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Dementia Prevention and Treatment

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Dementia Prevention and Treatment
A Narrative Review

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IMPORTANCE Dementia affects 10% of those 65 years or older and 35% of those 90 years or older, often with profound cognitive, behavioral, and functional consequences. As the baby boomers and subsequent generations age, effective preventive and treatment strategies will assume increasing importance.

OBSERVATIONS Preventive measures are aimed at modifiable risk factors, many of which have been identified. To date, no randomized clinical trial data conclusively confirm that interventions of any kind can prevent dementia. Nevertheless, addressing risk factors may have other health benefits and should be considered. Alzheimer disease can be treated with cholinesterase inhibitors, memantine, and antiamyloid immunomodulators, with the last modestly slowing cognitive and functional decline in people with mild cognitive impairment or mild dementia due to Alzheimer disease. Cholinesterase inhibitors and memantine may benefit persons with other types of dementia, including dementia with Lewy bodies, Parkinson disease dementia, vascular dementia, and dementia due to traumatic brain injury. Behavioral and psychological symptoms of dementia are best treated with nonpharmacologic management, including identifying and mitigating the underlying causes and individually tailored behavioral approaches. Psychotropic medications have minimal evidence of efficacy for treating these symptoms and are associated with increased mortality and clinically meaningful risks of falls and cognitive decline. Several emerging prevention and treatment strategies hold promise to improve dementia care in the future.

CONCLUSIONS AND RELEVANCE Although current prevention and treatment approaches to dementia have been less than optimally successful, substantial investments in dementia research will undoubtedly provide new answers to reducing the burden of dementia worldwide.

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Dementia, which has both cognitive deficits and functional consequences,[1] is a disorder of aging with prevalence ranging from 3% among those 65 to 70 years old to 35% among those 90 years and older.[2] As the baby boomers (born between 1946 and 1964) age over the next 3 decades, the effect of dementia will be monumental, with the number of individuals in the US with Alzheimer disease (AD) expected to double above the current estimate of 6.7 million.[3] From a global perspective, more than 55 million people have dementia worldwide—more than 60% of whom live in low- and middle-income countries—with nearly 10 million new cases each year.[4]

The most common cause of dementia is AD, which accounts for an estimated 60% to 80% of cases. Other causes of dementia include vascular (approximately 5%-10%), frontotemporal degeneration (3% of those with onset 65 years or older and 10% of those with onset younger than 65 years), and Lewy body disease (approximately 5%), although Lewy body disease may be underdiagnosed in clinical practice. Moreover, more than 50% of those diagnosed with AD have mixed dementia with more than 1 identifiable cause.[3]

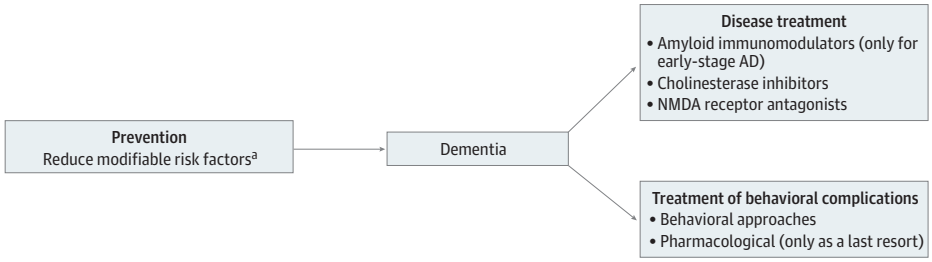
Beyond its effects on patients, dementia affects caregivers, with at least 11 million providing care in the US in 2022.[3] The toll of dementia caregiving can be enormous—up to 40% report depressive symptoms,[5] and 30% regularly feel completely overwhelmed[6]; their role and needs must also be considered in the care of the patient.

