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The Costs of Untreated Agitation

A Literature Review

Spring 2021

Introduction

It is no longer a secret that dementia presents one of the greatest health and economic challenges of the 21st century. Collaborations among academic, scientific, and advocacy organizations have propelled dementia awareness to national governments, the G20, the World Health Organization, and even the Academy Awards.[1] Yet as our collective awareness grows, we are failing to recognize one of the disease's most consequential symptoms—agitation—and its costs.

While much remains unknown about the costs of treated and untreated agitation, we do have a blueprint and a strategy for moving forward. In 2010, Alzheimer's Disease International (ADI) issued a pioneering report that transformed the global dialogue on dementia. For the first time, ADI offered a comprehensive assessment of the costs of dementia. In the executive summary, ADI wrote:

> ***The total estimated worldwide costs of dementia are US$604 billion in 2010…Costs were attributed to informal care (unpaid care provided by family and others), direct costs of social care (provided by community care professionals, and in residential home settings), and the direct costs of medical care (the costs of treating dementia and other conditions in primary and secondary care). Costs of informal care and the direct costs of social care generally contribute similar proportions of total costs, while the direct medical costs are much lower.***[2]

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[1] Julianne Moore, 2015. 87th Academy Awards, award for Best Actress, Still Alice.

[2] Wimo A, and Prince M. World Alzheimer's Report 2010: The Global Economic Impact of Dementia. Alzheimer's Disease International. 2010. https://www.alz.org/documents/national/world_alzheimer_report_2010_summary(1).pdf

In subsequent years, ADI and other advocates, academics, and health economists have revisited the question of global dementia costs, continuing to implement the ADI model of direct and indirect costs.

We embrace this perspective. The unique consequences of dementia demand a broad assessment. Yet while ADI's work has shaped our understanding of the costs of dementia, we do not yet have a sufficient grasp of the costs of untreated agitation due to Alzheimer's. This is a gap in our knowledge – and it needs to be filled.

Agitation, in particular, can drive costs in a multitude of ways:

- **Those living with agitation are 20% more likely to be institutionalized.**[3]
- **Agitation raises informal care costs, which total €445 per month in the home care setting and €561 per month in the institutional long-term care setting across 8 European countries.**[4] **In the US, the cost of care for those with behavioral and psychological symptoms of dementia is $1,298 per month.**[5]
- **Interventions that significantly impact agitation can be costly. In the UK, care costs including such interventions can reach £15,000 over 3 months for those at the most severe agitation levels.**[6]
- **In 2015, the excess cost associated with agitation was nearly £2 billion in the UK alone.**[7]

As we have seen before, many steps are needed to appreciate the direct and indirect costs of dementia. With agitation, the first step involves systematically gathering and organizing the available scientific literature on agitation in dementia, which is the beginning of a much larger project that the

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[3] Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, et al. Institutionalization risk and costs associated with agitation in Alzheimer's disease. *Alzheimers Dement (N Y)*. 2019;5:851-861. Published 2019 Nov 23. doi:10.1016/j.trci.2019.10.004

[4] Costa N, Wübker A, De Mauléon A, et al. Costs of Care of Agitation Associated With Dementia in 8 European Countries: Results From the RightTimePlaceCare Study. *J Am Med Dir Assoc*. 2018;19(1):95.e1-95.e10. doi:10.1016/j.jamda.2017.10.013

[5] Hermann N, Lanctot K, Sambrook R, et al. The Contribution of Neuropsychiatric Symptoms to the Cost of Dementia Care. *Int J Geriatr Psychiatry*. 2006;21(10):972-6. Doi:10.1002/gps.1594

[6] Livingston G, Kelly L, Lewis-Holmes E, et al. A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioral interventions for managing agitation in older adults with dementia. *Health Technol Assess*. 2014;18(39):1-vi. doi:10.3310/hta18390

[7] Morris S, Patel N, Baio G, et al. Monetary costs of agitation in older adults with Alzheimer's disease in the UK: prospective cohort study. *BMJ Open*. 2015;5(3):e007382. Published 2015 Mar 13. doi:10.1136/bmjopen-2014-007382

Global Council on Alzheimer's Disease (GCAD) plans to undertake in the years ahead.

Our knowledge and understanding of agitation associated with dementia is limited but growing. We hope this literature review contributes to a broadening and deepening perspective of this underappreciated symptom of dementia, which can lead to more effective methods of diagnosis and treatment.

Signed,

Mary Michael

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The goal of this literature review is to begin to assess the costs of untreated agitation. By design, this project strives to balance the hard economic numbers of direct costs with the human toll of intangible costs. But even this broader understanding of costs falls short. The human story gets quickly lost in conversations about dollars and cents. We are therefore pleased that Meryl Comer – advocate, author, care partner, and champion for women's brain health – shares her story on caring for a husband with Alzheimer's-related agitation. Her story won't alter bottom-line calculations. But it provides an essential voice on what agitation truly costs.

Many times, personal stories involving Alzheimer's gloss over the unseemly details of the journey. It is our version of pain management. But it does not do justice to the cruelty of the disease and the behavioral changes, like agitation, that isolate and demean the very dignity of a loved one that as a caregiver you vow to protect. It is a secret we too often keep, even from other family members, until an uncontrolled and alarming episode threatens us harm as well.

