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Symptoms and Treatment Needs of People with Dementia-Related Psychosis: A Mixed-Methods Study of the Patient Experience

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ABSTRACT

Objectives: This study describes the person-centered experience and impact of symptoms and the treatment needs of dementia-related psychosis (DRP) from a patient and care partner perspective.

Methods: Qualitative interviews and a quantitative survey were used to collect patient experience data from persons with DRP or their care partners.

Results: Sixteen participants (1 person with DRP, 15 care partners) completed the qualitative interview; 212 participants (26 persons with DRP, 186 care partners) completed the quantitative survey. The most commonly reported symptoms were visual hallucinations, auditory hallucinations, persecutory delusions, and distortion of senses. The most common impacts were difficulty differentiating what is real from what is not real, increased anxiety, and effects on personal relationships. Current treatments were less than moderately helpful, and the ability to distinguish what is real from what is not real and overall symptom improvement were described as the most important benefits of an ideal treatment.

Conclusions: Patient experience data provide insights into urgent therapeutic needs of patients by describing the nature, frequency, and severity of symptoms and the impacts they have on individuals' lives.

Clinical Implications: Patient experience data demonstrate an unmet need for treatments to reduce the symptoms and impacts of DRP.

KEYWORDS

Hallucinations; delusions; patient experience data; dementia; dementia-related psychosis

Introduction

Hallucinations and delusions associated with dementia-related psychosis are frequently reported in persons with common subtypes of dementia, including Alzheimer's disease (AD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia (VaD) (Ballard et al., 2000; Johnson, Watts, Chapin, Anderson, & Burns, 2011; Lyketsos et al., 2002; Mendez, Shapira, Woods, Licht, & Saul, 2008; Mourik et al., 2004). Although the subtypes of dementia are caused by different pathological brain changes, mixed pathology is commonly present in individuals, and patients experience similar psychotic symptoms (Aarsland, Taylor, & Weintraub, 2014; Brenowitz et al., 2017; Elahi & Miller, 2017; J. A. Schneider, Arvanitakis, Bang, & Bennett, 2007).

Historically, diagnostic criteria for dementia-related psychosis have been limited by a lack of specificity and consensus on the definitions of the associated symptoms (Cummings et al., 2020). A recent publication on clinical recommendations for dementia-related psychosis defined hallucinations as perceptions of objects or events that occur without an external stimulus and delusions as fixed false beliefs that the patient believes to be true (Cummings et al., 2020; Ravina et al., 2007). However, there have been no person-centered studies on the experience of hallucinations and delusions, the timing of these symptoms over the course of dementia, or the impacts these symptoms have on patients' lives.

Recent studies have shed light on the burden associated with dementia-related psychosis. Dementia-related psychosis was associated with a significantly higher comorbidity burden and increased healthcare resource use and costs relative

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to dementia alone (Frazer, Abler, Halpern, Skoog, & Rashid, 2021). The presence of psychosis in dementia is also associated with a higher risk of disease progression to severe dementia, a higher likelihood of entering long-term care, and increased risk of death (Peters et al., 2015; Steinberg et al., 2008; Wetmore et al., 2021). A recent retrospective cohort study reported that within 2 years of developing psychosis, approximately 16% of dementia patients entered long-term care and approximately 50% had died (Wetmore et al., 2021). Hallucinations, in particular, are associated with a 1.6- and 1.5-times higher risk of institutionalization and death, respectively (Scarmeas et al., 2005), and with reduced quality of life, subjective wellbeing and life satisfaction (Choi et al., 2021). Furthermore, dementia-related psychosis is associated with a significant increase in care partner burden (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999; Cummings et al., 2018; Jeste & Finkel, 2000), and much of the responsibility of caring for individuals with dementia-related psychosis falls on family members. One study found that over 80% of care hours for individuals with probable dementia are provided informally by family care partners (Friedman, Shih, Langa, & Hurd, 2015).

There are no therapies currently approved by the U.S. Food and Drug Administration (FDA) for treating dementia-related psychosis (Cummings et al., 2018). Persons with dementia are often treated on a short-term basis with existing antipsychotic medications; however, these are associated with known risks and uncertain benefit (Kales, Gitlin, & Lyketsos, 2015; L. S. Schneider, Dagerman, & Insel, 2005; L. S. Schneider et al., 2006). A 1.6- to 1.7-fold increase in mortality among older persons with dementia-related psychosis who are taking antipsychotics prompted the FDA to issue a boxed warning for these drugs on the basis of short-term studies (Lenzer, 2005; Mathis et al., 2017; Reus et al., 2016; L. S. Schneider et al., 2005). In a longer-term placebo controlled study, a reduction in survival was also observed in persons taking antipsychotics compared to placebo (Ballard et al., 2009). Consistent with these known risks, the American Psychiatric Association cautions that non-emergency antipsychotic medication should be used only for the treatment of agitation or psychosis in

persons with dementia when symptoms are severe, are dangerous, or cause significant distress to the person with dementia (Reus et al., 2016).

Individuals living with a condition and their family members can provide valuable understanding of the needs that drive patient-focused drug development. The FDA's patient-focused drug development initiatives aim to facilitate and encourage the systematic collection of patient experience data to address unmet treatment needs (Chalasan, Vaidya, & Mullin, 2018; Kuehn, 2019; Mullin, Vaidya, & Chalasan, 2019). Specifically, the patient and care partner perspectives of the signs, symptoms, impacts, needs, and treatment priorities of those living with a given disease are useful for informing the development of more targeted treatment options and for facilitating the identification and classification of signs and symptoms (Chalasan et al., 2018). There are no published studies that describe the symptoms, current treatment patterns, and existing treatment needs of persons with dementia-related psychosis from a patient or care partner perspective. Such accounts are needed to effectively identify and prioritize treatment of the most impactful symptoms of dementia-related psychosis. This study aimed to address this literature gap by characterizing the impact of psychosis symptoms, treatment needs, clinically important outcomes, and preferences for benefits and risks of treatment in persons with dementia-related psychosis.