Despite the promise of amyloid immunomodulators for AD, it is likely that most persons with dementia will not be eligible for these at the time of diagnosis; moreover, the clinical effectiveness and duration of effect of these drugs remain uncertain. In this review, we summarize the current evidence and explore emerging science on the prevention and treatment of dementia to inform clinical decision-making (**Figure**).

Methods

This Narrative Review draws from several systematic reviews published between 2018 and 2023, including the 2020

Figure. Prevention and Treatment of Dementia



AD indicates Alzheimer disease; NMDA, *N*-methyl-D-aspartate.

[a] Many risk factors are potentially modifiable, but few have clinical trial evidence that modification reduces risk.

Table 1. Estimated Percentages of Dementia Attributable to Modifiable Risk Factors[a]

Risk factor	Relative risk for dementia (95% CI)	Risk factor prevalence, %	Dementia attributable to each risk factor, %
Less education	1.6 (1.3-2.0)	40.0	7.1
Hearing loss	1.9 (1.4-2.7)	31.7	8.2
Traumatic brain injury	1.8 (1.5-2.2)	12.1	3.4
Hypertension	1.6 (1.2-2.2)	8.9	1.9
Alcohol (>21 units/wk)	1.2 (1.1-1.3)	11.8	0.8
Obesity (BMI ≥30)	1.6 (1.3-1.9)	3.4	0.7
Smoking	1.6 (1.2-2.2)	27.4	5.2
Depression	1.9 (1.6-2.3)	13.2	3.9
Social isolation	1.6 (1.3-1.9)	11.0	3.5
Physical inactivity	1.4 (1.2-1.7)	17.7	1.6
Diabetes	1.5 (1.3-1.8)	6.4	1.1
Air pollution	1.1 (1.1-1.1)	75.0	2.3
All modifiable risk factors	NA	NA	39.7

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.

[a] Data are from the 2020 report of the *Lancet* Commission.[7]

Lancet Commission review[7] and the Alzheimer's Association's *Alzheimer's Disease Facts and Figures*,[3] which is updated annually. We augmented these reviews by searching PubMed for each topic heading of the *Lancet* review plus other topics we were aware of, adding new studies published from January 2020 to August 2023. We excluded validation studies, opinion pieces, and editorials. When drawing conclusions, emphasis was placed on meta-analyses of clinical trials (eg, Cochrane reviews), individual clinical trials, and, when clinical trial data were unavailable, meta-analyses of observational studies.

Prevention

Most of the evidence supporting strategies to prevent dementia is based on observational studies, and the few randomized clinical trials (RCTs) have important limitations. Preventive measures are aimed at reduction of modifiable risk factors, including social determinants of health. In 2019, the World Health Organization published guidelines on risk reduction of cognitive decline and dementia,[8] and in 2020, the *Lancet* Commission identified 12 modifiable risk factors that account for an estimated 40% of dementia risk worldwide (**Table 1**).[7] None of these risk factors has a relative risk that exceeds 1.9. Moreover, conclusive RCT evidence is lacking that modification of any risk factor can prevent dementia. Nevertheless, several potentially valuable interventions can be initiated in midlife or later life that may have beneficial effects for individual patients (**Table 2**).[9-39]

Education/Cognitive Stimulation

Higher levels of education in childhood and late adolescence appear to be most important for late-life cognition.[40] The effects of education and cognitive stimulation in later life are more difficult to ascertain because of the possibility of reverse causation (ie, people do not participate in these activities because they already have cognitive impairment). Systematic reviews of interventions, such as computerized cognitive training, have failed to find convincing evidence of improvement of cognition,[41] though some have demonstrated improvement on the specific tasks trained.[9]

Hearing Aids

Evidence on treating hearing loss as a means of preventing dementia is mixed. A meta-analysis of mostly observational studies concluded that hearing aids and cochlear implants led to a 19% reduction in cognitive decline,[10] but a recent clinical trial of a hearing intervention failed to demonstrate a benefit on cognition at 3 years.[11]