My husband has long-forgotten me, but I am constant as his copilot and guardian.

The demons and terror of his world define mine. Any challenge is self-defeating. I play into his reality and pretend his fate and our life together are not doomed. His doctor has told me to "Call 911 if he gets too dangerous."

What is not uncommon in dementia is an episodic personality shift to something more aggressive, egocentric, emotionally abusive, and potentially harmful. It is the pendulum along which our lives swing. Lucidity is progressively diminished and intermittently punctured by high level of irritability or sudden inexplicable rage. Whatever haunts our loved one taunts and tests us.

The behaviors associated with agitation take an indelible emotional toll on those living with dementia and those who care for them. But agitation left unmanaged is the most urgent trigger for institutional care even when our first choice is to keep our loved one home. The ensuing costs to families are bankrupting and the societal burden is expediential and staggering.

This literature review on dementia and agitation shows how little we know about how to manage the intersection where the scaffolding of one's identity begins to fall apart. But it is a necessary first step if we are ever to treat the ravages of dementia, the festering pandemic of aging populations worldwide.

Meryl Comer

Chair & Co-Founder,
Global Alliance on Women's
Brain Health/a UsA2 Enterprise

Author of "Slow Dancing With A Stranger:
Lost and Found in the Age of Alzheimer's"

Voices from the Community

"We found a perfect nursing home that claim[ed] to specialise in dementia. They went to the hospital to assess [my dad] and have refused to take him. Due to his dementia he can become agitated and has tried to kick doors and shouted at staff. So they said they can't take him due to his challenging behaviour."

Comment posted on Alzheimer's Society forum

"We had an agitated dementia patient have a serious sentinel event from a fall because DESPITE nursing staff and the doctors and the family begging for 1:1 constant observation, administration did not think upping staff was warranted. And then three days later, a similar [incident] (less serious injuries) occurred to a similar [patient]."

Comment posted by a nurse on Reddit

"I have no idea what to do."

Comment posted on Alzheimer's Society forum

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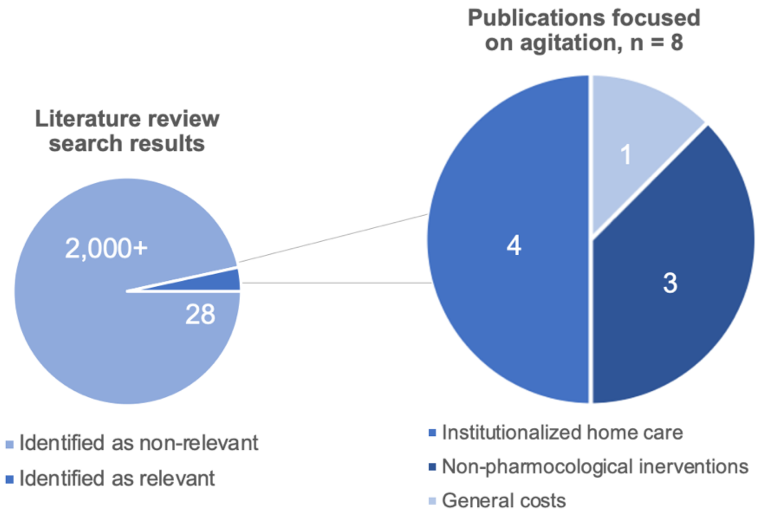
RESEARCH METHODOLOGY AND FINDINGS:

Lack of Consistent Evidence on the Costs of Agitation

Our literature review finds relatively few studies that assess the specific costs of agitation in Alzheimer's disease (AD), especially in a consistent and generalizable way. Our research examined studies published in English from January 2000 to April 2020 that report qualitative and quantitative analyses of direct and indirect costs of agitation in AD. Key words used as search terms included but were not limited to: "agitation in Alzheimer's disease," "neuropsychiatric symptoms of Alzheimer's disease," "cost of formal and informal care," "total healthcare costs," "cost of managed care," "long-term care" and "economic costs associated to delirium in Parkinson's disease."

> **"There is inadequate understanding of these costs—which are likely immense, but largely unknown."**



A total of 28 publications were identified as relevant (see annotated bibliography, p. 9-24 for more information). Our research was conducted between May and June of 2020.

Key insights from the literature:

- **The US lags behind the UK and EU.** Of the eight publications that directly estimate the costs of agitation, only two examined costs in the US.
- **Untreated & unknown.** The small set of analyses that focus on the costs of agitation look only at treated agitation. The costs of untreated agitation are not estimated. This is true both in Europe and the U.S. It is possible that non-English-language publications estimate the costs in other countries.
- **Little consensus, less consistency.** There is dramatic variation in cost estimates of agitation. Many factors contribute to these differences. Costs vary significantly across different settings, levels of agitation, health systems, geographies, and other factors.
- **Limited generalizability:** Given variation in geographic and study setting as well as differentiation in systems of care, cost analyses have limited generalizability to broader environments.

This literature review contributes to GCAD's work by examining specific questions about the costs of agitation. After a review of the scientific and academic literature, we conclude there is inadequate understanding of these costs—which are likely immense, but largely unknown. Furthermore, after discussing this inadequacy with economic and cost-modelling experts, a consensus emerged that the first step to understanding the costs of agitation was to examine the current literature to assess what we know, what we don't know, and what we need to know. This would apply to both treated and untreated agitation in AD. We present this literature review as the foundation for greater action to assess the costs of agitation, which can then motivate action to address this important, but largely overlooked, health challenge. This initial research provides a starting point and framework to drive further analysis, stimulate discussions of agitation, and advance towards meaningful progress on this critically important health challenge.

