age-associated cognitive decline (AACD) [47]. A subjective assessment of this comprehensive range of normal dementia has been published [48, 49]. Two frailty phenotypes were described from the elemental concepts [50], where one of the phenotypes is specified by a multi-domain concept. Also, this reflection presents cognizance, mindset, tactile debilitation, constant sicknesses, inabilities, and social conditions to actual parts [51, 52]. And the second one is the one-dimensional concept which is described by physical phenotypes [17]. The benchmarks of these phenotypes involve contracting (weight reduction), shortcomings (handgrip strength), weakness or helpless endurance (self-detailed), disregard (step speed), tranquil-like state (kilocalories used week after week). Within this system, lots of actual debilitations and non-actual constituents are not readily tolerated. The Fried models have

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been applied in large scale epidemiological investigations, chiefly in the United States, Canada, and Europe [17, 42, 53-55].

6. DEMENTIA MANIFESTATION

Several factors can coexist that lead to the manifestation of dementia. Studies suggest that anti-depressant drugs are associated with a potential reason underpinning dementia. Earlier stage dementia may result from late-onset depression [17].

Cognitive

- Irregular memory loss.
- Loss of word sense.
- Forgetting several events, like a family outing, paying a necessary bill, and so on.
- Memory loss in using a once familiar instrument like a microwave, iron, computer, and so on.

Psychological

- Depression, apathy, delusion.
- Lack of emotions and feelings or activities, like not being willing to participate in having a meal.

Physical

- Movement disability, seizures.
- Involuntary rhythmic shaking.

Behavioral

- Withdrawal from social involvement.
- Inability to respond.
- Walking out of one’s home at or after midnight.

Sleep

- Dream enacting behavior.
- Running or flying during the time of dreaming.

These manifestations do not occur in all types of dementia; each individual manifests not all examples provided here. Several less common images that are not listed may appear [17].

7. TOOLS OF SCREENING AND DIAGNOSIS

The Mini-Mental State Examination (MMSE) [13, 17, 53] and Montreal Cognitive Assessment (MoCA) [56, 57] are neuropsychological screening tests that are widely used to evaluate patients. Additionally, there are locally adapted screening tests exemplified by

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the Korean Dementia Screening Questionnaire (KDSQ) [13, 56, 58, 59] commonly used in caregiver interviews in Korea. In the present study, a prediction model was developed to help screen for cognitive dysfunction. This model included patient evaluations (MMSE and MoCA scores), caregiver or informant interviews (KDSQ results), and clinical evaluations (including essential demographic data). The MMSE, MoCA, and KDSQ were administered as neuropsychological screening tests in this study.

The MMSE is the most commonly used test for cognitive impairment screening and can be performed relatively quickly [21, 22]. Possible scores range from 0 to 30 points, where higher scores indicate better cognitive function. The MMSE is the most appropriate test for detecting moderate and severe cognitive dysfunction. The MMSE examines the following six cognitive domains: orientation in time, orientation in place, memory registration, memory recall, attention and calculation, and language and visuospatial function [53]. The MoCA is the most widely used screening test for cognitive dysfunction, including Mild cognitive impairment (MCI) and the early stages of dementia. The MoCA has higher sensitivity than the MMSE for detecting early-stage cognitive decline [57, 60]. The Groningen Frailty Indicator (GFI) is a screening tool used to determine the level of frailty [58]. It consists of fifteen items and focuses on the loss of function and resources in four domains: physical (nine elements), cognitive (one item), social (three elements), and psychological (two items). Most items are answered with ‘yes’ or ‘no.’ The option ‘sometimes’ is added for cognitive and psychosocial items, with scores on the GFI ranging from zero to fifteen. The original cut-off value of ≥4 has been used to indicate frailty [60].

8. DIAGNOSTIC APPROACH

Neurodegenerative proteinopathies are involved in and mechanistically underpin most primary dementias, where an accumulation of misfolded proteins contributes to neuronal loss, neuroinflammation, and glial cell activation. The specific type of protein engaged in the pathophysiology defines each proteinopathy [57]. In determining the health status of older adults, frailty evaluation is a pivotal method. It is conceivable to isolate the clinical strategies utilized by geriatricians to decide feebleness (*i.e.*, fragility) into two classes: using a questionnaire-based approach or evaluating the subject's physical results [61, 62]. In general, frailty is a clinical condition associated with a higher risk of adverse effects such as falls, injury, institutionalization, and death [59]. Fragility in more seasoned grown-ups prompts expanded vulnerability to stressors and is a perceived pointer to numerous antagonistic impacts in this age group. Clinical assessment, intellectual screening, research facility appraisal, and underlying imaging can now effectively analyze dementia. It is imperative to embrace laboratory studies to preclude clinical reasons for underpinning psychological/cognitive impairments, such as hypothyroidism, weakness, electrolyte problems, nutrient B12 insufficiency, and hyperglycemia [63, 64], all of which are potentially reversible. By the presence of at least the aggregate model characterizes delicacy; weight reduction, weariness, low energy utilization, lazy strolling speed, and low strength of handgrip. The cumulative deficit model defines frailty based on the accumulation of several symptoms, sensory deficiencies, clinical signs, disorders, disabilities, and irregular outcomes from the laboratory tests [62]. The following techniques can also be used:

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8.1. Cognitive Assessments and Neuropsychology

These appraisals are utilized to evaluate memory, critical thinking, language abilities, math abilities, and other mental working abilities (Fig. 1).

8.2. Laboratory Test

Testing an individual's blood and other fluids and checking levels of different chemicals, hormones, and vitamins can help diagnose or rule out potential causes of symptoms. Mini strokes, cancers, and other conditions that may partly underpin dementia may, for example, be detected by these tests (Fig. 1).

8.3. Psychiatric Testing

Such assessment will help choose whether the manifestations of an individual are instigated or added to by unhappiness/anguish/desolation or any other emotional wellness issues (Fig. 1).

8.4 Genetic Testing

Albeit inheriting dementia directly (via a single--gene mutation) is hugely rare, genes are widely considered to play some role in almost all cases of dementia. For example, some forms of frontotemporal dementia are inherited, and select mutations in presenilin-1 and amyloid precursor protein are responsible for associated early-onset forms of AD. A genetic test in these cases will permit individuals to know whether they are in danger of dementia [63]. For the most part, fragility is a condition encompassing multiple indications, including weight reduction, weakness, health depletion, slow speed of strolling, and physical inactivity [64]. To observe signs of the presence of a functional and psychological incapacity, the early identification of dementia onset includes an exhaustive cross-examination [65, 66] (Fig. 1).