Treatment of Cardiovascular Risk Factors

Observational studies[13] and a Cochrane review of clinical trials[14] examining the association of blood pressure control with prevention of dementia had conflicting results. In the SPRINT MIND trial,[12] intensive treatment of blood pressure to a target of less than 120 mm Hg vs 140 mm Hg reduced incident probable dementia by 17%, but this was not a statistically significant finding. However, secondary outcomes of mild cognitive impairment

Table 2. Evidence Behind Preventive Measures for Cognitive Decline, Mild Cognitive Impairment (MCI), or Dementia

Preventive measure	Outcome(s)	Study design	Conclusion(s)
Single factor			
Cognitive training	Cognition	SR[9]	Improvement on specific tasks trained
Hearing treatment	Cognition/dementia	OM[10]	Less decline/reduced risk
	Cognition	RCT[11]	No effect
Treatment of hypertension	MCI	RCT[12]	Reduced risk
	Dementia	RCT[12]	No effect
	MCI or dementia	RCT[12]	Reduced risk
	Dementia	OM[13]	Reduced risk
	Cognitive impairment or dementia	SR[14]	No association
Statins	Cognitive decline or dementia	SR[15]	No association
Aspirin	Dementia	RCT[16]	No effect
Alcohol	Dementia	OM[17,18]	Lower risk for occasional, light to moderate, and moderate to heavy drinkers
		OS,[19] SR[20]	Higher risk for heavy drinkers
Diet			
DASH and MIND diets	Dementia	OM[21]	Reduced risk
MIND diet	Cognition/MRI findings of dementia	RCT[22]	No effect
Weight loss	Cognition	SR and TM[23]	Improved memory and attention
Smoking cessation	Dementia	OS[24]	Reduced risk
Treatment of depression	Cognition	SR and TM[25]	Improved psychomotor speed and delayed recall
Treatment of obstructive sleep apnea	Dementia	OS[26]	Reduced incidence of Alzheimer disease
Prevention of delirium	Dementia	Simulation[27]	Reduced risk
Increased social activity	Dementia	OM[28]	Reduced risk
	Cognition	SR[29]	Improvement on some tests
Exercise	Alzheimer disease and dementia	OM[30,31]	Reduced risk
	Cognitive function	SR and TM[32]	Improved or maintained global cognition
Treatment of diabetes			
Metformin	Cognitive impairment	TM[33,34]	Mixed; 1 showed protective effect,[33] the other did not[34]
Intensive control	Cognitive decline	SR[35]	No effect
Multifactorial			
Exercise and cognitive training	Cognition	SR and TM[36]	Modest improvement
Aerobic exercise cognitive stimulation	Cognition	RCT[37]	Improved though inconsistent effects
Cardiovascular risk factors, cognitive training, exercise, and diet	Cognition	RCT[38]	Improved
Personalized risk-reduction strategy	Cognition	RCT[39]	Improved

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; MIND, Mediterranean–DASH Intervention for Neurodegenerative Delay; MRI, magnetic resonance imaging; OM, observational meta-analysis; OS, observational study; RCT, randomized clinical trial; SR, systematic review; TM, treatment meta-analysis.

(MCI) or MCI or dementia demonstrated similar reductions in risk and were statistically significant. The use of statins to reduce cognitive decline or dementia was not supported in a Cochrane review,[15] nor was aspirin protective in a large clinical trial.[16]

Diet

Observational studies support the protective effect of a Mediterranean diet, the DASH (Dietary Approaches to Stop Hypertension) diet, and a hybrid of the 2 called the MIND diet.[21] However, a recent clinical trial comparing 3 years of a MIND diet with a control diet with mild caloric restriction did not demonstrate differences in global cognition or magnetic resonance imaging (MRI) findings of dementia.[22] Among mostly middle-aged persons with overweight and obesity, weight loss was associated with improved attention and memory.[23]

