SPECIAL ARTICLE

State of the Science: Apathy As a Model for Investigating Behavioral and Psychological Symptoms in Dementia

Lauren Massimo, PhD, CRNP,† Helen C. Kales, MD,‡ and Ann Kolanowski, PhD, RN**

Apathy is one of the most common and pervasive of the behavioral and psychological symptoms of dementia (BPSDs). Apathy has profound consequences for morbidity, mortality, and caregiver burden. Treatment of apathy has been hindered because of poor understanding of the mechanisms underlying this heterogeneous syndrome. Research has demonstrated that apathy is associated with disruption of the frontal-striatal system in individuals with neurodegenerative disease. As with other BPSDs, these neural mechanisms alone do not completely account for the syndrome; individual, caregiver, and environmental factors also contribute to apathy. In this article, we modify a current conceptual model of the factors contributing to BPSDs to examine determinants of apathy. This integrative model provides a more complete and theoretically informed understanding of apathy, allowing for greater insight into potential targets for research, intervention, and care. We end by proposing an agenda for moving the science of BPSDs in general, and apathy in particular, forward. **J Am Geriatr Soc 66:S4–S12, 2018.**

Key words: apathy; goal-directed behavior; behavioral and psychological symptoms of dementia

Behavioral and psychological symptoms of dementia (BPSDs) include changes in behavior, perceptions, thought content, and mood disturbances such as apathy and agitation.[1] They are among the most troubling symptoms accompanying neurodegenerative disease and contribute to many negative outcomes.[2,3] Significant challenges in the management of BPSDs include heterogeneity of presentation; complexity of underlying neurocognitive dysfunction; and variety of precipitating individual, caregiver, and environmental determinants.

We discuss apathy as a prototype BPSD. We chose this focus for several reasons. First, apathy is one of the most prevalent and persistent BPSDs across all neurodegenerative diseases.[4–6] Second, as with many BPSDs, apathy is a conceptually heterogenous syndrome with varied presentations, leading to the need to avoid "one size fits all" approaches to management. Third, there is a larger body of literature on potential causative mechanisms than for other BPSDs, indicating that neuroanatomical dysfunction in part explains the syndrome,[7,8] although as with other BPSDs, neural mechanisms alone do not account for the syndrome; determinants of apathy may also include individual, caregiver, and environmental factors.[1,9] We modify a current conceptual model[1] of the factors precipitating BPSDs to examine mechanisms associated with apathy. Using the latest findings related to the neurocognitive dysfunction underlying apathy, we extend the model specifically for this particular syndrome. This integrative model provides a more complete and theoretically informed understanding of apathy, allowing for greater insight into potential targets for research, intervention, and improvement in care. Development and testing of similar models for other BPSDs is recommended. We end by proposing an agenda for moving the science of BPSDs in general, and apathy in particular, forward.

DEFINITION OF APATHY

The word apathy derives from the Greek word pathos or passion. While describing a state of indifference or inertia,[10] over time, the concept of apathy has undergone changes in meaning but remains vaguely defined and broadly applied.[11] In 1990, Marin defined apathy as a state of motivational impairment,[12] suggesting that apathy is a syndrome resulting from psychiatric, neurological, or medical disorders. Although this definition represented an advance, lack of motivation is difficult to quantify, and it is not the only cause of apathetic behavior.

From the *College of Nursing, Pennsylvania State University, University Park; †Frontotemporal Degeneration Center, Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and the ‡Program for Positive Aging, Department of Psychiatry, University of Michigan, Ann Arbor, Michigan.

Address correspondence to Lauren Massimo, PhD, University of Pennsylvania 3400 Spruce Street, 3 West Gates, Philadelphia, PA 19104. E-mail: lmassimo@upenn.edu

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Table 1. Recommendations for Future Research to Advance Knowledge About Apathy

