



Published in final edited form as:

Drugs Aging. 2017 June ; 34(6): 425–436. doi:10.1007/s40266-017-0462-x.

Weight Loss in Patients with Dementia: Considering the Potential Impact of Pharmacotherapy

Bart A. A. Franx¹, Ilse A. C. Arnoldussen¹, Amanda J. Kiliaan¹, Deborah R. Gustafson^{2,3,4}

Deborah R. Gustafson: deborah.gustafson@neuro.gu.se

¹Department of Anatomy, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands ²Department of Neurology, Section for NeuroEpidemiology, State University of New York, Downstate Medical Center, 450 Clarkson Avenue, Box 1213, Brooklyn, NY 11203, USA ³Neuropsychiatric Epidemiology Unit (EPINEP), Institute for Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden ⁴Department of Health and Education, University of Skövde, Skövde, Sweden

Abstract

Unintentional body weight loss is common in patients with dementia and is linked to cognitive impairment and poorer disease outcomes. It is proposed that some dementia medications with market approval, while aiming to improve cognitive and functional outcomes of a patient with dementia, are associated with reported body weight or body mass index loss. This review presents evidence in the published literature on body weight loss in dementia, describes selected theories behind body weight loss, evaluates the potential impact of approved dementia pharmacotherapies on body weight, considers the potential role for medical foods, understands the potential influence of treatments for neuropsychiatric symptoms and signs, and finally, summarizes this important area.

1 Introduction

Dementia is a clinical syndrome characterized by progressive deterioration of cognitive abilities stemming from neurodegenerative and/or ischemic pathologies. Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (LBD), and frontotemporal dementia (FTD) are the most common subtypes [1]. The prevalence of dementia is growing rapidly. It has been estimated that worldwide, 46.8 million people lived with dementia in 2015 [2]. This number is expected to double every 20 years without the development of

Correspondence to: Deborah R. Gustafson, deborah.gustafson@neuro.gu.se.

Compliance with Ethical Standards

Conflict of interest

Bart A.A. Franx, Ilse A.C. Arnoldussen, Amanda J. Kiliaan, and Deborah R. Gustafson have no conflicts of interest directly relevant to the content of this article. No support was obtained specifically for writing or publishing this review. Dr. Kiliaan and Dr. Gustafson were Investigators in LipiDiDiet, a multicenter translational project funded by the European Commission (<http://www.lipididiet.eu>). Dr. Kiliaan performed animal experiments using Fortysyn Connect[®]. Dr. Gustafson analyzed epidemiological data on the association between dementia and adiposity, cardiovascular risk factors, and the APOE genotype. Neither Dr. Kiliaan nor Dr. Gustafson was directly involved in the clinical trial of Souvenaid[®] in patients with biomarker-based mild cognitive impairment.

therapeutic or preventive strategies [2]. The burden of dementia on society and healthcare systems is equally staggering. Total worldwide costs of US\$818 billion were estimated for 2015, which are expected to exceed US\$1 and US\$2 trillion thresholds by 2018 and 2030, respectively [3].

An intense search for effective dementia medications targeting potential etiologies and symptoms throughout the DOI dementia course is ongoing. Available pharmacologic interventions for dementia do not address the underlying etiology, but instead are symptomatic and designed to slow cognitive decline and improve the deteriorating functional status that characterizes dementia. While these treatments can be effective, some may have considerable side effects such as body weight (BW) or body mass index (BMI) loss. In general, epidemiologic studies have described a paradoxical life course association of BMI in association with dementia such that overweight and obesity in mid-life increase the risk for dementia, while a decline in BW or BMI and/or underweight (BMI <20 kg/m²) may precede and/or accompany dementia onset [4, 5], as well as continue to predict dementia course and outcomes after diagnosis [6, 7]. Thus, medications that cause iatrogenic BW or BMI loss may provoke adverse outcomes in a frail elderly patient, such as one with dementia.

Here, we explore the published literature on BW loss in dementia, describe selected theories behind BW loss, evaluate the potential impact of approved dementia pharmacotherapies on BW, consider the potential role for medical foods, understand the potential influence of treatments for neuropsychiatric symptoms and signs, and finally, summarize this important area. To identify relevant studies that describe BW in patients who received drugs that treat dementia symptoms, we searched PubMed and Web of Science for English publications with the terms ‘dementia’, ‘Alzheimer’, ‘donepezil’, ‘galantamine’, ‘ri-vastigmine’, ‘memantine’, ‘body weight’, ‘nutritional status’, ‘body mass index (BMI)’, and ‘weight loss’ with no date restrictions on 31 July, 2016.