Methods

Design and eligibility

This observational, noninterventional, prospective study collected and analyzed qualitative interviews and quantitative online survey data, using a mixed-methods approach aligned with the FDA's patient-focused drug development initiatives. Data were collected from persons with dementia-related psychosis as well as care partners of persons with dementia-related psychosis in the United States. This study incorporated elements of both quantitative (close-ended) and qualitative (open-ended) data collection in parallel. Results of in-depth qualitative interviews and pilot testing allowed refinement and confirmation of the breadth of the

quantitative survey content. Further, qualitative results were used to inform interpretation and categorize quantitative survey results, and data from each method were given equal weight in the final interpretation of the data. The ability to compare the detailed responses from the qualitative interviews provided greater insights into survey responses while the survey approach facilitated data collection in a much larger sample than typically feasible via interview alone. Topics of interest were informed by the FDA's priorities for person-centered research, and data were available from exploratory market research studies (not published) that contributed to an understanding of areas of focus for meaningful research. All participants provided informed consent either electronically at the beginning of the survey for the quantitative component or as part of a consent discussion at the outset of the qualitative interview. Qualitative interview participants were provided with an informed consent document to review prior to their scheduled interview and verbally confirmed receipt, understanding, and willingness to participate before the interview began. The overall study was reviewed by the RTI institutional review board (IRB), and the quantitative component was also reviewed by the UsAgainstAlzheimer's IRB for the A-LIST What Matters Most Insight Series. Both determined that the study (including both the quantitative survey and the qualitative interview) was exempt from IRB oversight under the revised Common Rule 2019 (United States Federal Government, 2021).

Both phases of the study recruited persons with or care partners of persons with one of the following disorders, which may be present with or without cerebrovascular disease: possible or probable AD, DLB, PDD, VaD, FTD, mild cognitive impairment, or mild dementia (quantitative only); dementias due to aging (quantitative only); brain trauma, including traumatic brain injury or chronic traumatic encephalopathy (quantitative only); other dementias; or dementias not otherwise specified. Notably, diagnostic criteria were physician-confirmed for the study interviews.

All participants were at least 18 years of age, able to read and write English, and had sufficient verbal and written ability to understand and answer questions and comply with procedures with corrective

measures (if applicable, such as hearing aids and reading glasses). Pairs of persons with dementia-related psychosis and care partners were not recruited; however, care partners of persons with dementia-related psychosis who participated were not explicitly excluded from participating. Care partner burden was beyond the scope of this study, and all questions in the qualitative interview and quantitative survey focused on the impacts of dementia-related psychosis on the person experiencing the symptoms.

Qualitative interview

The qualitative component of this study consisted of a prospective, observational, noninterventional in-depth telephone interview. Interview participants were recruited through physician referrals organized by the Global Market Research Group (Carlsbad, CA). Physicians identified potentially eligible individuals and referred them to Global Market Research Group staff, who screened for individuals who were eligible and interested in participating and scheduled a telephone interview. All telephone interview participants received an informed consent document from the recruitment firm ahead of their scheduled interview to ensure voluntary participation. Qualitative interview participants were persons or care partners of persons who met the criteria for all-cause dementia (AD, DLB, PDD, VaD, or FTD) according to National Institute on Aging – Alzheimer's Association guidelines (McKhann et al., 2011) and had psychotic symptoms for at least 2 months (new-onset symptoms were permitted). Eligibility was determined on the basis of chart review and clinician confirmation. Care partners participating included individuals who provided at least 20 hours per week of direct in-person care for an individual with dementia-related psychosis. Participants in the qualitative interview were ineligible for participation in the quantitative survey.

Semistructured interview discussion guides were developed largely on the basis of concepts included within the Hallucination and Delusions domains of the Scale for the Assessment of Positive Symptoms, as well as other key concepts of interest identified through market research studies including in-office listening sessions and in-home visits with care

partners and patients. The semi-structured interview guide was used as a topic guide to increase consistency of the data collected to allow comparability among the interviews but also to facilitate a dialogue between the participant and the interviewer where the interviewer could pursue additional lines of conversation and ideas. Sixty-minute interviews were conducted by research staff at RTI Health Solutions (Durham, NC) between October 29, 2019, and December 13, 2019. Transcripts of interviews were analyzed for dominant trends, themes, and patterns in participants' responses using constant comparative analysis, and concept saturation was documented using a concept summary grid. Results were used to confirm the comprehensiveness of the study survey and aid in interpretation of survey results by providing details of the experience described in participant's own words. Descriptive statistics of data obtained during screening (e.g., demographic attributes) were computed, quality-checked, and summarized.

Quantitative survey

The quantitative component consisted of an online survey that was completed by a convenience sample of English-speaking persons with self-reported dementia-related psychosis or care partners of persons with care partner-reported dementia-related psychosis. Participants were recruited by the advocacy groups UsAgainstAlzheimer's and the Lewy Body Dementia Association. These groups created awareness of the research effort by providing information summarizing the purpose of the study along with relevant contact information for the recruitment firm through e-mails, advertisements on their websites or social media, and through web-based survey links directly to members of the advocacy groups. The survey was developed by Acadia Pharmaceuticals Inc. and RTI Health Solutions in collaboration with advocacy partners and was administered from November 14, 2019, to January 21, 2020. Respondents completed an initial web-based screening survey, and eligible participants were permitted to move directly to the survey itself. The online questionnaire consisted of 35 closed-ended items regarding medical history;

occurrence, severity, frequency, and impact of symptoms; treatments taken; effectiveness of treatments taken; and desired treatment benefits (see **Supplemental Material**). The survey was rigorously pilot-tested and refined on the basis of telephone-based cognitive debriefing interviews conducted by experienced qualitative research staff at RTI Health Solutions with a small set of 10 advocacy group members, including persons with dementia-related psychosis, care partners, and subject matter experts, prior to launch. Content of the survey questions was further confirmed through results of qualitative interviews. Within the survey, participants were given definitions of common types of symptoms of dementia-related psychosis, including hallucinations, delusions, distortion of senses, paranoid delusions or false beliefs, lack of trust for loved ones, delusions about infidelity, visual hallucinations, and auditory hallucinations (see **Supplemental Table S1**). Respondents were specifically asked to rate the severity of symptoms with a visual analog scale (VAS) of 1 ("very mild") to 5 ("very severe") and the effectiveness of current treatments with a VAS of 0 ("not at all well") to 5 ("extremely well"). Respondents were also asked to rank prespecified impacts of symptoms of dementia-related psychosis from most impactful to least impactful and prespecified benefits of an ideal treatment from most desirable to least desirable (see **Supplemental Material**).