General Recommendation	Evidence of or Rationale for Recommendation
Prospective clinical trials are needed with apathy as a primary outcome together with important secondary outcomes, such as function.	With few exceptions, apathy has been investigated as a secondary outcome in retrospective studies
Novel technology approaches including activity-monitoring devices and eye trackers are necessary for more objective measurement of apathy.	The individual, caregiver or provider often measures apathy subjectively.
Use of a uniform operational definition of apathy[10] and a standard measure specific to the definition would enhance precision and facilitate comparison across studies.	Apathy has been described and measured inconsistently in the literature.
Recruitment of well-characterized samples that meet criteria for specific types of neurodegenerative disease.	The pathophysiology of apathy may not be the same across the neurodegenerative disease spectrum.
Continued study of the neurobiological basis of different apathy components using neuroimaging techniques.	Without greater neurobiological specificity, it will be difficult to understand the neuroanatomical associations with specific apathy symptoms. Greater specificity of apathy subtypes will also help investigators to more precisely identify treatment targets and to determine who is likely to respond to specific treatments.
Longitudinal studies of apathy are needed to allow for sufficient time to observe potential treatment effects.	Intervention trials need to be long enough to detect clinically relevant effects in the treatment arm and to observe the likelihood of worsening apathy in the control arm. In addition, given apathy's association with conversion to mild cognitive impairment and Alzheimer's disease, intervention studies should examine whether efficacious treatments delay this conversion.
Investigators should consider stabilization of apathy severity to be an important outcome of intervention, in addition to delay in emergence or reduction of apathy.	Apathy worsens as dementia progresses, and it is likely that the type and severity of dementia influences response to pharmacotherapy.
Studies that combine biological and psychosocial approaches are needed to treat apathy more successfully.	There is a general lack of high-quality research to support the use of nonpharmacological approaches.
Strong conceptual frameworks that go beyond condition-specific indicators of treatment success and include person-centered goals are needed to guide future studies of apathy.	Few, if any, intervention studies include outcomes that reflect goals and preferences meaningful to people with apathy or their caregivers. The lived experience of neurodegenerative disease can provide important ecological insight into meaningful and achievable outcomes, such as ability to maintain social and physical activity.

In 2006, Levy and DuBois proposed defining apathy as "the quantitative reduction of self-generated voluntary and purposeful behaviors."[13] Consistent with a model of apathy associated with a deficit in 1 of the 3 determinants of goal-directed behavior, Levy and DuBois proposed 3 underlying mechanisms responsible for apathy: diminished emotional-affective processing (motivation), impaired cognitive processing of plans of action (planning), and difficulty in initiating behavior (initiation). In this definition, apathy can occur when any one of these processes is disrupted. From this perspective, it is possible to observe and measure the various forms of apathy.[7]

An international task force published a consensus on the diagnostic criteria for apathy in neurodegenerative conditions[10] that may resolve some of the discrepancies in identifying apathy. In these criteria, apathy is described as a syndrome with cognitive, affective, and behavioral dimensions. To meet criteria for apathy, the individual must display the core feature of diminished motivation and have a reduction in 2 of the 3 following domains: goal-directed self-initiated or environment-stimulated behavior, goal-directed cognitive behavior, and emotional response. Clinical evaluations of individuals with apathy are challenging because of the variability in each individual's goals, interests, and emotional displays. Diagnostic criteria such as those that the international task force[10] proposed are necessary to operationalize this heterogeneous syndrome for reliable diagnosis and for distinguishing from other syndromes such as depression, and there is a need for the classification of apathy based on the underlying neural mechanisms that are foundational to the development and testing of more precise targeted treatments for apathy (Table 1).

PREVALENCE

Apathy is a common behavior in neurodegenerative disorders such as Alzheimer's disease (AD), frontotemporal degeneration (FTD), Lewy body disease (LBD), and Parkinson's disease (PD). In AD, the prevalence rate of apathy has been estimated to be between 51% and 80%.[14–16] Abnormal social behavior is a hallmark symptom of FTD, and apathy is the most prevalent behavioral disorder, occurring in 90.5% of individuals with mild FTD and 100% of those with moderate and severe disease.[17] The frequency of apathy in PD and PD-spectrum disorders such as LBD may also be substantial, although estimates of prevalence vary more widely than in AD—from 12% to 70%.[18–21]

Apathy is also one of the most persistent BPSDs. Data from a population-based longitudinal study found that apathy was among the most stable of symptoms, having a 62% probability of continuing to be exhibited after 1 year.[4] In this study, apathy also had a strong association with disability, poor health, and mortality.

