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GERIATRIC DISORDERS (W MCDONALD, SECTION EDITOR)

Cognitive and Neuropsychiatric Impairments in Alzheimer's Disease: Current Treatment Strategies

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Abstract This update on Alzheimer's disease (AD) discusses treatment strategies for cognitive and neuropsychiatric symptoms (such as agitation, psychosis, anxiety, and depression) common in this illness, emphasizing in particular nonpharmacologic strategies such as cognitive interventions, physical exercise, and psychotherapy. We provide an overview of cognitive enhancers and their combination strategies and medications commonly used for treatment of neuropsychiatric symptoms in AD. Finally, we give recommendations for providing support to caregivers and suggest how to identify caregiver/patient pairs most in need of intensive dementia care services.

Keywords Alzheimer's disease · Caregiver support · Cooperative dementia care · Cognitive interventions · Neuropsychiatric symptoms · Agitation · Cognitive enhancers

Introduction

Approximately 5.2 million Americans have Alzheimer's disease (AD) and related dementias, a number expected to increase significantly over time [1]. These costly neurodegenerative diseases impact the patients' quality of life and longevity, radically changing the lives of patients' families and loved ones. As a disease that progressively impairs diverse brain functions, AD affects much more than memory and everyday self-management. Communication, language, mood, behavior regulation, sleep, and eventually even motor function will deteriorate. In the USA, the estimated health and social care costs for patients with AD is $172 billion per year [2]. Recently, considerable progress has been made in identifying cerebrospinal fluid (CSF) biomarkers and imaging findings that, in conjunction with cognitive testing, may help identify those at risk for developing dementia due to AD [3]. Research is also focusing on identifying treatments for AD other than the commonly used acetylcholinesterase (AChE) inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonist, including tau-based medications, nutritional supplements, and medical foods [4]. Even without definitive medical treatment, however, those who are living with AD and their family care partners may be greatly helped by effective multimodal interventions. This review provides an update on the latest treatment strategies in AD, emphasizing in particular the strategies that help care partners manage their own stress and patients' evolving problems.

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Common Problems Seen in Alzheimer's and Their Treatment

Cognitive Impairment

Pharmacological Approaches

Enough data have accumulated on the effects of acetylcholinesterase inhibitors (AChEIs) to be able to recommend them with confidence for treatment of AD. A recent meta-analysis

confirms the efficacy of these medications for stabilization of cognition and function, while highlighting what we know about the adverse events common with their use, including nausea, vomiting, diarrhea, and anorexia. These side effects are caused by the pro-parasympathetic nervous system activation that occurs with the use of AChEIs [5]. Beyond their effects on the gastrointestinal system, less well publicized is the associated risk of bradycardia, which further places patients taking AChEIs at risk for falls, syncope, pacemaker placement, and other adverse consequences of abnormally low heart rate [6].

Inhibition of AChE emerged as a therapeutic target with the discovery that large cholinergic neurons in the brain, with their wide projections and importance to many cognitive processes, degenerate in AD. The therapeutic action of AChEIs is believed to promote cholinergic neurotransmission, but also to increase the production of some growth factors and reduce the deposition of beta amyloid and formation of senile plagues, two characteristic pathologic processes found in the brains of patients affected by AD [7]. It is hypothesized that AChEIs exert positive effects on attention and arousal systems [8], as well as on language abilities [9], in addition to the stabilization of cognition and function that can be seen clinically.

Memantine, lacking the procholinergic mechanism of action, is not known to cause gastrointestinal side effects common to AChEIs. Memantine targets the dysfunction in glutamatergic transmission and may exert some neuroprotective effects in the brains of AD patients [10].

Over the years since the AChEIs and memantine were approved for treatment of AD, questions have existed as to the degree of their clinical usefulness and the duration of their beneficial effects. A study examining the existing evidence from randomized placebo controlled trials and long-term observational studies helps guide clinical practice. Evidence suggests that the efficacy of AChEIs may last for several years in some patients, benefits are greatest when treatment begins early in the course of the disease, and efficacy can be observed at all stages of dementia [11•, 12], while memantine's therapeutic effect is more readily observed in moderate to severe disease [12].