2 Body Weight Loss in Dementia

Unintentional BW loss is a prominent clinical feature in some individuals with dementia [7–9]. For example, data indicate that 30–40% of patients with dementia may experience clinically significant weight loss [10–12]. Body weight loss in dementia may be characteristic of reduced nutritional status, which is partially explained by a reduced food intake [11]. It has been shown that 14–45% of community-dwelling patients with mild-to-moderate AD, and up to 68% of patients with severe AD, are at risk of malnutrition [13–15]. Body weight loss is also observed in transgenic mouse models of dementia that recapitulate underlying neurodegenerative pathologies [16–20], albeit inconsistently [21, 22], as this loss may also be explained by model-specific developmental problems [16] or strain-specific genetic effects [23].

Unintentional BW loss is detrimental for the frail elderly because it is associated with higher rates of mortality [24–27], institutionalization [28], adverse health outcomes, decline in functional status, and overall poorer quality of life [29, 30]. In elderly with dementia, unintentional BW loss is associated with syndrome severity [7, 31–33], higher rates of

institutionalization [34], a higher incidence of behavioral problems [35], and ultimately mortality [6, 36–38]. In contrast, a BMI equal to or higher than overweight ($\geq 25.0 \text{ kg/m}^2$) has been associated with reduced mortality in dementia [39, 40]. Thus, it appears that low or healthy adult BMI can lead to poorer health outcomes in patients with dementia, while a higher BMI may be protective.

As aforementioned, several epidemiologic studies report a paradoxical association of BW or BMI in dementia. Most of these studies use traditional categories of BMI as follows: underweight, $<20.00 \text{ kg/m}^2$; healthy body size, $20.00\text{--}24.99 \text{ kg/m}^2$; overweight, $25.00\text{--}29.99 \text{ kg/m}^2$; and obese $\geq 30.00 \text{ kg/m}^2$. An overweight or obese state in midlife may increase dementia risk in late life [4, 41–43]. Strikingly, a subsequent decline in BW or BMI in late life (e.g., $>4\%$ per year [44]) towards the underweight or even healthy BMI range precedes a dementia diagnosis by years, and may signify a prodromal phase, [9, 45–48] and/or accompany dementia [4, 8, 49–51]. In other words, the epidemiology suggests that during mid-life, an increased BMI or central adiposity [52, 53], increases the risk for dementia in old age, while in late life, a decline in body weight to a BMI within the underweight or even healthy range is associated with a higher risk of dementia in the years to come. Supporting evidence of the significance of BW loss during prodromal dementia are observations of unintentional BW loss from mid- to late-life increasing the risk for mild cognitive impairment (MCI) [54]. The elderly with MCI are often malnourished compared with their cognitively intact peers [55]; and patients with MCI that are losing BW show more accelerated progression towards dementia [44, 56, 57]. In summary, it is clear that BW and BMI are intricately linked with dementia before and after diagnosis, and that BW or BMI loss or underweight can lead to poorer health outcomes in dementia.

3 Theories of Body Weight Loss in Dementia

Numerous explanations have been put forth to explain associations observed between malnutrition, BW loss, cognitive decline, and dementia [58, 59]. First, patients with dementia can experience BW loss from reduced energy intake owing to their decreased mental status, which causes them to simply forget or refuse to eat [60]. This may result from impairments in episodic memory and attention that are associated with medial temporal lobe atrophy [11]. Second, changes in behavior, such as repetitive actions and other behavioral disorders may both demand larger amounts of energy and reduce energy intake. Third, sensory changes such as deterioration of the olfactory bulb and/or diminished gustatory perception can contribute to weight loss as a result of cholinergic deficits [58]. Fourth, dysphagia, or difficulties swallowing, may reduce energy intake [61]. Fifth, hypermetabolism, defined as an elevated basal metabolic rate of $>10\%$ [in energy (e.g., kJ) per unit time], is suggested to cause BW loss. Studies in patients with AD show increased [62], but also reduced [63] and no change [64, 65] in energy metabolism. However, hypermetabolism and BW loss were observed in a transgenic mouse model of AD using calorimetric cages [19]. Still, it remains unclear whether hypermetabolism is a feature of all or a subset of AD cases.

