Factors Associated With Behavioral and Psychological Symptoms of Dementia: Prospective Observational Study Using Actigraphy

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Abstract

Background: Although disclosing the predictors of different behavioral and psychological symptoms of dementia (BPSD) is the first step in developing person-centered interventions, current understanding is limited, as it considers BPSD as a homogeneous construct. This fails to account for their heterogeneity and hinders development of interventions that address the underlying causes of the target BPSD subsyndromes. Moreover, understanding the influence of proximal factors—circadian rhythm–related factors (ie, sleep and activity levels) and physical and psychosocial unmet needs states—on BPSD subsyndromes is limited, due to the challenges of obtaining objective and/or continuous time-varying measures.

Objective: The aim of this study was to explore factors associated with BPSD subsyndromes among community-dwelling older adults with dementia, considering sets of background and proximal factors (ie, actigraphy-measured sleep and physical activity levels and diary-based caregiver-perceived symptom triggers), guided by the need-driven dementia-compromised behavior model.

Methods: A prospective observational study design was employed. Study participants included 145 older adults with dementia living at home. The mean age at baseline was 81.2 (SD 6.01) years and the sample consisted of 86 (59.3%) women. BPSD were measured with a BPSD diary kept by caregivers and were categorized into seven subsyndromes. Independent variables consisted of background characteristics and proximal factors (ie, sleep and physical activity levels measured using actigraphy and caregiver-reported contributing factors assessed using a BPSD diary). Generalized linear mixed models (GLMMs) were used to examine the factors that predicted the occurrence of BPSD subsyndromes. We compared the models based on the Akaike information criterion, the Bayesian information criterion, and likelihood ratio testing.

Results: Compared to the GLMMs with only background factors, the addition of actigraphy and diary-based data improved model fit for every BPSD subsyndrome. The number of hours of nighttime sleep was a predictor of the next day’s sleep and nighttime behaviors (odds ratio [OR] 0.9, 95% CI 0.8-1.0; P=.005), and the amount of energy expenditure was a predictor for euphoria or elation (OR 0.02, 95% CI 0.0-0.5; P=.02). All subsyndromes, except for euphoria or elation, were significantly associated with hunger or thirst and urination or bowel movements, and all BPSD subsyndromes showed an association with environmental change. Age, marital status, premorbid personality, and taking sedatives were predictors of specific BPSD subsyndromes.
Conclusions: BPSD are clinically heterogeneous, and their occurrence can be predicted by different contributing factors. Our results for various BPSD suggest a critical window for timely intervention and care planning. Findings from this study will help devise symptom-targeted and individualized interventions to prevent and manage BPSD and facilitate personalized dementia care.

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KEYWORDS
behavioral and psychological symptoms; dementia; older adults; actigraphy; sleep; activity; risk factors

Introduction

Behavioral and psychological symptoms of dementia (BPSD) constitute a core and prevalent feature of Alzheimer disease and related dementia [1], with most patients experiencing one or more types of symptoms over the course of the disease [2]. BPSD refer to frequently occurring symptoms of disturbed perception through content, mood, or behavior [3], which manifest into a wide range of forms, such as agitation, aggression, depression, apathy, wandering, and socially inappropriate behaviors [1]. Increasingly recognized as the most challenging aspect of dementia, BPSD present adverse outcomes, including decreased functioning and accelerated disease progression [4], and, if poorly managed, an increased risk of nursing home placement [5] and hospitalization [4,6,7]. BPSD are also associated with an increased burden on, and decreased quality of life of, caregivers [8-10].

Although BPSD are associated with neurological mechanisms of neurocognitive disease to some extent, previous studies have revealed that the actual occurrence of symptoms can be attributed to diverse personal factors (eg, medical conditions, premorbid personality, and physical and psychological unmet needs), social factors (eg, communication with caregivers, caregivers’ stress and depression, and lack of social activities), and environmental factors (eg, overstimulation and lack of established routines), rather than to neurocognitive impairment alone [11,12]. While a few studies have provided evidence that supports frequent co-occurrence of individual BPSD, others have contended that BPSD are distinct and heterogeneous and have different determinants and consequences [13-15]. Determining key factors that predict the different types of BPSD is the first step, since it would guide the determination of which strategies should be chosen to target the underlying causes and ultimately prevent or manage the symptoms [12,16,17].

We based this study on the need-driven dementia-compromised behavior (NDB) model [18]. In the NDB model, BPSD arise from the interaction of two types of factors: (1) relatively stable background factors, including sociodemographic characteristics; neurological, cognitive, and functional status; underlying health; and personality traits, and (2) proximal factors, which are fluctuating and changing states of physical and psychological unmet needs and immediate environmental conditions. To further explain stress-related proximal factors, we incorporated the progressively lowered stress threshold (PLST) model [19], which posits that individuals with dementia are increasingly unable to manage stress, as the threshold for stress tolerance lowers as the disease progresses. If heightened perceived stressors accumulate, then exceed the stress threshold, the person with dementia starts to exhibit BPSD [19-21]. The PLST model recognizes circadian rhythms as a factor that influences the stress threshold level and accordingly postulates that impaired sleep and inadequate physical activity level are among the stressors that consequently trigger BPSD [22,23].

Previous studies have recommended person-centered nonpharmacological interventions as the first-line treatment modality for managing BPSD given the limited efficacy and undesired adverse effects of antipsychotics [24-26]. However, the effect size of the existing nonpharmacological interventions for BPSD has been small [27]. Thus, caregivers and providers continue to struggle to implement the most effective interventions targeting the underlying cause of certain types of BPSD due to limited evidence for target symptoms [28]. Moreover, current knowledge of BPSD is limited, since most existing studies considered BPSD imprecisely as a unitary construct by using measures that aggregated symptoms, which failed to account for the heterogeneity of different types of BPSD [12,14,29]. Although a range of factors have been associated with BPSD occurrence in the literature, most studies focused on only one aspect by testing the effect of a single intervention, such as music therapy, environmental modification, or structured recreational activities [30,31]. A recent scoping review highlighted a gap in the research, namely that diverse factors, including personal, social, and environmental, have been studied only for depression [12]. Surprisingly, few predictive models in existing studies accounted jointly for the diverse factors [32,33].

A few studies found that sleep problems are associated with depression [34,35], apathy [35,36], agitation [37,38], and aggression [39]; however, efforts have been limited by the use of proxy-rated instruments for disturbed sleep [34,35,39]. Since caregiver-reported sleep measures require systemic and continuous observation of sleep behaviors, such a resource-intensive and time-consuming assessment may be infeasible in real-time care settings [40]. Further, as Blytt et al found significant discrepancies between proxy-rated sleep and actigraphy measures, proxy raters may underreport and fail to recognize sleep disturbances as compared with those measured by actigraphy [41].

Although physical activity has increasingly gained attention as a nonpharmacological approach to managing BPSD [42], few studies have examined the influence of physical activity on BPSD using observational rating instruments to measure activity level [43,44]. A study reported that physical activity objectively measured using actigraphy was significantly correlated with agitation and aggression but did not account for other potential factors [45]. In summary, surprisingly little is known about the
influence of circadian rhythms, including sleep and physical activity levels, on BPSD among community-dwelling older adults with dementia. This is due to the limited number of methodologically rigorous studies using objective measures, such as actigraphy, and accounting for personal, social, and environmental factors within a single study.

Understanding factors that predict BPSD subsyndromes is important not only for establishing early care planning for symptom prevention and management but for selecting the most effective person-centered interventions. Thus, this study explored factors associated with BPSD subsyndromes among community-dwelling older adults with dementia, considering background and proximal factors (ie, actigraphy-measured sleep and physical activity levels and diary-based caregiver-perceived symptom triggers), guided by the NDB model.

**Methods**

**Design**

This exploratory study employed a prospective observational design with two waves of data collection. Within each wave, background factors were collected at baseline, and repeated measures were collected for proximal factors over approximately 14 days. Reporting of this study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [46].

**Participants and Setting**

Older adults with dementia living at home were recruited from outpatient neurology clinics at two tertiary hospitals and daycare centers in Seoul and the Gyeonggi region in Korea. Inclusion criteria for older adults with dementia were as follows: aged at least 65 years, a diagnosis of dementia by a physician, a Mini–Mental State Examination (MMSE) score of less than 24, and exhibition of BPSD at least once a week, as screened using the Korean version of the Neuropsychiatric Inventory at baseline [47]. The primary caregivers who provided the majority of care for the recruited older adults with dementia, lived in the same home, and were able to read and write in Korean were also included.