9. ENSURING THE CAUSES OF DEMENTIA BY PATHOLOGICAL AND CLINICAL EXAMINATIONS

Evaluation of exact causes has required a variety of tools that are used for clinical and neurological examinations. Pathologic examination, history, cognitive features are the primary tool sets used for dementia. Amyloid-beta (Aβ) peptide plaques together with neurofibrillary tangles containing hyperphosphorylated tau protein in the cortex and hippocampus, visual impairment, and anomia have been associated with and included in pathologic examinations of AD. Studies show that dementia related to cerebrovascular disease often associates with intracerebral hemorrhage, atherosclerosis, and focal brain atrophy. Similarly, LBD often correlates with brain atrophy [67].

10. BARRIERS TO DIAGNOSIS AND TREATMENT

The provision of dementia care has become highly scrutinized with the increase in the prevalence of dementia disorders and the growing vital impact of dementia on health care services, with primary care physicians (PCP) being at the center of such focus [53]. The two main problems found to impede the diagnosis of dementia are the inability or anxiety of people with dementia to accept or recognize symptoms, and the capacity of health and

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social care practitioners to identify and diagnose dementia, particularly during the earliest stages [68]. It can be mentally demanding but gratifying to evaluate and manage dementia. However, caregivers that provide dementia treatment can often face particular obstacles that cause frustration unless such obstructions are accepted and resolved [69]. Patients with dementia are at a high risk of inadequate postoperative care for pain, primarily because they cannot express or communicate their pain perception [70]. When dementia is diagnosed early in the disease process, there is a greater potential opportunity for treatment to preserve patient function and postpone deterioration as well as for family education about the disease and its care.

On the other hand, primary care providers frequently experience difficulties making early diagnoses [71]. Currently, dementia is diagnosed primarily based on a clinician's suspicions grounded on patient symptoms or caregiver concerns, and it is mainly done in a primary care context [72]. In the primary care setting, where provider-patient encounters are generally brief and patients often present with various symptoms and other issues, diagnosing dementia in older people can occasionally be problematic. Early dementia symptoms, such as memory loss, may not be seen during a typical office visit, unless specifically checked [64]. As a result, it's not unexpected that numerous studies show primary care clinicians making delayed and unreported dementia diagnoses [30, 73, 74]. While these practice-related concerns are valid, they should not be confused with an inability to objectively distinguish between typical age-related memory deficits and dementia [75]. Because of the potential for injury and expenditure, missed and delayed diagnoses in medicine have recently attracted more attention in the patient safety literature [76-80]. When diagnoses are accidentally delayed, incorrect, or missing entirely, these events are reported to occur [81]. Dementia diagnosis that is missed or delayed results in missed treatment opportunities and increases the burden on patients and caregivers. This study aimed to learn more about the prevalence of missing and delayed dementia diagnoses in primary care and determine the factors that contribute to these issues. We only looked at trials that focused on overcoming barriers to accurate and timely diagnosis, rather than screening, primarily because the advantages of routinely screening asymptomatic people are unknown, and any early detection technique must overcome these obstacles to succeed [72]. Only around half of dementia cases are diagnosed by doctors. The purpose of this study was to see how PCPs assess patients for dementia and to see what difficulties there are in diagnosing dementia in the primary care context. In 18 focus groups, 78 physicians from three geographic locations took part. The failure to notice and respond to dementia symptoms and a perceived lack of necessity to determine a particular diagnosis, time constraints and negative attitudes regarding the importance of assessment and diagnosis were all highlighted as barriers. These hurdles thwart clinicians from diagnosing dementia and, as a result, from providing tangible assistance to patients with dementia symptoms or their caregivers [64].

11. OVERCOMING THE BARRIERS

Frailty can be considered a development of a non-specific state of vulnerability, indicating a transitional physiological decline across many systems. A current understanding is that this multidimensional condition refers to physical, psychological, cognitive, and social factors and that this ‘combination’ needs to be considered in its description and treatment

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[82]. Screening evaluations, for example, the Mini-Mental Condition Examination, provide a quick and straightforward appraisal of orientation, attention, memory, language, and visual-spatial skills that can be time-dependently assessed. Whereas they will not give a firm diagnosis of dementia, they can be effectively used to select individuals that warrant further, more specific evaluation. Separating mild psychological impairments from dementia is essential, as potentially treatable depression and other disorders can negatively impact such relatively simple dementia evaluations. A soundly based early diagnosis of dementia provides more potential time to initiate treatment to maintain patient function and delay decline for supporting family, education-focused towards achieving effective disease management [83]. AD evaluation, like other dementias, requires a dependable battery of tests that includes a neuropsychological assessment; be that as it may, even when such evaluations are utilized across society and time-dependently, difficulties can be experienced [84]. For older adults with end-stage dementia, there is an urgent need to expand palliative care coverage [85]. In the pathogenesis of disability in older people with diabetes, frailty is a mediator, and it is recommended to assess regular activities of daily living. Frailty is a complex process that time-dependently develops from a solid, healthy state to a pre-frail level, followed by frailty and, ultimately, impairment and disability. A multimodal intervention that combines a proper diet, exercise preparation, appropriate glycemic regulation, and the potential use of suitable hypoglycemic medicines may aid delay or prevent progression to disability [86].

PCPs hence assume a fundamental role in conveying appropriate care for individuals with dementia and, in some cases, can even be considered parental figures. However, several obstacles hinder them from providing the best possible care [85, 87]. Cognitive decline can often be linked to late-life depression. Depressive symptoms are frequently related to or even precede dementia. Furthermore, depressive disorders raise the probability of moderate cognitive impairment and dementia persisting. The current evidence and future perspectives on the integration and value of clinical assessments, neuropsychological, neurochemical, and neuroimaging biomarkers for the etiological classification of dementia versus depression syndrome, and the prognosis of depression relating to dementia risk are presented here. Finally, we review the evidence for medication and psychotherapy in the treatment of depression in demented patients. Large-scale collaborative research is urgently needed to explain the function and interplay of clinical and biological aspects in elderly people with depressive disorders who are at high risk of dementia. We recommend that the precision medicine paradigm be introduced to this research sector to address impediments to successful medication development [88].

12. THERAPEUTIC APPROACH

In elderly individuals, dementia denotes a critical health complication: a progressive decline in cognition, day-to-day functioning, and behavior. All of these result in incapacitation [89].

12.1. Pharmacologic Intervention for Dementia

An ultimate goal is to manage the dementia severity. In trying to achieve this, pharmacologic and non-pharmacologic treatment approaches are required to attain the actual objective.

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Studies suggest that multiple potential pharmacologic treatment approaches should best be considered to manage dementia.