Sixth, neuroendocrine dysregulation in dementia may also give rise to BW loss. Because the biggest component of BW or BMI loss is loss of adipose tissue [66, 67], discussion of

adipose as the largest endocrine organ in the body deserves attention. Adipose tissue secretes hundreds of cytokines, peptides, and hormones, collectively referred to as adipokines, which interact with the brain to control energy metabolism and other brain functions [68–70]. Leptin is secreted by adipocytes [71], expressed in the brain [72, 73], and is present in the blood and cerebrospinal fluid in quantities that are proportional to body fat mass [74–77]. In the brain, leptin regulates food intake and energy expenditure by acting on the hypothalamus through a negative feedback loop [78, 79]. Leptin also supports hippocampal neurogenesis, axonal growth, and learning and memory processes [79–81]. Analogous to the evidence that low adiposity, measured as BMI in the underweight ranges, may be associated with a higher risk for dementia in the elderly [4, 8, 49–51], multiple studies associate low plasma leptin (after adjusting for BW) with an increased risk for AD [82, 83] and cognitive decline [84, 85] later in life. Furthermore, when AD manifests clinically, plasma leptin may be markedly reduced independently of BMI [86, 87] (although stable levels have also been reported [88, 89]). Because in vitro experiments and in vivo animal studies show that leptin is neurotrophic and neuroprotective in both healthy neuronal tissue and AD-stricken brains [90–93], it is plausible that disrupted leptin signaling may contribute to AD pathology. Strikingly, by employing a mouse model that mimics the toxic amyloid- β peptide aggregation pathology of AD, it has been demonstrated that the ensuing morbidly low BW and a low plasma leptin level were associated with inhibited leptin signaling in the brain and aberrant responses of hypothalamic neurons, symptoms that progressively worsened as the amyloid- β burden increased [94]. Thus, these data presented on leptin are an example of the potentially tremendous role of the fat-brain axis in aging-associated changes in both brain and periphery. Owing to the large amount of accumulated adipose tissue in most adults aged 65 years and older who are entering a period of increasing dementia risk, the impact of adipose tissue loss as a result of aging, aging brain, and iatrogenic instigators is meaningful.

Finally, other theories of BW loss not discussed here, are those consequent to dementia, such as the presence of multi-morbidities, adverse effects of other medications unrelated to dementia, loss of autonomy, and changing socio-environmental factors [58, 95].

4 Pharmacotherapies for Dementia: Effects on Body Weight and Body Mass Index

The US Food and Drug Administration (FDA) has currently approved four unique formulations for the treatment of dementia: donepezil, rivastigmine, galantamine, and memantine [96]. Donepezil, rivastigmine, and galantamine are acetylcholinesterase inhibitors (AChEIs) and vary only slightly in pharmacological properties. Acetylcholinesterase inhibitors are at the forefront of symptomatic treatment for AD and LBD [97], diseases that are most often characterized by a loss of cholinergic neurons in the brain, reducing the amount of acetylcholine available for neurotransmission, leading to a deficient cholinergic system [98]. Acetylcholinesterase inhibitors bind to brain cholinesterase enzymes in a reversible manner and inhibit them from breaking down acetylcholine at the synapse level. Thus, AChEIs increase the level and duration of neurotransmitter action in forebrain regions, in an attempt to compensate for the loss of functioning cholinergic neurons [99]. Most systematic reviews and meta-analyses that assess

the efficacy of AChEIs report modest improvements in cognitive function and other benefits in patients with mild-to-moderate AD or LBD [100–102], but marginal effects of uncertain significance in VaD [103].

Despite the positive cognitive effects of AChEIs, numerous phase IV clinical trials note an unintentional side effect that may be cause for concern. In a meta-analysis of AChEI treatment in AD, it was shown that there was an almost three-fold higher odds of the adverse event, BW loss, among patient groups taking AChEIs compared with placebo treatment groups. Furthermore, this BW loss was associated with adverse gastrointestinal side effects [100]. Notably, AChEIs induce dose-dependent nausea, vomiting, anorexia, and diarrhea [100, 104–106] caused by cholinergic hyperstimulation of the internal muscarinic receptor in the gastrointestinal tract [106, 107]. Thus, AChEIs may influence nutritional status through adverse effects on the peripheral nervous system leading to BW loss [108].

