Published in final edited form as:

J Am Geriatr Soc. 2018 April ; 66(Suppl 1): S13–S16. doi:10.1111/jgs.15325.

Commentary on Apathy as a Model for Investigating Behavioral and Psychological Symptoms in Dementia

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Keywords

Dementia; Apathy; Behavioral and psychological symptoms of dementia

Behavioral and psychological symptoms in dementia (BPSD) are a core, prevalent and persistent feature of Alzheimer's disease and related dementias.¹ Widely considered one of the most difficult aspects of clinical management of dementia, these symptoms are associated with significant caregiver strain^{2–4} and place patients at increased risk for institutionalization.^{5–7} In this *JAGS Supplement*, Massimo, Kales and Kolanowski present a comprehensive summary of the state of the science on apathy—a common, persistent and impactful BPSD exhibited in dementia and other neurodegenerative diseases.⁸ Although evidence suggests that apathy is both the most common and persistent BPSD, it is often underrecognized and undertreated.^{2,9} Even when apathy is recognized, clinicians and families face the additional challenge of identifying adequate treatments. Both pharmacologic and non-pharmacologic interventions currently lack the precision needed to target specific apathy subtypes and their underlying mechanisms; neither do they take into account common comorbidities, such as depression, that frequently complicate the management of BPSD.^{8,10–13}

Although the void in readily accessible, tailored treatments for apathy remains, it is not because of lack of progress. On the contrary, apathy is perhaps the best-characterized of BPSDs. This largely reflects increased attention toward apathy as a risk factor for poor cognitive performance, hastened cognitive decline and transitions from mild cognitive impairment (MCI) to dementia.^{14,15} The extent and consistency of poor cognitive outcomes associated with apathy has sparked interest in apathy as a potential target for disease-modifying therapies for Alzheimer's disease—a global public health priority.^{16,17} Consequentially, substantial advancements in apathy research have been made in the past decade including refined definitions, diagnostic criteria and the identification of well-defined

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Conflicts of Interest: The author has no conflicts of interest related to this manuscript.

Author Contributions: The author is solely responsible for this work.

neurobiological correlates.¹⁸ Findings from a range of neuroimaging and neuroanatomical studies offer support for the involvement of the anterior cingulate circuit in the development of apathy.¹⁹ Genetic studies involving patients with Alzheimer's disease have found that presence of the apolipoprotein epsilon 4 allele (APOE ε4) is associated with an increased risk for apathy as well as progression from MCI to dementia.^{20–22} These represent critically important advances and prompt us to reconsider and reevaluate how we address management of a complex BPSD like apathy in a way that is responsive both to the heterogeneity of neurodegenerative disease presentation and apathy's multifactorial determinants.

Toward this end, Massimo and colleagues have described a conceptual framework to guide thinking and research on apathy. This framework builds logically upon an existing model and has clear potential to serve as a much-needed exemplar for advancing a more integrated biopsychosocial research agenda in response to the biopsychosocial etiology of apathy and possibly, other BPSDs. Provided available evidence on underlying neuropathological features of apathy, effectiveness of existing pharmacologic/non-pharmacologic treatments and ongoing neuromodulation interventional studies, the field is well positioned to move toward the development of multimodal interventions and therapies. This commentary aims to build upon the recommendations outlined by Massimo and colleagues based on this adapted conceptual framework by presenting further considerations for intervention research. Secondly, this commentary aims to identify supportive preconditions to advancing this research, and important steps on the path toward a research agenda that is both responsive to real-world challenges and meaningful to individual patients and families.

Further Considerations for Intervention Research

Despite the expanse of existing research on apathy, significant knowledge gaps remain. These gaps will best be addressed with the development and use of more consistent, objective measures of apathy in future research, greater attention to comorbidities, consideration of the heterogeneity across different neurocognitive disorders and apathy subtypes, and the development of multimodal intervention trials of sufficient duration that employ sensitive outcome measures that are responsive to the heterogeneity and anticipated course of apathy. With respect to the latter, and referring to the proposed model, we can hypothesize that such interventions will more likely be successful if they enhance the precision and targeting of individualized treatments. Specifically, emerging interventions should: (1) capitalize on existing knowledge about neurobiological correlates of dementia (thus, targeting a previously untapped underlying mechanism of apathy presentation), (2) build in structures to facilitate individualization based on personal abilities, interests, and apathy subtype, (3) aim to target underlying mechanisms of distinct symptom clusters and patterns (thus, avoiding the “one size fits all” pitfall), and (4) integrate multiple modalities. While some interventions have tested multiple components, these are largely unimodality approaches, which integrate only non-pharmacologic or only pharmacologic approaches. Integration of multiple components in these interventions can potentially target distinct mechanisms of apathy, albeit not necessarily intentionally or in a systematic manner. Successfully implementing trials with this degree of complexity while maintaining flexibility for individual tailoring will require expanded adoption of complex trial designs and novel analytic approaches.

