The impact of mild behavioral impairment on the prognosis of geriatric depression: preliminary results

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Our study aimed to examine how the presence of Mild Behavioral Impairment (MBI) symptoms influenced the outcome of late-life depression (LLD). Twenty-nine elderly (≥ 60 years) depressive patients, including eleven (37.9%) with MBI, were recruited and followed-up on average for 33.41 ± 8.24 weeks. Psychiatric symptoms severity and global functioning were assessed, respectively, using the Brief Psychiatric Rating Scale (BPRS) and the Global Assessment of Functioning (GAF) scale. BPRS total score significantly decreased from baseline to follow-up ($P < 0.001$, d = 1.33). The presence of MBI had no significant effect on mood and cognitive symptoms improvement. On the contrary, while a significant increase in GAF score was observed in patients without MBI ($P = 0.001$, d = 1.01), no significant improvement of global functioning was detected in those with MBI ($P = 0.154$, d = 0.34) after 6-month follow-up. The presence of MBI in patients with LLD may negatively affect long-term outcome, slowing or preventing functional improvement. ***Int Clin Psychopharmacol*** **39: 305–312 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.**

International Clinical Psychopharmacology 2024, **39**:305–312

Keywords: aging, behavioral symptoms, cognitive dysfunction, depression, neuropsychiatry

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Received 31 August 2023 **Accepted** 28 September 2023.

Introduction

Late-life depression (LLD) represents a primary public health problem. The population is growing older, so the elderly with psychiatric disorders, including depression, will increase both in absolute number and in proportion (United Nations, 2019). Depression in late life has disabling consequences and leads to significant familiar and economic burden (Zivin *et al*., 2013). Because of the clinical and pathogenetic heterogeneity as well as the common overlap with multiple comorbid medical and psychiatric conditions (Leyhe *et al*., 2017), the treatment of LLD is challenging and its prognosis is highly variable.

LLD is commonly associated with cognitive impairment and several overlapping complex pathophysiological substrates might partly explain the frequent co-occurrence of the two conditions (i.e. vascular risk factors, secretion of corticosteroid hormones, neuroinflammation, neurotrophin deficiency) (Linnemann and Lang, 2020). Whether a neurodegenerative process is present or not seems to have a substantial impact on the treatment outcome of LLD. Though antidepressant drugs typically demonstrated a limited effectiveness in LLD (Morimoto *et al*., 2015), a particularly poor response has been shown in LLD patients who have structural brain abnormalities and cognitive impairment (Alexopoulos *et al*., 2000; Sheline *et al*., 2012; Kalayam *et al*., 1999).

Extensive literature supports the existence of a vascular depression diagnostic subtype characterized by white matter hyperintensities (WMHs), cognitive dysfunction (specifically executive dysfunction) and poor response to antidepressant therapy (Alexopoulos *et al*., 1997; Taylor *et al*., 2013; Elefante *et al*., 2022; Herrmann *et al*., 2008). For instance, it has been reported that executive dysfunctions without memory impairment conferred a higher risk of relapse and recurrence to patients with LLD treated with tricyclic antidepressants (Alexopoulos *et al*., 2000). The same research group also observed that the presence of WMHs in cortico-striato-limbic networks were associated with treatment resistance to selective serotonin reuptake inhibitors (SSRIs) in patients with LLD (Alexopoulos *et al*., 2008). More recently, significant associations between late life depressive symptoms and cerebral amyloid angiopathy (Smith *et al*., 2021), and between global

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neuropsychiatric symptom (NPS) burden and greater WMH volume (Miao *et al*., 2021b) have been reported.

The nature of the relationship between LLD and cognitive impairment is not completely understood (Byers and Yaffe, 2011). Some authors consider LLD merely as a risk factor for dementia, whereas others suggested that the onset of depressive symptoms in late life may be a disease marker, reflecting a prodromal phase of neurodegenerative processes (Diniz *et al*., 2013; Cherbuin *et al*., 2015; Kessing 2012).