Since the market approval of AChEIs, the association between AChEI treatment and BW loss has been investigated. One group observed a 23% risk of BW loss in individuals with dementia taking AChEIs [109], while others concluded AChEI treatment is protective against BW loss seen in dementia [110] (however, the latter study lacked a control group). Crucially, in a meta-analysis of 25 clinical AChEI trials and others, an increased risk of BW loss was observed for every AChEI [111, 112]. This provided the first report of pooled estimates of effect addressing whether AChEIs may cause BW loss in dementia. While there are also reports of patients regaining BW after AChEI discontinuation [104, 105], no randomized controlled trials (RCT) assessing discontinuation have been conducted.

Memantine, the fourth compound currently approved by the FDA for the management of dementia, is a partial N-Methyl D-Aspartate receptor (NMDAR) antagonist. In dementia, an excitotoxic mechanism, partially owing to excess glutamate causing over-activation of NMDARs, triggers various neurotoxic events that lead to necrosis or apoptosis. Memantine works through uncompetitive blocking of the glutamatergic NMDARs when they are excessively open, blocking the imminent excitotoxic cascade [113]. Despite a paucity of evidence and high heterogeneity among studies, memantine is associated with clinical benefits on cognitive, functional, and global outcome scales in patients with mild-to-severe AD [114–116], although efficacy in mild AD has been disputed [117]. Minimal benefits have been detected in VaD [114] and FTD [118], but not in LBD [119, 120].

Studies that pooled trial data of adverse events have reported no significant difference between memantine and placebo groups in drop-out rates or the incidence of adverse events [114, 116, 121], and no significant effects were found on BW loss and other adverse events that are associated with AChEIs [114, 116, 121]. There is the caveat with memantine as with all dementia medications, however, that the BW of those prescribed may have already dropped to such low levels that no further influence of the medication is observed on BW. This is however, speculative, as to our knowledge, no data exist on this important point. Overall, memantine displays a better safety and tolerability profile than AChEIs [121].

5 Potential Role for Medical Foods

The pursuit of novel dementia treatments has led to the development of novel nutritional interventions such as medical foods. Medical foods are not dietary supplements owing to legal definitions, and variation exists cross-nationally as to whether a medical prescription is necessary for their use, thus complying with the pharmacotherapy framework of this review [122]. The term medical food is defined as “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation” [123]. In contrast, dietary supplements are products (e.g., capsules, liquids, or soft gels) that contain a dietary ingredient intended to add to the nutritional value of the diet [122]. Both medical foods and nutritional supplements have been developed to improve dementia outcomes, but for the sake of brevity and the focus of this review on pharmacotherapies, only medical foods are discussed here. (For systematic appraisals on the effectiveness of nutritional supplements in dementia, the reader is directed elsewhere [124–126]).

Treatment rationales for medical foods are based on specific micronutrient needs that arise from underlying disease pathologies, and that may not be met by simply modifying the usual diet. Of high relevance for this review, medical foods may also provide a way to combat BW loss. For AD, three medical foods are being developed that claim to offer symptomatic relief: Axona[®], CerefolinNAC[®], and Souvenaid[®]. Axona[®] provides a ketogenic agent that targets metabolic deficiencies in AD [127]. Results from a multi-center RCT show that APOE-4 (an important AD-susceptibility gene) negative patients with mild-to-moderate AD taking Axona[®], improve on the Alzheimer’s Diseases Assessment Scale-Cognitive subscale after 90 days [128]. It should be noted that 23% of patients in the treatment arm discontinued the trial because of adverse events, mostly related to the gas- trointestinal system. CerefolinNAC[®] addresses the hyperhomocysteinemia and oxidative stress associated with disorders such as MCI and AD. CerefolinNAC[®] increases the bioavailability of folate and vitamin B₁₂. One prospective case–control study has shown that CerefolinNAC[®] significantly slows cognitive decline in dementia disorders compared with no treatment [129]. Unfortunately, there are a paucity of published studies on the treatment effects of Axona[®] and CerefolinNAC[®], and these studies have not addressed patient BW or nutritional status.