OUTCOMES

Apathy has profound consequences. Accumulating evidence suggests that it is associated with a variety of undesirable outcomes, such as poor insight, poor cognitive performance, lower functional autonomy, and even greater mortality.[22–25] Apathy has also been identified as an independent risk factor for the development of cognitive impairment in older adults with normal cognition[26,27] and for conversion to dementia in individuals with mild cognitive impairment (MCI).[28,29] These findings suggest that apathy contributes to global decline in cognition and everyday function and thus support the need to identify individuals who are at risk of developing it.

PERSPECTIVES OF FAMILY AND PROFESSIONAL CAREGIVERS

People with neurodegenerative disease tend to be unconcerned about their apathetic behavior, but it is distressing for their family caregivers.[30] Emotional blunting and lack of response associated with apathy reduce the relational exchange between the caregiver and care recipient. Caregivers often misinterpret apathy as oppositional or volitional behavior.[31] Spousal caregivers report a loss of connection to their spouse with apathy that may be related to impaired emotional responsiveness seen in the syndrome.[32] In a study of family caregivers, spousal apathy had the greatest effect on deterioration of the marital relationship.[33]

In contrast, formal caregivers may not see apathy as a significant problem. A recent study of nursing staff in general hospitals reported a high frequency of BPSDs in individuals with dementia, but they did not endorse apathy or indifference as a distressing symptom.[34] Similar findings have been reported in long-term care settings.[35] Nursing home staff view withdrawal as common in residents, but rarely is it deemed distressing to staff. Staff distress was also not associated with dependency in activities of daily living, a core feature of apathy. Perhaps in the resource-stressed nursing home environment, "doing for" a resident is perceived as more expedient than encouraging self-care. Staff in Australian nursing homes did not endorse lack of motivation as a challenging behavior,[36] a finding similar to that reported previously.[37] In the latter study, many staff, like family caregivers, viewed symptoms as deliberate, but unlike family caregivers, formal caregivers did not report high levels of associated distress.

OVERLAP WITH DEPRESSION

Depression and apathy are distinct syndromes that are often confused. Symptoms common to apathy and depression include anhedonia, hypersomnia, and fatigue.[31,38] A study that attempted to differentiate apathy from depression in individuals with AD using factor analysis of the Hamilton Depression Scale found that psychomotor retardation, agitation, and poor appetite were construed as apathy factors. Symptoms such as sad mood, guilt, suicidal ideation, anxiety, and insomnia loaded as a sadness factor, suggesting that they were more commonly found in people with depression.[39] Other symptoms such as self-criticism and negative thoughts about the future are common in people with depression, but absent in individuals with apathy, who tend to show a lack of concern.[40] This is consistent with similar findings that suggest that apathy is a discrete syndrome separate from depression.[31] Because apathy is so common in dementia, efforts to distinguish it from depression are imperative for guiding treatment decisions.

MEASUREMENTS

There are several apathy assessment tools for use in cognitively impaired individuals. Traditional instruments to assess for apathy in neurodegenerative disease include rating scales that commonly rely on proxy report (for review, see[41]). Thus, apathy is most often assessed in the context of the caregivers' perspective and may therefore be subject to caregiver confounds such as burden and strain that may affect the evaluation.[42,43]

Because apathy is associated with a reduction in motor behavior, others have proposed the use of objective measurements such as ambulatory actigraphy and computer-based measurements of apathy.[7,43–45] Continued work in this area is important for the development of an empirically based, objective approach that elucidates mechanisms contributing to apathy (Table 1). Lastly, use of instruments that include subscales to measure domains of apathy would increase the targeted treatment of apathy.[41,46]

CONCEPTUAL FRAMEWORK FOR EXAMINING APATHY

We propose an adaptation of Kales and colleagues' BPSD conceptual model[1] to better understand apathy (Figure 1). Factors identified in the original conceptual model are those that may directly cause (neurodegeneration) or indirectly trigger BPSD. The original conceptual model describes how interactions between the person with dementia, caregiver, and environment can trigger BPSD in the context of underlying neurodegeneration.[9,47,48] Because this is a conceptual model, the factors listed include those with a significant evidence base as well as those that are hypothesized to be important from practice-based experience. The model is highly useful because it details the etiological complexity of BPSDs needed for a thorough clinical assessment and why it is likely that no single pharmacological or nonpharmacological approach can be used as a "magic bullet" for treatment. The model also serves as a basis for researchers to consider in studying the effect of potential etiological causes and triggers of BPSDs; these studies can lead to better, more customized interventions than those that we have currently. Because BPSDs are heterogeneous in their phenotypes (e.g., depression, psychosis, agitation), have different evidence bases, and may have different underlying etiologies (e.g., different brain regions involved), we believe that there is further utility to adapting the model for specific BPSDs such as apathy.