Alcohol Consumption and Smoking

The evidence on alcohol use and subsequent dementia is mixed. Many studies suggest that light to moderate drinking has a protective effect compared with abstinence.[17,18] Some,[19,20] but not all,[17] studies suggest that heavy drinking or alcohol use disorders increase dementia risk. In a longitudinal study, tobacco smoking cessation was associated with reduced risk of dementia over the subsequent 8 years.[24]

Table 3. US Food and Drug Administration (FDA)–Approved Dementia-Specific Pharmacological Treatments for Alzheimer Disease (AD) Dementia

Medication class/medications	FDA-approved indication	Adverse effects
Acetylcholinesterase inhibitors		
Donepezil	Mild, moderate, or severe dementia due to AD	GI upset, nausea, vomiting, diarrhea, vivid dreams, weight loss, bradycardia, syncope, increased GI bleeding/peptic ulcer risk with donepezil, and contact dermatitis with patch only
Rivastigmine	Mild, moderate, or severe dementia due to AD	
Galantamine	Mild or moderate dementia due to AD	
NMDA inhibitor memantine	Moderate or severe dementia due to AD	Dizziness, confusion, anxiety, hypotension, hypertension, diarrhea, and agitation
Amyloid immunomodulators		
Aducanumab[a]	Mild cognitive impairment and mild dementia due to AD	ARIA
Lecanemab		ARIA, infusion reaction, and headache
Donanemab[b]		ARIA, infusion reaction, and headache

Abbreviations: ARIA, amyloid-related imaging abnormalities; GI, gastrointestinal; NMDA, *N*-methyl-D-aspartate.

[a] Provisional FDA approval and will not be available after November 2024.

[b] Under consideration for FDA approval.

Depression

The relationship between depression and dementia is complicated. Depression can be a predictor of future dementia, a prodrome or presenting symptom of dementia, or a concurrent illness. Moreover, observational studies generally have not distinguished between treated and untreated depression. Although treatment of major depression with antidepressants can improve psychomotor speed and delayed recall,[25] to our knowledge, no RCT has demonstrated that treatment of depression prevents dementia.

Sleep

In longitudinal studies, sleep disturbances have been associated with increased risk for all-cause dementia, AD, and vascular dementia.[42] Specific sleep disorders were associated with different types of dementia, including insomnia (AD) and sleep-disordered breathing (all-cause, AD, and vascular). Retrospective observational data suggest that treatment of obstructive sleep apnea with positive airway pressure can reduce the incidence of dementia and AD specifically.[26] Although obstructive sleep apnea is associated with increased AD cerebrospinal fluid biomarkers, clinical trial evidence is lacking that treatment with continuous positive airway pressure can reverse these changes.[43]

Delirium Prevention

Delirium, an acute confusional state that affects up to 50% of hospitalized adults and up to 80% in the intensive care unit, is a potentially modifiable independent risk factor for the subsequent development of dementia.[44] Delirium is independently associated with cognitive decline and dementia in older adults[45] and accelerates the trajectory of cognitive decline in those with dementia.[46] Moreover, delirium may be preventable in about 50% of cases through multicomponent targeted intervention strategies.[47,48] A simulation estimated that 6 new cases of dementia could be prevented per 1000 patients receiving a nonpharmacologic delirium prevention approach.[27]

Social Isolation

Longitudinal studies have shown that frequent social contact in middle and early old age was associated with decreased dementia risk, but dementia may cause social isolation rather than the reverse.[28] A systematic review of interventions to increase social activity that included 3 RCTs with a total of 586 participants demonstrated small improvements on some cognitive tests.[29]

Physical Activity/Exercise

Meta-analyses of observational studies of exercise indicated benefit of exercise on prevention of AD and dementia.[30,31] The timing of physical activity may be important. Midlife physical activity has not been shown to be associated with cognitive performance,[49,50] whereas later life physical activity has,[30] although reverse causation is a possible explanation. A multicomponent exercise intervention that included strength training improved cognition in a RCT, especially for those with MCI.[32]