Data analyses included descriptive statistics of responses to individual questions. For continuous-type data, the mean, standard deviation, median, and range were presented. For categorical data, frequencies and percentages were reported. Each question was analyzed individually among those participants who responded; no imputation of missing data was performed.

Results

Participant characteristics

The in-depth qualitative interview was completed by one person with dementia-related psychosis and 15 care partners (**Table 1**). The majority of qualitative interviews described persons with dementia-

Table 1. Characteristics of people with dementia-related psychosis in the qualitative interview.

Characteristic	Person with dementia-related psychosis (n = 1)	Care partner (n = 15)
Male, n (%) ^a	1	10 (66.7)
Age, mean (range), years	81	85.5 (60–89)
Duration of dementia, n (%)		
>6 months to 1 year	1	1 (6.7)
>1 to 3 years	–	7 (46.7)
>3 to 5 years	–	4 (26.7)
>5 years	–	3 (20.0)
Dementia diagnosis, n (%)		
PDD	1	3 (20.0)
AD	–	9 (60.0)
VaD	–	3 (20.0)
Relationship to person with dementia, n (%)		
Friend	–	5 (33.3)
Spouse (wife)	–	4 (26.7)
Daughter	–	3 (20.0)
Niece, daughter-in-law, or son-in-law	–	3 (20.0)
Race/ethnicity, n (%)		
Caucasian	1	8 (53.3)
Mixed race	–	1 (6.7)
Puerto Rican	–	1 (6.7)
Hispanic or Latino	–	6 (40.0)
Education, n (%)		
Less than high school	1	–
Some high school, high school, or other equivalent	–	7 (46.7)
Some college	–	4 (26.7)
College degree	–	4 (26.7)
Some graduate school	–	1 (6.7)

Note. Dashes indicate no data. AD = Alzheimer's disease; PDD = Parkinson's disease dementia; VaD = vascular dementia.

^aSex of person with dementia.

related psychosis who were male and white or Latino. Most had been diagnosed with AD, PDD, or VaD. Ten of the 15 care partners who participated were family members.

The quantitative online survey was completed by a total of 212 eligible individuals: 26 persons with dementia and 186 care partners (Table 2). On average, self-reporting persons with dementia-related psychosis were younger (mean age of 64.6 years vs. 78.1 years) and more likely to be earlier in their disease state than persons for whom care partners completed the survey (span of time since dementia diagnosis for the cohort: previous 10 years vs. previous 24 years). While no self-reporting persons lived in a long-term care facility, 21.0% of those for whom a care partner answered the survey lived in an assisted living community, a nursing facility, or a rehabilitation center. The most common dementia diagnoses in the care partner report group were DLB and AD; in the patient self-report group, DLB and mild

Table 2. Characteristics of people with dementia-related psychosis in the quantitative survey.

Characteristic	Person with dementia-related psychosis (n = 26)	Caregiver (n = 186)
Male, n (%) ^a	15 (57.7)	91 (48.9)
Age, mean (range), years	64.6 (49–84)	78.1 (55–97)
Dementia diagnosis, median	2017	2016
Dementia diagnosis, date range	2010–2019	1996–2019
Dementia type, n (%) ^b		
AD	6 (23.1)	91 (48.9)
PDD	1 (3.8)	32 (17.2)
DLB	13 (50.0)	71 (38.2)
FTD	2 (7.7)	7 (3.8)
VaD	1 (3.8)	18 (9.7)
MCI or mild dementia	11 (42.3)	27 (14.5)
Other (brain trauma, other, aging)	7 (26.9)	53 (28.5)
Race, n (%)		
Caucasian	21 (80.8)	167 (89.8)
Hispanic or Latino	2 (7.7)	8 (4.3)
Black or African American	2 (7.7)	5 (2.7)
Mixed race or other	1 (3.8)	4 (2.2)
Living situation of person with dementia, n (%)		
With spouse/partner	17 (65.4)	101 (54.3)
With children	5 (19.2)	29 (15.6)
Alone	6 (23.1)	19 (10.2)
Assisted living community, nursing facility, or a rehabilitation community	0 (0)	39 (21.0)
Other	1 (3.8)	26 (14.0)
Education, n (%)		
Less than high school	1 (3.8)	16 (8.7)
Some high school, high school, or other equivalent	2 (7.7)	55 (30.1)
Technical school/certification	5 (19.2)	11 (6.0)
Some college	4 (15.4)	21 (11.5)
College degree	6 (23.1)	44 (24.0)
Graduate degree	8 (30.8)	36 (19.7)

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia-spectrum disorder; MCI = mild cognitive impairment; PDD = Parkinson's disease dementia; VaD = vascular dementia.

^aSex of person with dementia. ^bReported by the participant; ≥1 subtype could be selected.

cognitive impairment or mild dementia were most common.

