

# BPSD Patterns in Patients With Severe Neuropsychiatric Disturbances

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## Brief Report

# BPSD Patterns in Patients With Severe Neuropsychiatric Disturbances: Insight From the RECAGE Study

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## ABSTRACT

**Objective:** Behavioral and psychological symptoms of dementia (BPSD) profiles vary depending on etiology in patients with mild-to-moderate BPSD. It is not known if similar differences exist in patients with severe BPSD. **Methods:** We analyzed data collected at baseline in 398 patients with severe BPSD (NPI  $\geq 32$ ) and defined diagnosis of dementia (Alzheimer's disease [AD] 297; Editorial accompaniment, please see page 640.

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frontotemporal dementia [FTD] 39; Lewy body disease/Parkinsonian dementia [LBD/PD] 31; and vascular dementia [VD] 31) included in the European multicenter cohort RECADE. **Results:** Mean total NPI was 52.11 (18.55). LBD/PD patients demonstrated more hallucinations, more anxiety and more delusions than patients with other dementia. FTD patients had less delusions and more disinhibition than patients with other neurodegenerative disorders. These profiles overlapped partially with those reported in the literature in patients with less severe symptoms. **Conclusion:** Patients with severe BPSD display different and specific profiles of neuropsychiatric symptoms depending on dementia etiology. (Am J Geriatr Psychiatry 2023; 31:633–639)

**Highlights**

• **What is the primary question addressed by this study?**

Do patients with severe behavioral and psychological symptoms of dementia show specific neuropsychiatric patterns on symptoms depending on etiology?

• **What is the main finding of this study?**

Patients with Lewy body dementia / Parkinson's disease dementia (LBD/PD) displayed more hallucinations, more delusion and more anxiety than patients with cognitive impairment of other origin while patients with frontotemporal dementia showed more disinhibition and less delusion.

• **What is the meaning of the finding?**

Different profiles were identified depending on etiology in patients with severe behavioral and psychological symptoms of dementia suggesting that precise characterization might be performed regardless of the severity of neuropsychiatric symptoms to adapt management.

**INTRODUCTION**

Behavioral and psychological symptoms of dementia (BPSD) have a dramatic impact on a patient's disease trajectory and caregiver's quality of life.<sup>1,2</sup> Indeed, BPSD is associated with increased risk of hospitalization, longer hospital stays and institutionalization, and are important determinants of caregiver's burden.<sup>1,3,4</sup>

The management of BPSD is difficult and relies on a combination of pharmacological and nonpharmacological approaches. Taking into account the small number of clinical trials, psychotropic drugs are generally used off-label with a high rate of adverse events.<sup>5</sup> Interestingly, it has been shown using dedicated scales, such as the Neuropsychiatric Inventory (NPI), that patients with various neurocognitive disorders and mild-to-moderate BPSD display distinct patterns of neuropsychiatric disturbances.<sup>6–9</sup> In addition, data suggest that these specific profiles persist at

the advanced stages of the disease despite variations in intensity over time.<sup>10,11</sup> Yet, it is not known whether different BPSD profiles are also observed in patients with severe BPSD, and, if so, whether these patterns are similar to those described in patients with milder BPSD. This is a key issue as patients with severe BPSD are usually treated with a combination of psychotropic drugs, that is, polypharmacy, which is a known risk factor for complications such as trauma<sup>12</sup> and functional decline.<sup>13</sup> In line with this, several studies have shown that the de-prescription of psychotropic drugs in patients with dementia is beneficial, while sometimes accompanied with BPSD resurgence.<sup>14–16</sup> Thus, better knowledge of the neuropsychiatric symptoms displayed by patients with severe BPSD might help improve management.

The present study aims at determining whether patients with severe BPSD due to different etiologies display specific patterns of neuropsychiatric disturbances. To do so, we characterized the BPSD clinical

profiles of patients with severe neuropsychiatric symptoms according to the causes of their dementia by analyzing data from the European multicenter study, RECACHE (REspectful Caring for AGitated Elderly).