High-dose donepezil (23 mg) has now been approved by the Food and Drug Administration (FDA) for treatment of moderate to severe AD, its safety and tolerability comparable to those of 10 mg for mild to moderate disease [13]. The mechanisms of action for AChEIs and memantine are complementary, illustrating the complex but vital interaction of the cholinergic and glutamatergic pathways [10], suggesting that the combination of these medications may be more effective than either alone. There is however still some uncertainty as to how effective the combination treatment is in clinical practice, with two recent meta-analyses showing somewhat conflicting results. A strong study from 2012, which included previously unpublished data, found a small cognitive benefit with combination therapy at 6 months, but no improvement in function [14]. A recent review recommended combination treatment more enthusiastically, basing this conclusion at least in part on theory and preclinical data [15]. Overall, given the lack of significant drug-drug interaction and the proposed synergistic mechanism of action as well as the available clinical data, combination therapy should be offered to appropriate patients. Table 1 provides further information on medications recommended and dosing.

Nutrition

We now know more about the effects of nutrition on AD, though less than necessary to promote widespread adoption. A review of existing evidence suggested that a combination of a specific medical food and adherence to a Mediterranean diet could slow cognitive decline in AD [16•].

Exercise

There has long been hope that exercise might prove to be beneficial in stabilizing the cognitive losses in AD; however, the existing evidence is heterogeneous in methods and, as with nutritional studies, should be interpreted with caution. The Cochrane review from 2013 examined 16 trials of exercise programs for older people with dementia, concluding that exercise programs may have a significant impact on cognitive functioning and ability to perform activities of daily living (ADLs), while possibly also reducing the burden on caregivers who supervise patients' participation or participate with them [17•].

A number of recent studies focus on the impact of exercise on the physical functioning and mobility of AD patients rather than on the cognitive and neuropsychiatric symptoms, with fairly positive results. A systematic review of 20 randomized controlled trials (RCT) of institutionalized and home-dwelling patients with AD concluded that intense physical activity, utilizing several types of exercise, and implemented for at least 3 months, may lead to improvements in mobility and functional ability for patients with dementia. As in the Cochrane review above, this study demonstrated the need for further investigation of the effect of physical activity on patients with AD, as the trials included in the review were few in number and heterogeneous in methods [18]. An earlier systematic review from 2010, while acknowledging the limitations of the present quality of evidence, cautiously recommended that exercise should be offered as an intervention at all stages of dementia, using varied activities, performed for 45-60 min, three times a week, for at least 12 weeks [19]. Many questions about the impact of exercise on dementia remain unanswered; among these are the practical problems inherent in getting many AD patients to engage in intensive exercise.

Table 1 Cognitive enhancers

Medication	Dosing guidelines	Notes
Donepezil	Initial dose 5 mg at bedtime Titrate to 10 mg once daily at 4-6 weeks For moderate to severe dementia, may titrate to 23 mg at 3 months	The only AChEI FDA approved for treatment of all stages of AD dementia (mild to severe)
Galantamine	Initial dose 4 mg twice a day Titrate to 8 mg twice a day at 4 weeks Titrate to 12 mg twice a day at 4 weeks	Extended-release capsules to provide once a day dosing are also available. Dosing adjustment recommended in renal and hepatic impairment
Rivastigmine	Initial dose 1.5 mg twice daily for 2 weeks Increase in increments of 1.5 mg twice daily every 2 weeks if well tolerated Maximum dose 12 mg a day	Dosing adjustment recommended in renal and hepatic impairment. Use caution when treating low-body-weight patients because of the high frequency of nausea and vomiting (oral form). The only AChEI FDA-approved for treatment of cognitive impairment in Parkinson's disease
Rivastigmine patch	Initial dose 4.6 mg/24 h topical once daily for 4 weeks Titrate to 9.5 mg/24 h topical once daily For severe dementia, may titrate to 13.3 mg/24 h topical once daily after 4 weeks at prior dose	Dosing adjustment recommended in hepatic but not in renal impairment. Use caution when treating low body weight patients. Dose adjustment may be needed in high-body-weight patients
Memantine	Initial dose 5 mg daily, at 1 week increase to 5 mg twice a day, in another week increase to 5 mg in the morning and 10 mg in the evening, and in another week increase to target dose of 10 mg twice a day or 20 mg once a day	FDA approved for use in moderate to severe AD Dose adjustment recommended in severe renal and hepatic impairment