The third medical food, Souvenaid[®], acts as a vehicle for the Fortasyn Connect formulation and was designed to deliver a specific combination of nutritional precursors and cofactors for phospholipid synthesis that are essential for the synthesis of neuronal membranes and synaptic function [130]. Deterioration of neuronal membranes and synaptic function have been shown to underlie cognitive decline in AD [131]. Therefore, this formulation is targeted to improve synaptic formation and function, with the ultimate goal of ameliorating cognitive symptoms in patients with AD [132].

Several industry-sponsored clinical trials assessing the efficacy of Fortasyn Connect at various stages of AD have been completed; however, evidence remains inconclusive.

Randomized controlled trials have reported modest positive outcomes for once-daily treatment on the measures of cognitive function in FTD [133] and mild AD [134, 135], while a much larger RCT of add-on treatment reported no effect in mild-to-moderate AD [136]. In addition, these studies noted that Souvenaid[®] was remarkably well tolerated by patients. In recognition of poor nutritional status often accompanying dementia, a secondary analysis was undertaken to examine the effect of Souvenaid[®] on BMI and functional abilities compared with an iso-caloric control product in mild AD. Overall, a small increase of marginal significance in BMI was reported in the active vs. control group after 24 weeks [137]. Thus, this study suggests that a medical food can increase BMI in patients with mild AD, although the underlying mechanism by which Souvenaid[®] contributes to a potential increase in BMI remains unknown.

At this moment, whether Souvenaid[®] can be an effective (add-on) treatment that may be beneficial to nutritional status in dementia remains an open question. There is no evidence from long-term clinical trials available yet, although a two-year RCT trial known as 'LipiDiDiet' has recently been completed in a population with prodromal AD (DR Gustafson and AJ Kiliaan are investigators on the LipiDiDiet team). Preliminary results indicate that Souvenaid[®] does not significantly benefit nor slow cognitive decline in the treatment group; however, various secondary measures such as medial temporal lobe atrophy and neuropsychological testing scores were significantly improved compared with the control group [138]. While too early to draw definitive conclusions regarding neuroprotective effects of Souvenaid[®], the prospect that a medical food intervention can positively affect early disease course, where conventional medication often fails, and alleviate potential side effects of traditional medications, is hopeful. While the LipiDiDiet study has been extended, more long-term clinical trials studying the effects of medical foods as interventions would be worthwhile.

6 Pharmacotherapies for the Treatment of Neuropsychiatric Symptoms of Dementia and their Effect on Body Weight

As aforementioned, AChEIs and NMDAR antagonists are the only medications with marketing approval for the treatment of dementia [96]. However, several other medications are prescribed to treat concomitant neuropsychiatric symptoms. These symptoms are referred to as behavioral and psychological symptoms of dementia (BPSD). These symptoms occur irrespective of dementia subtype and include a wide array of non-cognitive disturbances such as agitation, aggression, hallucinations, and depression [139]. Behavioral and psychological symptoms of dementia are associated with high levels of distress and poor outcomes for the patient and caregiver, as well as increased use of healthcare resources [139]. Behavioral and psychological symptoms of dementia are therefore a meaningful intervention target [140, 141]; and unexpected benefits may arise from BPSD medications. For example, dronabinol, a synthetic cannabinoid used to decrease nausea and improve appetite in patients with human immunodeficiency virus, is used as an off-label treatment for BPSD-related aggression and agitation in the elderly. Interestingly, a placebo-controlled crossover study and a non-randomized retrospective study also suggest that it may alleviate anorexia [142, 143]. However, BW did not change in a more recent RCT [144], hence it is

not yet possible to draw conclusions. Herein, antidepressants and antipsychotics are briefly discussed as they are more frequently used as an off-label treatment for BPSD.