Along with the rising interest in the dementia prodromal stages, several studies focused on identifying NPS in elderly patients as potential markers of later neurodegeneration (Brodaty *et al*., 2012; Geda *et al*., 2014; Masters *et al*., 2015). NPS include mood disorders, anxiety, psychosis, neurovegetative disorders (sleep and appetite disturbances) and behavioral alterations such as agitation and aggression (Lyketsos *et al*., 2011).

Although NPS are considered a predominant clinical manifestation of the behavioral-variant frontotemporal dementia and the frontal variant of Alzheimer's disease (AD), these symptoms are actually almost ubiquitous in all dementia subtypes. In fact, NPS have been observed in 97% of AD patients in the first five years after diagnosis (Steinberg *et al*., 2010) and can also be present in subjects with Mild Cognitive Impairment (MCI) and in individuals without cognitive deficits (Feldman *et al*., 2004). The onset of NPS in cognitively normal patients during old age may represent an early manifestation of neurodegeneration and may indicate progression along the continuum of neurodegenerative pathology (Masters *et al*., 2015; Peters *et al*., 2015). Understanding whether NPS may allow an early identification of neurodegenerative processes might help potentially slow down cognitive decline. In fact, both symptomatic agents and dementia disease-modifying therapies (available and under study) address the very early stages of the illness (Beshir *et al*., 2022).

Recently, the construct of Mild Behavioral Impairment (MBI) was formulated to help identify individuals at greater risk of cognitive decline (Ismail *et al*., 2016). MBI refers to a late-onset neurobehavioral syndrome in which NPS, lasting at least 6 months and not better identified by other psychiatric disorders, could represent early markers of neurodegenerative diseases. A change in the patient's behavior that is visible to others and a significant impairment in interpersonal, social or occupational functioning is required for the identification of MBI. Of note, the alterations in functioning must be attributable to NPS and not to cognitive symptoms or to other intercurrent psychiatric disorders. MCI may be present, but dementia is considered an exclusion criterion and the patient's independence must be maintained with minimal help or assistance.

MBI can be evaluated through the MBI-checklist (MBI-C), a standardized clinical assessment tool exploring 5 domains (reduction of drive or motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception or thought content) (Ismail *et al*., 2017).

In a recent study in dementia-free memory clinic patients, MBI-C impulse dyscontrol and motivation domains demonstrated associations with medial temporal lobe atrophy, showing that NPS can be present in the absence of frontal pathology (Matuskova *et al*., 2021). As the medial temporal lobes are affected early in AD, the use of MBI-C might have utility for early recognition of people at risk. The neurodegenerative nature of MBI has been confirmed by several studies in dementia-free patients, demonstrating associations with β-amyloid (Lussier *et al*., 2020; Miao *et al*., 2021a), phospho-tau (Johansson *et al*., 2021; Ghahremani *et al*., 2022), gray and white matter atrophy (Gill *et al*., 2021), and neurofilament light chain, a validated biomarker of axonal damage and neurodegeneration (Naude *et al*., 2020).

Although MBI is considered a promising construct for neurobiological research, the relationships between MBI and late-life psychiatric disorders are yet to be fully established (Ismail *et al*., 2018). In a cross-sectional study on individuals aged ≥50 years referred to our psychogeriatric service, we found that MBI often co-occurred with psychiatric conditions such as mood and anxiety disorders. In particular, we observed that MBI patients have a higher age at the onset of psychiatric symptoms, especially depression, and greater motor retardation and apathy with respect to patients without MBI (Elefante *et al*., 2023). However, no studies have been conducted on the clinical implications of the presence of MBI in the outcome of major psychiatric disorders. Specifically, we hypothesize that the occurrence of symptoms belonging to MBI domains may have an impact on the outcome of patients treated for LLD. In a previous analysis, we observed that the presence of MBI was associated with less improvement of functioning, but not symptom severity, after at least 2 months of follow-up in 25 patients treated for LLD (Elefante *et al*., 2022). Since the lack of short-term improvement may be indicative either of a longer delay in the recovery process or of persistent functional deficits, in this preliminary study, we aimed to assess whether changes in symptoms and functioning may be differentially observed, depending on the MBI status, in LLD patients followed over at least 6 months.