12.1.1. Approved Pharmacologic Treatments for Dementia Attributed to Alzheimer's Disease—Dementia associated with probable AD is one of the most common forms of dementia. Anticholinesterases have become a standard of care in the light of the cholinergic hypothesis and the known cholinergic deficits associated with the disease.

The cholinesterase inhibitors donepezil, galantamine, and rivastigmine represent the choice for symptomatic treatment for patients with AD. All have demonstrated beneficial actions on standard cognition and global function measures in mild to moderately affected patients, but are mainly considered ineffective in advanced disease. Consideration of which to initially try often associates with PCP preference, availability, and cost. All are generally considered well-tolerated at recommended doses - when administered with caution and appropriately titrated to their optimal dose. Their expected level of “improvement” and impact on clinical outcomes for patients with Alzheimer’s can be considered “modest” and purely symptomatic. Futhermore, when no benefits are attained using one cholinesterase inhibitor, switching to one of the other two within this class may prove favorable.

The initial Donepezil recommended dose to use is 5 mg once/day for six weeks, which, if tolerated and needed, may be elevated to 10 mg (generally for three months) and, ultimately, potentially up to 23 mg once/day (albeit this latter dose can be associated with substantially higher gastrointestinal adverse effects). Rivastigmine can be used for mild to moderate stages of AD orally at 1.5 mg twice daily for two weeks - titrating carefully and as needed to a maximum recommended dose of 6 mg twice daily. Alternatively, it can be administered as a transdermal patch at 4.6 mg/24 h once/day for four weeks, with the possibility for a titrated elevation to 9.5 mg or 13.3 mg once/day, if required and tolerated. Finally, Galantamine immediate-release is initiated at 4 mg twice daily for four weeks that can, as needed (depending on tolerability), be titrated to a target dose range, 8mg twice daily and, ultimately, to 12 mg twice daily after four further weeks. In several cases, anticholinesterases are combined when administered to moderate to severe cases with memantine (particularly for donepezil). Whereas combination therapy has demonstrated statistically significant effects on cognition and global clinical impression, the clinical relevance of these effects remains somewhat academic and uncertain. The use of all of these drugs is associated with well-known, common adverse effects that include nausea, vomiting, loss of appetite, increased bowel movements, insomnia, seizure disorders, and urinary tract obstruction, and are contraindicated in patients with bradycardia, headache, constipation, confusion, and dizziness [67] (Fig. 1).

There appears to be less consensus on the utility of cholinesterase inhibitors in patients with other forms of dementia. Consequently, regulatory approval for use in non-Alzheimer’s diagnoses is more variable. Nevertheless, use in vascular dementia (VD), Parkinson’s disease (PD) dementia, and dementia with Lewy Bodies has been described. Benefits, at best, can be considered “modest,” and their clinical relevance is often questioned. In other dementias, such as those associated with Frontotemporal dementia, Huntington disease, and

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multiple sclerosis, in aggregate, studies thus far have yet to provide any substantial support of their utility.

12.2. Exercise and Motor Rehabilitation

Several prospective types of research recommended that consistent physical activity may improve cognitive function and decrease the threat of Alzheimer's and other dementias. Potentially, their onset or progression is delayed (Fig. 1) [14, 17, 90-92], but studies to definitively demonstrate this are lacking. A population-based study reported that modest strength midlife bodily activity was significantly associated with a reduced threat of dementia [93]. Exercise has been recognized to develop physical health and well-being, and in patients with AD or dementia, it augmented performance in the actions of daily living [90, 94]. The positive effect of exercise programs in reducing the progression of dependence in activities of daily living (ADL) in people with dementia was supported in a review that included seventeen randomized controlled trials but disclosed limited proof of advantage for the remaining consequences [95]. Recently, a review on the link between fitness, physical activity, and grey matter volume reported that randomized interventions and cross-sectional studies steadily support a favorable alteration in the prefrontal cortex size and hippocampus after a moderate level of exercise in older adults [96]. The brain-derived neurotrophic factor, neurotrophins, provides a common pathway of these mechanisms and may facilitate the exercise-driven brain actions, initiate neuronal plasticity, support cognition, and safeguard neurons against insult [96-98].

12.3. Memantine: A Therapeutic Approach in Treating Alzheimer's Disease and Vascular Dementia

Initially developed as an antidiabetic drug in the 1960s that proved ineffective, Memantine was later clinically developed for neurological disorders in Germany and, ultimately was approved by the regulatory authorities in Europe and the US in 2002 and 2003, respectively, for modest to severe AD. It acts as an uncompetitive antagonist of the N-methyl-D-aspartate (N-MDA) receptor; thereby, potentially mitigating its over-activation. Numerous clinical studies have now demonstrated that Memantine can be effective and safe, primarily in AD [99]. Several preclinical studies provided data suggesting that it positively influences developing AD brain neuropathology potentially by reducing Aβ production, aggregation, and downstream neurotoxic consequences, in part through the cordon of extra-synaptic NMDA receptors [100]. However, whether or not such actions translate to humans with Alzheimer's remains an open question. The recommended starting dose of memantine is 5 mg once daily, with upward titration in 5 mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and ultimately to 20 mg/day (10 mg twice daily) - with a minimum interval between dose increases of one week. A daily dose of 20 mg has also been used in patients suffering from mild to moderate levels of VD. Memantine has been reported to impact cognition favorably across different cognitive scales, with generally no worsening global behavior and functioning. Additionally, it is usually well-tolerated compared to placebo concerning its side effect profile [101].

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12.4. Rational Therapeutic Methodology to Frontotemporal Dementia

Frontotemporal dementia is a clinical condition described by progressive worsening of decision-making abilities, control of language, and behavior, with relative early sparing of memory [102].

The disorder encompasses a spectrum of neurode-generative diseases with different cellular mechanisms and brain regions and various clinical courses and prognoses. Still, all are accompanied by varying degrees of frontal and temporal lobe neuronal loss, atrophy, and gliosis. Different molecular pathologies can be involved that include predominant proteins that abnormally accumulate in cells and can comprise tau, the transactive response DNA binding protein of 43 kDa (TDP43), or fused in sarcoma (FUS) protein, or Ewing sarcoma protein and TATA-binding protein-associated factor 15 (TAF15). Mutations in the granulin gene can result in frontotemporal dementia consequent to progranulin haploinsufficiency. In this light, agents that can elevate progranulin generation and secretion are potential therapeutics. Suberoylanilide hydroxamic acid (SAHA) has been reported as a potential therapeutic in neurodegenerative disorders and a potential medication for treating frontotemporal dementia [103]. Treatment with SAHA, a histone deacetylase blocker at protein and mRNA levels, amplified the progranulin production in cortical neurons [104]. Across a series of cellular and animal studies, SAHA has reported favorable actions. Adeno-associated virus-derived progranulin was conveyed to the lysosome, improved LAMP-1 (Lysosomal-associated membrane protein 1) assembly in Grn−/− mice, and mitigated abnormal activity of cathepsin D. These data provide information about progranulin biology and support the therapeutic strategy of progranulin-boosting for neuronal ceroid lipofuscinosis and FTD as a result of mutations in GRN (Mutations in progranulin) [103, 105].