In the specific case of apathy, integrating advances made in understanding impairments in goal-directed behavior and their related neural mechanisms presents an

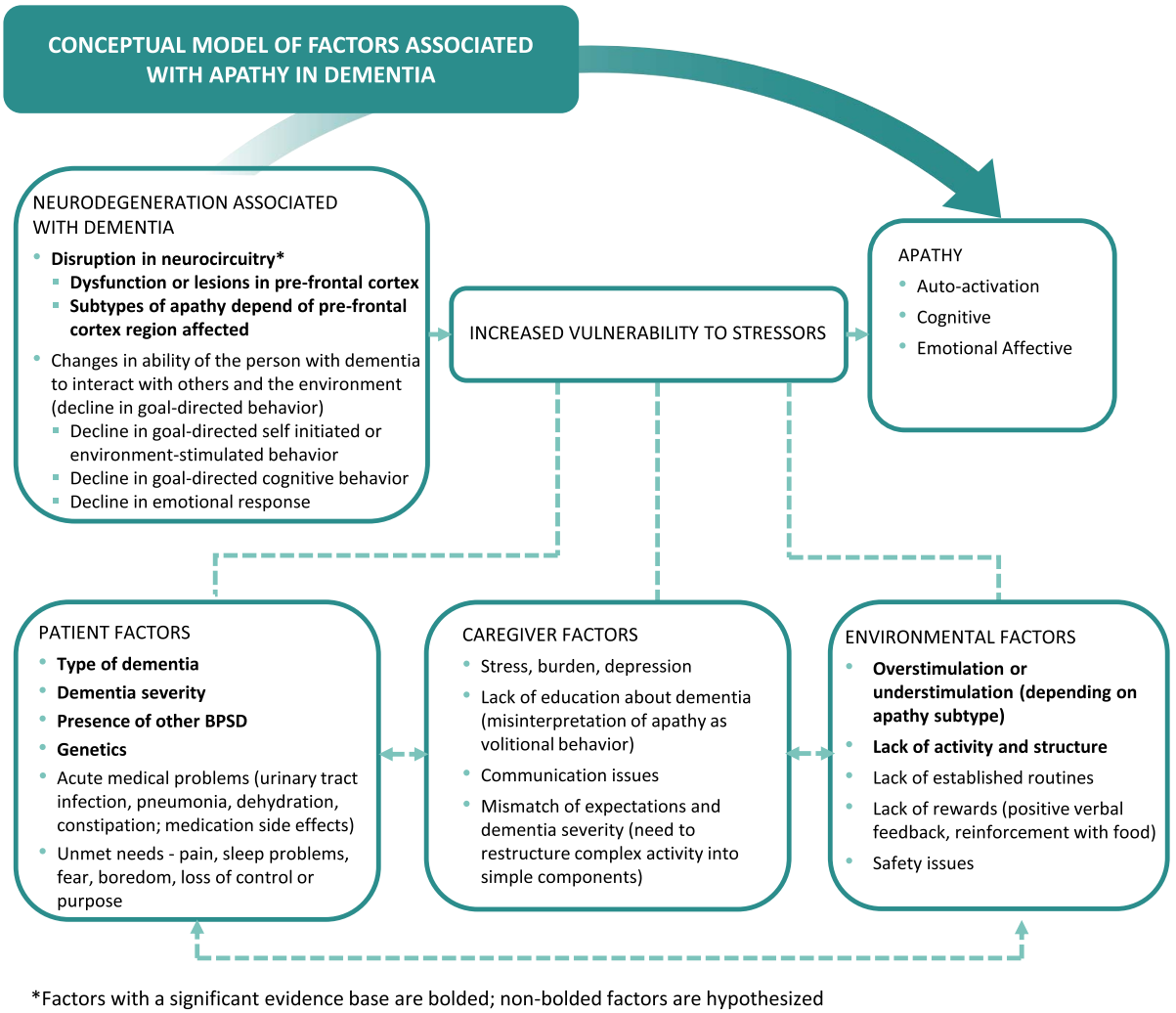

Figure 1. Conceptual framework for examining apathy.