**Procedure**

The Institutional Review Board of the affiliated institutions approved this study. Participants were recruited via on-site visits between June 2018 and June 2019. We conducted the second-wave data collection for participants who agreed to continue in the study between July 2019 and June 2020. The assessment and data collection were conducted by research staff that included registered nurses with a master’s degree and registered nurse research assistants with a bachelor’s degree. The research staff with a master’s degree taught the data collection protocol and trained the research assistants in on-site data collection. The research staff then contacted potential participants and explained the study purpose and procedures. All data collection was conducted at the participants’ homes. After obtaining written informed consent at baseline from caregivers who were screened for eligibility, family caregivers completed a structured questionnaire consisting of sociodemographic information and standardized scales for physical and neuropsychological assessments, with assistance from the research staff. Following the baseline assessments, we placed an actigraphy device on the participants’ wrists, and primary caregivers logged the BPSD manifestations into the BPSD diary on a daily basis for 14 consecutive days.

**Measures**

**Outcome Measure: BPSD**

Although the Neuropsychiatric Inventory [48] is a widely used tool to measure BPSD, its 2-week retrospective rating likely results in recall bias, since its rating reliability is dependent on caregiver training [49]. Therefore, we developed a BPSD diary, adapted from the Neuropsychiatric Inventory, to detect 12 behavioral and psychological symptoms commonly observed in patients with dementia on a daily basis: delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, elation or euphoria, apathy or indifference, disinhibition, irritability or lability, aberrant motor behavior, sleep and nighttime behavior, and appetite or eating disorders. The BPSD diary is a structured, easy-to-use checklist that allows a caregiver to record the presence and severity (ie, mild, moderate, and severe) of individual symptoms.

Although BPSD encompass heterogeneous symptoms, clustering a number of individual symptoms that are highly correlated and contiguently co-occur allows for a more meaningful interpretation of the study findings [17,50]. Moreover, use of subsyndromes rather than 12 individual symptoms can increase power, as the number of participants who endorse the symptom cluster will increase [51]. Since euphoria or elation, aberrant motor behavior, sleep and nighttime behavior, and appetite or eating disorders did not load on any clusters in previous studies [50-54], we included them as individual symptoms. The remaining eight symptoms were clustered as follows, based on results from factor analyses reported in the literature: (1) psychotic symptoms (hallucination and delusion), (2) affective symptoms (depression, anxiety, and apathy), and (3) hyperactivity (agitation or aggression, disinhibition, and irritability) [51,53-55].

**Proximal Factors**

**Sleep and Physical Activity**

Sleep and physical activity were objectively measured using actigraphy (the wGT3X-BT activity monitor; ActiGraph, LLC). Wrist actigraphy has been shown to be a reliable method by which to objectively measure sleep-wake cycles and is suitable for older adults with dementia [56,57]. Participants were asked to wear actigraphy devices on their nondominant wrist for 14 consecutive days starting on the day of the first visit. ActiLife software (version 6.13.3; ActiGraph, LLC) was used to evaluate actigraphy data and provide standard indices of sleep duration and fragmentation using vector magnitude counts in 60-second epoch data. We applied the Cole-Kripke algorithm to score a 1-minute epoch as asleep or awake [58]. We defined nighttime sleep as the time between 8 PM and 8 AM. We used total sleep time (TST) at night and wake time after sleep onset (WASO) at night as sleep parameters. The previous night’s sleep parameters were used as potential predictors of BPSD occurring the following day. We also used actigraphy-derived energy
expenditure (kcal burned × 100/hour) as a parameter of activity level. Energy expenditure measured for 24 hours was used as a potential predictor of BPSD occurring on the same day, which reflected the physical conditions during the day when BPSD were exhibited.

**Physiological Unmet Needs States and Interpersonal and Environmental Triggers**

We used a checklist, embedded within the BPSD diary, to assess contributing factors that family caregivers considered to be immediate triggers for symptoms that encompassed physiological unmet needs states and interpersonal and environmental triggers. On the checklist, the triggers were specifically listed as follows: hunger or thirst, urination or bowel movement, pain or discomfort, sleep disturbance, noise, light, temperature, interpersonal trigger related to a person or persons who were present when the symptom occurred, environmental change, and other. Caregivers were asked to check all contributing factors that were present on the same day when the BPSD were present on this daily-basis symptom checklist. When caregivers checked the “other” option, they were asked to provide a brief description of the triggers. Diary-based caregiver-reported contributing factors that were observed immediately prior to BPSD occurrence were used as potential predictors of BPSD occurring on the same day.

**Background Factors**

**Sociodemographic and Health Information**

Participants provided demographic data, including age, gender, marital status, and education level. Dementia diagnosis and neurological and psychiatric medications were obtained via medical chart review or interviews with family caregivers and staff at the recruitment sites.

**Cognitive and Functional Status**

The Korean version of the MMSE (K-MMSE) was administered to evaluate cognitive functioning at baseline. The highest total score is 30 points, with a higher score indicating better cognitive function [59]. The Cronbach α score for Korean older adults with dementia was .91 [60]. The Korean version of the Activities of Daily Living scale (K-ADL) was administered to measure baseline functional status. This measure consists of seven items that are rated on a 3-point Likert scale, with higher scores indicating more severe dependency. The K-ADL has been validated for Korean older adults with dementia who participated in the first wave. During the second wave of data collection, out of 64 eligible participants, 5 (8%) were excluded from the analysis due to no available actigraphy data (n=3) and no available BPSD diary data (n=2). Consequently, this study included a total of 145 older adults with dementia who participated in the first wave.

**Personality Type**

A family caregiver informant was asked to rate his or her family member’s premorbid personality using the Korean version of the Big Five Inventory (BFI-K) [62]. The BFI-K consists of 15 items that are rated on a 5-point Likert scale, which assess five domains of personality features, namely openness, conscientiousness, neuroticism, extroversion, and agreeableness. The instrument is known to be reliable, with Cronbach α scores ranging from .67 to .82 in a Korean sample [62].

**Statistical Analysis**

For descriptive statistics, categorical variables were expressed as the number of dementia patients by percentage, while continuous variables were presented as means and SDs. We used two-sample independent t tests and Fisher exact tests to compare the difference between data from waves 1 and 2 (Tables S1-S3 in Multimedia Appendix 1). We used generalized linear mixed models (GLMMs) to explore factors predictive of BPSD subsyndromes, with estimation of odds ratios (ORs) and 95% CIs. The GLMM, a commonly used random-effects model, was well suited to this analysis because the approach permits random effects and is suitable for nonnormal or discrete outcomes that are repeatedly measured for each subject [63,64]. All models included a random effect of participant with a random intercept to account for heterogeneity among individuals; all other factors were modeled as fixed effects [65]. Once we decided on the variables to be included in the final model based on clinical and theoretical relevance, we then calculated variance inflation factors to assess multicollinearity among variables. We found that the data were suitable for regression analyses, given that all variance inflation factors were <5, which indicated that no multicollinearity could be detected (Multimedia Appendix 2).

**Results**

**Background Characteristics**

During the first wave of data collection, we initially recruited 166 eligible participants. Out of these participants, 18 (10.8%) were lost to follow-up due to refusal to wear the actigraphy devices (n=10), hospitalization or emergency room visits (n=6), death (n=1), and absence of family caregivers at home during the study period (n=1). A total of 3 (1.8%) participants were excluded from the analysis due to no available actigraphy data. During the second wave of data collection, out of 64 eligible participants, 5 (8%) were excluded from the analysis due to no available actigraphy data (n=3) and no available BPSD diary data (n=2). Consequently, this study included a total of 145 older adults with dementia who participated in the first wave.
Of the 145 participants, 59 (40.7%) older adults with dementia continued to participate in the second wave. At baseline for the first wave, the participants’ mean age was 81.23 (SD 6.01) years, with a female to male ratio of approximately 3:2 (86/145, 59.3% female). Education level for most participants was elementary school or below. Participants had moderate cognitive impairment, as indicated by the K-MMSE mean score of 17.28 (SD 5.5); the mean score of the K-ADL was 10.57 (SD 3.6). Background characteristics of the 145 participants in the first wave at baseline are illustrated in Table 1; these characteristics are presented separately for the first and second waves in Table S1 in Multimedia Appendix 1.