Symptoms of dementia-related psychosis

The most commonly reported symptoms of dementia-related psychosis reported by interview participants were visual hallucinations (15 of 16; 93.8%) (Figure 1). Dominant trends related to visual hallucinations in the qualitative interviews included reports of seeing a person in the home who was not really there or seeing an animal or object out of context that was not really there (Table 3). Two examples from the qualitative interviews are described. In the first example, during a qualitative interview, a care partner (friend) described a dialogue with a person with dementia-related

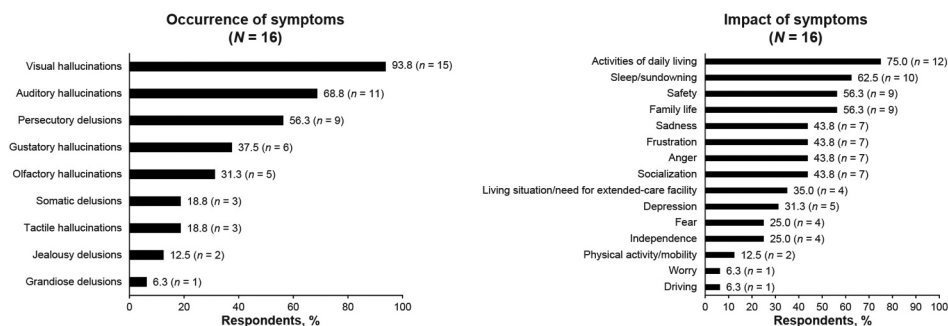


Figure 1. Qualitative interview: Percent of participants who reported each type of symptom and impact of symptoms. *Note.* “Sundowning” refers to a state of confusion occurring in the late afternoon and spanning into the night, which may cause problems sleeping or increases in behavioral problems.

psychosis in which the person said, “*There’s nobody here. he’ll get a little nervous and start claiming, ‘Yes, he’s here, don’t you see him?’*” In a second example, a person with dementia-related psychosis described a vivid example of a hallucination as follows, “*It looked like a person. It didn’t look like no statue, but it looked like a person. And I just took a swing. If it was a person, I would have laid them out. One incident, I pried my eyes open and I see a young woman, a young teenager or whatever. I pried my eyes open and she just kept staring at me and I said ‘I’ll be damned.’ I know actually, I know it wasn’t real.*”

Auditory hallucinations were also commonly reported (11 of 16; 68.8%) (Figure 1). Common themes regarding auditory hallucinations in the qualitative interviews included descriptions of hearing voices calling out to the person with dementia-related psychosis or hearing someone breaking into the house. One friend of a person with dementia-related psychosis reported “*he’ll just say [...] ‘Someone’s calling me, I hear someone still calling me.’ And I’m like, ‘Nobody’s in the room.’*” More than half of respondents (9 of 16) also described persecutory delusions, for example, beliefs that money had been stolen or that family members were trying to trick the individual with dementia-related psychosis. Interview participants also commonly reported agitation, aggression, anxious behavior, impaired cognition, confusion, and paranoid behavior associated with their descriptions of symptoms.

Self-reports and care partner reports from the quantitative online survey revealed similar results. Visual hallucinations (88.5%), auditory

hallucinations (53.8%), distortion of senses (53.8%), and paranoid delusions (38.5%) were the most common symptoms reported by persons with dementia-related psychosis. Paranoid delusions (75.8%), visual hallucinations (75.3%), and lack of trust for loved ones (52.2%) were the most common symptoms reported by care partners (Figure 2).

Interview participants indicated that the frequency of symptoms varied on a daily basis and that specific events or situations – such as noises, photographs, movies, leaving the home, unfamiliar settings, or changes in light levels – seemed to trigger hallucinations or delusions. Fourteen care partners indicated that the frequency and severity of symptoms worsened with time as the disease progressed.

In the quantitative survey, visual hallucinations were reported as occurring weekly by 53.8% of persons with dementia-related psychosis and 52.7% of care partners; auditory hallucinations were reported as occurring weekly by 30.8% of persons with dementia-related psychosis and 29.0% of care partners; and paranoid delusions were reported as occurring weekly by 15.4% of persons with dementia-related psychosis and 58.6% of care partners. Approximately half of care partners (100 of 186; 53.8%) reported that individuals were not at all comfortable or were only a little comfortable discussing the symptoms of dementia-related psychosis with those closest to them. Five of 26 (19.2%) persons with dementia-related psychosis reported that they were not at all comfortable or only a little comfortable discussing their symptoms with those closest to them; however, this may be a reflection of the less severe disease progression observed in self-reports.

Table 3. Selected qualitative accounts.