DISCUSSION

A Comprehensive Approach for Future Research

As experts and researchers look to improve understanding of the costs of agitation in Alzheimer's disease, research on the overall costs of Alzheimer's disease (AD) provides a valuable model. We advocate for a similar, comprehensive approach to estimating the costs of agitation—accounting for direct, indirect, and intangible costs.

For example, Castro et al. define costs of dementia as "the result of all goods and services that are given up to prevent, diagnose, treat, and otherwise cope with dementia." This includes direct costs (e.g., hospital resources, medical services, drugs, social services, family payment to formal caregivers); indirect costs (e.g., loss of income by the person living with AD and loss or reduction for family members or carers); and intangible costs (e.g., those related to pain or deterioration of the person living with AD or caregiver's quality of life).

El-Hayek et al. expand this approach to include additional socioeconomic costs related to AD. The authors concede that it is difficult to gauge the value of programs, policies, or interventions vis-à-vis AD, and they recognize that costs accumulate years before a person receives a dementia diagnosis. They also emphasize that it is difficult to make generalizations about costs across cities, states, provinces, and countries, given the unique circumstances from one place to the next.

We believe the methods established through these research efforts can inform how we assess costs of treated and untreated agitation in AD.

CONCLUSION

Opportunities and Next Steps

Our goal in this literature review is to advance the discussion of the costs of treated and untreated agitation in Alzheimer's disease. While there is much we do not know, we have collected and analyzed the evidence that is available in the current scientific literature.

Goals:

1. **To increase recognition of costs of agitation in Alzheimer's disease**
2. **To provide researchers and other experts with the background they need to move forward with cost modeling**
3. **To establish a framework for discussion, debate, and collaboration**
4. **To lay the foundation for effective social listening and solicitation of community perspective**

Further research on the costs of agitation is necessary. By assessing the current need for evidence and providing a framework for future efforts, we aim to galvanize research, collaboration, and, ultimately, effective responses to agitation in Alzheimer's disease.

Annotated Bibliography

This annotated bibliography reviews the relevant academic and scientific literature related to the costs of agitation in Alzheimer's disease. For each resource, we provide a brief description of the study, its methods, findings and constraints, and how it can support the overall discussion on agitation in Alzheimer's disease. Resources are listed alphabetically by author last name and divided into primary and secondary resources.

Primary Resources:

1. **Buylova Gola A, Morris S, Davis S, et al. Healthcare utilization, and monetary costs associated with agitation in UK care home residents with advanced dementia: a prospective cohort study. *International Psychogeriatrics*. 2020;32(3):359-370. doi: 10.1017/S1041610219002059**

   The study conducts a cost analysis, including health and social care costs, to calculate the monetary costs associated with agitation in care home residents with advanced dementia in the United Kingdom. Costs assessed include costs for the UK National Health Service, costs for personal social services, and costs to society. This study aims to fill a gap in the literature, as little is known about the costs of agitation in advanced stages of dementia.

   This article will be used in the discussion of costs of agitation pertaining to the care home setting. A limitation of this study is that the population of interest is based specifically in the UK, limiting the generalizability of results to other geographies. However, methods of data analysis may be adapted for future studies.

2. **Castro DM, Dillon C, Machnicki G, Allegri RF. The economic cost of Alzheimer's disease: Family or public health burden? *Dement Neuropsychol*. 2010;4(4):262-267. doi:10.1590/S1980-57642010DN40400003, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5619058/**

This article reviews the overall economic costs of Alzheimer's disease (AD) by resources deployed to prevent, diagnose, treat, and manage AD, as well as its impact on health systems and society. The authors define cost of dementia to society as "the result of all goods and services that are given up to prevent, diagnose, treat, and otherwise cope with dementia". These costs are broken down into direct costs (e.g., hospital resources, medical services, drugs, social services, and family payment to formal caregivers); indirect costs (e.g., loss of income by the patient and loss or reduction for family members or careers); and intangible costs (e.g., those related to pain or deterioration of patient and caregivers' quality of life).

While this article does not focus on the costs of agitation, specifically, it discusses cost modifiers including neuropsychiatric symptoms. In one study referenced, Hermann, Lanctot, Sambrook et al (2006) found that total costs multiplied when neuropsychiatric symptoms were present, as evaluated with the Neuropsychiatric Inventory (NPI). In this study, there was no difference found in drug-associated costs; the highest total costs for these patients were due to a greater proportion of indirect costs. Additionally, there was a significant association between costs and baseline NPI.

These results will be used in discussion of different attributed costs and how researchers have studied economic impact in the past. Additionally, this article can provide additional context for the overall costs of Alzheimer's disease and how it has been studied in the past. See article's references for additional resources on the cost of Alzheimer's disease.