Methods

Participants

Participants were enrolled among patients attending the psychogeriatric outpatient service of the Psychiatry Unit 2 at Pisa University Hospital (Italy) between June 2020 and March 2022, according to the following inclusion criteria: 1) age ≥ 60 years; 2) diagnosis of current depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). Patients diagnosed with

dementia, Parkinson's disease or other neurodegenerative parkinsonism were excluded. 44 subjects were recruited, of which 29 had been followed-up for at least 6 months (median [weeks] = 32, range = 26–62, interquartile range = 28–35; mean ± SD = 33.41 ± 8.24) and were included in this study. 15 patients were lost at follow-up after 6 months (attrition rate = 34.1%): 7 had never a follow-up visit, the latter 8 had follow-up assessments on average up to 15.12 ± 9.17 weeks (median = 19, range = 3–24, interquartile range = 5.5–23). All subjects provided written, informed consent for data collection to be analyzed and presented anonymously in aggregate form. The study was carried out in accordance with the Declaration of Helsinki. The protocol was approved by the Ethical Committee of the University of Pisa (N. 22537_Perugi).

Assessment

All patients were evaluated by psychiatric trainees with at least 2 years of experience in the field of psychogeriatrics, under senior psychiatrist supervision. Educational history, marital status, family history of psychiatric and neurodegenerative conditions, medical comorbidity (including MCI), current and lifetime psychiatric conditions according to DSM-5 criteria and course features were all investigated at baseline (American Psychiatric Association, 2013). The Clinical Global Impression - Severity scale (CGI-S) was used as a proxy of psychiatric illness severity according to clinician's judgement at baseline (Guy, 1976). The Brief Psychiatric Rating Scale, Extended Version (BPRS) and the Global Assessment of Functioning (GAF) scale were used, respectively, to rate symptoms severity and functioning level, both at baseline and at each follow-up assessment (Ventura *et al.*, 1993; Jones *et al.*, 1995). BPRS subscales were derived according to the model proposed by Velligan and colleagues (Velligan *et al.*, 2005). Moreover, according to our usual clinical routine, Mini-Mental State Examination (MMSE) was also administered (Folstein *et al.*, 1975), whenever possible, at baseline and at follow-up approximately every 4 to 6 months to monitor cognitive impairments.

The presence of MBI was explored according to a multi-step protocol. First, MBI-C interview was administered in person to the patient and the patient's caregiver (Elefante *et al.*, 2019). Given that all patients were also diagnosed with current depressive episode, specific MBI features such as the age of onset, severity, and qualitative pattern of NPSs were emphasized during the interview. For example, in comparison to psychiatric disorders identified by DSM-5, NPSs pertaining to MBI show distinct qualitative characteristics and a different course. Consistently with the MBI definition (Ismail *et al.*, 2016), NPSs were rated as present only if they represented a clear change from the patient's usual behavior or personality, including during previous depressive episodes (i.e. new-onset symptoms), had a persistent course (≥6 months), and did not occur before the age of 50 years. Thus, MBI criteria permit a distinction between DSM-5 mental disorders and late-onset psychiatric symptoms. As previously suggested (Mallo *et al.*, 2018; Kassam *et al.*, 2022), a cutoff of 6.5 (i.e. ≥ 7) was used to identify patients screening positive for high level of NPS. MBI-C findings, clinical history and medical files of patients screening positive for MBI were then discussed with two senior psychiatrists (CE, LL) who reexamined the patient and provided a consensus for the presence of MBI.