12.5. The Therapeutic Use of Doll Therapy in Dementia

Data from study reports have revealed that doll therapy positively impacts persons who have dementia, resulting in a lessening in concern-related behaviors and attachment and a significant drop in anxiety and agitation levels [106]. Doll therapy resulted in a decline in behavioral and psychological symptom scores and related caregiver distress. However, it did not benefit behaviors such as eating [17]. Consequently, doll therapy has been recommended as a treatment option to mitigate suffering and support comfort in some dementia groups potentially. Despite these reassuring benefits, the practice of doll therapy is understood poorly, and ethical concerns have been expressed that question its use in dementia [107].

12.6. Therapeutic Efficacy of Vincamine in Dementia

Vincamine is a monoterpenoid indole alkaloid present in the leaves of Vinca (lesser periwinkle).

Marketed in Europe as a prescription medication for treating primary degenerative and VD, it is permitted as a dietary supplement in the US (in adults for six months or less). Although used in humans over several decades, the exact mechanisms of action and their effects are relatively unknown. In general, vincamine is considered a peripheral vasodilator that potentially increases blood flow to the brain. Efficacy of vincamine has been reported

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to be statistically superior to placebo in patients suffering from mild to moderate levels of dementia having vascular and degenerative etiology [84]. Treatment with vincamine was associated with a rise in the global cerebral blood flow level and a decline in initial right-left asymmetry of hemispheric means [108]. Still, more studies are warranted to evaluate its actual potential clinical value.

12.7. Essential Oil from Bergamot as a Novel Therapeutic Approach in Dementia

Several preclinical reports have reported that the essential oil derived from bergamot has remarkable neurobiological properties [109] and can favorably impact synaptic transmission, modify electroencephalographic activity, and provide neuroprotective and analgesic properties. The indication is that essential oil derived from bergamot generates anxiolytic-like effects devoid of sedation, similar to benzodiazepines but *via* a different mechanism that likely involves glutamatergic system modulation, with the potential to benefit patients with dementia. There is supportive evidence suggesting that dementia patients respond to benzodiazepines in case of agitation and aggression as chemical restraints that can reduce behavioral complications [110]. Past studies of bergamot essential oil have mainly involved its use in 'aromatherapy' involving its inhalation - often when combined with other oils (such as from lavender [*Lavandula angustifolia*], sweet orange [*Citrus sinensis*], sandalwood [*Santalum austrocaladonicum*] or frankincense [*Boswellia carterii*]. Whereas the results from available clinical studies have proved favorable and well-tolerated, a truly randomized, 'double-blind,' placebo-controlled clinical trial would present difficulties due to the scent of the oil. However, nanotechnology-based delivery of bergamot essential oil has recently been published and could support potential future clinical studies [111] concerning agitation and pain in severe dementia.

12.8. Dance/Movement Therapy in Dementia

Dance/movement therapy (DMT) is a non-pharmacologic but cost-effective treatment strategy for dementia. This treatment technique aims to improve the quality of life and may lessen cognitive decline [112]. Dance movement therapy may be beneficial for dementia patients as it embodies an intervention that can potentially address the complex interactions encompassed by physical, emotional, social, and cognitive processes; however, the effectiveness of this intervention remains unclear [113]. Furthermore, explicitly clarifying how this intervention form is put together and delivered is essential for defining the required elements for an optimal treatment strategy and evaluating past published studies involving it. DMT has been noted as favorable in treating depression; however, clinical studies in old-aged adults with declining cognitive abilities suggest positive outcomes but require more extensive and more detailed trials [114]. The potential risk factor of falling during dancing should, notably, be kept in mind before instigating this activity.

13. CERTAIN DIETARY COMPOUNDS EXHIBIT NEUROPROTECTIVE EFFECTS BY MODULATING PTEN AND BRCA1 ACTIVITY

Due to a lack of reliable treatment options, brain dysfunction and dementia have become an increasing public health concern. Several disease-protective factors, such as physical activity, sleep, and dietary patterns, have been highlighted by epidemiological research

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[115]. Among these factors, nutritional choices may provide specific neuroprotective effects. In particular, dietary choices may alter AKT/PTEN and BRCA1 signaling and, thereby, potentially prevent neurodegenerative diseases or reduce progression. Of numerous natural dietary products evaluated, an ingredient derived from the root of *Curcuma longa*, curcumin, present in culinary turmeric, may potentially reverse the effects of dementia on memory [116]. Curcumin's potential neuroprotective effects are considered mediated by modifying the PI3K/AKT signaling pathway [117]. Curcumin’s bioavailability and stability have somewhat limited well-controlled clinical trials; however, new formulations may remedy this to evaluate its actual potential value in dementia and neurodegenerative disorders [118]. Kaempferol is a flavonol present in several plants, including grapefruit and edible berries, which has been shown to demonstrate neuroprotective effects in a rat animal model [119], and Kaempferol protects neurons through activation of AKT signaling [120]. A neuroprotective ingredient of a Chinese medicinal herb, *Herbaepimedium*, Icariin, reduces PTEN expression following PI3K/AKT signaling [121].

Furthermore, specific components of the rosemary herb appear to prevent the expression of PTEN in K562 myeloid cells [122]. In contrast to this, the expression levels of PTEN are increased following treatment with Ginsenoside [123, 124]. These represent examples of natural products of potential interest in neurodegeneration/dementia. However, a sound preclinical basis should be assembled that rigorously optimizes the conditions for their clinical translation to support their evaluation in patients with dementia and neurodegenerative disorders.

14. PREVENTION OF DEMENTIA AND FRAILTY

Around fifty million individuals live with dementia, and this number is anticipated to rise to one hundred fifty-two million by 2050 [125]. The strategy of ‘avoidance’ of environmental and physical challenges that may impact and increase the risk of dementia and frailty is clearly wise, as such risk factors become better characterized. In this light, numerous activities can potentially detrimentally impact health, cognition, and countless associated factors, and not all risk factors can be circumvented, for example, common infections. In this light, the implementation of healthy lifestyle choices can potentially be beneficial when instigated sufficiently early across not only dementia and frailty but also numerous other medical conditions [116].