3. **Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, et al. Institutionalization risk and costs associated with agitation in Alzheimer's disease. *Alzheimers Dement (N Y)*. 2019;5:851-861. Published 2019 Nov 23. doi:10.1016/j.trci.2019.10.004**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6881649/

This study serves as a retrospective analysis of the National Alzheimer's Coordinating Center Uniform Data set to assess the incremental risk and costs associated with agitation in individuals with Alzheimer's disease. The study defines agitation in line with the NPI Questionnaire and estimates the incremental costs of institutionalization associated with agitation in individuals with the disease. Of the 11,384 individuals included in the study, 6603 had agitation; compared with individuals without agitation, those with agitation were 20% more likely to be institutionalized. The total incremental cost of institutionalization associated with agitation was $4.3 billion ($50,588/individual).

This study serves as a source for discussion on the costs of institutionalization of those with agitation in Alzheimer's. It also references studies conducted globally on different cost analyses of dementia, including components specific to agitation and care. Discussion of these articles, as well, can be included in our analyses and support our discussion of the literature.

4. **Costa N, Wübker A, De Mauléon A, et al. Costs of Care of Agitation Associated With Dementia in 8 European Countries: Results From the RightTimePlaceCare Study. *J Am Med Dir Assoc*. 2018;19(1):95.e1-95.e10. doi:10.1016/j.jamda.2017.10.013 https://pubmed.ncbi.nlm.nih.gov/29275939/**

   This paper estimates the additional societal costs for people living with dementia with agitation in home care and institutional long-term care settings across 8 European countries. Results indicated that the total monthly mean cost differences due to agitation were €445 in the home care setting and €561 in the institutional long-term care setting. Informal care costs were the main drivers in the home care group and institutional care costs were the main drivers in the institutional long-term care settings.

   This review provides further background to the already modeled costs of nonpharmacological interventions to treat agitation, contributing to work that reviews the cost of treated agitation. The limitation to this study is that factors are analyzed in the context of Europe, leaving a gap for similar analyses in the US.

5. **El-Hayek YH, Wiley RE, Khoury CP, et al. Tip of the Iceberg: Assessing the Global Socioeconomic Costs of Alzheimer's Disease and Related Dementias and Strategic Implications for Stakeholders. *J Alzheimers Dis*. 2019;70(2):323-341. doi:10.3233/JAD-190426https://content.iospress.com/articles/journal-of-alzheimers-disease/jad190426**

   This review catalogues the different socioeconomic costs related to Alzheimer's disease and related dementias that are described in the literature; assesses the challenges and gaps of existing approaches to measuring these costs; and analyzes and discusses the implications for stakeholders to generate reliable data that can guide evidence-based decision making. This review finds that it is generally difficult to gauge the true value of programs, policies, or interventions for Alzheimer's disease and dementia, given the long-term, progressive nature of the disease and its socioeconomic impact beyond the patient and formal healthcare system.

   In this review, three cost-types were assessed: direct, indirect, and intangible costs. Direct costs included both medical (e.g., medication and hospitalization) and social/non-medical (e.g., residential care) costs for patients and caregivers. These costs were measured using administrative data sets (e.g., insurance claims) or standardized questions (e.g., Resource Utilization in Dementia Questionnaire) that quantify self-reported resource use. Indirect costs referred to resource lost or invested for which no money was exchanged. The two approaches to quantifying the cost of informal care relied on the value of informal estimates of the time caregivers spent in the provision of care: the replacement cost and the opportunity cost. Intangible costs were referred to as non-material costs that are not typically covered in economic analyses and stem from the deterioration of social, psychological, and physical domains of quality of life, and/or exacerbation of comorbid illness.

The authors note several challenges in measuring direct costs; for example, medical insurance claims may not capture the full direct costs, such as household out-of-pocket expenses or the costs borne by other insurers. Additional self-reported data is biased and difficult to standardize. Despite these challenges, the authors find that direct costs for of Alzheimer's and other dementias are substantial and increase over time or with disease severity. Direct costs may begin to accumulate several years prior to dementia diagnosis and are often driven primarily by social care costs. Additionally, out-of-pocket expenditures are high, exceed those of individuals without dementia, and are disproportionately borne by women and minorities.

Similarly, there is great variability in how the literature measures informal costs; however, the authors demonstrate a direct association between costs and disease severity. There is also evidence that indirect costs of dementia may be elevated many years prior to diagnosis.

Finally, in terms of intangible costs, the authors identify several studies that demonstrate a strong correlation between caregiving and health status of the caregiver. Additionally, the subjective burden experienced by informal caregivers generally increased with disease severity. This suggests that both quality of life and caregiver burden may be impacted several years before dementia is formally diagnosed.

Although this study discusses the broad economic impacts of dementia, it can serve as foundational research to investigate the costs of agitation. First it acknowledges the extent of research already conducted on the global economic costs of dementia, broken down by category. Second, it indicates that broad analyses of dementia may be missing several symptoms that can affects an increase in cost such as agitation. This indicates the need for further research to understand the role of agitation in the costs of dementia. Third, the article helps justify the need to understand the costs of untreated agitation. As this paper mentions, several costs begin to accumulate before the diagnosis of dementia; one would therefore assume that several costs begin to accumulate before the onset of agitation as a symptom of dementia.

6. **Hermann N, Lanctot K, Sambrook R, et al. The Contribution of Neuropsychiatric Symptoms to the Cost of Dementia Care. *Int J Geriatr Psychiatry*. 2006;21(10):972-6. Doi:10.1002/gps.1594**

This study estimates the contribution of behavioral and psychological symptoms of dementia (BPSD) to the costs of care. Results indicate that the total cost of care was $1,298 per month, and there was a significant independent relationship between cost and BPSD. The incremental cost of a one-point increase in the NPI score was significant at $30 per month (95% CI: $19-41). These results demonstrate that BPSD contributes significantly to the overall costs of dementia care.