Table 1. Background characteristics of older adults with dementia in the first wave at baseline.

| Variable                      | Value (N=145) |  |
|-------------------------------|---------------|---|
| Age (years), mean (SD)        | 81.23 (6.01)  |   |
| Gender, n (%)                 |               |   |
| Male                          | 59 (40.7)     |   |
| Female                        | 86 (59.3)     |   |
| Marital status, n (%)         |               |   |
| Married                       | 86 (59.3)     |   |
| Bereaved or divorced          | 59 (40.7)     |   |
| Education level, n (%)        |               |   |
| Elementary school or below    | 73 (50.3)     |   |
| Middle school                 | 14 (9.7)      |   |
| High school                   | 34 (23.4)     |   |
| College or above              | 24 (16.6)     |   |
| Total K-ADL^a score, mean (SD)| 10.57 (3.63)  |   |
| Total K-MMSE^b score, mean (SD)| 17.28 (5.51)  |   |
| Big Five Inventory score, mean (SD) |            |   |
| Openness                      | 8.60 (2.96)   |   |
| Conscientiousness             | 11.66 (2.73)  |   |
| Neuroticism                   | 7.74 (2.87)   |   |
| Extroversion                  | 8.49 (1.87)   |   |
| Agreeableness                 | 10.92 (2.96)  |   |
| Sedative (yes), n (%)         | 51 (35.2)     |   |
| Dementia type, n (%)          |               |   |
| Alzheimer disease             | 71 (49.0)     |   |
| Lewy body dementia            | 60 (41.4)     |   |
| Vascular dementia             | 23 (15.9)     |   |
| Other dementia                | 31 (21.4)     |   |

^aK-ADL: Korean version of the Activities of Daily Living scale.
^bK-MMSE: Korean version of the Mini–Mental State Examination.

Descriptive Statistics for BPSD Occurrence and Proximal Factors

Summary statistics of BPSD and proximal factors for the 2354 days that encompassed the first and second waves are presented in Table 2; these factors are presented separately for the first and second waves in Table S2 in Multimedia Appendix 1. Caregivers completed the BPSD diaries and participants wore actigraphy devices for a mean of 11.5 (SD 3.5) days. Of the 2354 days during which the symptoms were measured, the most frequently occurring BPSD subsyndrome was affective symptoms (n=548, 23.3%), followed by hyperactivity symptoms (n=350, 14.9%) and sleep and nighttime behaviors (n=275, 11.7%). Euphoria or elation (n=108, 4.6%) and aberrant motor behaviors (n=103, 4.4%) were relatively infrequent. The prevalence of BPSD across participants is also presented in Table S3 in Multimedia Appendix 1. The prevalence of affective symptoms was the highest (82/145, 56.6%), followed by hyperactivity (70/145, 48.3%).
The mean TST at night was 6.4 (SD 2.5) hours, and the mean WASO at night was 0.4 (SD 0.4) hours. The mean energy expenditure (100 kcal/hour) was 0.21 (SD 0.14). Among the diverse set of caregiver-reported contributing factors, the most frequently reported factor was sleep disturbance (276/2354, 11.7%). Urination or bowel movement (220/2354, 9.3%), pain or discomfort (190/2354, 8.1%), and interpersonal triggers (171/2354, 7.3%) were also relatively frequent.

Table 2. Summary statistics of BPSD subsyndromes and proximal factors.

| Value (N=2354 days) |
|---------------------|
| BPSD subsyndromes, n (%) |
| Days of recording BPSD and actigraphy per person, mean (SD) | 11.54 (3.50) |
| Psychotic symptoms | 234 (9.9) |
| Affective symptoms | 548 (23.3) |
| Hyperactivity symptoms | 350 (14.9) |
| Euphoria or elation | 108 (4.6) |
| Aberrant motor behavior | 103 (4.4) |
| Sleep and nighttime behavior | 275 (11.7) |
| Appetite or eating disorders | 193 (8.2) |

Proximal factors

| Sleep- and energy-related factors, mean (SD) |
|--------------------------------------------|
| Total sleep time (hours at night) | 6.44 (2.52) |
| Wake time after sleep onset (hours at night) | 0.43 (0.36) |
| Energy expenditure (100 kcal/hour) | 0.21 (0.14) |

| Caregiver-reported contributing factors, n (%) |
|-----------------------------------------------|
| Hunger or thirst | 149 (6.3) |
| Urination or bowel movement | 220 (9.3) |
| Pain or discomfort | 190 (8.1) |
| Sleep disturbance | 276 (11.7) |
| Noise | 76 (3.2) |
| Light | 69 (2.9) |
| Temperature | 103 (4.4) |
| Interpersonal trigger | 171 (7.3) |
| Environmental change | 87 (3.7) |
| Other | 238 (10.1) |

aBPSD: behavioral and psychological symptoms of dementia.

GLMMs Predicting BPSD Subsyndromes From Background and Proximal Factors

In the first step, the GLMMs for each BPSD subsyndrome were assessed with only background factors included in the models (Model 1; see results in Tables S1 and S2 in Multimedia Appendix 3). Based on Model 1, proximal factors—actigraphy-measured sleep and activity levels and diary-based caregiver-reported symptom triggers—were entered into Model 2. Table 3 presents $P$ values of the likelihood ratio tests as well as the respective AIC and BIC scores for Models 1 and 2 for each BPSD subsyndrome. Likelihood ratio testing comparing Model 1, which consisted of only background factors, with Model 2 (ie, the full model), which included both background and proximal factors, showed that the full model had superior fit for every subsyndrome ($P<.001$). Goodness-of-fit statistics (ie, lower AIC and BIC values) indicated that models for every subsyndrome improved with the addition of proximal factors.
Table 3. Comparisons of generalized linear mixed models.

| Outcomes (BPSD<sup>a</sup> subsyndromes) | Background factors (Model 1) | Background factors + proximal factors (Model 2) | P value<sup>b</sup> |
|-----------------------------------------|------------------------------|-----------------------------------------------|-------------------|
|                                         | AIC<sup>c</sup>              | BIC<sup>d</sup>                              | AIC               | BIC               |
| Psychotic symptoms                     | 872.94                       | 993.98                                       | 756.84            | 952.81            | <.001 |
| Affective symptoms                     | 1683.85                      | 1804.89                                     | 1379.99           | 1575.96           | <.001 |
| Hyperactivity symptoms                 | 1278.41                      | 1399.46                                     | 1064.87           | 1260.84           | <.001 |
| Euphoria or elation                    | 689.12                       | 810.17                                      | 587.68            | 783.65            | <.001 |
| Aberrant motor behaviors               | 525.33                       | 646.37                                      | 442.19            | 638.16            | <.001 |
| Sleep and nighttime behaviors          | 1215.43                      | 1336.47                                     | 957.22            | 1153.20           | <.001 |
| Appetite or eating disorders           | 882.84                       | 1003.88                                     | 792.87            | 988.84            | <.001 |

<sup>a</sup>BPSD: behavioral and psychological symptoms of dementia.

<sup>b</sup>P values were calculated by the likelihood ratio test.

<sup>c</sup>AIC: Akaike information criterion.

<sup>d</sup>BIC: Bayesian information criterion.

Factors Predictive of BPSD Subsyndromes

The results of the GLMMs of background and proximal factors as predictors of BPSD subsyndromes are depicted in forest plots in Figures 1 and 2 and displayed in Tables S1 and S2 in Multimedia Appendix 4. The results are also summarized below for each subsyndrome.

**Figure 1.** Forest plots of odds ratios (with 95% CIs shown as whiskers) for the influence of background and proximal factors on psychotic symptoms, affective symptoms, hyperactivity symptoms, and euphoria or elation. ADL: Activities of Daily Living scale; MMSE: Mini–Mental State Examination; BFI: Big Five Inventory; ref.: reference; WASO: wake time after sleep onset.
Figure 2. Forest plots of odds ratios (with 95% CIs shown as whiskers) for the influence of background and proximal factors on aberrant motor behavior, sleep and nighttime behaviors, and appetite or eating disorders. ADL: Activities of Daily Living scale; MMSE: Mini–Mental State Examination; BFI: Big Five Inventory; ref.: reference; WASO: wake time after sleep onset.