Statistical analysis

All the analyses were performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) in September 2022. Descriptive statistics were used to describe demographic and clinical characteristics of the sample. Comparative analyses of baseline variables between the groups were first conducted using *tableone* package. Continuous variables were compared using Student's *t*-test (or Mann–Whitney-Wilcoxon test), after normality checking using Shapiro-Wilk test. Pearson's chi-squared test or, when appropriate, Fisher's exact test was used for comparison of categorical variables, with pairwise Fisher's exact test for post-hoc comparisons. Two-way mixed analysis of variance (ANOVA) from *rstatix* package was used to compare group changes in BPRS total score, BPRS Depression/Anxiety subscale according to Velligan and colleagues (Velligan *et al.*, 2005), and GAF score from baseline to follow-up (Jones *et al.*, 1995), including MBI diagnosis as a between-subjects factor and time (i.e. baseline vs. follow-up) as a within-subjects factor. To fix non-normality of residuals in the mixed ANOVA on BPRS total score, one extreme outlier (i.e. value exceeding the third quartile by three times the interquartile range) from the MBI group was removed from the sample. Pairwise one-sample Student's *t*-tests were used as post-hoc contrasts. Finally, since the normality of residuals assumption was not met for MMSE total scores, pairwise Wilcoxon rank sum tests were conducted to compare baseline and follow-up MMSE total scores within groups (paired tests) and MMSE total scores between groups at baseline and at follow-up (unpaired tests). Last observation carried forward method was used in cases where the MMSE total score was missing. Even though all patients' baseline MMSE scores have been included, 10 patients' end-of-follow-up MMSE values were lacking. For 6 patients we replaced the end-of-follow-up MMSE score with the MMSE score of a visit between the baseline and the end-of-follow-up. For 4 patients, instead, we replaced the end-of-follow-up MMSE score with the baseline MMSE score. Given the limited sample size and the exploratory nature of the analyses, a statistical significance threshold of $P < 0.10$ was set for all the analyses.

Results

Our sample was composed of 29 patients with a diagnosis of current depressive episode. Age ranged between 60

and 88 years, with a mean of 74.21 ± 7.93 years (median = 74, interquartile range = 69–80). Almost two-thirds of patients were female (N = 18, 62.1%) and most were married (N = 15, 51.7%) or widowed (N = 10, 34.5%) (Table 1). Recurrent major depressive disorder, bipolar disorder type 1 and bipolar disorder type 2 were equally represented, with 7 patients (24.1%) being affected by each. Four subjects were at their first depressive episode (13.8%), while the latter four were diagnosed with cyclothymic disorder and major depressive episodes (N = 2, 6.9%) or with other specified bipolar disorder (N = 2, 6.9%). Anxiety disorder comorbidity was common (N = 17, 58.6%). Notably, in more than half of patients the onset of mood disorders was after the age of 40 (N = 15, 51.7%) and in two-fifths of the sample it was after the age of 50 (N = 12, 41.4%).

Overall, 11 patients were identified as high-level MBI (37.9%). Only few significant differences between patients with and without MBI emerged (Table 1). Patients with MBI had a significantly higher number of school years (Wilcoxon r = 0.32, $P = 0.085$) and were more frequently married than widowed (post-hoc contrast: $P = 0.018$, $p_{fdr} = 0.106$). Interestingly, first-degree family history for psychiatric disorders was significantly less common in patients with MBI than in those without (54.5% vs. 88.9%, $P = 0.071$). No significant differences between groups were found for age, gender, follow-up duration, psychiatric diagnoses, medical comorbidity, family history of neurodegenerative disorders, age at onset of symptoms and mood disorders, baseline cognition assessed through MMSE, and baseline episode severity measured by CGI-S, GAF score and BPRS total score and subscales.