Please note that the descriptions of side effects and dosing adjustments above are not exhaustive. Thorough review of dosing and recommendations is recommended prior to initiating treatment

Cognitive Stimulation and Training

There is considerable interest in cognitive interventions for AD, which include cognitive training (CT), cognitive stimulation (CS), and cognitive rehabilitation (CR). Table 2 describes these strategies. A recent systematic review that summarized only high-quality randomized controlled trials of cognitive interventions in AD found that them to be very few in number, limiting conclusions about their efficacy and which patients may benefit. However, the available trials demonstrate the potential for these interventions to improve global cognitive functioning in a cost effective manner. These trials also boasted good adherence and completion rates [20•]. Another recent systematic review analyzed 12 randomized controlled trials of CT, including both AD and vascular dementia patients and, in some studies, involved participation of family caregivers. This review found no significant effects on either cognitive or noncognitive outcomes. One high-quality RCT of CR for AD showed improvements in comparison to a control condition, based on achievement of patient-derived personal goals [21]. A more recent well-designed study of patients with mild AD, all of whom were treated with AChEIs, found differences between those who received "client-centered" global stimulation (falling under the CS category of cognitive interventions) or CT and those in the control group. Instrumental activities of daily living (IADL) and ADL performance increased in patients who received client-centered global stimulation and CT. CT further stimulated many cognitive functions and led to better performance in language processing [22]. Another valuable study tested CT lasting 4-5 h a day, for 10 days, in 21 adults with early AD, leading to significant improvement in working memory, sustained and switching attention, and performance on practiced and unpracticed tasks [23], indicating that intensive cognitive interventions may be particularly effective. So far there is no evidence that commercially marketed brain training games are effective in AD [24].

Table 2 Cognitive interventions

Cognitive intervention type	Definition of the cognitive intervention
Cognitive training (CT)	Practice on a set of standard tasks to increase particular cognitive function, meant to support accomplishment of ADL/IADL
Cognitive rehabilitation (CR)	Individualized treatment; therapist works with the patient and family to devise strategies to identify and address personally relevant goals, with less emphasis on particular cognitive functions
Cognitive stimulation (CS)	Engagement in a range of activities designed to enhance general cognitive and social functioning, administered in a group setting

Adapted from [25]

To date, the quality of evidence regarding the use of cognitive stimulation and training methods remains low to

moderate, and the search continues to determine which type of cognitive exercises would benefit the patients with AD in different stages of the disease. However, given the low risk and potentially significant benefit on patient's functioning, we are able to recommend cognitive interventions of either of the types described in Table 2, particularly to patients with mild AD. For those in later stages of the disease, there may be more benefit from interventions based on individually determined goals, such as CR.

Neuropsychiatric Symptoms

Agitation, psychosis, depression, and anxiety are common in dementia [26••] and negatively impact the quality of life of the patients with AD and their caregivers. They are the major precipitant of institutionalization [27, 28].

Successful treatment interventions involve careful assessment of contributing physiological, psychological, and environmental factors. Multidimensional treatment approaches that are flexible and tailored to the individual and the environment tend to yield the best outcomes. The recommendation is to start with nonpharmacologic approaches and caregiver support and to add pharmacologic interventions when necessary [29, 30]. Often, in cases of severe agitation where the risk of injury is high, medications are started together with behavioral interventions, at a low dose, and while avoiding polypharmacy. Medication selection is based on the specific symptom target, the severity of symptoms, and side effect profiles. Behavioral symptoms tend to run a natural course and dissipate with time, so eventually careful dose reductions should be considered [31].