Psychotic Symptoms

Regarding proximal factors, patients were more likely to exhibit psychotic symptoms on the same day if they were exposed to environmental change (OR 14.7, 95% CI 5.3-40.8; \( P < .001 \)) or inadequate light (OR 7.8, 95% CI 1.5-40.7; \( P = .02 \)). Patients were more likely to exhibit psychotic symptoms (OR 8.8, 95% CI 3.6-21.7; \( P < .001 \)) if they had sleep disturbance observed and reported by caregivers as well as pain or discomfort (OR 4.4, 95% CI 1.9-10.3; \( P < .001 \)), urination or bowel movement–related problems (OR 3.1, 95% CI 1.4-6.9; \( P = .005 \)), or hunger or thirst (OR 2.6, 95% CI 1.1-6.4; \( P = .03 \)).

Background factors significantly associated with psychotic symptoms were educational attainment at the middle school level (OR 10.2, 95% CI 1.5-70.1; \( P = .02 \)), greater impairment in activities of daily living (ADLs) (OR 1.3, 95% CI 1.1-1.7; \( P = .01 \)), taking sedatives (OR 4.6, 95% CI 1.0-21.1; \( P = .049 \)), and high conscientiousness traits (OR 0.8, 95% CI 0.6-1.0; \( P = .02 \)).

Affective Symptoms

Of environmental condition–related proximal factors, increased likelihood of affective symptoms was significantly associated with noise (OR 12.1, 95% CI 4.5-32.4; \( P < .001 \)), inadequate light (OR 5.1, 95% CI 1.5-17.4; \( P = .01 \)), inadequate temperature (OR 2.9, 95% CI 1.2-7.1; \( P = .02 \)), and being exposed to environmental change (OR 2.4, 95% CI 1.2-4.9; \( P = .02 \)). Of proximal factors associated with physical unmet needs states, affective symptoms were more likely to be exhibited by patients with pain or discomfort (OR 8.6, 95% CI 4.6-16.4; \( P < .001 \)), sleep disturbance (OR 5.3, 95% CI 3.3-8.7; \( P < .001 \)), urination or bowel movement problems (OR 3.5, 95% CI 2.0-6.1; \( P < .001 \)), or hunger or thirst (OR 2.3, 95% CI 1.2-4.6; \( P = .02 \)). Interpersonal triggers related to a person or persons who were
present with the patients with dementia were also significantly associated with an increased likelihood of affective symptoms (OR 8.4, 95% CI 4.8-14.6; P<.001).

Background factors significantly associated with affective symptoms included agreeable personality traits (OR 1.2, 95% CI 1.0-1.3; P=.03), greater impairment in ADLs (OR 1.1, 95% CI 1.0-1.3; P=.03), and educational attainment at the middle school level (OR 0.2, 95% CI 0.0-0.6; P=.005).

**Hyperactivity Symptoms**

With respect to proximal factors, patients were more likely to exhibit hyperactivity symptoms if they experienced pain or discomfort (OR 8.8, 95% CI 4.6-16.9; P<.001), hunger or thirst (OR 4.5, 95% CI 2.1-9.5; P<.001), urination or bowel movement problems (OR 4.2, 95% CI 2.2-8.0; P<.001), or sleep disturbance (OR 3.0, 95% CI 1.7-5.2; P<.001). Increased likelihood of hyperactivity symptoms was also predicted by being exposed to noise (OR 8.5, 95% CI 3.2-22.6; P<.001) and environmental change (OR 4.9, 95% CI 2.1-11.8; P<.001). Interpersonal triggers also increased the predicted odds of hyperactivity symptoms (OR 7.6, 95% CI 4.0-14.4; P<.001).

Background factors that increased the predicted odds of hyperactivity symptoms were greater impairment in ADLs (OR 1.1, 95% CI 1.0-1.3; P=.04) and taking sedatives (OR 2.5, 95% CI 1.1-5.9; P=.03).

**Euphoria or Elation**

Regarding proximal factors, patients with greater levels of energy expenditure (100 kcal/hour) measured by actigraphy were less likely to exhibit euphoria or elation on the same day (OR 0.02, 95% CI 0.0-0.5; P=.02). In contrast, patients who were exposed to environmental change (OR 19.7, 95% CI 7.5-51.7; P<.001) or interpersonal triggers (OR 13.0, 95% CI 6.0-28.4; P<.001) were more likely to show symptoms of euphoria or elation.

Background factors significantly associated with euphoria or elation included diagnosis of Alzheimer disease (OR 5.7, 95% CI 1.4-23.6; P=.02), bereavement or divorced status (OR 4.9, 95% CI 1.4-17.1; P=.01), and high conscientiousness traits (OR 1.3, 95% CI 1.0-1.6; P=.046).

**Aberrant Motor Behaviors**

Of proximal factors, environmental condition–related factors that increased the likelihood of aberrant motor behaviors were being exposed to noise (OR 21.6, 95% CI 5.0-93.5; P<.001), inadequate temperature (OR 5.8, 95% CI 1.6-21.3; P=.008), and environmental change (OR 5.6, 95% CI 1.2-26.6; P=.03). In contrast, light was significantly associated with decreased likelihood of such behaviors (OR 0.1, 95% CI 0.0-0.8; P=.03). Patients were more likely to exhibit BSDP behaviors if they had pain or discomfort (OR 18.0, 95% CI 6.9-47.1; P<.001), sleep disturbance (OR 6.4, 95% CI 2.7-14.9; P<.001), hunger or thirst (OR 3.6, 95% CI 1.1-11.2; P=.03), or urination or bowel movement problems (OR 3.2, 95% CI 1.2-8.3; P=.02).

Background factors significantly associated with aberrant motor behaviors were greater impairment in ADLs (OR 1.3, 95% CI 1.1-1.6; P=.01), higher K-MMSE score (OR 1.2, 95% CI 1.0-1.3; P=.048), older age (OR 0.9, 95% CI 0.8-1.0; P=.02), high extroversion traits (OR 0.7, 95% CI 0.5-0.9; P=.01), and taking sedatives (OR 0.2, 95% CI 0.0-0.7; P=.02).

**Sleep and Nighttime Behaviors**

Among proximal factors, greater numbers of total nighttime sleep hours measured by actigraphy were significantly associated with decreased likelihood of sleep and nighttime behaviors occurring the next day (OR 0.9, 95% CI 0.8-1.0; P=.005). In contrast, patients were more likely to exhibit sleep and nighttime behaviors given sleep disturbance observed and reported by caregivers (OR 19.4, 95% CI 11.6-32.7; P<.001), urination or bowel movement problems (OR 7.7, 95% CI 4.0-14.7; P<.001), or hunger or thirst (OR 4.6, 95% CI 2.2-9.6; P<.001). Increased odds of sleep and nighttime behaviors were also associated with environmental change (OR 5.9, 95% CI 2.4-14.6; P<.001), inadequate temperature (OR 4.0, 95% CI 1.6-10.2; P=.003), and noise (OR 2.7, 95% CI 1.0-6.8; P=.04). None of the background factors were significantly associated with the likelihood of sleep and nighttime behaviors.

**Appetite or Eating Disorders**

Of proximal factors, increased likelihood of appetite or eating disorders was associated with exposure to environmental change (OR 11.1, 95% CI 4.2-29.3; P<.001), inadequate lighting (OR 3.4, 95% CI 1.1-10.8; P=.03), and inadequate temperature (OR 2.9, 95% CI 1.1-8.0; P=.04). Patients were also more likely to exhibit appetite or eating disorders on the same day if they experienced hunger or thirst (OR 8.5, 95% CI 4.0-18.1; P<.001) or urination or bowel movement problems (OR 6.0, 95% CI 2.9-12.6; P<.001). Interpersonal triggers also predicted an increased likelihood of appetite or eating disorders (OR 2.2, 95% CI 1.0-4.6; P=.04). The openness trait was the only background factor that significantly predicted appetite or eating disorders (OR 1.3, 95% CI 1.1-1.6; P=.003).