14.1. Physical Activity

Individuals who exercise tend to have significantly higher levels of neurotrophic factors involved in neurological health. Meta-investigations of longitudinal observational investigations of 1-21 years duration demonstrated exercise to be related to a decreased risk of dementia [126]. A further evaluation of detailed surveys indicates that there is persuading evidence that actual physical work can, in part, provide some safeguard against AD development [127]. Abbott and colleagues reported that men who stroll for two miles or more each day were less likely to develop dementia than non-walkers (less than 0.25 miles daily) over six years [122]. In general, there is a decrease in the risk of dementia in those subjects who undertook physical activities consistently, but not in those who

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didn't practice regularly [90]. A meta-investigation suggested that individuals who were not dynamic beforehand could achieve a favorable response after participating in physical activities for just four months [91], implying that although beneficial over the long-term, a later lifestyle change can still potentially prove valuable.

14.2. Pharmacological Methodologies

An investigation of 755 individuals with mild psychological impairments and a background marked by dismay from the Australian longitudinal Alzheimer's Illness Neuroimaging Activity evaluated the impact of specific serotonin reuptake inhibitor (SSRI) treatment and reported that over four years of such treatment related to a postponement to clinically analyzed AD [124]. In an examination that evaluated donepezil (10 mg) as well 2000 IU of vitamin E daily over a three year duration in relation to the rate of progression of mild cognitive impairment (MCI) to AD, although no significant differences were noted for either agent over the three year study duration, there was a positive signal for donepezil in the first year of dosing and through the entire study in subjects who were apolipoprotein E4 carriers [124]. Several examinations have revealed that combination of memantine together with an acetylcholinesterase inhibitor (donepezil) can positively impact outcome measures [128].

14.3. Social Networks

A 28-year follow-up examination of 10308 people in the UK suggests that more progressive social contact during late middle age is associated with a modest reduction in dementia-related risk, independent of monetary and alternate lifestyle factors [129]. In theory, one might expect that the social network of an individual would facilitate engagement in potentially beneficial social activities and provide access to social support (whether meeting friends, attending functions, volunteering/participating in occupational duties or group recreational activities and potentially gaining emotional/informational support) to beneficially impact cognitive outcomes. However, how to specifically measure this and evaluate past studies incorporating various different designs, terminologies and measures is difficult. Furthermore, numerous social factors can impact the opportunity to social network, as can race and ethnicity. In this light, there has been relatively minimal sound confirmation of the effects of social mediations on dementia in quality RCTs (Randomized Controlled Trials), and a comprehensive, systematic review of the available literature is that of Kelly and colleagues [130]. In synopsis, they conclude that strong social relationships benefit older adults' cognitive functioning, and point out that changes in social relationships could represent a consequence of cognitive decline, as opposed to a cause of it as a failing memory or poorer cognitive function might result in a reduced ability to function socially. Clearly more work needs to be undertaken on this topic as a there is a likely defensive consequence of social contact on potential dementia development, and more recurrent contact may help converse cognitive reserve [129, 131]. In another report, it was found that five social affiliation subdomains were negatively associated with incident dementia, proposing that improvement of these social relationships may potentially prevent dementia [132].

14.4. Mediterranean Diet

In older individuals, the Mediterranean diet (MeDi) might also provide properties that mitigate cognitive decline as it is associated with several foods and nutrients, including

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monounsaturated fatty acids, fish, vitamins B12 and folate, antioxidants, and moderate quantities of alcohol that potentially safeguard against dementia or cognitive dysfunction [116]. To lower the risk of cognitive decline or dementia, MeDi has been recommended by the WHO (World Health Organization) as it may aid and certainly cannot harm the consumer. In this regard, polyunsaturated fatty acid, vitamin B, vitamin E, and multi-complex supplementation should not be included [117].

14.5. Vitamins

It is known that select vitamins and minerals have numerous essential roles within the nervous system and positively impact the brain's health. It has been recommended that supplements containing vitamins and minerals might be beneficial in sustaining cognitive function and deferring the onset of dementia [119]. The homocysteine (Hcy) hypothesis of dementia has gained popularity because dietary supplementation with folic acid and vitamin B12 can effectively lower homocysteine levels [120] and, thereby, potentially reduce the onset of dementia [121]. Several cross-sectional and prospective studies have evaluated the relationship between homocysteine and cognitive deficit, dementia, and B vitamins [122]. The impact of vitamin D on the central nervous system has been progressively elucidated, and it appears that it can facilitate neural mechanisms of potential protection against AD [52]. In this light, maintaining sufficiently high vitamin D concentrations throughout life may signify a potential means to reduce the likelihood of developing neurological disorders associated with age [133-136].

14.6. Cognitive Activity

Whereas the neuronal integrity, concerning the structure and volume of the brain, can potentially be safeguarded by physical activity, cognitive activity emphasizes the functioning and plasticity of the neural circuits within the brain (Fig. 1) and, likewise, requires to be optimized throughout life. Cognitive reserve across brain regions is vital for neuronal integrity and cognitive activity, particularly concerning offsetting neurodegenerative disorders and dementia [123]. Mental exercise and training have been identified as promising approaches later in life [124]. The Sequential Multiple Assignment Randomized Trial (SMART) revealed that increasing the training level progressively over time was more successful at postponing cognitive decline than using a stable and standardized training routine [137]. Watching television, for instance, is considered an example of a passive cognitive activity of questionable value. In this regard, studies have essentially determined that watching television raises the odds of dementia and mortality [129, 130]. In humans, functional MRI (Magnetic resonance imaging) has revealed that mental activities are, in large part, associated with a reduction in atrophy of the hippocampus and specifies a complex time-dependent alteration in the function of cortical projections [44, 132].

15. CLINICAL MANAGEMENT

Several conditions are frequently considered to contribute to the causation of dementia [138, 139], which, as noted previously, can arise as a result of both AD and other brain disorders. For instance, 38% of patients had AD and infarcts, 30% had pure AD, 12% had VD, and 11% had AD with either PD or LBD at necropsy [140]. In this light, more effective dementia

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management can potentially be instigated based on the prevailing reason underpinning dementia [76]. Although management of dementia is complicated, a multifaceted approach that encompasses an exact diagnosis and pays attention to preliminary signs and symptoms, education, and support of care providers is likely to work out best. To achieve this, a versatile team approach is required [141, 142]. As noted earlier, cholinesterase inhibitors (ChEIs) have been considered a treatment option for AD with cerebrovascular disease as well as specific other forms of dementia (Fig. 1) [76]. There is also preliminary evidence for a beneficial effect of galantamine in treating AD with cerebrovascular disease [143]. The ChEIs are sometimes recommended as a treatment option for dementia associated with PD, although further research is required. Recent evidence supports the potential use of donepezil and rivastigmine in the case of dementia associated with PD and VD [144, 145], but here too, further research is required. Finally, Donepezil can be considered a treatment option for VD [143]. Beyond this and of more potential relevance to frailty, evidence supports that 34 weeks of physical exercise increases physical and social activity. Patients that received 250mg of calcium, 60mg of iron, and 3mg of thiamine per day were reported to demonstrate a reduced homocysteine level. Improved functional measures have been described as a consequence of daily intake of 400mg folic acid and S-adenosylmethionine, 600mg N-acetyl cysteine, 30IU Vitamin-E, and 6mg Vitamin B_{12}. Finally, oral fluid supplements of 500Kcal/day may effectively increase the BMI and weight of treated patients [146].