Amid burgeoning methodological guidance for the design, implementation and evaluation of complex interventions, there is ample opportunity to apply these approaches in intervention trials for apathy. Many of these evolving designs aim to circumvent the long timelines, excessive costs and delayed translation of findings from clinical trials. They do this by enabling interventions to be more responsive to individual needs and contexts while maintaining design controls. Given the need for accessible, individualized interventions in the here and now, pragmatic and adaptive trial designs are particularly promising approaches for more efficient and translatable discoveries. Pragmatic trials are tested in real world contexts and frequently have less stringent eligibility criteria and group randomization models.^{23,24} Pragmatic trials are recognized by the National Institutes on Aging (NIA) as a helpful approach to bolstering inclusion of older adults in research. The NIA recently opened new funding mechanisms for pragmatic trial designs. Adaptive clinical trials extend this flexibility by adapting intervention dose, eligibility criteria, and protocols—and in some cases—outcome measures in accordance with an a-priori trial protocol.²⁵ For example, an adaptive trial design might apply a protocol wherein the type or dose of a specific non-pharmacologic therapy provided to participants is adjusted based upon their specific apathy subtype profile or responsiveness to therapies throughout the intervention. A key benefit of adaptive trials is the potential to reduce exposure to interventions, sample requirements and trial duration as compared to fixed sample trial designs.²⁵

There is a clear need for intervention research that better addresses apathy in the heterogeneous contexts in which families and clinicians encounter it. In addition to the development of new objective measures of apathy, standardized measures that characterize other diagnostic challenges with apathy would support a more comprehensive classification from which to inform practice. Incorporation of measures of apathy that more closely reflect clinical presentation in trials will also help in addressing the need for more sensitive outcome measures. A particular challenge is the co-occurrence of depression, which is also prevalent across many neurodegenerative diseases. Differential diagnosis can be challenging for clinicians given that key features of apathy, including hypersomnia, diminished insight and psychomotor retardation, are also common in depression.²⁹ Furthermore, apathy subtypes vary within and across different neurodegenerative diseases,¹³ providing an important opportunity to tailor treatments toward specific neurocognitive deficits. Absent standardized classification of these subtypes, however, clinicians will still ultimately lack necessary guidance from intervention trials.

Suggested Supportive Preconditions for Intervention Research

It should be self-evident that, to address all of these factors, certain preconditions in the form of new systems, contexts and supports for advancing multimodal interventions will need to be put into place. The infrastructure should be equipped to address environmental, caregiving and personal determinants of apathy. To support the development of impactful multimodal interventions for apathy, two specific preconditions requiring consideration include (1) strengthened collaborations to facilitate construction of larger, well-characterized samples that integrate relevant variables across determinant categories including neuroimaging data, and (2) integration of apathy into longitudinal preclinical trials.

Assembling sufficiently characterized samples for well-powered trials will almost certainly require that investigative teams expand collaborative efforts. Provided the high costs of neuroimaging and requisite expertise for addressing biological, psychological and social determinants of apathy, it is reasonable to consider opportunities to align, rather than recreate already sparse resources. Specific steps for strengthening collaborative systems and contexts for future apathy research include: increasing and expanding shared data-use agreements and integration of new measurements of apathy into existing prospective cohorts, particularly among pre-clinical trials. Additionally, expanded engagement with existing clinical trial registries and creation of multi-site studies with a greater emphasis on non-cognitive symptoms would support proposed priorities for intervention research on apathy. These efforts would be ideally orchestrated by federal funding initiatives to support pooled data from clinical trials examining BPSDs, and apathy in particular, as a potentially modifiable risk factor. Agreements to incorporate variables relevant to personal, caregiving and environmental determinants specific to apathy in cohort studies would also help in informing future targets for intervention. Another notable benefit of pooling data is the opportunity to increase sample sizes across similar research cohorts, thus maximizing opportunities for empirical testing of individualized approaches. Institutionally supported partnerships may also effectively facilitate similar data-sharing agreements. While pooled resources and data sharing are likely critical to assembling sufficiently diverse, well-characterized cohorts with neuroimaging data, reaching this goal is not without other logistical challenges, principally navigating ethical approvals and data storage infrastructures.