**Discussion**

**Principal Findings**

Although BPSD are recognized to arise from background and proximal factors, it is unclear exactly how the different BPSD subsyndromes are influenced by specific proximal factors, such as sleep and physical activity levels and physical and psychosocial unmet needs states. This study explored factors associated with BPSD subsyndromes among community-dwelling older adults with dementia, including sets of background and proximal factors (ie, actigraphy-measured sleep and activity levels and diary-based caregiver-perceived symptom triggers) guided by the NDB model. This research expanded upon the limited previous research by using actigraphy and diary-based assessments, thereby enabling the collection of objective and/or continuous time-varying proximal data.

**The Effects of Proximal Factors on the Occurrence of BPSD Subsyndromes**

Our results demonstrated that BPSD subsyndromes were predictable based on proximal factors, including actigraphy-measured sleep and activity levels and diary-based...
caregiver-reported symptom triggers. The models to predict BPSD subsyndromes demonstrated better predictive ability when both background and proximal factors served as predictors in the models compared to those with only background factors. While BPSD have been largely considered unpredictable [17] and few previous studies have considered the impact of preventative approaches to BPSD [11], our results support a paradigm shift to an individualized approach to BPSD subsyndromes through prediction and early prevention. In particular, caregiver-reported physical, psychosocial, and environmental triggers largely influenced most subsyndromes, except for euphoria or elation. This suggests that, despite the unmodifiable nature of background factors, most BPSD can be prevented through early identification of at-risk individuals and timely assessment of targeted physical and psychosocial unmet needs.

However, it remains unclear as to which BPSD subsyndromes are under circadian control (ie, influenced by sleep and activity levels). In this study, greater nighttime sleep hours were associated with a lower likelihood of sleep and nighttime behaviors, manifested as nighttime awakening or excessive daytime napping, occurring the next day. This finding is consistent with previous studies, in that sleep problems are both a risk factor and a symptom outcome [66,67]. In previous studies, the association between sleep disturbance and BPSD has been inconsistent and variable among different BPSD. For example, a previous study of a Korean sample found that more severe sleep impairment, measured by the Korean version of the Pittsburgh Sleep Quality Index (PSQI) [68], was significantly associated with apathy or indifference, but not with other types of symptoms [69]. In another study conducted in China, the total scores of the PSQI and its subscales were significantly correlated with depression, apathy, and sleep and nighttime behaviors [35]. Moreover, one study of a hospitalized sample noted that the average number of sleep minutes significantly predicted agitation and irritability [37]; another study of nursing home residents with severe dementia found that a greater number of nighttime sleep hours was a predictor of daytime aggressive behaviors [70]. One possible explanation for the nonsignificant relationship between sleep parameters and aggression in our study could lie in the differences in sample characteristics. Given that the mean K-MMSE score in our sample indicated moderate cognitive impairment, nighttime sleep perhaps affects aggression when cognitive impairment is severe. Regarding the activity level, euphoria or elation was associated with energy expenditure measured by actigraphy. A previous study showed that an increased physical activity level was associated with an increased likelihood of agitation and aggression in hospitalized patients with severe dementia [45]. This may be because increased physical activities could reflect heightened agitation and aggressive symptoms per se rather than physical exercise. To summarize, it still remains unclear as to which BPSD subsyndromes are under circadian control. The inconsistent results among prior studies call for further research to build on extant knowledge.

**Implications for Different Approaches to Heterogeneous BPSD Subsyndromes**

While the NDB model explains the effect of the interplay between background and proximal factors on the broad construct of BPSD [71], the findings from this study extend the NDB model by indicating which specific background and proximal factors exert their effects on which specific BPSD subsyndromes. For example, while a greater number of nighttime sleep hours was associated with attenuated likelihood of sleep and nighttime behaviors occurring the next day, nighttime sleep hours did not influence other BPSD subsyndromes. While physical unmet needs states (eg, pain or discomfort, sleep disturbance, and hunger or thirst) and physical environmental conditions (eg, noise and lighting) were significant factors associated with affective symptoms, they were not found to influence symptoms of euphoria or elation. Instead, actigraphy-measured energy expenditure was a proximal factor that predicted euphoria or elation, whereas it did not influence any other symptoms. Thus, the results underscore that etiological-based differentiated interventions are needed to focus on the factors underlying the target BPSD subsyndromes [17].

Accordingly, our study provides empirical evidence regarding the heterogeneity of BPSD [13-15] by revealing the distinct underlying predictors for the seven BPSD subsyndromes. Results showed that there were multiple predictors of all BPSD; however, the mechanisms underlying how a set of neurobiological, psychosocial, and environmental factors interplay and subsequently result in specific symptoms remain elusive [72]. Since the etiopathogenesis of BPSD is complex, multifactorial, and variable depending on the BPSD subsyndromes or individual symptoms [12,72], it is challenging for health care providers and caregivers to decide which interventions should be used to manage certain types of symptoms. Several interventional algorithms have been proposed to simplify complex information on the relationships among multifactorial factors and make it usable, such as the Describe, Investigate, Create, and Evaluate (DICE) approach [11,73] and the BPSD–Describe and Measure, Analyze, Treat, and Evaluate (DATE) algorithm [72]. Although the algorithms have been helpful for caregivers to simplify the complex nature of heterogeneous BPSD trajectories, further research is needed to develop predictive models that will guide health care providers and caregivers to move toward personalized BPSD care. Our study represents a starting point for developing more data-driven predictive algorithms tailored to BPSD subsyndromes to advance more precise BPSD care.

**Advancing BPSD Research and Practice by Leveraging Digital Health Technologies**

The results also facilitate the use of technological advances to achieve personalized BPSD care. Assessment of BPSD has largely relied on information reported by informal or formal caregivers, which has resulted in information bias and caregiver burden [74]. While the traditional nomothetic approach to assessment of BPSD has limitations in terms of capturing the unique trajectories of BPSD manifestations and their contexts, human behavior and psychology research has considered idiographic approaches to capture prospective and...
time-dependent variation within individuals [75]. Our study demonstrates the potential of using real-world data to measure fluctuating contextual information by leveraging digital health technologies to advance BPSD research and practice using an idiographic and personalized approach. Although concerns may exist regarding applying actigraphy to patients with dementia, our results demonstrated the feasibility of assessing sleep and activity levels using actigraphy in individuals with dementia, as evidenced by relatively low attrition rates and low amounts of missing data.

Along with the objectively measured actigraphy data, the results of the GLMMs revealed the large magnitude of the associations between diary-based caregiver-perceived symptom triggers and BPSD subsyndromes, which indicates the importance of collateral information from caregivers for predicting BPSD subsyndromes. Information and communications technologies (ICTs) can be a solution to complement paper-based symptom diaries by allowing the collection of high-frequency contextual information on BPSD that is episodic and evolves over time [76]. Future studies could adopt mobile app–based symptom diaries, which would facilitate the tracking and monitoring of BPSD by using push notifications to ensure measurements are not missed and to assist caregivers in easily checking symptoms anywhere and anytime with their mobile phones. Ecological momentary assessment (EMA) [77] is a promising tool that could be incorporated into mobile app–based symptom diaries. EMA data collected using electronic diaries could capture the momentary aspects of BPSD occurrence, rather than relying on recall over time and how BPSD manifestations vary over time and situations through repeated assessments [77]. Moreover, integrating prediction models into digital devices, such as smartphones, or connecting them to electronic health records could further improve the clinical utility of prediction models.

**Limitations**

Several limitations should be noted. First, we used a proxy measure of BPSD based on caregivers’ reporting, rather than direct observation of symptoms, which may have introduced observer and recall bias. Second, because BPSD and caregiver-reporting contributing factors were checked on a daily rather than episodic basis, caregivers could check multiple types of symptoms and related triggers if different types of symptoms were observed within a day. This may have made it difficult to identify the caregiver-reported factors that contributed to specific types of BPSD that occurred during the day. Future mobile app–based symptom diaries that collect episodic data would make it possible to disentangle aggregated proximal factors and symptoms that occur within a day. Finally, although it was not within the scope of this study, the bidirectionality of the relationships between proximal factors and BPSD is unclear in the current literature. A more thorough understanding of the reciprocal effects of sleep and physical activity levels with BPSD is needed to understand the mechanisms that underly the associations.