Nonpharmacologic and pharmacologic interventions can, in theory, be readily combined as potential mechanisms and toxicities associated with each likely do not overlap, and such combinations could be effective in the management of LBD and other disorders. Pharmacologic treatment of LBD has thus far resulted in relatively limited evidence for efficacy and potential increased risk of morbidity and mortality. In this light, initiating a nonpharmacologic approach first would be warranted. In this regard, promising evidence for exercise, cognitive training, and educational programs for the caregiver to manage agitation and psychosis (Fig. 1) have been reported [141]. Cognition, global function, and living activities could then potentially be improved by the use of ChEIs. In this manner, a pharmacologic approach could be carefully and increasingly initiated with nonpharmacologic ones in a time-dependent manner as the severity of dementia demands [147, 148].

As noted previously, frailty - operationally defined by Fried *et al.* [163] as experiencing three out of five phenotypic conditions denoting compromised energetics: low grip strength, low energy, low physical activity, reduced waking speed, and unintended weight loss - can potentially have its signs decreased by the early introduction of regular physical activity. Additionally, there is increasing evidence that a healthy diet and lifestyle from midlife can reduce the risk of frailty. In this light, avoiding smoking, reducing alcohol consumption, and increasing physical activity can provide potential benefits (Fig. 1) [149]. Multifaceted physical training with a specific duration, vitamin D supplements, appropriate nutrition, and cognitive training, likewise, may decrease frailty (Fig. 1) [150-152]. In a multifaceted study, physical exercise was performed three times per week (30 to 45 minutes) for five months [153]. Patients with a BMI greater than $35kg/m^2$ lost as much as 0.5-1kg weight per week, or 8-10% of their initial body weight by six months [149]. Different interventions can

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be combined and individualized in primary care of frailty, depending on patient need and accessibility - for example, a combination of strength exercise and protein supplementation. In a Korean randomized controlled trial focused on preventing or mitigating frailty, a recommended 1.5g/kg per day of protein was suggested as essential for benefit. Although contact with family did not provide strong evidence as a preventing factor in the study of frailty management, contact with friends proved beneficial to prevent frailty [154]. A significant factor in the direction of frailty is to reduce unwarranted polypharmacy. In this regard, the most widely used tools, like Beers, STOPP-START, and Laroche criteria, effectively reduce polypharmacy in frail patients [153, 155, 156].

16. NUTRITION AND PHYSICAL ACTIVITY

Weight loss and malnutrition are commonly seen in patients with dementia and frailty [126, 157-160]. In this light, nutrition maintenance is a crucial factor in well-being. Weight loss can be caused by a gradual loss of eating skills that accompanies increasing functional impairments, ultimately resulting in reduced food intake. Weight loss and anorexia can result from a declining ability to swallow, leading to turning away foods with aging. This can create a self-propagating negative cycle of lowered food intake, reduced energy, micronutrient deficiency, and increased frailty and dementia [161]. It is possible to increase body weight in severely affected patients by high-calorie concentrates [76] and dietary supplements [162] to aid in maintaining the status of nutrition [163]. Supplementing any nutrient is insufficient for preventing or treating frailty; instead, a range of nutrients should be present in food and meals of frail patients [76]. For patients with dementia and frailty, it has been recommended that 692 kcal/day to 500 kcal/day [164] are required [165]. For six months, 500kcal has been suggested, comprising approximately 45% carbohydrates, 30% proteins, and 25% fat that ultimately provide an enhanced level of vitamin E, B12, C, folate, zinc, and copper. For 12 months, 6mg Vitamin-B_{12}, 400 mg folic acid has been be recommended [166].

Although, as noted previously, homocysteine levels can increase in various forms of dementia, consumption of resveratrol in red grapes [167, 168] and fats can potentially act as a protective factor [169] *via* their antioxidant properties [168, 170]. Homocysteine can potentially be lowered to 26% by consuming 0.25mg folic acid and 2.5mg vitamin B-complex daily. For such patients, intake of protein-rich food or a Mediterranean diet [3, 171]containing meat, oily fish, vegetables, and dairy products to support muscle mass ultimately should be considered as a way to increase body weight [39, 41, 172]. In general, growing evidence concludes that effective outcomes derive from a combination of nutritional support and multicomponent [173] physical activity [3, 171]. As noted previously, physical activity or exercise can potentially support an increase in muscle bulk/mass, strength [40] and decrease frailty and dementia, if instigated early enough. Physical exercise regimens should best comprise aerobic and balance exercises that are feasible and individualized to the patient. For aerobic exercise, walking outside for, example, 30- 40 minutes per day, minimum, of four days/week is recommended - but only for individuals for which falls and unlikely. Balance exercise can consist of 15 exercises undertaken for 25 minutes a day and four days/week at home. These can be focused on strengthening arms and legs, or coordination and balance, depending on the patient's needs [174]. As noted for elderly

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patients, physical activity can be beneficial but may increase the risk of injury, falls, and fractures - and hence must be appropriately instigated [175, 176]. In this light physical exercise as a non-pharmacological approach should best be adapted to disable patients to support their potential utility and benefit. Strong, physically, and stable patients may profit from a short walk or specified movements (like hand to knee touches, shoulder exercises, the lifting of knees or legs, *etc.*). Patients who are only capable of poor or limited movement can conduct standing or sitting exercises (including lower extremities for 5 minutes). Patients unable to move lower extremities may potentially perform upper body exercises (*e.g.*, pulling/pushing exercises with hands - including forward and backward extensions). Patients mainly unable to move can conduct training while sitting or reclining (*i.e.*, relaxation movements, deep breathing and stretching) [177].