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## METHODS

### Subjects

RECACHE is a European prospective longitudinal multicenter study evaluating the long-term effectiveness of Special Care Units for patients with dementia and BPSD. The study has been described in details previously in a dedicated publication.<sup>17</sup> Briefly, patients were included in RECACHE based on BPSD severity (Neuropsychiatric Inventory (NPI)  $\geq 32/144$ ) and cognitive status (mini mental status evaluation [MMSE]  $\leq 24/30$ ). Patients with a single definite clinical diagnosis were included in the present study (excluding patients classified as having dementia due to multiple etiologies or dementia not otherwise specified) and divided into four diagnostic groups: Alzheimer's disease (AD); Frontotemporal dementia (FTD); Vascular dementia (VD); and Lewy body dementia/Parkinson's disease dementia (LBD/PD). Diagnoses were provided by managing physicians and were not centrally reviewed.

### Neuropsychological and Behavioral Evaluation

During the baseline visit, demographic data and information on the neurocognitive disease were collected. Cognitive status was assessed using the MMSE and the profile and severity of BPSD were evaluated using the NPI-12 item. The NPI-12 item covers the following subdomains: 1) delusion, 2) hallucinations, 3) agitation/aggression, 4) depression/dysphoria, 5) anxiety, 6) elation/euphoria, 7) apathy, 8) disinhibition, 9) irritability, 10) aberrant motor behavior, 11) sleep, 12) appetite, and eating disorder. Each subdomain was evaluated based on a score that reflects both the frequency and severity (frequency  $\times$  severity).

### Patterns of BPSD

The 12 NPI items were included into a principal component analysis (PCA) with varimax rotation.

The number of components was determined by examination of the scree plot (Supplementary Fig. 1) and retaining components with eigenvalues above 1.0 (Supplementary Table 2). Factors loadings above 0.4 were used to interpret the derived scores (Supplementary Table 1). Four components were identified: Component 1 represented agitation/aggression and Irritability; Component 2 delusion, hallucinations and, to a lesser extent, Aberrant motor behavior; Component 3 apathy, sleep and appetite and eating disorders; and Component 4 depression/dysphoria, anxiety, elation/euphoria (negative load) and, to a lesser extent, disinhibition (negative load).

### Statistical Analyses

Values were expressed as mean (standard deviation) or percentage. Comparisons between quantitative variables were performed using analysis of variance (ANOVA) followed by Tukey's post-hoc test. Qualitative variables were compared using Chi squared. Statistical significance was assumed at  $p < 0.05$ . PCA was performed using STATA 16 and other analyses using JASP 0.16.2.<sup>18</sup>

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## RESULTS

The RECACHE study enrolled 518 community-dwelling patients with dementia and severe BPSD in 11 centers from 6 European countries. Among those, 398 patients had a single definite diagnosis: 297 AD, 39 FTD, 31 LBD/PD and 31 VD, and comprised our study sample. The study flowchart is displayed in Supplementary Figure 2. Demographic and baseline characteristics are summarized in Table 1. FTD patients were younger than patients with other diagnoses without further differences between groups. AD patients were more often women than FTD and VD patients. VD patients were less educated than FTD and AD patients. Duration of the disease and MMSE at inclusion did not differ between groups.

Total NPI and NPI sub-scores are shown in Table 1 and Figure 1. Patients with LBD/PD showed higher global BPSD burden compared to AD and FTD patients. Regarding mean NPI sub-scores, LBD/PD patients showed significantly higher levels of delusion than all other groups while FTD patients displayed significantly lower levels than other groups

**TABLE 1. Demographic, Cognitive and Neuropsychological Data of Patients Included in the Study Depending of the Diagnosis, Expressed as Mean (95% CI) or Percentage.**