opportunity to further improve the utility of the model for research. Thus, we have elaborated on the model to include underlying neurocognitive dysfunction thought to contribute to apathy, as well as how apathy subtypes may contribute to symptom heterogeneity (Figure 1). Ideally, this can advance the field in three ways. First, it provides researchers and clinicians with an opportunity to consider apathy as arising directly from disruptions in neurocircuitry or indirectly when such disruptions in neurocircuitry lower the threshold for (increase vulnerability to) specific personal, caregiver, and environmental stressors. Second, it suggests distinct pathways for intervention. Third, it can point the way toward additional iterations of the model for other BPSDs such as depression or psychosis, with specific attention to the neural and nonneural mechanisms pertinent to those syndromes.

In terms of neurocircuitry disruption, according to the model that Levy and DuBmois proposed, apathy is the result of dysfunction in the frontal cortex or structures in the basal ganglia.[13] Three goal-directed behavior processes map onto 3 distinct brain regions that work together in a large-scale neural network associated with apathy. In particular, 3 functional neuroanatomical loops underlie goal-directed behavior in the frontal area (anterior cingulate circuit, dorsolateral prefrontal circuit, orbitofrontal circuit) and appear to capture information from internal and external environments needed for enacting goal-directed behavior and performing possible actions.[13] Because each circuit is functionally separate in supporting individual goal-directed behavior components, it may be possible to distinguish different apathetic profiles or subtypes based on underlying neurocognitive dysfunction.[13,49,50]

Although the underpinnings of apathy are neurobiological in nature, personal, caregiver, and environmental factors may exacerbate or trigger apathy symptoms. A granular understanding of symptom subtype and determinants are critical to the development of effective care strategies that are person and caregiver centered.[49]

A recent scoping review focusing on BPSDs followed the Kales conceptual model of BPSDs and used the categories of personal, caregiver, and environmental determinants as a guide for searching the literature for high-quality, low-bias studies addressing causes or determinants of behavioral symptoms. High quality was defined using Gough's Weight of Evidence Framework[51] and low bias

using the Cochrane Collaboration bias tool.[52] This review found 16 high-quality, low-bias studies addressing the causes or determinants of apathy.[9] The operational definition of apathy varied according to study. The most common instrument used to measure it was the apathy subscale of the Neuropsychiatric Inventory.[53] Informant report was used most often to rate apathy, which is not surprising given that reduced insight often co-occurs with apathy.[54,55]

Personal Factors

Although apathy is prevalent across dementia types, there are also some limited and inconsistent data on rates according to type. One study found that apathy is more common in behavioral variant FTD than AD. [56] Another study found that apathy is more common in early- than late-onset AD.[57] A third study of individuals with AD and vascular dementia found that apathy is more common in those with vascular dementia, but the results were not statistically significant.[58] In another study, apathy was most frequent in Dementia with Lewy Bodies (DLB), but again, the results were not statistically significant.[59]

The review found strong evidence that apathy is related to the severity of cognitive impairment in dementia. Apathy was associated with more severe cognitive impairment according to the Mini-Mental State Examination[60,61] and the Clinical Dementia Rating Scale.[62] A prior study examining specific cognitive deficits in individuals with AD found that apathy was associated with greater severity of frontal lobe–related cognitive deficits.[63]

Several other individual-level determinants have also been implicated, including the presence of other BPSDs.[61] In AD, baseline apathy and antidepressant use are also associated with increasing apathy over time.[64]

Biological factors appear to be most strongly associated with apathy. A number of studies have shown that neuroanatomical changes in grey and white matter are associated with apathy.[61,64] Apathy also appears to be associated with genetic factors, including apolipoprotein E ϵ4 in individuals with AD[57,65] and c9ORF72 in individuals with FTD.[66] Other biological factors (e.g., cerebral spinal fluid biomarkers in AD) do not appear to be associated with apathy.[64] Finally, sex does not appear to be related to apathy.[60]