Symptom severity and impacts
<i>"you're in your house and you see that, and it's a person in your house. It looked like a person. It didn't look like no statue, but it looked like a person. And I just took a good kick and a good swing. If it was a person, I would have laid them out . . . One incident, I pried my eyes open and I see a young woman, a young teenager or whatever. I pried my eyes open and she just kept staring at me and I said, 'I'll be damned.' I know actually, I know it wasn't real." [Person with dementia-related psychosis]</i>
<i>"There's nobody here.' . . . he'll get a little nervous and start claiming, 'Yes, he's here, don't you see him?'" [Care partner – friend]</i>
<i>"he'll just say, 'We got to go to the front room,' or 'Someone's calling me. I hear someone still calling me.' And I'm like, 'Nobody's in the room.' And really nobody's in the house sometimes when he's hearing these voices." [Care partner – friend]</i>
<i>"Well, the big thing is they're stealing [. . .] they're trying to steal this and it's like there's nobody there and even the family members who he would never accuse anybody of something like that, he'll accuse them of stealing." [Care partner – daughter]</i>
<i>"he has a couple times told me he saw somebody dead or a circle on the wall." [Care partner – wife]</i>
<i>"every time he passed a mirror he talks to the person in the mirror and he really thinks it's another person, he thinks it's his buddy. At one point, he got mad because wherever we went the person followed us." [Care partner – wife]</i>
<i>"I want to run out the door sometimes, I really want to escape and run out the door." [Care partner – wife]</i>
<i>"she's now starting to get her days and nights mixed up. She's up all night, and she just won't go to sleep" [Care partner – friend]</i>
Current treatment/side effects of current treatment
<i>"He is sleeping in longer than usual." [Care partner – family friend]</i>
<i>"But then it has all these other side effects that . . . whoa, I'd rather not take it. So you're saying you're going to help me, but then I'm going to have nightmares or I'm going to have this. I'm going to have that. And it's like, 'Never mind. I think my dad was right. Don't take it.' Because there's so many side effects that these medications have. That you take it for one thing, and then it just disrupts another thing." [Care partner – niece]</i>
<i>"[Do] any of them work? I don't know. It's almost like people with dementia, they really don't fit into a category of mental illness. It's like they're their own little entity." [Care partner – wife]</i>
<i>"It was controlling his sleep, has a lot to do with it. So if he sleeps, he's more rested, he's more calm. But the days that he doesn't sleep, he gets more agitated during the day." [Care partner – wife]</i>
How an ideal treatment would help
<i>"I think his emotions. He gets very stressed. He gets very antsy in his episodes [. . .]. It'll help him not having to go through that stress." [Care partner – family friend]</i>
<i>"Stop the repetitive thoughts, [. . .] break the cycle and stop the thoughts that get him there in the first place. Oh, God, it would be like you could actually keep your loved one at home and wouldn't have to put him into a home. And bankrupt the family [. . .]. Because I think everything else you can pretty much keep them at home." [Care partner – wife]</i>
<i>"When he's having these delusions, there are days when he's really sad [. . .]. Well I think just seeing him happy and being normal a little bit again. Coming back to being himself again. I know that this is a disease, and it's a sickness, and it's not his fault. But I would love to see him come back as himself. And even if it's not 100%, but be my husband again." [Care partner – wife]</i>
<i>"Well, we would live better. We would be able to go out more, we'd be able to get along better. [. . .] I would take him more often to my kids' house. Sometimes, I go there and I worry because I don't want him lashing out or anything." [Care partner – wife]</i>
<i>"Well, if he could realize it's himself in the mirror and if he could rest at night [. . .]. I mean, we're up every night a couple of times at night and sometimes that's when he gets . . . that's when he can get aggressive because that's when he feels like he needs to do something, go get gas, go to work, go help somebody, and he gets frustrated when he can't get out of the house. And then he's mad at me because I'm the one. I'm the one that's doing all of this and so that's when it gets ugly." [Care partner – wife]</i>

Persons with dementia-related psychosis rated visual hallucinations (mean, 3.27 of 5) and distortion of senses (mean, 3.25 of 5) as the most severe symptoms, while care partners rated paranoid delusions (mean, 3.65 of 5), followed by delusions about infidelity (mean, 3.73 of 5) and lack of trust for loved ones (mean, 3.39 of 5), as the most severe (Figure 3).

Impacts of dementia-related psychosis

Qualitative interview participants commonly described symptoms of dementia-related psychosis as impacting activities of daily living (12 of 16; 75.0%), for example, by causing individuals to refuse to participate or allow for assistance with daily aspects of self-care or medication administration or by creating additional household chores. Two additional common themes of the qualitative interviews, reported by more than half of participants were impacts of symptoms on sleep (10 of 16; 62.5%) and safety (9 of 16; 56.3%). For example, one friend of a person with dementia-related psychosis said *"she's now starting to get her days and nights mixed up. She's up all night, and she just won't go to sleep."* Symptoms also impacted participants' family life (9 of 16; 56.3%), for example, by creating difficult familial interactions due to fixed paranoid delusions about family members. These impacts, particularly those affecting daily living and safety, also influenced living situations for persons with dementia-related psychosis and contributed to the need for additional care partner support. The wife of one person with dementia-related psychosis shared *"I want to run out the door sometimes, I really want to escape and run out the door."*

In the quantitative survey, 60.9% of self-reports indicated that visual hallucinations were the most impactful symptom (Figure 4). Consistent with interview results described above, persons who reported visual hallucinations as the most impactful symptom ($n = 14$) indicated that these hallucinations hindered everyday activities by causing the individual to avoid people (71.4%) and to avoid driving (71.4%), to feel less confident in going about daily activities (64.3%), and to feel that their

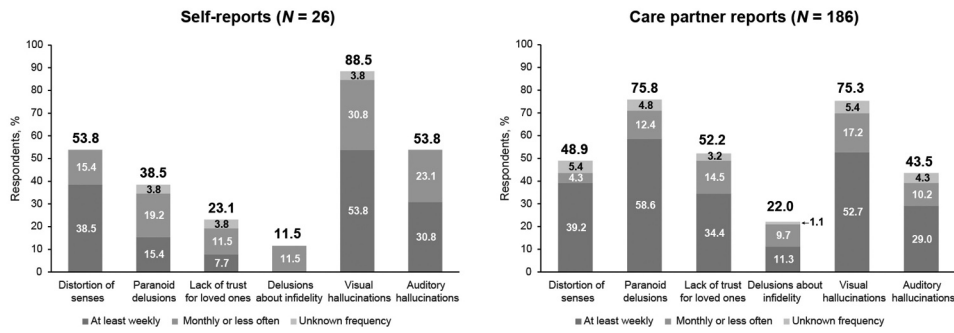


Figure 2. % of participants who reported each type of symptom and recent symptom frequency. *Note.* Percentages may not sum to the total percentage for each symptom because of rounding.

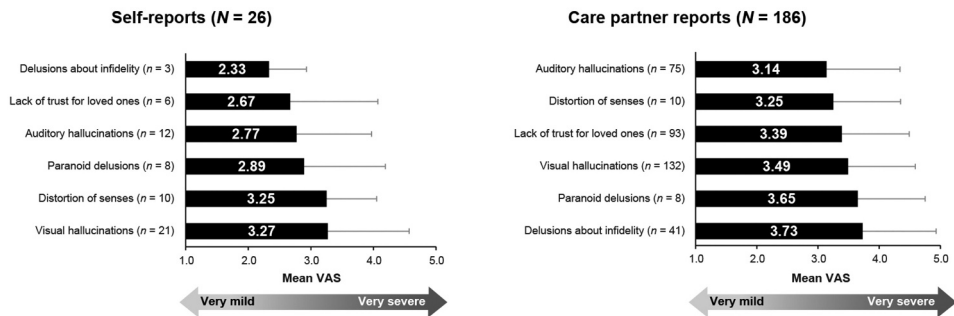


Figure 3. Symptom severity reported using a visual analog scale. *Note.* Scale ratings ranged from 1 (“very mild”) to 5 (“very severe”). Whisker lines indicate standard deviations. VAS = Visual Analog Scale.