6.1 Antidepressants

Increased appetite and BW gain are well-known side effects of antidepressants. Antidepressants are routinely prescribed to treat agitation or depressive symptoms that appear in dementia and use is reported almost twice as high among AD patients compared with controls [145]. However, the orexigenic effect of antidepressants in patients with dementia is rarely addressed. Mirtazapine, a noradrenergic antagonist, has potent orexigenic effects [146]. Of all marketed antidepressants, mirtazapine is associated with maximum BW gain, an effect strongly predicted by the H₁-histamine receptor antagonistic action of this drug type [147]. The orexigenic effect of mirtazapine warrants off-label prescriptions to treat anorexia and underweight in various conditions [148, 149], but only a handful of retrospective open-label studies have investigated whether antidepressants such as mirtazapine alleviate BW loss in patients with dementia. One report documented three AD cases with co-morbid depression who regained appetite and BW within weeks after initiating mirtazapine [150]. Another study examined the impact of various antidepressants on nutritional parameters in the institutionalized elderly with and without dementia. All patients, irrespective of dementia status, experienced BW gain and lower risk of malnutrition when taking antidepressants (except for selective serotonin reuptake inhibitors [SSRIs]) [151]. The third and final retrospective open-label study investigated whether mirtazapine alleviated BW loss in AD, and observed a mean BW increase of 4.6% after 6 months [152]. Of note, these studies were not placebo controlled, and sample sizes were underpowered and highly heterogeneous (e.g., many patients also received AChEIs [151]).

Management of BPSD with pharmacological agents is an important but complex component of dementia treatment owing to a lack of treatment options and possible adverse interactions caused by concomitant use of other types of medications. Despite the scarcity and varied quality of clinical practice guidelines for the management of BPSD, there is advancement. Recent systematic comparison and appraisal of BPSD guidelines concluded there was sufficient agreement for the use of antidepressants to manage co-morbid depression in BPSD [153]. However, only SSRIs were considered. Mirtazapine may be preferable in BPSD because SSRIs are associated with a high propensity for drug–drug interactions [154]. Unlike mirtazapine, SSRIs and tricyclic antidepressants are associated with many serotonin-related adverse effects, including nausea, insomnia, headaches, anxiety, and sexual dysfunction [155]. In contrast, mirtazapine is less likely to cause drug–drug interactions and overall has a more favorable side-effect profile than other classes of antidepressant medications [146]. Particularly because of the latter, mirtazapine has been recommended as treatment for depression in dementia over other antidepressants [156]. Of note, studies have suggested that second-generation antidepressants in general appear less effective in elderly populations, and that there is no substantial difference between the efficacy of mirtazapine, sertraline (SSRI), and placebo in the treatment of primary co-morbid depression symptoms in BPSD [157, 158]. However, a follow-up cost-effectiveness study concluded that mirtazapine treatment may carry more benefits over placebo or sertraline in terms of

improving quality of life and reducing unpaid care time and cost, potentially caused by improving insomnia and anxiety [159].

6.2 Antipsychotics

Antipsychotics, most often second-generation antipsychotics (SGAs), are another class of medications prescribed for the pharmacological treatment of BPSD. Second-generation antipsychotics are commonly used to manage typical symptoms such as aggression and psychosis, and do so with modest efficacy [160]. In addition, SGAs are associated with an increased risk for BW gain and metabolic side effects related to morbidity in adults, such as diabetes mellitus and hyperlipidemia [161]. Similar to the orexigenic property of antidepressants, H₁ receptor affinity of antipsychotic agents was found to be a strong predictor of these effects [162]. The relationship between metabolic side effects and antipsychotic treatment for the elderly with dementia was investigated in a meta-analysis of 27 studies [163]. It was concluded that, owing to a paucity of publications and relatively short trial durations, limited evidence indicates a possible association between BW gain and antipsychotic drug use in patients with mild-to-moderate dementia. This relationship was more convincing for SGAs, and no significant effects on glucose homeostasis or lipid metabolism were found [163].

While BW gain resulting from SGA use might be considered helpful in elderly populations where BW loss is common and detrimental, it can easily be overshadowed by several SGA-associated adverse effects. First, SGA treatment in elderly patients with dementia is linked to a 1.7-fold increased risk for cardiovascular events and mortality compared with placebo [164]. Therefore, the FDA actively warns against off-label prescription of antipsychotics in elderly patients [165] and nearly all clinical BPSD guidelines recommend caution and timely discontinuation [153]. Second, drug–drug interactions need to be considered. For example, if a BPSD patient taking an antipsychotic agent requires an opioid analgesic, there will be an increased risk of sedation, dizziness, and falls [166]. Third, because antipsychotics interact in part with dopaminergic pathways, they cannot be readily applied in every clinical case of dementia. For instance, treatment of psychosis with SGAs in Parkinson's disease dementia is difficult, considering certain SGAs can exacerbate parkinsonian symptoms [167], which is possibly evidenced by the higher risk of bone fractures associated with SGA prescription in Parkinson's disease dementia [168].