This paper can provide numeric values for the cost of BPSD of dementia. However, we still cannot discern which costs are attributed to agitation.

7. **Kales H. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369. https://doi.org/10.1136/bmj.h369.**

   This article reviews the assessment and management techniques for BPSD of dementia, concluding that there is no one-size-fits-all treatment. Generally, non-pharmacological treatments for BPSD should be used first, particularly those involving partner intervention.

   This article can support discussion of different treatment methods and related direct or indirect costs for persons exhibiting BPSD, such as agitation. For instance, this article notes that non-pharmacological approaches involving family caregiver interventions have the strongest evidence base of success, though there may be additional indirect costs accrued.

8. **Koenig AM, Arnold SE, Streim JE. Agitation and Irritability in Alzheimer's Disease: Evidenced-Based Treatments and the Black-Box Warning. *Curr Psychiatry Rep*. 2016;18(1):3. doi:10.1007/s11920-015-0640-7 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6483820/**

   This review describes common behavioral symptoms of Alzheimer’s disease (AD) – with a particular focus on the challenging symptoms of agitation and irritability – and discusses evidence-based approaches to their management.

   This review can support the discussion of prevalence and burden of agitation in Alzheimer’s disease and non-pharmacological and pharmacological approaches to treatment, as well as provide qualitative insights into the presentation of untreated agitation.

9. **Livingston G, Barber J, Marston L et al. Clinical and cost-effectiveness of the Managing Agitation and Raising Quality of Life (MARQUE) intervention for agitation in people with dementia in care homes: a single-blind, cluster-randomized controlled trial. *Lancet Psychiatry*. 2019;6:293-304. doi: 10.1016/ S2215-0366(19)30045-8 https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(19)30045-8/fulltext**

   This study a examines a parallel-group, cluster-randomized controlled trial in 20 care homes across England to assess whether the Managing Agitation and Raising Quality of Life (MARQUE) intervention reduced agitation in residents with dementia after 8 months compared to treatment as usual (TAU).

   This article can support the discussion of interventions for agitation and provide context to issues of pragmatism, scalability, and cost-effectiveness of interventions. However, the paper’s findings may be limited, as study findings are dependent on specific healthcare infrastructure characteristics and geographic regions, therefore limiting the generalizability of the data collected to other geographies.

10. Livingston G, Kelly L, Lewis-Holmes E, et al. Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. *Br J Psychiatry*. 2014;205(6):436-442. doi:10.1192/bjp.bp.113.141119
https://pubmed.ncbi.nlm.nih.gov/25452601/

This study systematically reviews randomized controlled trial evidence regarding non-pharmacological interventions for agitation in dementia. The authors review 33 studies fitting predetermined criteria, and assess their validity and calculated standardized effect sizes (SES). The authors find that person-centered care, communication skills training, and adapted dementia care mapping decreased symptomatic and severe agitation in care homes immediately and for up to 6 months afterwards. Activities and music therapy by protocol decreased overall agitation, and sensory intervention decreased clinically significant agitation. Aromatherapy and light therapy did not demonstrate efficacy in decreasing agitation.

This study can help outline the different nonpharmacological interventions used to treat agitation, supporting the discussion of the cost of treated agitation through nonpharmacological intervention.

11. Livingston G, Kelly L, Lewis-Holmes E, et al. A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioral interventions for managing agitation in older adults with dementia. *Health Technol Assess*. 2014;18(39):1-vi. doi:10.3310/hta18390
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4781145/

This study reviews and synthesizes evidence for clinical effectiveness and cost-effectiveness of non-pharmacological interventions for reducing agitation in dementia, considering dementia severity, the setting, the person with whom the intervention is implemented, whether the effects are immediate or longer term, and cost-effectiveness.

The study finds costs of interventions that significantly impacted agitation were activities (£80-696), music therapy (£13-27) sensory interventions (£3-527) and training paid caregivers in person-centered care or communication skills with or without behavioral management training and DCM, (£31-339). Among the 11 interventions that were evaluated using the Cohen-Mansfield Agitation Inventory (CMAI), the incremental cost per unit reduction in CMAI score ranged from £162 to £3480 for activities, £4 for music therapy, £24-143 for sensory interventions, and £6-62 for training paid caregivers in person-centered care or communication skills with or without behavioral management training or DCM. Health and social care costs ranged from around £7,000 over 3 months in people without clinically significant agitation symptoms to around £15,000 to the most severe agitation levels.

This review provides further background to the already modeled costs of nonpharmacological interventions to treat agitation, contributing to work that reviews the cost of treated agitation. However, the study focuses only on the UK, with a gap for similar analyses in the US.

12. **Morris S, Patel N, Baio G, et al. Monetary costs of agitation in older adults with Alzheimer's disease in the UK: prospective cohort study. *BMJ Open*. 2015;5(3):e007382. Published 2015 Mar 13. doi:10.1136/bmjopen-2014-007382**
    https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4360590/

    This study calculates the monetary costs associated with agitation in older adults with Alzheimer's disease in the UK from a National Health Service and personal social service perspective. The study recruited 224 participants with Alzheimer's disease and followed up for 54 months. The primary outcome studied was health and social care costs, including accommodation costs and costs of contacts with health and social care services. Agitation, in this study, was assessed using the Neuropsychiatric Inventory agitation score.