It is important to rule out culprits other than AD itself that may be causing neuropsychiatric symptoms, particularly new or decompensated medical disorders and drug side effects. Commonly overlooked etiologies include constipation, dehydration, hypoxia, pain, upper respiratory infections, urinary tract infections, and dental abscesses. Over the counter medications, substance use, and pain medications also significantly impact the functioning of patients with AD. Anticholinergic load is additive and of particular importance in this population given their vulnerability to delirium. The impact of psychiatric disorders and uncorrected sensory deficits must also be assessed when planning treatment.

a) Agitation and Psychosis

The term agitation refers to disruptive motor or vocal activity (e.g., yelling, physical aggression, pacing) and tends to occur in more advanced stages of cognitive impairment [32]. Psychotic symptoms occur in up to 51 % of patients with AD and often contribute to the development of disruptive agitation [33]. Hallucinations may be auditory or visual, though the latter are more common in dementia with Lewy bodies and Parkinson's disease dementia.

Delusions in AD tend to be cognitively based. Memory deficits may lead to beliefs that misplaced objects have been stolen. Agnosia may result in misidentification syndromes: that the identity of a person has changed, that a person has been replaced by an imposter (Capgras syndrome), or that the patient's house is not their home. Less commonly, the patient may come to believe that he or she is being poisoned or that their spouse is unfaithful.

Identifying and modifying factors that precipitate and exacerbate agitation tend to be effective. It is also an important psychoeducational tool for caregivers who thus learn to recognize troublesome patterns. For example, agitation may be caused by boredom/lack of appropriately engaging activities, loneliness, and pain: addressing these needs may minimize disruptive behavior [34]. Cognitively impaired patients may become agitated while others help them with ADLs, and allowing them to remain as independent as possible in these activities is important. Examples include person-centered showering (an intervention focused on resident comfort and preferences), the towel bath (an in-bed bag bath method in which the resident remains covered at all times), prevention of constipation, and toileting routines [35]. It is essential to use simple language and visual cues to improve communication and minimize frustration. Instituting predictable routines, eliminating unnecessary stimulation and novelty, and maximizing the patients' remaining abilities can help reduce agitation.

If hallucinations or delusions are not distressing to the patient, it is preferable not to treat them with medications. Rather, education and finding nonpharmacologic adaptive strategies provide more benefit. If these symptoms impair quality of life, a low dose of an atypical antipsychotic medication can be tried.

Medications should be considered particularly if problem behaviors are frequent or aggressive with potential for injury. Infrequent or sporadic behaviors usually do not require daily medications.

AChEIs and memantine may help delay progression of functional deficits and emergence of neuropsychiatric symptoms [36, 37]. Memantine may have some benefits relative to placebo for agitation and psychosis as well as for global behavioral measures [38].

Antipsychotics are not approved by the FDA for the management of agitation in AD, though they are commonly used off-label. Published efficacy studies show only modest benefit over placebo [39–42]. In addition, The Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease (CATIE-AD) study cast serious doubt over the benefit of treating agitation and psychosis with atypical antipsychotics [43]. In this trial, no difference was found among the treatment groups or placebo, and authors concluded that side effects offset the small advantages in efficacy for these drugs. In

April 2005, a meta-analysis of 17 placebo-controlled trials reported that the risk of mortality was 1.6-1.7 times greater in elderly dementia patients treated with atypical antipsychotic medications, primarily because of cardiovascular effects or infection [44]. This precipitated the "black box" warning that the use of atypical agents for the treatment of behavioral symptoms in elderly patients with dementia is associated with increased mortality. Other significant adverse effects include extrapyramidal symptoms, sedation, and metabolic syndrome. Anticholinergic side effects are troublesome in this population and may aggravate agitation.

If a trial of antipsychotics is warranted because of the severity of the symptoms, atypical agents are preferred because of their improved side effect profile and tolerability [45]. Written informed consent should be obtained from responsible individuals (usually family members) and therapeutic and side effects fully documented.

Clinical trials of antidepressants for agitation have shown mixed results. There is some new evidence for the efficacy of the selective serotonin reuptake inhibitor (SSRI) citalopram. A multisite randomized double-blind clinical trial of citalopram (the CitAD trial) showed superiority over placebo for reducing agitation in AD patients [46•]. The target dose in this trial was 30 mg daily, which exceeds the current FDA advisory limit of 20 mg in older adults because of a dose-dependent risk for QTc prolongation. Citalopram was associated with a slightly greater decline in cognition. Common side effects of SSRIs include nausea, diarrhea, and anorexia; these could be problematic in the elderly if they contribute to discomfort and weight loss.