17. IMPLICATIONS AND CHALLENGES FOR HEALTH CARE POLICY

Numerous challenges are faced by healthcare workers involved in the management/treatment of dementia and frailty patients. Psychological trauma, as well as a fear for one's safety, are examples of such challenges. Agitation and aggression are not uncommon in patients with dementia. There is growing appreciation that these can result in assaults by some dementia patients on the people around them and, particularly, on caregivers. Studies on this topic have, in part, been compromised by a past lack of a clear definition of precisely what constitutes physical aggression or a hostile action. Whether this involves physical contact or an attempt at physical contact, or, indeed, a threat of physical contact and aggression - as an assault may result in a major or minor injury, or, certainly, no damage of any kind. Similarly, physical aggression towards property can provoke fear of assault or danger to a caregiver [178]. However, as health care workers take such types of behaviors and both actual and perceived violence as part of their job [35], reports on their incidence can vary widely. In this light, rates of violence/aggression by dementia care recipients against their caretakers are approximated at more than 20% [178]. O'Leary and colleagues [179] have reported that the frequency of violence and aggression does not differ by either gender or the type of dementia. Nevertheless, numerous studies have focused on male veterans (quite possibly due to the availability of data from institutions related to the care of veterans - that are predominantly male). There is no such thing as an 'aggression gene,' but there appears to be some correlation between premorbid aggressiveness and the occurrence of violent behavior in those with advanced dementia [178]. The incidence of violence/aggression varies wildly across studies [178], with some [180] as high as 65% of care-recipients demonstrating attack of some kind (46.4% physical and 17.5% sexual aggression); and 40.4% of these exhibited premorbid aggressive behaviors. In evaluating such studies, however, it should be considered that the demonstration of aggression and violence are often amongst the most potent factors predicting nursing home placement and thus may, in part, bias such data analyses deriving from them. Nevertheless, aggression and violence must be considered significant challenges in dementia healthcare; evaluating the triggers and providing coping advice is essential concerning healthcare providers.

Potential triggers often involve unresolved pain, frustrated communication due to vision and hearing impairments, unexpected environmental changes, unanticipated or excessive noise, and activity, a lack of privacy or space, sleep issues, the quality of the relationship

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with care providers, and others [181]. As noted, factors such as a premorbid aggressive personality trait and depression can add to this. The early recognition of triggers of aggression and their mitigation before violence associates with the caregiver's experience, with a risk of assault for less experienced workers [182]. Hence, the training for health care providers for dementia care has been highly recommended [183]. Wharton and colleagues [178] review several training programs and recommend adapting them to the informal elderly healthcare setting. Clearly, non-pharmacological management is the first option for mitigating behavioral and psychological symptoms of dementia, but, once exhausted, the selection of available pharmacological options depends on a patient's comorbidities, the manifestation of symptoms as well as personal tolerance to medications.

Prior studies suggest that anticholinesterase use in AD and LBD may help delay the onset of neuropsychiatric symptoms [184]. However, should they occur and not prove to be resolvable, several studies provide low- to moderate-quality evidence that supports the utility of anti-depressants, anti-psychotics, or anti-epileptics in combination with anticholinesterases [185]. Study findings are pretty mixed, with varying recommendations for treatment of this challenging elderly patient population that are often already taking a combination of medications [186]. Currently, there is no definitive FDA-approved medication to treat agitation and aggression in the elderly with dementia. Although, certainly, there are a selection of approved medications that can potentially mitigate delusions, paranoid behavior, agitation, disinhibited behaviors and such like conditions that can potentially be used 'off label' - these should be used with caution. Thus future studies are needed to build an evidence base for the real-world effectiveness and potential adverse actions of available medications [185].

As noted earlier, the expansion of the world's aging population has created an accompanying rise in the number of older adults with frailty that has resulted in an overwhelming attendant pressure on healthcare programs worldwide [187]. This has resulted in unmet care needs, falls and fractures in the frail elderly, excessive hospitalizations, reduced quality of life, and injury/illness resulting from medical care (*i.e.*, iatrogenic complications), ultimately, premature mortality [52]. Other adverse outcomes, such as dementia and disability [188, 189], can, likewise, occur and balloon health care costs [149]. The excessive heterogeneity found in the course of physical frailty, before any treatment, and various initial deficiency indices result in different frailty trajectories. Understanding the complex underlying biological process that leads to a defect is valuable when selecting treatment options and instigating them. In this regard, a personalized medicine approach targeting the multiple organ systems associated with frailty likely results in the best outcomes. However, this often requires time, more initial healthcare resources, and the heterogeneity found in prognosis and response to treatment can reduce the accuracy in predicting which individuals will or will not experience improvements or adverse outcomes; again impacting cost-effectiveness [31].

Numerous interventions for the clinical management of frailty exist, including physical activity/exercise, protein-calorie supplementation, and particularly important the "de-prescription" of unnecessary medications - especially as the elderly and frail have the most extraordinary heterogeneity in how they handle any precise prescriptions. However,

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the effectiveness of such interventions has yet to be supported by a robust evidence base. Therefore, we need to accumulate more evidence-based knowledge about which intervention approaches are most effective in frailty and determine whether they are cost-effective, practical, and acceptable to the elderly with frailty [33]. Instigating the best-personalized strategy at the earliest time possible, optimally during a pre-frail state or time, would likely provide the best outcome [190].

17.1. Government Policies

As age is directly associated with the onset of dementia and frailty, the aging of society has made their treatment a global challenge. Rising costs in public healthcare, and particularly chronic healthcare, are critically stretching the government resources of many nations at a time when they are hugely fragile, consequent of the COVID-19 pandemic. This can negatively impact economic growth and lower the living standard, particularly during a current labor shortage. Different countries are trying to cope with this global challenge by developing and utilizing other policies personalized to their nation's perceived requirements and available resources. However, there are commonalities across countries in need. Examples of such programs include the Australian residential aging policy [191, 192] select pension policies in the UK [193], an adaptation policy in Europe [194], and an aging care policy in the Arab region [195]. In China, the government has initiated an aging policy focused on supporting a basic lifestyle and providing rights and well-being for the elderly. It has become increasingly clear that such policies may derive from different segments within a government and local and central governments. Coordination in such cases is key to reducing the risk of policy failure and evaluating which are more and less successful time-dependently to support further implementation of the former [196, 197] In Latin American countries, like Argentina, Mexico, Chile, and Costa Rica, initially implemented charity-based approaches to combat poverty and illness have gradually been replaced by a 'rights-based approach' to support well-being, and recent reforms are now emphasizing the need for a national evidence-based policy. A common requirement across policies from many nations is predictability and redundancy to ensure that a fundamental level of required healthcare is met and adapted to meet local needs. Definitive measures are needed to monitor healthcare in the elderly that can be broadly used across and between nations to allow comparisons and evidence-based decision-making.