7 Discussion and Perspectives

The evidence presented in this review demonstrates that unintentional BW loss in dementia is problematic, and that the association between AChEI treatment and BW loss is a concern. See Fig. 1 for an illustration of factors involved in BW loss in dementia. Importantly, there is increasing evidence that AChEIs, prescribed to relieve cognitive symptoms of dementia, are associated with two or even three times the risk of clinically significant BW loss [111]. In a vulnerable population where BW loss and poor nutritional status are predictive of adverse outcomes, clinicians need to consider these risks when evaluating their choice to prescribe an AChEI. In contrast, memantine has shown no significant relationship with BW loss [114, 116, 121]. Thus, although the cognitive benefits of memantine in AD, FTD, and VaD may be

small, the absence of effects on BW may make memantine a more suitable treatment option for elderly patients in whom BW loss is a hazard. However, we acknowledge that memantine may be more likely prescribed among those with more severe dementias, and thus for those who have already lost a substantial amount of BW.

Common pharmacotherapies for the treatment of BPSD have demonstrated orexigenic effects in patients with dementia. Mirtazapine, which has a mild side-effect profile that reduces insomnia and increases appetite [146], could be a primary candidate for BPSD treatment when BW loss or malnutrition are concerns. To our knowledge, there is currently no consensus on the use of mirtazapine for treatment of BPSD. Future experimental studies on the orexigenic effect of mirtazapine in the elderly are critical to establish whether mirtazapine is a viable treatment option. Second-generation antipsychotics seem to have a similar effect on BW, but the potential benefit is overshadowed by their more serious adverse effects [164, 165].

Maintaining a healthy BW in individuals with dementia is an integral part of patient care. Decreased nutritional and energy intakes contribute to BW loss [11, 65], which suggests promising avenues for non-pharmacological interventions such as medical foods. Systematic appraisals have indicated that nutritional supplements can improve nutritional status [125, 126], and the same may hold for medical foods [137]. In addition, other lifestyle and social factors may be improved to enhance the quality of the dining experience for the elderly. The introduction of an aquarium in the dining area of residents with long-term dementia increased food intake by 25% and significantly improved BW [169]. There is also interest in other modifiable lifestyle factors, including transformation of usual diets such as adopting the Mediterranean dietary pattern or enhancing essential fatty acid intake [170]. Evidence on single and mixed food-based interventions that improve BW in dementia remain scarce. Future research in this area will benefit both patients and caregivers.

Finally, as a reminder, there is ample evidence that excess BW is associated with serious morbidities in adult populations [171, 172], while among the elderly, BMI in the overweight or obese range appears to positively affect survival [39, 40, 50]. The protective effect of higher BMI on mortality in later life, in contrast to middle age, is frequently termed the 'obesity paradox', and has been observed in other conditions, such as coronary artery disease and stroke [173, 174]. However, an obesity paradox is not consistently observed across studies in association with cognition and dementia; and with the global pandemic of obesity and emergence of new medications, it is unclear what associations will be observed in the very near future. Whether low adiposity or BW loss in dementia should be treated with interventions promoting BW gain has no straightforward answer and requires a personalized medicine approach.

8 Conclusion

More research is needed in clinical and pre-clinical areas of BW, BMI, and dementia. First, studies of body composition and metabolic aspects of adipose tissue are needed to clarify what BW and BMI represent in association with brain health. Second, definitions of optimal BW and BMI are needed for healthy brain and peripheral aging. Third, the relative

influences of other factors, such as environmental, sensory, and physical function, need to be addressed more comprehensively and quantified for better use in models of aging. Finally, not only do dementia medications require further inquiry, but other medications, in addition to the role of polypharmacy in peripheral (BW loss) and brain health and disorders.

Acknowledgments

Funding

Support for this review is as follows: DR Gustafson, State University of New York, Downstate Medical Center institutional research funds and the Swedish Research Council for Health, Working Life and Welfare, AGECAP 2013–2300, 2013–2496; AA Franx, IC Arnoldussen, AJ Kiliaan AJ, EFRO project BriteN (PROJ-00405). The Women's Interagency HIV Study (WIHS), National Institute of Allergy and Infectious Diseases (U01-AI-35004, U01-AI-31834, U01-AI-34994, U01-AI-34989, U01-AI-34993, and U01-AI-42590).