	AD (n=297)	FTD (n=39)	LBD/PD (n=31)	VD (n=31)	F	P
Age (years)	77.45 (7.99)	71.62 (8.92)	78.29 (6.02)	80.07 (9.02)	7.869	<0.001
Education (years)	9.341 (4.56)	10.08 (4.47)	8.81 (3.84)	6.97 (3.28)	3.342	<b>0.019</b>
Female gender (%)	60.3	41.03	51.61	32.26		<b>0.005</b>
Age at diagnosis (years)	74.5 (8.34)	68.67 (8.68)	75.52 (6.72)	77 (9.25)	7.276	<0.001
Duration (years)	2.95 (3.24)	2.95 (3.15)	2.77 (3)	3.07 (2.7)	0.045	0.99
MMSE	15.2 (6.29)	15.92 (7.63)	14.07 (6.17)	16.97 (4.83)	1.260	0.288
Total NPI	51.39 (17.97)	48.41 (12.77)	62.32 (24.46)	53.45 (20.71)	3.938	<b>0.009</b>
NPI subdomain A – Delusion	4.54 (4.21)	1.98 (3.68)	6.94 (4.76)	3.65 (2.25)	8.816	<0.001
NPI subdomain B – Hallucinations	1.8 (3.2)	0.69 (4.87)	5.77 (4.86)	1.90 (3.13)	16.493	<0.001
NPI subdomain C - Agitation/Aggression	5.59 (3.87)	6 (4.09)	5.9 (4.8)	7.13 (4.33)	1.427	0.234
NPI subdomain D - Depression/Dysphoria	5.24 (3.69)	5.10 (3.49)	6.87 (4.21)	5.55 (3.39)	1.924	0.125
NPI subdomain E – Anxiety	5.47 (4.06)	5.03 (4.73)	8.48 (3.36)	5.48 (4.18)	5.483	<b>0.001</b>
NPI subdomain F - Elation/Euphoria	1.14 (2.52)	1.08 (2.25)	1.26 (2.22)	1.29 (2.8)	0.067	0.978
NPI subdomain G – Apathy	7.26 (4.16)	8.72 (3.69)	6.52 (4.42)	6.90 (4.13)	2.923	<b>0.034</b>
NPI subdomain H – Disinhibition	2.4 (3.4)	4.4 (4.27)	2.1 (2.97)	2.48 (2.98)	4.178	<b>0.006</b>
NPI subdomain I – Irritability	4.96 (3.73)	3.9 (4.15)	5.81 (4.94)	6.19 (4.54)	2.401	0.067
NPI subdomain J – Aberrant motor behaviour	5.3 (4.23)	4.05 (4.25)	5.58 (5.28)	4.26 (3.96)	1.507	0.212
NPI subdomain K – Sleep	3.68 (3.72)	3.13 (3.65)	3.39 (4.38)	4.52 (4.46)	0.822	0.482
NPI subdomain L – Appetite and eating disorder	3.83 (4.09)	4.33 (4.25)	3.71 (4.91)	4.1 (4.02)	0.216	0.885
Principal component analysis						
Component 1 (Agi, Irr)	-0.04 (1.27)	-0.08 (1.29)	0.23 (1.67)	0.32 (1.49)	1.051	0.370
Component 2 (De, Hal, Mot)	0.03 (1.21)	-0.80 (0.98)	1.10 (1.72)	-0.19 (1.08)	21.082	<0.001
Component 3 (Dis, Sle, Eat)	-0.05 (1.24)	0.36 (0.96)	-0.13 (1.46)	-0.03 (1.52)	1.310	0.271
Component 4 (Dep, Anx, Ela*, Dis*)	-0.05 (1.19)	-0.15 (1.31)	0.65 (1.23)	0.03 (1.14)	3.401	<b>0.018</b>

P values ≤ 0,5 are indicated in bold.

except for VD. LBD/PD patients also showed mean higher levels of hallucinations and anxiety as compared to other groups. FTD patients showed higher levels of disinhibition than AD and LBD/PD groups. No differences between groups were observed regarding other NPI sub-scores.

Results of the PCA are displayed in Supplementary Table 1 and Supplementary Figure 3. When examining BPSD patterns, LBD/PD patients had higher scores for Component 2 (delusion, hallucination) than all other groups and for Component 4 (anxiety, depression, lack of euphoria) than AD and FTD patients. FTD patients had lower scores for Component 2 (delusion, hallucination) than AD and LBD/PD patients. There were no significant differences between groups for Components 1 (aggression, irritability) and 3 (apathy, sleep, eating disorder).