**Conclusions**

In conclusion, this prospective study demonstrated that BPSD are clinically heterogeneous, and their occurrence can be predicted by different contributing factors. Our results for various BPSD suggest a critical window for timely intervention and care planning. These findings represent the starting point for the establishment of a prediction model tailored to specific symptoms. However, further studies with larger samples are needed to confirm these findings. Nonetheless, these findings will assist in devising symptom-targeted and individualized interventions to prevent and manage different types of BPSD and to ultimately facilitate personalized dementia care.

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**Authors’ Contributions**

EC contributed to the study concept and design. SK, SH, EK, JHL, and BSY were responsible for acquisition of the data. EC, BK, and S-JH analyzed and interpreted the data and drafted the manuscript. All authors participated in the interpretation of the results and revision of the manuscript. All authors have read and approved the final manuscript.

**Conflicts of Interest**

None declared.

**Multimedia Appendix 1**

Background characteristics of older adults with dementia, summary statistics of behavioral and psychological symptoms of dementia (BPSD) and proximal factors, and summary statistics for the prevalence of BPSD subsyndromes.

[DOCX File, 23 KB-Multimedia Appendix 1]

**Multimedia Appendix 2**

Summary statistics for the prevalence of behavioral and psychological symptoms of dementia (BPSD) subsyndromes.

[DOCX File, 17 KB-Multimedia Appendix 2]
Multimedia Appendix 3

Results of generalized linear mixed models (GLMMs) for psychotic, affective, and hyperactivity symptoms and euphoria or elation (Model 1) and results of GLMMs for aberrant motor behaviors, sleep and nighttime behaviors, and appetite or eating disorders (Model 1).

[DOCX File, 21 KB-Multimedia Appendix 3]

Multimedia Appendix 4

Results of generalized linear mixed models (GLMMs) for psychotic, affective, and hyperactivity symptoms and euphoria or elation (Model 2, full model) and results of GLMMs for aberrant motor behaviors, sleep and nighttime behaviors, and appetite or eating disorders (Model 2, full model).

[DOCX File, 26 KB-Multimedia Appendix 4]

References

1. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, et al. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Dement 2011 Sep;7(5):532-539 [FREE Full text] [doi: 10.1016/j.jalz.2011.05.2410] [Medline: 21889116]

2. Zhao Q, Tan L, Wang H, Jiang T, Tan M, Tan L, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. J Affect Disord 2016 Jan 15;190:264-271. [doi: 10.1016/j.jad.2015.09.069] [Medline: 26540080]

3. Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and symptoms of dementia: A consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr 1996;8 Suppl 3:497-500. [doi: 10.1017/s1041610296000943] [Medline: 9154615]

4. Wancata J, Windhaber J, Krautgartner M, Alexandrowicz R. The consequences of non-cognitive symptoms of dementia in medical hospital departments. Int J Psychiatry Med 2003;33(3):257-271. [doi: 10.2190/ABXK-FMWG-98YP-D1CU] [Medline: 15089007]

5. Zuidema S, Koopmans R, Verhey F. Prevalence and predictors of neuropsychiatric symptoms in cognitively impaired nursing home patients. J Geriatr Psychiatry Neurol 2007 Mar;20(1):41-49. [doi: 10.1177/0891988706292762] [Medline: 17341770]

6. Herrmann N, Lancot KL, Sambrook R, Lesnikova N, Hébert R, McCracken P, et al. The contribution of neuropsychiatric symptoms to the cost of dementia care. Int J Geriatr Psychiatry 2006 Oct;21(10):972-976. [doi: 10.1002/gps.1594] [Medline: 16955429]

7. O'Brien JA, Caro JJ. Alzheimer's disease and other dementia in nursing homes: Levels of management and cost. Int Psychogeriatr 2001 Sep;13(3):347-358. [doi: 10.1017/s1041610201007736] [Medline: 11768381]

8. Kunik ME, Snow AL, Davila JA, McNeese T, Steele AB, Balasubramanyam V, et al. Consequences of aggressive behavior in patients with dementia. J Neuropsychiatry Clin Neurosci 2010;22(1):40-47. [doi: 10.1176/jnp.2010.22.1.40] [Medline: 20160208]

9. Ornstein K, Gaugler JE. The problem with "problem behaviors": A systematic review of the association between individual patient behavioral and psychological symptoms and caregiver depression and burden within the dementia patient-caregiver dyad. Int Psychogeriatr 2012 Oct;24(10):1536-1552 [FREE Full text] [doi: 10.1017/S1041610212000737] [Medline: 22612881]

10. Baharudin AD, Din NC, Subramaniam P, Razali R. The associations between behavioral-psychological symptoms of dementia (BPSD) and coping strategy, burden of care and personality style among low-income caregivers of patients with dementia. BMC Public Health 2019 Jun 13;19(Suppl 4):447 [FREE Full text] [doi: 10.1186/s12889-019-6868-2] [Medline: 31196141]

11. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ 2015 Mar 02;350:h369 [FREE Full text] [doi: 10.1136/bmj.h369] [Medline: 25731881]

12. Kolanowski A, Boltz M, Galik E, Gitlin LN, Kales HC, Resnick B, et al. Determinants of behavioral and psychological symptoms of dementia: A scoping review of the evidence. Nurs Outlook 2017;65(5):515-529 [FREE Full text] [doi: 10.1016/j.outlook.2017.06.006] [Medline: 28826872]

13. Volicer L. Review of programs for persons facing death with dementia. HealthCare (Basel) 2019 Apr 15;7(2):1-12 [FREE Full text] [doi: 10.3390/healthcare7020062] [Medline: 30991668]

14. Volicer L, Galik E. Agitation and aggression are 2 different syndromes in persons with dementia. J Am Med Dir Assoc 2018 Dec;19(12):1035-1038. [doi: 10.1016/j.jamda.2018.07.014] [Medline: 30197272]

15. Kang B, Karel MJ, Corazzini KN, McConnell ES. A mixed methods study on the manifestations of behavioural symptoms of dementia among veterans with and without posttraumatic stress disorder. J Adv Nurs 2021 May 30:3176-3188. [doi: 10.1111/jan.14864] [Medline: 33969916]

16. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA 2012 Nov 21;308(19):2020-2029 [FREE Full text] [doi: 10.1001/jama.2012.36918] [Medline: 23168825]
17. Tanev KS, Winokur A, Pitman RK. Sleep patterns and neuropsychiatric symptoms in hospitalized patients with dementia. Front Neurol 2012;3:73 [FREE Full text] [doi: 10.3389/fneur.2012.00073] [Medline: 22586419]

18. Algase DL, Beck C, Kolanowski A, Whall A, Berent S, Richards K, et al. Need-driven dementia-compromised behavior: An alternative view of disruptive behavior. Am J Alzheimers Dis Other Demen 2016 Sep;41(6):10-19. [doi: 10.1177/153331759601100603]

19. Hall GR, Buckwalter KC. Progressively lowered stress threshold: A conceptual model for care of adults with Alzheimer's disease. Arch Psychiatr Nurs 1987 Dec;1(6):399-406. [Medline: 3426250]

20. Smith M, Hall GR, Gerdner L, Buckwalter KC. Application of the progressively lowered stress threshold model across the continuum of care. Nurs Clin North Am 2006 Mar;41(1):57-81, vi. [doi: 10.1016/cnur.2005.09.006] [Medline: 16492454]

21. Smith M, Gerdner LA, Hall GR, Buckwalter KC. History, development, and future of the progressively lowered stress threshold: A conceptual model for dementia care. J Am Geriatr Soc 2004 Oct;52(10):1755-1760. [doi: 10.1111/j.1532-5415.2004.52473.x] [Medline: 15450057]

22. Richards KC, Beck CK. Progressively lowered stress threshold model: Understanding behavioral symptoms of dementia. J Am Geriatr Soc 2004 Oct;52(10):1774-1775. [doi: 10.1111/j.1532-5415.2004.52477.x] [Medline: 15450062]

23. Volcier L, Hurley AC. Management of behavioral symptoms in progressive degenerative dementias. J Gerontol A Biol Sci Med Sci 2003 Sep;58(9):M837-M845. [doi: 10.1093/gerona/58.9.m837] [Medline: 14528041]