    Findings indicate that among people with Alzheimer's disease, health and social care costs varied significantly by the level of agitation, from £29,000 over a 12-month period in people with no agitation symptoms to nearly £57,000 at the most severe levels of agitation. On average, agitation symptoms accounted for 12% of the health and social care costs of Alzheimer's disease. The excess cost associated with agitation was nearly £2 billion a year across all people with Alzheimer's disease in the UK. In the discussion of this article, the author references Murman et al, which found that after controlling for cognitive impairment and comorbidities behavioral symptoms measured using the NPI significantly increased total direct costs.

    This article can support the discussion of monetary costs associated with agitation in Alzheimer's disease. A limitation of this study is that the population of interest is based specifically in the UK, limiting the generalizability of results to other geographies. However, methods of data analyses may be adapted for future studies.

13. **Okura T, Langa KM. Caregiver burden and neuropsychiatric symptoms in older adults with cognitive impairment: The Aging, Demographics and Memory Study (ADAMS). *Alzheimer Dis Assoc Disord*. 2011;25(2):116-121. Doi:10.1097/WAD.0b013e318203f208.**
    https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3100441/

    This study estimates the quantity of informal care associated with neuropsychiatric symptoms in older adults with cognitive impairment. This study uses data collected in the Aging, Demographics and Memory Study (ADAMS) (2005) in the United States. The study measures the presence of neuropsychiatric symptoms, cognitive category, and hours per week of active health and supervision. The study finds that a greater number and increased severity of psychiatric symptoms was independently associated with increased quantity of informal care, even after adjusting for potential confounders (i.e. severity of cognitive impairment and medical comorbidities). The authors also identify individual neuropsychiatric symptoms among those with cognitive impairment no dementia (CIND) and dementia that significantly increased the caregiving burden on family members.

This study will be important in the discussion of caregiver burden as a factor of indirect costs for the treatment of agitation. Although no monetary value was given for time spent providing informal care, the researchers reference a similar study that was able to quantify the average number of hours caregivers provided weekly to help with functional limitations (Beeri M, Werner P, Davidson M, Noy S 2002); this study will also be useful in this discussion.

14. **Panca M, Livingston G, Barber J, et al. Healthcare resource utilisation and costs of agitation in people with dementia living in care homes in England - The Managing Agitation and Raising QUality of LifE in Dementia (MARQUE) study. *PLoS One*. 2019;14(2):e0211953. doi:10.1371/journal.pone.0211953**
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0211953

    This study calculates the cost of agitation in people with dementia living in care homes. The authors analyze baseline data from 1,424 residents with dementia living in care homes, part of the Managing Agitation and Raising Quality of life in dementia (MARQUE) study, who had Cohen-Mansfield Agitation Inventory (CMAI) scores. Specifically, the researchers investigate the relationship between residents' health and social care costs and severity of agitation based on the CMAI total score. Additionally, the study assesses resource utilization and compares the costs of residents with and without clinically significant symptoms of agitation.

    The authors find that agitation, defined by the CMAI, was a significant predictor of costs; on average, a one-point increase in the CMAI predicted a 0.5% increase in the annual costs. The excess annual cost associated with agitation per resident with dementia was £1,125.35.

    This article can support discussion of monetary costs associated with agitation in Alzheimer's disease in a care home setting. A limitation of this study is that the population of interest is based specifically in the UK, limiting the generalizability of results to other geographies. However, methods of data analyses may be adapted for future studies.

15. **Prince M, Comas-Herrera A, Knapp M et al. World Alzheimer Report 2016 Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future. *Alzheimer's Disease International*. 2016.**
https://www.alz.co.uk/research/WorldAlzheimerReport2016.pdf

    This report reviews the state of healthcare for dementia around the world and recommends improvements. The authors note that an estimated 90% of people with dementia will develop some form of behavioral and psychological symptoms of dementia (depression, anxiety, hallucinations, delusions, wandering, agitation, aggression), and that over half of people with dementia remain agitated and distressed towards the end of life.

This report can support the discussion of the cost of treated agitation in Alzheimer's disease and help provide additional context for the skewed costs of care, particularly in the end stages of disease.

16. **Research Protocol: Non-pharmacological interventions for Agitation and Aggression in Dementia**
https://effectivehealthcare.ahrq.gov/products/dementia-agitation-aggression/research-protocol#toc_js_1

    This systematic review provides background information on the prevalence and cost of dementia and proposes four theoretical frameworks to explain the etiology of behavioral disorders in those with dementia. This article will help support discussion of nonpharmacological interventions identified for managing agitation and/or aggression in dementia and provide additional commentary on some of the costs of treated agitation.