Diabetes

A Cochrane review found no benefit of intensive control compared with standard diabetes management on cognitive decline at 5 years.[35] Meta-analyses of the association of metformin use with cognitive impairment have been mixed.[33,34]

Multifactorial Interventions

Various multifactorial interventions have demonstrated benefits on cognition.[36,37] The 2-year Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[38] reported that a combination of diet, exercise, cognitive training, and management of cardiovascular risk factors improved cognition in healthy older adults who were at increased risk of cognitive decline; participants were not followed up long enough to determine the effect on dementia prevention. In the Systematic Multi-Domain Alzheimer Risk Reduction Trial (SMARRT), a personalized multifactorial intervention led to modest improvements in cognitive composite score, risk factors, and quality of life compared with a health education control group.[39]

What to Watch For

Ongoing RCTs will likely provide more clarity on the role of combined lifestyle interventions (US POINTER),[51] statin therapy (PREVENTABLE),[52] and the provision of hearing aids (HearCog)[53] on preventing dementia.

Table 4. Approved Alzheimer Disease (AD) Medications Used for Non-AD Dementias[a]

Medication class/medications	Non-AD dementia	Status
Acetylcholinesterase inhibitors		
Donepezil	DLB, VaD, PDD, and TBI	First-line therapy in UK and approved in Japan for DLB
Rivastigmine	DLB and PDD	First-line therapy in UK for DLB and approved in US and UK for PDD
Galantamine	Severe AD, DLB, and PDD	More RCT data needed to determine efficacy for DLB
NMDA inhibitor memantine	DLB, VaD, PDD, and TBI	May provide small benefit for DLB, VaD, and PDD; further studies needed
Amyloid immunomodulators		
Aducanumab	Mixed dementia	None of these medications have been tested in mixed dementia (eg, DLB-AD or VaD-AD)
Lecanemab		
Donanemab		

Abbreviations: DLB, dementia with Lewy bodies; NMDA, *N*-methyl-D-aspartate; PDD, Parkinson disease dementia; RCT, randomized clinical trial; TBI, traumatic brain injury; VaD, vascular dementia.

[a] Off label except where noted.

Disease Treatment

Appropriate treatment of dementia is guided by the cause of dementia and the stage. In 2011, the National Institute on Aging and Alzheimer's Association classified AD into 3 stages: (1) preclinical, in which cognition is normal and AD is defined by abnormal biomarkers; (2) MCI, in which cognition is impaired but function is intact and biomarkers may help inform prognosis; and (3) AD dementia, in which cognition and function are impaired and biomarkers may be helpful in excluding AD as cause.[54,55] In 2018, the National Institute on Aging and Alzheimer's Association proposed the AT(N) schema for AD, a clinically agnostic, biologically based classification of AD anchored by key biomarkers: amyloid (A), tau (T), and neurodegeneration (N).[56] A new framework for diagnosis and staging of AD is currently under consideration and includes incorporation of plasma biomarkers and classification criteria to accommodate nonequivalence between fluid and imaging biomarkers.[57] Similarly, research and clinical definitions of MCI and dementia stages have been outlined for dementia with Lewy bodies,[58] Parkinson disease,[59] frontotemporal degeneration,[60] and vascular cognitive impairment.[61] The recent approval of new medications for AD and the growing expansion of development pipelines with potentially more effective drug treatments across all dementia-related conditions will require specialists and primary care clinicians alike to be able to identify and start treatments earlier in the disease course.