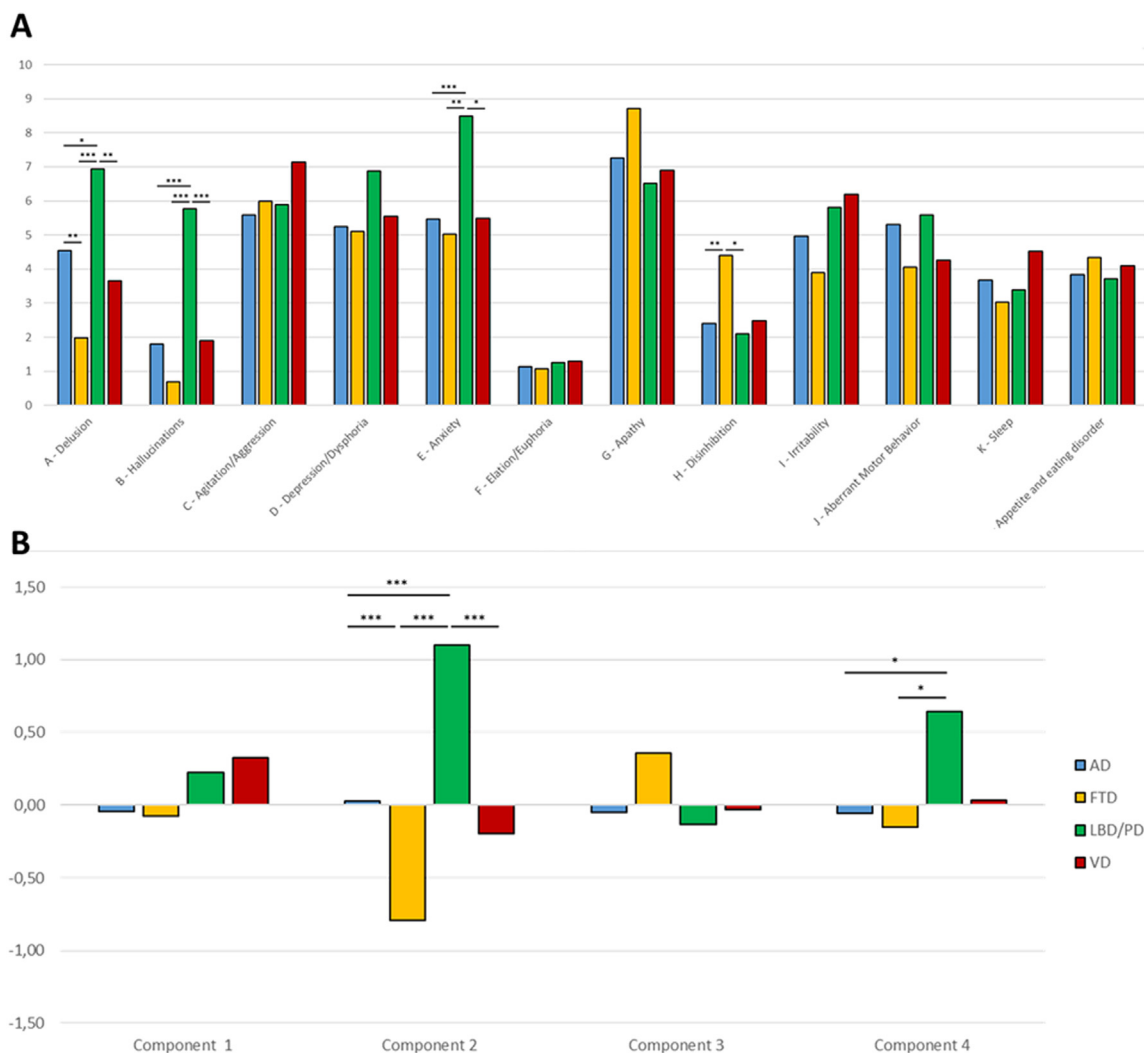
## DISCUSSION

In this study, we performed a comparative analysis of neuropsychiatric symptoms in community-dwelling patients with dementia and severe BPSD and