In light of the overwhelming evidence that Alzheimer's disease, in particular, begins decades prior to clinical symptoms, it behooves us to seek opportunities to study apathy in the pre-clinical disease context. To date, the majority of these trials have focused predominantly on cognitive symptoms. Longitudinal pre-clinical trials are also likely to already have robustly characterized samples with detailed medical, cognitive and neuroimaging data that can support investigators in addressing multifactorial determinants. Through greater alignment of resources, we can construct the needed systems and expertise to assemble sufficiently diverse and characterized samples needed to address the research priorities identified by Massimo and colleagues.

Important Steps in the Path Ahead

Unfortunately, individuals living with dementia and their family members cannot wait to benefit from the findings from pre-clinical trials and longitudinal research studies. As there are currently no disease modifying treatments for delaying progression of dementia, it is ethically imperative for us to also focus on the determinants that we can address in the here and now. Principal among these is the influence of caregiving factors on apathy subtypes as illustrated by the framework proposed in the Massimo and colleagues. While we know that family and informal caregivers are greatly distressed by apathy, evidence suggests that formal caregivers do not experience apathy as an important or actionable symptom.^{26,27} If we are to develop translatable interventions that caregivers will respond to, engage in and sustain, we must rectify the apparent disconnect among the perceptions of apathy held by formal caregivers, expert clinicians and researchers, and family members. Furthermore, it is

unclear what motivates informal caregivers to engage in novel apathy interventions. For example, what outcomes are they seeking and what changes in the individual with dementia are meaningful to them? If we cannot design and frame interventions that align with meaningful outcomes for patients and family members, we cannot be optimistic about their uptake and utility in practice.

Clinicians who have cared for people with dementia and other neurodegenerative diseases are likely aware of another ethical imperative that merits investigation in partnership with people living with dementia and their families. Despite the potential for apathy as a potential target for slowing or delaying disease progression, some formal and informal caregivers might describe apathy (in particular, loss of insight) among individuals in moderate to advanced disease stages as a blessing rather than a curse. This may be particularly true for families who have experienced significant difficulty managing a range of BPSDs that posed care challenges, such as care resistance or aggressive behaviors. Research clearly indicates that apathy may complicate the grieving process, in particular for spouses; however, there has been little research that has explored how someone living with dementia perceives the experience of apathy and the importance, risks and benefits of different treatment approaches.^{28–31} While these may seem like tangential diversions from the more rigorous pursuit of symptom resolution, the answers to these questions are ultimately needed to shape and refine targeting and intensity of apathy interventions. Thus far, these conversations and the development of consensus statements and research agendas have taken place without direct involvement from the people most affected by apathy and targeted to benefit from the research.

In summary, recent advances in research on apathy provide a unique opportunity to make considerable progress in symptom science and management of other BPSDs. These advances almost certainly require the creation of new collaborative efforts and systems and more diverse, well-characterized research cohorts that take into account, rather than dismiss, the heterogeneity of underlying pathology and comorbidities. Probably the most important future direction is for researchers to use strong theoretical frameworks that capture the heterogeneity we now know characterizes apathy and to avail themselves of novel trial designs when testing interventions for apathy that provide needed flexibility in real world settings. The conceptual model presented by Massimo and colleagues provides an ideal and accessible framework for informing the development of interventions that go beyond singular, one-size fits all approaches/modalities and incorporates pharmacotherapy, non-pharmacological treatments and neuromodulation. Development and testing of multimodal interventions may be aided by novel trial designs that afford the flexibility needed to accommodate responsiveness to modifiable and multifactorial determinants of apathy that vary substantially across individuals. Ultimate translation of these interventions will further require an expanded understanding of the unique needs and goals of people living with dementia and their formal and informal caregivers.

Acknowledgments

Sponsor's Role: This work was supported in part by the National Institute on Aging under award number P50AG033514. The content is solely the responsibility of the author and does not necessarily represent the official views of the NIH.

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