AD is treated with cholinesterase inhibitors (CIs) donepezil, rivastigmine, and galantamine and *N*-methyl-D-aspartate receptor antagonist memantine. CIs increase acetylcholine availability, which is important for memory function, and memantine reduces excitotoxic damage to neurons and resulting agitation and irritability.[62] Donepezil and rivastigmine are approved to treat mild to severe dementia due to AD, whereas galantamine is approved for mild to moderate AD dementia. Memantine is approved for moderate to severe AD dementia (**Table 3**). When they were first approved, the efficacy of CIs was challenged for multiple reasons, including use of cognitive scales during the trials that were not used in clinical practice, the variability of cognitive benefit across patients, and that despite a statistically significant difference between drug and placebo groups in their change from baseline scores, the effect size was still small and the clinical importance not clear.[63] It was also not known whether long-term use would accompany desired outcomes, such as delay in institutionalization. It is now established that response to CIs is complex and affected by many factors, including but not limited to signs of cholinergic deficit, stage of disease, rate of disease progression, presence of apathy, concomitant diseases, and education level.[64] CIs are associated with modest but persistent cognitive benefits over several years and reduced mortality,[65,66] and both CIs and memantine have demonstrated prolonged time to institutionalization and reduced caregiver burden.[66,67]

New immunomodulators targeting β-amyloid plaques and protofibrils, hallmark neuropathological features of AD, are now approved by the US Food and Drug Administration (FDA) for persons with MCI or early AD. Aducanumab, lecanemab, and donanemab indisputably reduce brain amyloid levels below the threshold level considered to be abnormal on amyloid positron emission tomography. However, evidence of clinical efficacy has been inconsistent and has prompted reconsideration of the amyloid hypothesis.[68] Many questions about amyloid remain unanswered, including its biological function and the reason behind its accumulation, the evidence of presymptomatic brain amyloid burden without universal cognitive decline, the discordance between location of deposition and cognitive deficits on clinical examination, and a more consistent relationship between phosphorylated tau accumulation and cognitive decline.[69-71] Lecanemab and donanemab are the first amyloid-targeting drugs to show a meaningfully slower rate of decline (27%-40%) in multiple cognitive and functional measures compared with placebo, as well as beneficial downstream effects on phosphorylated tau.[72,73] It is estimated that these medications (Table 3) may slow disease progression by about 5 months, but it is difficult to know whether they will produce a clinically important and sustained benefit in any particular individual.[74] Aducanumab's effect on reduction of cognitive and functional decline is inconclusive, leading to its provisional FDA approval designation in 2021. As of November 2024, aducanumab will no longer be available in the US.

The most noteworthy adverse effects of amyloid immunomodulatory drugs are vasogenic brain edema and brain bleeding in the form of microhemorrhages or macrohemorrhages or superficial siderosis (amyloid-related imaging abnormalities [ARIA], namely ARIA-E [edema] or ARIA-H [hemorrhagic]).[75] Risk of ARIA greatly increases with apolipoprotein E ε4 genotype, particularly homozygotes. Symptoms may include confusion, headache, seizure, or focal neurological signs. ARIA is asymptomatic in about 70% of people and requires close MRI and clinical monitoring, particularly in the first 5 months of treatment, though ARIA can occur at any time throughout the treatment period. The frequency of surveillance MRIs to check for ARIA during treat-

ment is before the 5th, 7th, and 12th (aducanumab) or 14th (lecanemab) doses. There are no standard protocols as to how often surveillance of a patient's clinical examination or routine laboratory tests should be carried out while receiving this therapy. If ARIA is suspected based on an abrupt change in neurological status, a brain MRI should be obtained as part of an emergent workup, and a clinical examination and MRI may need to be repeated monthly until neurological symptoms and changes on the MRI resolve. Appropriate use recommendations have been published for these medications and provide guidance on administration and management of their routine use and common adverse effects.[76,77] The process to determine a patient's appropriateness to receive amyloid immunotherapy is substantial and includes cognitive testing to rule out moderate or severe dementia, proof of elevated brain amyloid, apolipoprotein E ε4 testing, and baseline brain MRI to evaluate for the presence of hemorrhages (1 macrohemorrhage or >4 microhemorrhages are exclusionary criteria to start treatment). Therapy requires monthly (aducanumab, donanemab) or twice monthly (lecanemab) infusions for up to 12 (donanemab) to 18 months (lecanemab) and possibly beyond (aducanumab), as well as serial surveillance MRIs for the first 4 to 5 months. In light of the high costs of these drugs and their administration, debate remains regarding the effectiveness and value of these amyloid immunomodulators.[78,79]