showed that these patients display distinct BPSD profiles depending on the underlying etiology. These findings corroborate and extend the results from earlier studies focused on patients with milder BPSD.<sup>2,6,9,11</sup> Indeed, Hirono et al. and Liu et al. performed similar comparisons between NPI sub-scores in AD, FTD and DLB patients with milder BPSD (mean total NPI 16.86 and 28.94, respectively, as compared to 52.11 in the present study) and found high levels of delusions and hallucinations in LBD patients and of disinhibition in FTD patients. However, the BPSD profiles observed in these past studies and the present only partially overlap as FTD patients showed more agitated BPSD profiles while DLB did not demonstrate significant anxiety in the previous studies.<sup>2,6</sup> Altogether, results from studies performed in patients with various magnitudes of BPSD load suggest that specific BPSD profiles are detectable early in the disease and persist but evolve with increasing severity, making precise and repeated characterization of these features mandatory.

Our results have important implications for clinical practice as they put the light on symptoms such as anxiety in LBD/PD patients, that had not been

**FIGURE 1. Comparison of NPI sub-scores [A] and of principal components [B] between AD, FTD, LBD/PD and VD patients. Only comparisons reaching significance are shown. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .**



previously identified as core BPSD symptoms in these diseases while they could benefit from targeted treatment.<sup>19,20</sup> In line with this, recent international clinical practice guidelines for the management of BPSD provide tailored recommendations of interventions and pharmacological treatments that take into account specific clinical presentations.<sup>21</sup> Additionally, patients with severe BPSD are at high risk of adverse or dangerous events<sup>4</sup> as psychotropic medications are associated with increased risk of complications including cognitive and functional decline and death. Those risks are even higher in patients receiving multiple psychotropic

drugs.<sup>12,13,16</sup> Consequently, several studies examined the benefit of treatment de-escalation.<sup>14,22</sup> These studies provided some evidence for a positive impact on the level of functioning but offered inconsistent conclusions regarding the risk of a rebound effect on neuropsychiatric symptoms.<sup>14,15</sup> The CHROME criteria (CHemical Restraints avOIDance METHodology) have been recently proposed to achieve the adequate prescription of psychotropic medications for the treatment of BPSD.<sup>23</sup> These criteria propose to use a syndrome-based rather than a symptom-based approach to improve diagnosis and, finally, prescription.

In research, recent clinical trials on pharmacological treatment for BPSD have followed a similar trend by selecting participants affected by specific cognitive diseases, BPSD types and severities.<sup>24,25</sup> Thus, the BPSD profiles unveiled by the present study will help refine inclusion and exclusion criteria for future trials focused on patients with severe BPSD.

The main strength of this study is its unique population of 500+ well-characterized community-dwelling patients with severe BPSD, prospectively recruited from 11 centers among 6 European countries, ensuring representativeness of really life and good external validity of our findings. However, this study as several limitations. We performed a high number of tests, which increases the risk of type I error. Additionally, the relatively small numbers of patients in the groups other than AD might have affected statistical power. Finally, the diagnoses were based on physician practice without the use of unified diagnostic criteria and some patients might have been misclassified.

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### CONCLUSION

Patients with severe BPSD display distinct BPSD profiles depending on dementia subtype. They should benefit from precise delineation of their profile of neuropsychiatric disturbances to ensure appropriate management.

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### AUTHOR CONTRIBUTIONS

*E. Cognat had the idea of the study, analyzed the data, wrote the draft and coordinated revision. S. Sabia analyzed*

*the data. A Fayel, J Dumurgier, M. Lilamand participated in the study conception. C. Paquet supervised the study. All authors contributed to data acquisition and revised the manuscript.*

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### DATA STATEMENT

*The data has not been previously presented orally or by poster at scientific meetings.*

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### DISCLOSURES

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### SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jagp.2023.03.014>.

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