CONCLUSION

Consequent to population aging, there is rising recognition that our knowledge base of the phenomenon of frailty and dementia is inadequate, particularly concerning the heterogeneity in their diagnosis, development, molecular underpinnings, and intervention. There are currently numerous potential interventions to support the clinical management of the frail and demented elderly, but which should most appropriately be implemented? When and under what conditions? Additionally, their predicted effectiveness remains largely open questions requiring more evidence-based knowledge. Whereas it often takes numerous years (sometimes decades) to develop practical, evidence-based personalized medicine approaches to target a single-gene or organ disease, it will, without doubt, take far longer to create a successful, stratified medicine approach to target, with predictive accuracy, a

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multi-organ system disorder - as underlies frailty or the end dementia deriving from a host of neurological disorders. To do so, we need to start now by developing feasible and cost-effective studies that can be longitudinally applied across cultures and identify and employ the most effective instruments and biomarkers. In the meantime, in the absence of a firm evidence base for interventions, ‘real life’ daily practice should best follow existing consensus guideline recommendations. Expected outcomes should be used across studies; predetermined techniques to reduce bias should be incorporated early. Additionally, training of healthcare individuals is critical, and outreach to organizations supporting the rights of the elderly is required to help ensure that the expectations of the research are met.

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
DLB	Dementia with LEWY Bodies
MCI-LB	Mild Cognitive Impairment with Lewy Bodies
ADNI	Alzheimer's Disease Neuroimaging Initiative
CVD	Cardiovascular Disease
MAPT	Multidomain Alzheimer Disease Preventive Trial
CHS	Cardiovascular Health Study
AAMI	Ageassociated Memory Impairment
CIND	Cognitive Impairment, No Dementia
AACD	Age-associated Cognitive Decline
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
KDSQ	Korean Dementia Screening Questionnaire
MCI	Mild Cognitive Impairment
GFI	Groningen Frailty Indicator
Aβ	Amyloid-Beta
PCP	Primary Care Physicians

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VD	vascular Dementia
PD	Parkinson's Disease
NMDA	N-Methyl-D-Aspartate
FUS	Fused in Sarcoma
TAF15	TATA-Binding Protein-Associated Factor 15
SAHA	Suberoylanilide Hydroxamic Acid
LAMP-1	Lysosomal-Associated Membrane Protein 1
DMT	Dance/Movement Therapy
SSRI	Specific Serotonin Reuptake Inhibitor
RCTs	Randomized Controlled Trials
MeDi	Mediterranean Diet
WHO	World Health Organization
Hcy	Homocysteine
SMART	Sequential Multiple Assignment Randomized Trial
MRI	Magnetic Resonance Imaging
ChEIs	Cholinesterase Inhibitors

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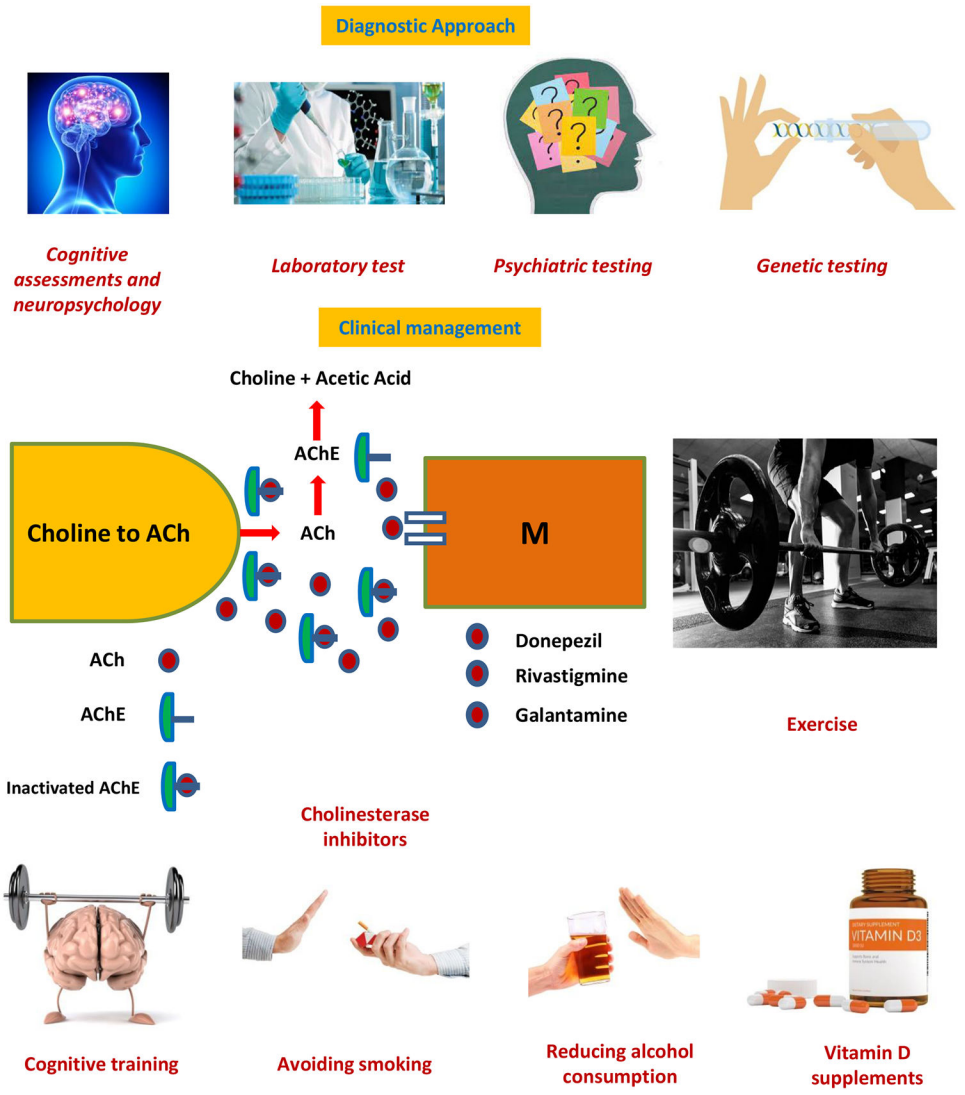

Fig. (1).

Diagnostic approaches and clinical management of dementia and frailty. Diagnostic approaches for dementia and frailty are cognitive assessments and neuropsychology, Laboratory, Psychiatric, and Genetic testing utilized to observe functional and psychological incapacity signs. In general, Acetyl Cholinesterase Inhibitors and multifaceted non-pharmacologic approaches are recommended to minimize dementia and frailty.