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Key Points

Body weight loss is common in adults with preclinical and clinical dementia, and linked to worsening cognitive impairment.

Some approved dementia medications are associated with loss of body weight.

In the elderly, more attention to polypharmacy targeting both brain and peripheral health and disorders is essential.

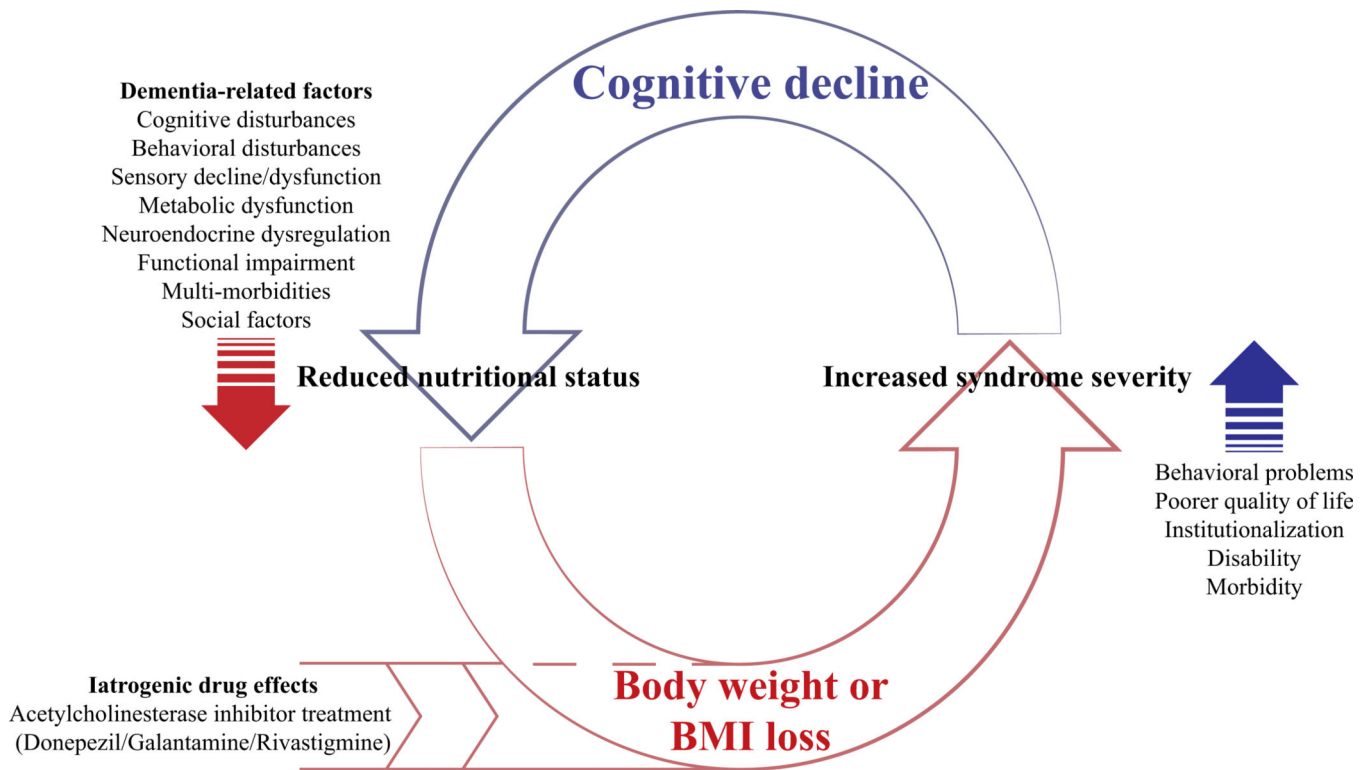


Fig. 1.

Vicious cycle of cognitive impairment and body weight or body mass index (BMI) loss and progression to dementia. Body weight or BMI loss is often an important correlate of dementia. In dementia, BW or BMI loss is associated with adverse health outcomes [6, 7, 31–38], cognitive decline, and cognitive impairment [44, 54, 56, 57], which evokes a deleterious cycle driving further BW or BMI loss. Acetylcholinesterase inhibitors approved for the symptomatic treatment of dementia contribute to BW or BMI loss [111, 112], most likely via side effects including nausea, anorexia, and vomiting, which are likely the result of cholinergic hyperstimulation [106, 107]