Caregiver Factors

In the prior scoping review[9], no high-quality evidence of any caregiver determinant was found, although in observational studies, it has long been noted that social interaction (or lack thereof) can affect apathy. Other than during personal care, nursing home residents spend much of their time "doing nothing," and negative affect and apathy have been observed during these unoccupied times.[67–70] In addition, structured interactions that involve caregivers, such as recreational activities (see discussion on environmental determinants), can reduce apathy and improve affect.[71]

More high-quality research is needed on the effect of caregiver factors, such as communication patterns, on apathy. For example, caregivers may misinterpret apathy as oppositional or volitional behavior,[32] which may lead to negative interactions. In long-term care settings,[34,35] staff may not intervene because they do not see apathetic behavior as problematic, leading to exacerbation of apathy.

Environmental Factors

The prior scoping review found 3 high-quality studies that evaluated environmental factors. In the first, individuals with AD participating in activities individualized to personality and physical ability[72] showed less apathy. Another study of individuals with AD participating in cognitive stimulation also showed positive effects on apathy.[73] A third study examining therapeutic conversation, also demonstrated decreases in apathy in individuals with AD.[74] Prior work in BPSDs suggests that individualized activities are better than one-size-fits-all interventions for engaging nursing home residents with dementia. For people with apathy, activities that individuals find personally interesting supply additional intrinsic motivation.[75] Because the environment is more modifiable than neurobiological deficits, such studies are extremely important.

To summarize, a recent rigorously conducted scoping review found that most prior studies of determinants have focused on person-related causes of apathy, particularly biological factors. The review found strong evidence of an association between apathy and neurodegeneration, although most studies previously conducted and considered for the review were in the area of person-related factors, with no high-quality caregiver studies found and only 3 high-quality environmental studies found. Additional work is needed to explore the caregiver and environmental factors that our adapted conceptual model suggested (Figure 1), particularly given their greater modifiability than most person-level factors, such as neurodegeneration.

INTERVENTIONS FOR APATHY

Pharmacotherapy, neuromodulation, and nonpharmacological approaches are among the interventions currently used for treating apathy. The evidence to support these interventions is modest, and there have been no widely accepted guidelines developed for the management of apathy. Treatment trial failures may relate to the commonly used simplified definition of apathy used in many trials (e.g., a lack of motivation); given that neuroanatomical evidence supports a multicomponent approach to apathy and that mechanisms underlying apathy are qualitatively different, different subtypes may require different interventions.[49] Again, this is where our adapted model will be useful for future trials.

Pharmacotherapy

Apathy is associated with neuropathological and neurochemical alterations to frontosubcortical circuits.[76] There are a number of neurotransmitters, receptors, and second messengers involved in the disruption of these circuits that form the basis for pharmacotherapy. The evidence for use of

pharmacological interventions in apathy has been systematically reviewed[46,76–78] and indicates modest efficacy. Few studies have been conducted, most are retrospective, and many do not have apathy as a primary outcome. Overall, cholinesterase inhibitors have the best evidence for symptomatic improvement, and there is some evidence for use of memantine. One clinical trial found no evidence for modafinil in reducing apathy or improving caregiver burden.[79] Although the evidence for most stimulants is limited, studies of the safety and efficacy of methylphenidate are more encouraging and support findings that apathy may represent dopaminergic dysfunction. For example, in a recent study of community-dwelling male veterans with mild AD, those receiving methylphenidate showed improvement in apathy scores over a 12-week period.[80] To clarify the clinical efficacy of methylphenidate, additional longitudinal studies such as the Apathy in Dementia Methylphenidate Trial 2[81] are underway to assess change in apathy and cognition in individuals with dementia. Finally, there is evidence that antidepressants and antiepileptics do not improve apathy and may actually be harmful.

Placebo-controlled trials with apathy as the primary target that will provide much needed additional data are underway. Because apathy has different components (behavioral, cognitive, affective), each with different underlying mechanisms, future investigations should examine separately the pharmacological effects on these aspects (Table 1).