17. **Ryu S, Katona C, Rive B, et al. Persistence of and Changes in Neuropsychiatric Symptoms in Alzheimer Disease over 6 months: the LASER-AD Study. *Am J Geriatr Psychiatry*. 2005;13(11):976-983. Doi:10.1097/00019442-200511000-00008.**
https://www.sciencedirect.com/science/article/abs/pii/S1064748112617679?via%3Dihub

    This study examines the persistence and change in severity of neuropsychiatric symptoms over 6 months in participants with Alzheimer's disease, and the relationship to initial severity, drug management, use of services, and cost of care. It finds that, of the 224 study participants, 93.8% had neuropsychiatric symptoms at baseline, with 80.4% who had persistent significant symptoms at 6-month follow-up. Those with at least one clinically significant symptom had higher care costs than those without. The study finds that clinically significant levels of neuropsychiatric symptoms were associated with greater costs of care. The relatively few associations found between specific psychiatric treatments and changes in neuropsychiatric symptoms reflect both undertreatment and the complexity of symptoms.
    This article can support the discussion of costs associated with neuropsychiatric symptoms in Alzheimer's.

18. **Aigbogun SM, Stellhorn R, Hartry A, et al., Treatment patterns and burden of behavioral disturbances in patients with dementia in the United States: a claims database analysis. *BMC Neurol*. 2019;19(33). Doi:10.1186/s12883-019-1260-3.**
https://link.springer.com/article/10.1186/s12883-019-1260-3#citeas

    This analysis characterizes the clinical and economic burden of behavioral disorders in dementia by examining the clinical characteristics, treatment patterns, and healthcare utilization and costs associated with agitation in patients with dementia using a large representative sample.

This study will be important in the review of the costs of formally treated agitation. The authors reference four studies that suggest an increase in economic burden associated with agitation. However, three of these analyses were conducted outside of the US, with only one being US-based. This study notes that healthcare resource utilization and costs were higher among patients with dementia and behavioral disorders compared with patients without behavioral disorders. This was quantified through hospitalizations, outpatient hospital/clinic visits, and the number of skilled nursing days. A limitation of this study was that the data collected was derived from claims data.

19. **Sano M, Soto M, Carrillo M et al. Identifying Better Outcome Measures to Improve Treatment of Agitation in Dementia: A Report from the EU/US/CTAD Task Force. *J Prev Alzheimers Dis*. 2018;5(2):98-102. Doi:10.14283/jpad.2018.15 http://www.jpreventionalzheimer.com/3126-identifying-better-outcome-measures-to-improve-treatment-of-agitation-in-dementia-a-report-from-the-euusctad-task-force.html**

    This article summarizes recommendations that emerged from the EU-US CTAD Task Force meeting in 2018. It provides a wealth of background information on agitation in dementia, including the clinical presentation, biological mechanisms, and available treatments, which can support the discussion of agitation.

20. **Wimo A, Gauthier S, and Prince M. Global Estimates of Informal Care. Alzheimer's Disease International. 2018.**
    https://www.alz.co.uk/adi/pdf/global-estimates-of-informal-care.pdf

    This report summarizes the global estimates of informal care in Alzheimer's disease. Family members and friends have great impact on the societal costs of dementia, since they undertake an extensive amount of unpaid informal care. However, it is difficult to translate this contribution into volume and economic terms. This report stratifies by hours per day, providing care or supervision and WHO region or country income status. From 2010 data, it was estimated that an average of 4.0 and 2.8 hours a day were spent on assisting in activities of daily living (ADLs) and supervision, respectively, in the US and Canada. Additionally, in the US and Canada, approximately 76% and 24% of persons living with dementia lived at home and in care homes, respectively.

    This report can provide an overall landscape of the proportional costs of informal care in North America for Alzheimer's disease, broadly. However, discussion of these statistics will be limited as they do not pertain to agitation, specifically.

Secondary Resources

21. **Alzheimer's Association. "Anxiety and Agitation." https://www.alz.org/help-support/caregiving/stages-behaviors/anxiety-agitation**

    This web page provides background information on anxiety and agitation as symptoms of dementia. Specifically, it lists possible causes, tips to prevent agitation, and ways caregivers can respond to people experiencing agitation and anxiety. This page may be helpful in the discussion of agitation in Alzheimer's.

22. **Alzheimer's Impact Movement. Costs of Alzheimer's to Medicare and Medicaid. 2020. https://act.alz.org/site/DocServer/2012_Costs_Fact_Sheet_version_2.pdf?docID=7161**

    This fact sheet itemizes the costs of Alzheimer's disease to Medicare and Medicaid. In 2020, the direct costs to American society of caring for those with Alzheimer's and other dementias is estimated to reach $305 billion; in the last five years of life, the costs of a person with dementia, on average, total more than $287,000. Additionally, in 2020, Medicare and Medicaid will spend an estimated $206 billion caring for those with Alzheimer's and other dementias.

    While this factsheet does not stratify costs by symptom, these statistics paint a larger picture of the total costs of treatment of Alzheimer's disease. By demonstrating that costs accrued in the last five years of life are more than 1.5 times the costs for a person with heart disease or cancer, it helps draw attention to the need for further analysis of costs in terms of symptom (i.e., agitation); treated or untreated symptoms; indirect, direct or intangible costs; and stages of the patient journey.

23. **Collier, S. What's the best way to manage agitation related to dementia? *Harvard Health Blog*. 2020. https://www.health.harvard.edu/blog/whats-the-best-way-to-manage-agitation-related-to-dementia-2020021418816**

    This article provides insights on how to care for people with dementia who exhibit symptoms of agitation. The author discusses aggression and agitation in dementia, reviews new research on the effects of nonpharmacological therapies, and offers tips to caregivers. This article can serve as an informational resource in the overall discussion of agitation and nonpharmacological interventions for agitation in Alzheimer's.