There are no FDA-approved medications for non-AD dementias (**Table 4**), with the exception of rivastigmine for mild to moderate dementia in patients with Parkinson disease and dementia with Lewy bodies.[80,81] Off-label use of CIs and memantine for dementia with Lewy bodies, vascular dementia, and dementia due to traumatic brain injury is common, and though evidence is weak,[82,83] there is some evidence to show a small benefit (Table 4).[84] CIs and memantine are not recommended in frontotemporal dementia due to lack of efficacy.[85]

What to Watch For

There are currently 141 individual treatments in trials for AD across 12 Common Alzheimer Disease Research Ontology mechanisms[86] as well as treatments for AD at the preclinical, asymptomatic stage. The AHEAD study[87] is currently evaluating the use of lecanemab in asymptomatic individuals with mild to moderately elevated brain amyloid levels. Tau-directed treatments include passive immunotherapies and small molecule tau aggregation inhibitors.[88] Ongoing studies are also targeting amyloid and tau simultaneously. Thirteen treatments are under investigation for dementia with Lewy bodies.[89] Current investigational medications for frontotemporal degeneration have been focused on people with identifiable genetic variations (*GRN*, *C9ORF72*), as well as on various mechanisms to suppress expression and pathological dysregulation of tau and progranulin pathways.[90]

Treatment of Behavioral and Psychological Complications

Although cognitive impairment is the clinical hallmark of dementia, behavioral and psychological symptoms of dementia (BPSD), such as apathy, delusions, and agitation, are common and often are the presenting symptoms.[91-93] BPSD is a fundamental aspect of the neurodegeneration that is present in all forms of dementia and may either arise from or be exacerbated by stressors present in patients (eg, acute infection, delirium), their caregivers (eg, communication style), or their environment (eg, excessive auditory stimuli).[94] Nearly all patients will exhibit these symptoms at some point during the course of dementia.[92]

When new BPSD occurs, a differential diagnosis should be generated (eg, using the DICE [Describe, Investigate, Create, and Evaluate] approach[95]) to help identify a potential underlying cause. There is a considerable evidence base supporting nonpharmacological interventions to address BPSD in persons living with dementia and associated caregiver distress.[96-98] Caregiver-focused interventions have the most consistent evidence base—including common elements such as skills training, psychoeducation, and activity tailoring—and reduce both frequency and severity of BPSD as well as the caregiver distress in response to such symptoms.[99] If distressing or dangerous symptoms remain, time-limited trials of pharmacotherapy targeting BPSD can be considered with clear, objective treatment goals in mind.[100] If a patient is already prescribed psychoactive medications yet the level of BPSD is severe enough to merit a new medication trial, this suggests that the current regimen is ineffective. Therefore, prior to prescribing new medications, consider a medication "cleanup" focused on deprescribing psychoactive medications. Following the approach outlined by Davies et al,[101] cognitive medications (ie, cholinesterase inhibitors and memantine) should be continued while medications specifically started for BPSD (as opposed to an underlying, preexisting psychiatric disorder) would be considered for discontinuation prior to starting a new medication. Clinicians might prioritize medications for discontinuation based on the evidence of harms, such as where a benzodiazepine or gabapentin is coprescribed with an opioid.[102,103] But even a medication perceived as relatively safe (eg, a serotonin reuptake inhibitor such as sertraline) could be causing gastrointestinal distress or akathisia that is manifesting as agitation in a patient with dementia.