Neuromodulation

Neuromodulation approaches to the treatment of apathy include repetitive transcranial stimulation and transcranial direct current stimulation. Both approaches are noninvasive and deliver magnetic fields through the skull, resulting in activation or inhibition of the underlying neuronal circuits involved with the generation of voluntary actions. Repetitive transcranial stimulation has been efficacious in the treatment of depression in cognitively intact individuals, but there is no strong evidence to support its efficacy for apathy or depression in people with dementia[59] In a recent randomized clinical trial, transcranial direct current stimulation had no effect on apathy in people with moderate AD.[82]

Nonpharmacological Approaches

Several systematic reviews provide evidence of the efficacy of customized activities (based on the individual's past history, preferences, and retained functional abilities).[78,83,84] These methodologically heterogeneous interventions include music therapy, customized activities, cognitive stimulation, multisensory behavioral therapy, art therapy, and therapeutic conversation. Theoretically, customized activities supply intrinsic motivation, a central feature of apathy, by capturing interest and providing reward. A challenge to the use of these interventions is that they can be complex and time consuming, making them difficult to reproduce and sustain.

There are limited data on the sustained effects of nonpharmacological interventions for apathy. Kolanowski and colleagues[85] found positive effects of individualized activities that extended 1 week after the intervention. Another trial of an individualized functional training program significantly reduced apathy 1 month after then intervention, but at 4 months, apathy levels had increased.[86] Given that apathy often worsens with dementia progression, it is likely that nonpharmacological treatment of apathy will require re-assessment and continuous programing.

Staff education (a month-long educational program using nonpharmacological approaches) was investigated in one study. Although nursing home residents' emotional blunting decreased, their level of interest did not increase.[87] The investigators noted that lack of staff access to information regarding resident preferences was a major barrier to implementing nonpharmacological interventions for apathy. Poor communication about resident preferences has been identified as a barrier to person-centered care.[88,89]

Similar to pharmacological studies, more research is needed that rigorously uses apathy diagnostic criteria and considers apathy subtypes to improve precision and effect sizes (Table 1). Again, our adapted model is well suited for this. For example, multisensory stimulation may be helpful in individuals with initiation difficulty, but worsen apathy in those with planning difficulties (by increasing distractibility). Studies are needed that determine optimal dosage and duration of interventions and test strategies to improve implementation and dissemination of evidence-based approaches. Finally, because nonpharmacological interventions have long been recommended as the first line of treatment for apathy, an updated review of guidelines[90] is needed given our current understanding of the determinants.

CONCLUSION

We suggest that apathy is a multicomponent phenomenon, emerging when there is dysfunction in any component of goal-directed behavior. This adds to a conceptual model of BPSD by Kales and colleagues that describes how interactions between a person with dementia, caregivers, and the environment may trigger BPSDs in the context of underlying neurodegeneration. Thus, it is likely that the pathophysiology of apathy is not a single mechanism but is instead multifaceted. It may be possible to identify selective impairments in goal-directed behavior that contribute to different clinical phenotypes or subtypes of apathy.[49] Understanding mechanisms underlying apathy such as neural mechanisms of goal-directed behavior in addition to factors such as those that Kales and colleagues proposed provide a necessary step forward in proactive, targeted treatment of apathy.

IMPLICATIONS FOR OTHER BPSDS

The focus here is on apathy in neurodegenerative disease, but the recommendations for advancing knowledge of this behavior has implications for other BPSDs. BPSD is an umbrella term for a variety and range of specific symptoms such as aggression, wandering, and depression. Primary measurement of BPSDs in the aggregate, that is, the number of symptoms displayed, has diluted the ability to detect important associations with other variables and the

effect of interventions on specific symptoms. There is a need for theoretically informed measures that provide greater precision in defining and measuring individual symptoms and syndromes.

Individual symptoms vary over time and according to type of dementia. Future studies including well-characterized samples that meet criteria for specific types of neurodegeneration and incorporation of advanced neuroimaging techniques and other biomarkers of neurodegenerative disease will help elucidate brain mechanisms that underlie specific symptoms.[91]

There are many factors in addition to neurodegenerative disease that precipitate BPSDs, including environmental context and the dyadic relationship with the caregiver. Strong conceptual frameworks that include these factors are needed to guide future research studies. Additional iteration of our apathy model for depressive or psychotic symptoms, with specific attention paid to the neural and nonneural mechanisms pertinent to those symptoms, would be most helpful.

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