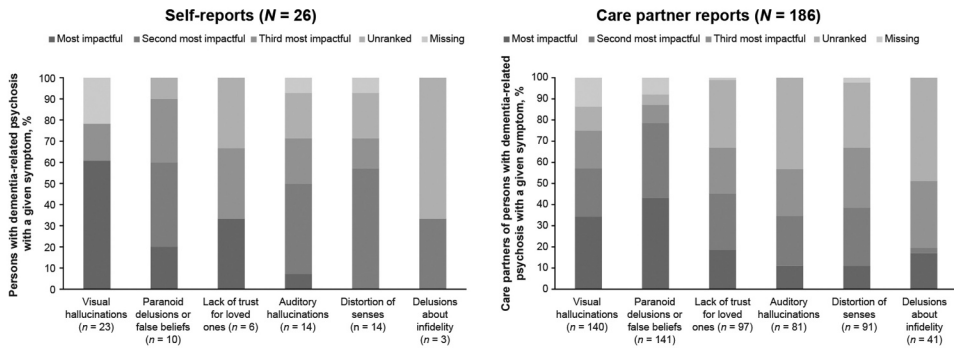


Figure 4. Rankings of patients' most impactful symptoms. *Note.* Additional information on types of impact is presented in Supplemental Tables S1 and S2.

engagement in social activities was affected (64.3%) (see **Supplemental Table S2**). Common emotional impacts of visual hallucinations included worry about the future (78.6%), substantial anxiety (64.3%), and making the person feel they are crazy (57.1%). Almost half (42.9%) of persons with dementia-related psychosis thought that visual hallucinations made it difficult to distinguish between what is real and what is not real. Distortion of senses was the second most impactful

symptom reported by persons with dementia-related psychosis ($n = 8$), with specific impacts of less confidence in going about their normal activities (75.0%), worry about the future (87.5%), and difficulty understanding what is real (62.5%) as a result of this symptom.

From the care partner perspective, paranoid delusions or false beliefs (43.3%), followed by visual hallucinations (34.3%), were most impactful (**Figure 4**). Care partners ($n = 61$) who rated

paranoid delusions or false beliefs as the most impactful symptom indicated that it affected all features of the individual's daily life and psychological/emotional health with direct impacts on daily activities (63.9%), participation in social activities (55.7%), ability to communicate (55.7%), and feeling less confident in going about their normal daily activities (54.1%) (see **Supplemental Table S3**). Care partners also reported that this symptom made it difficult for individuals to know what is real (85.2%), caused the individual a lot of anxiety (85.2%), impacted the individual's relationships (67.2%), and frightened the individual (60.7%). Impacts of additional symptoms ranked as most impactful to third most impactful for both self-reports and care partner reports are presented in **Supplemental Tables S2–S3**.

Treatment patterns for dementia-related psychosis

In the qualitative interviews, 6 of the care partners were not aware of current medications for dementia-related psychosis; the remaining 9 reported that the person's treatment included atypical antipsychotics, antidepressants, anxiolytics, and/or benzodiazepines. Participants commonly expressed concern about side effects and a lack of efficacy of current treatments (Table 3).

The quantitative survey revealed that many individuals were not receiving treatment for their dementia-related psychosis (42% of both self-reports and care partner reports). Among those receiving treatment, common therapies included use of atypical antipsychotics, reported by 26.9%

of persons with dementia-related psychosis and 40.9% of care partners (Figure 5). Use of psychological or behavioral therapy was reported by 23.1% of self-reports and 7.5% of care partner reports. Participants indicated that current treatment methods were less than moderately helpful in treating the most impactful symptoms, with a median VAS score of 2.00 out of 5 reported by persons with dementia-related psychosis and care partners (VAS range = 0 ["not well at all"] to 5 ["extremely well"]). The mean VAS score (standard deviation) was 2.33 (1.0) for self-reports ($n = 15$) and 2.40 (1.3) for care partner reports ($n = 104$).

Discontinuation of a treatment was reported by 11 persons with dementia-related psychosis (42.3%) and 115 care partners (61.8%). Among those who reported discontinuation, the most common specific reasons given were side effects (27.3% of self-reports, 31.3% of care partner reports), doctor's recommendation (27.3% of self-reports, 13.9% of care partner reports), or lack of symptom improvement (9.1% of self-reports, 27.8% of care partner reports) (see **Supplemental Figure S1**).

Existing treatment needs and desired treatment benefits

Qualitative interview participants indicated a need for treatment to improve symptoms and the ability to know what is real versus not real (Table 3). Participants indicated that improvements related to impacts of dementia-related psychosis symptoms that would be most desired would include improving the person's ability to sleep, socialize with/visit

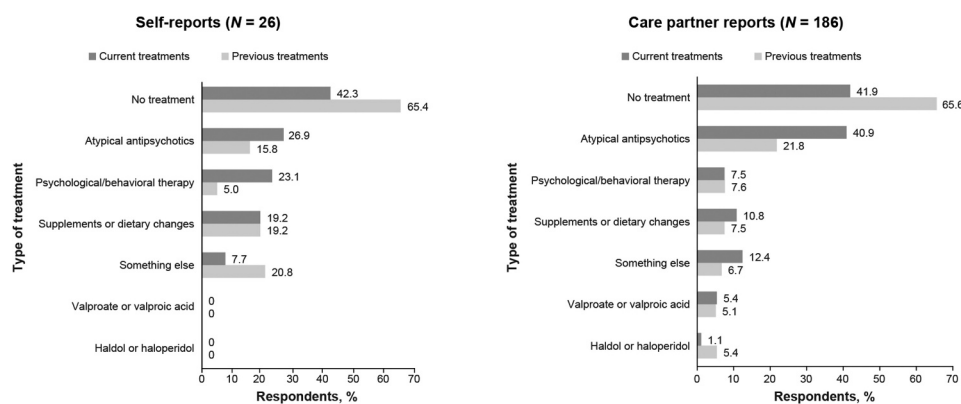


Figure 5. Treatment history and current treatments for persons with dementia-related psychosis. *Note.* Participants could report more than one treatment.