Enhanced behavioral responses to norepinephrine may contribute to agitation in dementia. In a randomized placebo controlled study, propranolol was shown to be superior to placebo and generally well tolerated, but behavioral effects decreased over time, limiting its clinical effectiveness [47]. A small pilot double-blind placebo controlled trial of prazosin demonstrated efficacy over placebo and good tolerability [48].

Due to the potential of benzodiazepines for causing worsening cognitive functioning and increasing the risk of falls, their use should be reserved for severe agitation when alternatives have not been successful. A limited trial of a short-acting benzodiazepine in these cases is preferred.

Recently, a retrospective chart review of using electroconvulsive therapy (ECT) for agitation in dementia was published [49•], demonstrating the efficacy and safety of this treatment. ECT should be reserved for patients with severe agitation in whom the added risk of worsening cognition can be justified. A small number of treatments can be effective.

b) Depression

Prevalence estimates of depression in AD vary between 26 to 50 % [50–52]. The best indicators of depression in dementia patients are persistent sad mood or decreased positive affect [52]. Vegetative signs such as insomnia, anorexia, and low energy are less reliable since they may arise from dementia and other problems. Depression increases the risk of sleep disturbances, agitation, and suicide [53–57] and may cause excess cognitive disability, further impacting function and increasing caregiver burden.

Nonpharmacologic interventions include decreasing social isolation, behavioral activation, exercise programs, and increasing pleasurable activities. Consideration of psychotherapy (e.g., problem-solving therapy) in patients with preserved insight should be promptly and consistently instituted [58–62]. Significant controversy regarding the use of antidepressants in dementia exists because of insufficient evidence regarding their efficacy [63–65, 66•]; however, SSRIs are frequently prescribed for cognitively impaired patients with depressive symptoms. SSRIs tend to be well tolerated, but close monitoring of efficacy vs. side effect burden is important.

c) Anxiety

Estimates of prevalence of anxiety in dementia vary from 2 % for panic disorder, 5 % for generalized anxiety disorder, and 70 % for nonspecific anxiety symptoms [67, 68]. Anxiety in dementia is associated with depression [69, 70], behavioral disturbances [68, 71], functional impairment [68], caregiver distress [72], and nursing home placement [73].

Nonpharmacologic interventions for treatment of anxiety include cognitive behavioral therapy [74], music therapy, increased socialization (e.g., attendance of day centers and day hospitals), person-centered care, memory aids such as keeping a diary, medication boxes to help take medications correctly, engaging in meaningful enjoyable activities, and managing physical and environmental problems [75].

There are very few systematic studies of medications for the treatment of anxiety in dementia. SSRIs continue to be considered the first choice, followed by mirtazapine [76], quetiapine [77], and buspirone [78]. Benzodiazepines should be avoided because of the potential to cause delirium and increase the risk of falls as well as issues related to tolerance and dependence.

Treating the Caregiver: An Opportunity Not to be Missed

When seeing a patient with AD, it is paramount to address the needs of his or her caregiver. Caregivers often feel the brunt of the dementia most acutely, seeing the person they care for gradually deteriorate while being called upon to take on increasingly complex roles, starting with supporting higher order IADLs in the earlier stages of the disease and basic physical care in the later stages. Despite experiencing some positive

consequences of caregiving such as companionship, enjoyment, and a sense of purpose [79], caregivers are prone to experiencing depression, anxiety, and emergence of medical problems related to increased stress levels. It is not surprising that many caregivers feel unprepared for the challenges they encounter; they are in great need of psychoeducation, support, and in many cases practical assistance. The National Plan to Address Alzheimer's Disease, updated in 2014, recognized the need to care for the dyad of the AD patient and his/her caregiver and called for improvement of access to services, dissemination of educational materials, and preparation of caregivers to provide the best care for their charges [80].