24. Lyketsos CG, Colenda CC, Beck C, Blank K, Doraiswamy MP, Kalunian DA, Task Force of American Association for Geriatric Psychiatry. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. Am J Geriatr Psychiatry 2006 Jul;14(7):561-572. [doi: 10.1097/01.JGP.0000221334.65330.55] [Medline: 16816009]

25. APA Work Group on Alzheimer's Disease and Other Dementias, Rabins PV, Blacker D, Rovner BW, Rummans T, Schneider LS, Steering Committee on Practice Guidelines, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry 2007 Dec;164(12 Suppl):5-56. [Medline: 18340692]

26. Reus VI, Fromholtz LJ, Eyler AE, Hilty DM, Horvitz-Lennon M, Jibson MD, et al. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. Am J Psychiatry 2016 May 01;173(5):543-546. [doi: 10.1176/appi.ajp.2015.173301] [Medline: 27133416]

27. Dyer SM, Harrison SL, Laver K, Whitehead C, Crotty M. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. Int Psychogeriatr 2018 Mar;30(3):295-309. [doi: 10.1017/S1041610217002344] [Medline: 29143695]

28. Kales HC, Gitlin LN, Lyketsos CG. When less is more, but still not enough: Why focusing on limiting antipsychotics in people with dementia is the wrong policy imperative. J Am Med Dir Assoc 2019 Sep;20(9):1074-1079 [FREE Full text] [doi: 10.1016/j.jamda.2019.05.022] [Medline: 31399358]

29. Gitlin L, Winter L, Dennis M, Hodgson N, Hauck W. Targeting and managing behavioral symptoms in individuals with dementia: A randomized trial of a nonpharmacological intervention. J Am Geriatr Soc 2010 Aug;58(8):1465-1474 [FREE Full text] [doi: 10.1111/j.1532-5415.2010.02971.x] [Medline: 20662955]

30. Majić T, Pluta JP, Mell T, Treusch Y, Gutzmann H, Rapp MA. Correlates of agitation and depression in nursing home residents with dementia. Int Psychogeriatr 2018;30(11):1779-1789. [doi: 10.1017/S104161021800066X] [Medline: 22591584]

31. Scales K, Zimmerman S, Miller SJ. Evidence-based nonpharmacological practices to address behavioral and psychological symptoms of dementia. Gerontologist 2018 Jan 18;58(suppl_1):S88-S102 [FREE Full text] [doi: 10.1093/gerona/58.1.m837] [Medline: 29361069]

32. Beck C, Richards K, Lambert C, Doan R, Landes RD, Whall A, et al. Factors associated with problematic vocalizations in nursing home residents with dementia. Gerontologist 2011 Jun;51(3):389-405 [FREE Full text] [doi: 10.1093/geront/gnq129] [Medline: 21292752]

33. Morgan RO, Sail KR, Snow AL, Davila JA, Fouladi NN, Kunik ME. Modeling causes of aggressive behavior in patients with dementia. Gerontologist 2013 Oct;53(5):738-747. [doi: 10.1093/geront/gns129] [Medline: 23103521]

34. Arbus C, Gardette V, Cantet CE, Andrieu S, Nourhashemi F, Schmitt L, REAL.FR Group. Incidence and predictive factors of depressive symptoms in Alzheimer's disease: The REAL.FR study. J Nutr Health Aging 2011 Aug;15(8):609-617. [doi: 10.1007/s12603-011-0061-1] [Medline: 21968854]

35. Zhou G, Liu S, Yu X, Zhao X, Ma L, Shan P. High prevalence of sleep disorders and behavioral and psychological symptoms of dementia in late-onset Alzheimer disease: A study in Eastern China. Medicine (Baltimore) 2019 Dec;98(50):e18405 [FREE Full text] [doi: 10.1097/MD.0000000000018405] [Medline: 31852160]

36. Mulin E, Zetzler JM, Friedman L, Le Duff F, Yesavage J, Robert PH, et al. Relationship between apathy and sleep disturbance in mild and moderate Alzheimer's disease: An actigraphic study. J Alzheimers Dis 2011;25(1):85-91. [doi: 10.3233/JAD-2011-101701] [Medline: 21335662]

37. Tanev KS, Winokur A, Pitman RK. Sleep patterns and neuropsychiatric symptoms in hospitalized patients with dementia. J Neuropsychiatry Clin Neurosci 2017;29(3):248-253 [FREE Full text] [doi: 10.1176/appi.neuropsych.16090166] [Medline: 28294708]
38. Rose K, Beck C, Tsai P, Liem P, Davila D, Kleban M. Sleep disturbances and nocturnal agitation behaviors in older adults with dementia. Sleep 2011;34(6):779-786. [doi: 10.5665/sleep.1048]

39. Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA. Sleep disturbance in mild to moderate Alzheimer's disease. Sleep Med 2005 Jul;6(4):347-352. [doi: 10.1016/j.sleep.2004.12.005] [Medline: 15978517]

40. Hjetland GJ, Nordhus IH, Pallesen S, Cummings J, Tractenberg RE, Thun E, et al. An actigraphy-based validation study of the sleep disorder inventory in nursing home patients. Front Psychiatry 2020;11:173 [Full text] [doi: 10.3389/fpsyg.2020.00173] [Medline: 32231600]

41. Blytt KM, Bjorvatn B, Husebo B, Flo E. Clinically significant discrepancies between sleep problems assessed by standard clinical tools and actigraphy. BMC Geriatr 2017 Oct 27;17(1):253 [Full text] [doi: 10.1186/s12877-017-0653-7] [Medline: 29078555]

42. Rolland Y, Pillard F, Klapouszczak A, Reynish E, Thomas D, Andrieu S, et al. Exercise program for nursing home residents with Alzheimer's disease: A 1-year randomized, controlled trial. J Am Geriatr Soc 2007 Feb;55(2):158-165. [doi: 10.1111/j.1532-5415.2007.01035.x] [Medline: 17302650]

43. Christofolletti G, Oliani MM, Bucken-Gobbi LT, Gobbi S, Beinotti F, Stella F. Physical activity attenuates neuropsychiatric disturbances and caregiver burden in patients with dementia. Clinics (Sao Paulo) 2011;66(4):613-618 [Full text] [doi: 10.1590/s1807-59322011000400015] [Medline: 21655755]

44. Woodhead EL, Zarit SH, Braungart ER, Rovine MR, Femia EE. Behavioral and psychological symptoms of dementia: The effects of physical activity at adult day service centers. Am J Alzheimers Dis Other Demen 2005;20(3):171-179 [Full text] [doi: 10.1177/1533317505020000314] [Medline: 16003933]

45. Ishimaru D, Tanaka H, Nagata Y, Takabatake S, Nishikawa T. Physical activity in severe dementia is associated with agitation rather than cognitive function. Am J Alzheimers Dis Other Demen 2020;35:1-7 [Full text] [doi: 10.1177/1533317519817397] [Medline: 31533445]

46. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet 2007 Oct 20;370(9596):1453-1457. [doi: 10.1016/S0140-6736(07)61602-X] [Medline: 18064739]

47. Choi SH, Na DL, Kwon HM, Yoon SJ, Jeong JH, Ha CK. The Korean version of the neuropsychiatric inventory: A scoring tool for neuropsychiatric disturbance in dementia patients. J Korean Med Sci 2000 Dec;15(6):609-615 [Full text] [doi: 10.3346/jkms.2000.15.6.609] [Medline: 11194184]

48. Cummings JL. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. Neurology 1997 May;48(5 Suppl 6):S10-S16. [Medline: 9153155]

49. Morganti F, Soli A, Savoldelli P, Belotti G. The Neuropsychiatric Inventory-Diary rating scale (NPI-Diary): A method for improving stability in assessing neuropsychiatric symptoms in dementia. Dement Geriatr Cogn Dis Extra 2018;8(3):306-320 [Full text] [doi: 10.1159/000490380] [Medline: 30323831]

50. Liew TM. Symptom clusters of neuropsychiatric symptoms in mild cognitive impairment and their comparative risks of dementia: A cohort study of 8530 older persons. J Am Med Dir Assoc 2019 Aug;20(8):1054.e1-1054.e9 [Full text] [doi: 10.1016/j.jamda.2019.02.012] [Medline: 30926409]