Although evidence of efficacy is lacking, psychotropic medications such as antidepressants, benzodiazepines, and antiepileptics are widely prescribed.[92,104] Atypical antipsychotics have modest evidence of efficacy.[105] Risperidone is approved for short-term use in both Canada (aggression or psychosis) and the UK (aggression) and is a potential first pharmacological treatment step for major, potentially dangerous symptoms that have not responded to behavioral approaches.[93] While quetiapine is the most widely prescribed antipsychotic for individuals with dementia,[94] it is among those with the least evidence of efficacy for BPSD.[99] Two other antipsychotics are worth noting: (1) brexpiprazole, which was recently FDA approved for agitation in persons with AD but has the same classwide safety concerns related to increased mortality as other antipsychotics, and (2) pimavanserin, a serotonin-receptor modulator that acts primarily as a selective 5-hydroxytryptamine receptor subtype 2A inverse agonist and antagonist rather than binding to D2 dopamine or histamine receptors.[106] Pimavanserin is FDA approved for the treatment of Parkinson disease psychosis (but not psychosis of AD) and has a potentially lower mortality risk than other atypical antipsychotics used for this indication.[107]

Although BPSD may resemble symptoms of psychiatric disorders in individuals without cognitive impairment, medications that are effective for these disorders are generally not effective for the same symptoms in dementia.[94] For example, a Cochrane meta-analysis of antidepressant studies for depression in persons living with dementia concluded that there is insufficient evidence of efficacy,[108] though citalopram can reduce agitation.[109] Antidepressants are also ineffec-

tive for apathy,[110,111] although methylphenidate may be beneficial.[112] Antiepileptic "mood stabilizers" (eg, valproic acid, carbamazepine) and trazodone are ineffective for irritability and agitation. Valproic acid merits particular mention because it is perceived as the leading alternative to antipsychotics for BPSD in long-term care settings[113] despite a Cochrane review recommending against its use in persons with dementia.[114]

Well-established safety concerns about medications for BPSD include an increased risk of fall-related injury for most psychotropics[115-117] and mortality for antipsychotics.[118] Less appreciated is the adverse effect on cognition in persons with dementia.[119,120] Clinicians should monitor for psychotropic changes during inpatient or subacute care[120,121] of persons living with dementia and continually reevaluate the balance of risks and benefits of these treatments.

What to Watch For

A trial of electroconvulsive therapy for agitation in moderate to severe dementia is underway,[122] along with a CitAD follow-up using escitalopram (S-CitAD)[123] and studies of cannabinoids.[124] On the nonpharmacological front, a trial of an online caregiver-directed platform based on DICE is underway.[125]

Limitations

When considering prevention, we confined this review to existing published data and did not conduct new analyses. Thus, we were unable to consider the effect of multiple contributors on risk but are able to provide some insight from several studies that address more than 1 risk factor.[36-39] We were also unable to compare the relative benefits of these interventions across strata of increasing age, where the balance of risks vs benefits may become less favorable. Although not covered here, key aspects of patient-centered care and health equity must be considered, including focusing on patient- or caregiver-identified goals, caregiver support, use of community-based services, housing and social issues, and advance directives and hospice.

Conclusions

Although numerous risk factors for developing dementia have been identified, convincing evidence that modification of these factors, either alone or in combination, can prevent dementia is lacking. AD can be treated with cholinesterase inhibitors, an *N*-methyl-D-aspartate antagonist, or β-amyloid immunomodulator medications, with the last modestly slowing cognitive and functional decline in people with MCI or mild dementia due to AD. Ongoing clinical trials will help to elucidate the long-term clinical efficacy, safety, and cost-effectiveness of these emerging treatments. Psychotropic medications have minimal evidence of efficacy for treating BPSD and are associated with notably increased risks of falls and cognitive decline. Ongoing and future research will undoubtedly provide new insights into prevention and treatment of dementia.

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