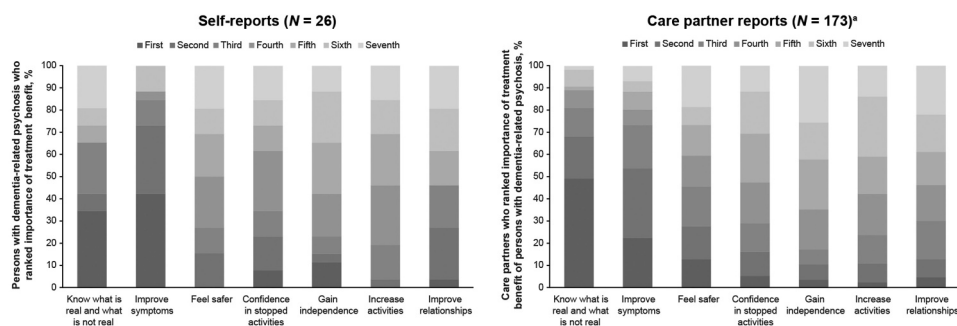


Figure 6. Ranking of benefits of an ideal treatment for dementia-related psychosis. ^aThirteen care partners did not respond to questions on the benefits of an ideal treatment.

relatives, and engage in day-to-day activities outside the home.

Similarly, in the quantitative survey, participants ranked the ability to distinguish what is real versus not real (34.6% of self-reports, 49.1% of care partner reports) and overall symptom improvement (42.3% of self-reports, 22.5% of care partner reports) as the most important benefits of an ideal treatment (Figure 6).

Discussion and implications

This study is the first to our knowledge to collect patient-experience data specifically about hallucinations and delusions associated with dementia-related psychosis. This study therefore used a mixed-methods approach to capture qualitative and quantitative data on the patient experience. Results provide insights into the most urgent therapeutic needs from a patient perspective by describing the nature, frequency, and severity of symptoms and the specific impacts they have on individuals' lives. Symptoms caused persons with dementia-related psychosis to question their understanding of reality and decreased their confidence in engaging fully with daily life, and current treatment options were not providing adequate symptom relief.

Qualitative and quantitative data presented here demonstrate that dementia-related psychosis is marked by the frequent occurrence of hallucinations and paranoid delusions. Detailed qualitative interviews revealed that symptoms caused individuals to doubt their own understanding of reality and the motives and actions of the people around

them, resulting in a reluctance to engage in everyday life. Participants indicated that symptoms had an impact on daily activities and social and emotional quality of life. In the qualitative interviews, impacts included decreased independence, family and social engagement, emotional quality of life, and security. Notably, participants described difficulties with the activities of daily living, sleep, family life, safety, and socializing, and their emotional states were often characterized by feelings of anger, frustration, and sadness. Results from the quantitative survey complement these interview findings. More than half of persons with dementia-related psychosis and care partners who completed the survey indicated that the most impactful symptoms made individuals less confident in going about daily activities, interfered with social engagement, induced worry about the future, made it difficult to understand what is real, or interfered with participation in social activities. Collectively, the impacts of hallucinations and delusions, particularly those related to independence and safety, often substantiated a need for 24-hour care partner support for the person with dementia-related psychosis and influenced considerations and concerns regarding future further-altered living situations or the need for placement in long-term care facilities.

The burdens of dementia-related psychosis are amplified by the poor prognosis of this condition. The presence of psychosis in persons with dementia is associated with worsening clinical outcomes, which include more rapid cognitive decline, decreased frontal executive function, institutionalization, and death (Fischer, Ismail, & Schweizer, 2012; Scarmeas et al., 2005; Wetmore et al., 2021).

In addition, dementia-related psychosis is associated with an increased comorbidity burden (Shim, Andes, Rashid, & Citrome, 2019; Vilalta-Franch, Lopez-Pousa, Calvo-Perxas, & Garre-Olmo, 2013; Zahodne, Ornstein, Cosentino, Devanand, & Stern, 2015). However, many individuals in both the qualitative and quantitative components were not receiving treatment, and those who were indicated that existing treatments were associated with concerning side effects or were not effective. Approximately one-third of participants indicated discontinuation of a treatment for dementia-related psychosis due to a lack of symptom improvement, side effects, or a doctor's recommendation.

The finding that many patients discontinued treatment due to side effects is consistent with the current literature regarding off-label use of atypical antipsychotics in elderly populations. Side effects of atypical antipsychotics include extrapyramidal symptoms (Ballard & Howard, 2006; Spindler, Galifianakis, Wilkinson, & Duda, 2013), orthostatic hypotension (Trigoboff et al., 2013), hematologic abnormalities (Ballard & Howard, 2006), metabolic disorders (Reynolds, 2011), and gastrointestinal, thrombo-embolic, and sedative effects (De Berardis et al., 2018). These agents are also associated with an increased risk for falls (and associated fractures) (Kuschel, Laflamme, & Moller, 2015), infection (Trigoboff et al., 2013), aspiration pneumonia (Hinkes, Quesada, Currier, & Gonzalez-Blanco, 1996; Saenger, Finch, & Francois, 2016; Trigoboff et al., 2013), and other serious complications in this vulnerable patient population (Ballard et al., 2009). The majority of these risks are serious and are communicated through warnings and precautions in FDA-approved labeling. Persons with Lewy body dementias may be particularly sensitive to adverse effects of antipsychotic use, with an increased risk of neuroleptic malignant syndrome noted in this population as well (Aarsland et al., 2005; McKeith, Fairbairn, Perry, Thompson, & Perry, 1992; Weintraub et al., 2016). Thus, there is a need for safe and effective therapies for persons with dementia-related psychosis.