51. Liew TM. Neuropsychiatric symptoms in cognitively normal older persons, and the association with Alzheimer's and non-Alzheimer's dementia. Alzheimers Res Ther 2020 Mar 31;12(1):35 [Full text] [doi: 10.1186/s12877-019-0623-7] [Medline: 32234066]

52. Canevelli M, Adali N, Voinis T, Soto ME, Bruno G, Cesari M, et al. Behavioral and psychological subsyndromes in Alzheimer's disease using the Neuropsychiatric Inventory. Int J Geriatr Psychiatry 2013 Aug;28(8):795-803. [doi: 10.1002/gps.3904] [Medline: 23147419]

53. van der Linde RM, Dening T, Matthews FE, Brayne C. Grouping of behavioural and psychological symptoms of dementia. Int J Geriatr Psychiatry 2014 Jun;29(6):562-568 [Full text] [doi: 10.1002/gps.4037] [Medline: 24677112]

54. van der Linde RM, Dening T, Stephan BCM, Prina AM, Evans E, Brayne C. Longitudinal course of behavioural and psychological symptoms of dementia: Systematic review. Br J Psychiatry 2016 Nov;209(5):366-377 [Full text] [doi: 10.1192/bjp.bp.114.148403] [Medline: 27491532]

55. Aalten P, de Vugt ME, Lousberg R, Korten E, Jaspers N, Senden B, et al. Behavioral problems in dementia: A factor analysis of the Neuropsychiatric Inventory. Dement Geriatr Cogn Disord 2003;15(2):99-105. [doi: 10.1159/000067972] [Medline: 12566599]

56. Camargos EF, Louzada FM, Nóbrega OT. Wrist actigraphy for measuring sleep in intervention studies with Alzheimer's disease patients: Application, usefulness, and challenges. Sleep Med Rev 2013 Dec;17(6):475-488. [doi: 10.1016/j.smrv.2013.01.006] [Medline: 23669093]

57. Figueiro MG, Hunter CM, Higgins P, Hornick T, Jones GE, Plitnick B, et al. Tailored lighting intervention for persons with dementia and caregivers living at home. Sleep Health 2015 Dec 01;1(4):322-330 [Full text] [doi: 10.1016/j.sleh.2015.09.003] [Medline: 27066526]

58. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. Sleep 1992 Oct;15(5):461-469. [Medline: 1455130]
59. Kang Y, Na D, Hahn S. A validity study on the Korean Mini-Mental State Examination (K-MMSE) in dementia patients [Article in Korean]. J Korean Neurol Assoc 1997;15(2):300-308 [FREE Full text]
60. Song JA, Park JW, Kim H. Impact of behavioral and psychological symptoms of dementia on caregiver burden in nursing homes [Article in Korean]. J Korean Gerontol Nurs 2013;15(1):62-74 [FREE Full text]
61. Won CW, Rho YG, Kim SY, Cho BR, Lee YS. The validity and reliability of Korean Activities of Daily Living (K-ADL) scale. J Korean Geriatr Soc 2002;6(2):98-106 [FREE Full text]
62. Kim J, Kim B, Ha M. Validation of a Korean version of the Big Five Inventory. J Hum Underst Couns 2011;32(1):47-65 [FREE Full text]
63. Sciandra M, Muggeo VMR, Lovison G. Subject-specific odds ratios in binomial GLMMs with continuous response. Stat Methods Appt 2007 Jul 6;17(3):309-320. [doi: 10.1007/s10260-007-0060-x]
64. Breslow NE, Clayton DG. Approximate inference in generalized linear mixed models. J Am Stat Assoc 2012 Dec 20;88(421):9-25. [doi: 10.1080/01621459.1993.10594284]
65. Snijders TAB, Bosker RJ. Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling. 2nd edition. London, UK: SAGE Publications Ltd; 2011.
66. Bubu OM, Brannick M, Mortimer J, Umasabor-Bubu O, Sebastião YV, Wen Y, et al. Sleep, cognitive impairment, and Alzheimer's disease: A systematic review and meta-analysis. Sleep 2017 Jan 01;40(1):1-18. [doi: 10.1093/sleep/zsw032] [Medline: 28364458]
67. Ooms S, Ju Y. Treatment of sleep disorders in dementia. Curr Treat Options Neurol 2016 Sep;18(9):40 [FREE Full text] [Medline: 27476067]
68. Sohn SI, Kim DH, Lee MY, Cho YW. The reliability and validity of the Korean version of the Pittsburgh Sleep Quality Index. Sleep Breath 2012 Sep;16(3):803-812. [doi: 10.1007/s11325-011-0579-9] [Medline: 21901299]
69. Shin H, Han HJ, Shin D, Park H, Lee Y, Park KH. Sleep problems associated with behavioral and psychological symptoms as well as cognitive functions in Alzheimer's disease. J Clin Neurol 2014 Jul;10(3):203-209 [FREE Full text] [doi: 10.3988/jcn.2014.10.3.203] [Medline: 25045372]
70. Whall AL, Colling KB, Kolanowski A, Kim H, Son Hong G, DeCicco B, et al. Factors associated with aggressive behavior among nursing home residents with dementia. Gerontologist 2008 Dec;48(6):721-731 [FREE Full text] [doi: 10.1093/geront/48.6.721] [Medline: 19139246]
71. Kolanowski AM. An overview of the need-driven dementia-compromised behavior model. J Gerontol Nurs 1999 Sep;25(9):7-9. [doi: 10.3928/0098-1943-19990901-05] [Medline: 10776138]
72. Tible OP, Riese F, Savaskan E, von Gunten A. Best practice in the management of behavioural and psychological symptoms of dementia. Ther Adv Neurol Disord 2017 Aug;10(8):297-309 [FREE Full text] [doi: 10.1177/1756285617712979] [Medline: 28781611]
73. Kales HC, Gitlin LN, Lyketsos CG, Detroit Expert Panel on Assessment and Management of Neuropsychiatric Symptoms of Dementia. Management of neuropsychiatric symptoms of dementia in clinical settings: Recommendations from a multidisciplinary expert panel. J Am Geriatr Soc 2014 Apr;62(4):762-769 [FREE Full text] [doi: 10.1111/jgs.12730] [Medline: 24635665]
74. Lyketsos CG. Neuropsychiatric symptoms in dementia: Overview and measurement challenges. J Prev Alzheimers Dis 2015 Sep;2(3):155-156 [FREE Full text] [doi: 10.14283/jpad.2015.60] [Medline: 26779454]
75. Qassem T, Tadros G, Moore P, Xhafa F. Emerging technologies for monitoring behavioural and psychological symptoms of dementia. In: Proceedings of the 9th International Conference on P2P, Parallel, Grid, Cloud and Internet Computing. 2014 Presented at: 9th International Conference on P2P, Parallel, Grid, Cloud and Internet Computing; November 8-10, 2014; Guangdong, China p. 8-10. [doi: 10.1109/pgecic.2014.82]
76. Piau A, Rumeau P, Nourhashemi F, Martin MS. Information and communication technologies, a promising way to support pharmacotherapy for the behavioral and psychological symptoms of dementia. Front Pharmacol 2019;10:1122 [FREE Full text] [doi: 10.3389/fphar.2019.01122] [Medline: 31632271]
77. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol 2008;4:1-32. [Medline: 18509902]

Abbreviations

ADL: activity of daily living
AIC: Akaike information criterion
BFI-K: Korean version of the Big Five Inventory
BIC: Bayes information criterion
BPSD: behavioral and psychological symptoms of dementia
DATE: Describe and Measure, Analyze, Treat, and Evaluate
DICE: Describe, Investigate, Create, and Evaluate
EMA: ecological momentary assessment
GLMM: generalized linear mixed model
ICT: information and communications technology
K-ADL: Korean version of the Activities of Daily Living scale
K-MMSE: Korean version of the Mini–Mental State Examination
MMSE: Mini–Mental State Examination
NDB: need-driven dementia-compromised behavior
NRF: National Research Foundation of Korea
OR: odds ratio
PLST: progressively lowered stress threshold
PSQI: Pittsburgh Sleep Quality Index
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
TST: total sleep time
WASO: wake time after sleep onset