24. **Ebersbach G, Wang IP, Klebe S, et al., Management of Delirium in Parkinson's Disease. *J Neural Transm* (Vienna). 2019;126(7):905-912. Doi:10.1007/s00702-019-01980-7. https://pubmed.ncbi.nlm.nih.gov/30725186/**

This paper serves as a review of management in delirium in Parkinson's disease. The authors define delirium as an acute and fluctuating disturbance of attention and awareness; pre-existing cognitive conditions or dementia are some of the most significant risk factors for developing delirium, and precipitating factors such as drug treatment, infections, trauma, or surgery may trigger delirium. The article examines pharmacotherapy aimed at treating delirium and nonpharmacological interventions available to prevent or palliate delirium, and calls for further development of instruments to detect and assess delirium in Parkinson's disease. This paper can serve as foundational information for potential discussion of delirium.

25. **IOS Press. "Analysis reveals economic cost of Alzheimer's disease and dementia are 'tip of the iceberg'." *ScienceDaily*. ScienceDaily, 30 July 2019. www.sciencedaily.com/releases/2019/07/190730092616.htm.**

    This article summarizes findings from a research review (El-Hayek Y, Wiley R, Khoury C, et al) highlighting the hidden costs of dementia, suggesting that traditional measures only show the 'tip of the iceberg' of the cost impact on society. The analysis examines the true cost of Alzheimer's disease and related dementias, finding that socioeconomic costs such as cost of healthcare for care partners/carers, reduced quality of life, and "hidden" costs that add up before diagnosis, are often overlooked by current estimates of the condition's economic impact. Some of dementia's hidden costs explored in this analysis include: caregivers' developing additional health conditions, such as anxiety or depression; families forced to cut back on spending or to use savings to support their loved ones; reduced quality of life for people with dementia and their care partners/carers; and costs that are incurred in the years before a diagnosis of impairment or dementia is made.

    This article indicates the extent of research already conducted to understand global costs of dementia, broadly, and it can help make the argument that specific costs may be due to agitation, requiring further research.

26. **Manappallil RG. Delirium in Parkinson's Disease: A Cocktail Diagnosis. *J Clin Diagn Res*. 2016;10(12):OD15-OD16. doi:10.7860/JCDR/2016/22248.9089 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5296489/?report=classic**

    This article examines mental disturbances described in patients with Parkinson's disease, with common symptoms including delirium and psychosis. Parkinson's Disease, a form of progressive neurodegenerative disorder, is often treated with Levodopa. This neurodegenerative disorder mostly affects elderly aged populations, and delirium has been reported in five to twenty-five percent of patients using Levodopa. Delirium has often been attributed to changes in environment, especially hospital stays and infections. There is a consensus that delirium increases with age, and rates as high as 60% have been reported in hospitalized elderly patients. Psychosis is usually due to drugs such as dopamine agonists.

This article serves as a case report, sharing the story of a 75-year old male who presented with delirium and ended up receiving a cocktail diagnosis, highlighting the need to look for other causes of delirium in patients with PD who also receive Levodopa treatment.

27. **Panza F, Solfrizzi V, Seripa D et al. Progresses in treating agitation: a major clinical challenge in Alzheimer's disease. *Expert Opin Pharmacother*. 2015;16(17):2581-2588. doi: 10.1517/14656566.2015.1092520 https://www.tandfonline.com/doi/pdf/10.1517/14656566.2015.1092520**

    This article reviews published literature, evaluates pharmacological interventions in Alzheimer's disease, and reviews clinical trials. It provides definitions for neuropsychiatric symptoms in dementia and behavioral and psychological symptoms, as well as commentary on current and alternative pharmacological approaches to the treatment of agitation in AD. This article can support discussion of agitation in AD and a brief review of current treatment options.

28. **Scarmeas N, Brandt J, Blacker D, et al. Disruptive behavior as a predictor in Alzheimer disease. *Arch Neurol*. 2007;64(12):1755-1761. doi:10.1001/archneur.64.12.1755**

    https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690610/

    This paper examines whether the presence of disruptive behavior has predictive value for important outcomes in Alzheimer's disease. Disruptive behavioral symptoms such as agitation, verbal and physical aggression, and wandering are well-recognized symptoms of AD, with reported frequencies ranging from 6-57% depending on symptom definition and stage of illness. Reports examining the association between disruptive behavioral symptoms vary; for example, some studies have reported an association between agitation and faster cognitive decline; between agitation and increased risk of institutionalization; and agitation and increased mortality risk. However, others fail to detect significant associations between disruptive behavior and cognition, function, institutionalization, and mortality. This makes it difficult to predict significant outcomes of disruptive behavioral symptoms.

    Findings from this study suggest that disruptive behavioral symptoms, including agitation, were extremely common, with more than 80% of study participants with Alzheimer's disease manifesting them at some point during study follow-up. Additionally, disruptive behavioral symptoms predicted cognitive and functional decline and were associated with a higher risk of institutionalization, even after adjusted for confounders.

    While this study does not include discussion of cost, it provides valuable insights into potential pathways and outcomes of agitation in AD, which should be considered when building economic models.

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