As yet, there is no clear evidence that pharmacological treatment of neuropsychiatric symptoms of AD reduces the burden of caregivers [81]. But, in a poignant wish list for a National Alzheimer's Agenda, a caregiver asked doctors to pay more attention to the words of caregivers during office visits, to provide them with more information about available supports, and to educate them about the progression of AD [82•]. Indeed, evidence is accumulating that psychoeducation, support, and tailored multimodal interventions targeting caregivers can be effective. So is the case management strategy, meant to provide individualized care for AD patients and their caregivers as well as improve the communication between the healthcare professionals and the caregivers [83]. One example of such a program is Partners in Dementia Care, which sought to enhance care coordination for veterans with dementia and their caregivers. Improvements in caregiver outcomes were seen after 6 months of intervention, with lesser levels of caregiver strain and depression, and fewer unmet needs [84•]. Randomized trials support the efficacy of care management in non-VA settings [85, 86].

The support for caregivers can come either directly from healthcare professionals and case managers, or from group meetings. In a study comparing cognitive behavioral group intervention with self-help manual and control, the group intervention was more effective at reducing caregivers' anxiety [87]. Some promise is also offered by technology-driven interventions for caregivers, though further evidence is needed before recommending them in clinical practice [88].

As regards the psychoeducational component, besides providing patients and their caregivers with information about AD and its progression, advice about care planning, advance directives, self-care for caregivers, patient management, problem-solving, and stress management training was found successful [79].

Overcoming Barriers to Delivering High-Quality Care for People With Dementia

A systematic review of coordinated care programs for AD patients and their caregivers shows that the results are still equivocal [89], and new models continue to appear. One innovative approach uses group visits for patients and caregivers together as a way to increase clinical capacity to deliver comprehensive care, targeting monitoring and treatment of cognitive and neuropsychiatric symptoms, management of medical comorbidities, and solutions for caregiver issues in conjunction with psychoeducation and group process. Such a clinic setting was shown to increase patient and caregiver satisfaction, and to be a positive experience for clinicians working in this model of care [90].

To help identify patient-caregiver dyads in need of such enhanced care, a simple tool such as the Dementia Services Mini-Screen can be utilized. Completed in 2 min or less, it identifies dyads experiencing high caregiver stress and high patient behavior problems who have correspondingly high levels of unmet medical and psychosocial care needs. These dyads are ideal candidates for multimodal, coordinated approaches to care [91•].

Major barriers to delivering best practices in dementia care are present in most contemporary health care environments, yet the components of high-quality dementia care are known and can be delivered using a variety of structured and coordinated approaches. Current efforts seek to create a consensus strong enough to motivate providers and healthcare systems to take the steps necessary to achieve this pressing goal [92].

Conclusions

AD is a progressive neurodegenerative disease that cannot be reversed and that inexorably leads to disability, loss of intellectual capacity, behavioral changes, decline in overall health, and death. None of the treatments available today can alter this prognosis. And yet, along the way, many interventions offer hope for temporary improvements in functioning, reduction in neuropsychiatric symptoms, sharper attention and memory, and correspondingly reduced distress for both patients with AD and their family caregivers. These interventions may offer patients more time spent positively engaged with family, friends, and enjoyable activities that sustain meaning and purpose. While the cognitive enhancing medications offer some promise, a great deal of interest in the last few years has been afforded to interventions such as changes in diet, physical activity, cognitive rehabilitation, and caregiver assistance, with successes in each of these categories of intervention. Also, despite high interest in identifying effective medications for treatment of neuropsychiatric symptoms, the key to successful treatment remains in thoughtful evaluation and individualized behavioral and nonpharmacologic strategies, including support of the caregiver. See Box 1 for a summary of recommendations for management of AD and related dementias.

Box 1. Recommendations for the management of AD

- Start treatment with AChEI as early as possible when AD is diagnosed
- Consider combination with memantine in moderate to severe stages of the disease
- Recommend and monitor balanced nutrition such as that based on the Mediterranean diet
- Recommend and monitor an exercise program of moderate intensity
- Recommend a cognitive intervention program, keeping in mind that as the dementia progresses, goals will change and must be adapted to each patient's individual needs
- Address neuropsychiatric symptoms emerging in the course of AD, using nonpharmacologic interventions first and, if these are insufficient, using medications selectively and sparingly
- Involve caregivers in management at each stage of the disease and identify and address their needs
- Identify caregiver-AD patient dyads with high unmet needs and prioritize their care
- For high-need/high-stress dyads, organize coordinated care management

Compliance with Ethics Guidelines

Conflict of Interest Anna Borisovskaya, Marcella Pascualy, and Soo Borson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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