Patient-experience data can provide a valuable understanding of the symptoms and treatment landscape of dementia-related psychosis, both to

inform the identification of persons with dementia across subtypes who need treatment and to inform drug development efforts to address unmet medical need (Chalasan et al., 2018; Fischer et al., 2020). This study is the first to our knowledge to use a person-centered approach to capture patient preferences about the most impactful, relevant, and important signs and symptoms and the potential acceptability of treatment benefit/risk outcomes. This information can be used by patients, families, and clinicians considering the severity of symptoms and making decisions about treatment priorities. Our results also demonstrate the critical importance of ensuring that clinicians who treat patients with dementia prioritize discussions with patients and family members to allow patients to freely discuss these symptoms in addition to the more classical assessments of cognitive decline and movement disorders. Persons with dementia-related psychosis and their care partners in this study ranked symptom improvement and the ability to distinguish reality from symptoms of psychosis as the most important benefits of a potential new treatment. A major impact of such treatment would be the confidence to more fully engage with life on practical, social, and emotional levels while remaining in a safe and stable living situation.

Collection of patient experience data from both persons with dementia-related psychosis and their care partners is a strength of the current study. This approach allows characterization of people at different stages of the disease, particularly as those with severe dementia may not be able to complete an interview/survey. Minor differences observed between symptoms and impacts reported by persons with dementia-related psychosis versus those reported by care partners could be related to differences in dementia severity. Persons with dementia-related psychosis for whom care partners completed this study were older, more likely to have had a dementia diagnosis for a longer period of time (ie, could be further along in the disease progression), less likely to have only mild cognitive impairment, and less likely to live independently relative to persons with dementia-related psychosis who completed the study independently. These characteristics may be more likely to be associated with more severe dementia and could influence the type of symptoms or level of insight into their

symptoms that patients in each group were most commonly experiencing. For instance, particularly in DLB, hallucinations often occur earlier in the progression of dementia when patients still have insight and can discuss their symptoms, whereas delusions occur later in the progression of dementia and can be more difficult for patients to be aware of and discuss (McKeith et al., 2017). Consistent with this, in the quantitative portion of this study, we observed a higher occurrence of hallucinations in self-reports and a higher occurrence of delusions in care partner reports. However, hallucinations still directly impacted the lives of patients with dementia-related psychosis, suggesting that even patients with less severe dementia could experience impactful hallucinations and/or delusions and benefit significantly from a safe and effective treatment. A greater percentage of care partners who completed the survey compared to persons with dementia-related psychosis who completed the survey also believed that individuals were generally uncomfortable discussing their symptoms. This is important in that strong stigma around experiencing psychosis and reduced confidence and increased social isolation reported in this study could prevent persons with dementia-related psychosis from talking to healthcare professionals or care partners about their symptoms. Publications that provide information on available treatments for dementia-related psychosis and increase awareness about dementia-related psychosis will help patients feel more comfortable discussing their symptoms and make them more likely to seek treatment to alleviate them.

This study has several limitations. Results are limited by the potential recall bias. The quantitative part of this study did not specifically exclude pairs of persons with dementia-related psychosis and their care partners, so it is possible that some pairs completed the survey, though the differences in characteristics reported in the two groups suggest that this was not common. Furthermore, most persons in the quantitative study reported a diagnosis of AD or Lewy body dementia (PD or DLB), and results may not be fully generalizable across all subtypes of dementia. External validity is also limited by the fact that a convenience sample and a self-selected sample were used for the qualitative and quantitative portions of the study, respectively. Because findings from the qualitative

interviewing portion of the study include primarily care partners and only 1 person with dementia-related psychosis, results may be biased toward what the care partner is able to observe about the individual's experience. Inclusion was also limited to individuals who could use the required technology; particularly for persons with dementia-related psychosis who participated, this could potentially skew results toward less severe dementias in these reports. Nonetheless, the consistency of the results from the qualitative interviews and quantitative survey as well as between self-reports and care partner reports supports the reliability of these findings.

The sample here is primarily white, and future research could expand upon these findings by collecting patient experience data from other racial and ethnic groups and examining similarities or differences in the patient experience of dementia-related psychosis based on ethnicity. Future studies could also directly capture care partners' perspectives and priorities with regard to symptom impacts and treatment needs, which may provide further insight into how to improve the lives of persons with dementia-related psychosis and their families.

Dementia-related psychosis is associated with considerable adverse outcomes for persons with dementia, and early identification and treatment could greatly improve outcomes (Fischer et al., 2020). Patient experience data from qualitative interviews describe hallucinations and delusions that have a substantial impact on the lives of individuals from a patient and care partner perspective and show that current treatment options do not address the most pressing symptoms. Quantitative analyses support these findings and clearly demonstrate that patients experience multiple types of symptoms and impacts of psychosis. A safe and effective therapy to improve symptoms and allow individuals to better distinguish reality from psychotic experiences is a strong, unmet clinical need.

Clinical implications

- Hallucinations and delusions caused persons with dementia-related psychosis to question their understanding of reality and decreased their confidence in engaging fully with daily life.

- Current treatment options did not address the most pressing symptoms of people with dementia-related psychosis.
- An ideal therapy would improve symptoms and allow individuals to better distinguish reality from psychotic experiences.

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Disclosure statement

Teresa Brandt, Bill Keller, and Victor Abler are employees of and may hold stock and/or stock options with Acadia Pharmaceuticals Inc.

Theresa Frangiosa is a consultant with Frangiosa & associates, LLC.

James Valentine works for Hyman, Phelps & McNamara, P. C., a law firm that represents Acadia Pharmaceuticals Inc.

Mark Price and Carla DeMuro are employees of RTI Health Solutions and RTI Health Solutions was hired by Acadia Pharmaceuticals Inc. to complete this work.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

All authors as well as the sponsor were involved in the design and conduct of the study; the collection, analysis, and interpretation of data; in the preparation of the manuscript; and in

the review or approval of the manuscript.

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