At follow-up, a significant main effect of time on BPRS total score was observed (F[1, 26] = 43.71, $P < 0.001$, $\eta_p^2 = 0.63$) (Table 2). Post-hoc contrast revealed that BPRS total score significantly decreased from baseline to follow-up (40.2 ± 6.9 vs. 31.6 ± 5.7; t = 7.06, $P < 0.001$, d = 1.33). There was no significant effect of MBI, indicating that BPRS total scores from patients with and without high level of MBI were similar overall (37.8 ± 8.4 vs. 34.8 ± 7.1; F[1, 26] = 2.05, $P = 0.164$, $\eta_p^2 = 0.07$). There was also no significant interaction effect between time and the presence of MBI (F[1, 26] = 0.01, $P = 0.916$, $\eta_p^2 = 0.00$). Descriptive statistics showed that BPRS total score was similar in patients with and without MBI both at baseline (42.1 ± 8.5 vs. 39.2 ± 5.9) and at follow-up (33.6 ± 6.0 vs. 30.4 ± 5.4).

Similarly, we observed a significant main effect of time on BPRS Depression/Anxiety subscale (F[1, 27] = 25.15, $P < 0.001$, $\eta_p^2 = 0.48$). Overall, depressive symptoms severity significantly decreased from baseline to follow-up (15.8 ± 3.4 vs. 11.5 ± 4.2; t = 5.42, $P < 0.001$, d = 1.01). Even in this case, there was no significant effect of MBI, indicating no differences in BPRS Depression/Anxiety subscale from patients with and without MBI (14.6 ± 4.9 vs. 13.0 ± 4.0; F[1, 27] = 1.88, $P = 0.182$, $\eta_p^2 = 0.065$). In addition, no significant interaction effect between time and MBI was detected (F[1, 27] = 2.48, $P = 0.127$, $\eta_p^2 = 0.08$). Based on descriptive statistics, depressive symptoms severity was similar in patients with and without MBI both at baseline (16.0 ± 4.2 vs. 15.6 ± 2.9) and at follow-up (13.3 ± 5.2 vs. 10.4 ± 3.1).

As for changes in global functioning, there was a significant main effect of time on GAF score (F[1, 27] = 12.99, $P = 0.001$, $\eta_p^2 = 0.33$), with post-hoc contrast revealing a significant improvement in GAF score over time (53.1 ± 15.6 at baseline vs. 65.2 ± 18.7 at follow-up; t = 4.00, $P < 0.001$, d = 0.74). A significant effect of MBI was also observed (F[1, 27] = 5.40, $P = 0.028$, $\eta_p^2 = 0.17$), with post-hoc contrast revealing significantly lower global functioning in patients with MBI compared to those without (51.4 ± 16.1 vs. 63.9 ± 17.8; t = 2.76, $P = 0.008$, d = 0.74). Finally, a significant interaction between time and MBI was identified (F[1,27] = 3.17, $P = 0.086$, $\eta_p^2 = 0.11$). Post-hoc comparisons showed that while no significant difference in GAF score was found at baseline between patients with and without MBI (48.6 ± 15.2 vs. 55.8 ± 15.6; t = 1.23, $P = 0.233$, d = 0.47), a large significant difference emerged at follow-up (54.1 ± 17.3 vs. 71.9 ± 16.5; t = 2.75, $P = 0.012$, d = 1.06). Moreover, while no significant improvement between baseline and follow-up was detected in patients with MBI (t = 1.54, $P = 0.154$, d = 0.34), a significant increase in GAF score was observed in those without MBI (t = 3.90, $P = 0.001$, d = 1.01). Consistently, GAF score change was significantly lower in patients with MBI than in those without (5.6 ± 11.7 vs. 16.1 ± 17.5, t = 1.96, $P = 0.061$, d = 0.72).

Finally, no significant changes in MMSE total scores over time were observed both in patients with MBI (r = 0.40, $P = 0.256$) and in those without (r = 0.12, $P = 0.620$). Moreover, no significant differences were observed in MMSE total scores between patients with and without MBI both at baseline (r = 0.067; Table 1) and at follow-up (28 [27, 30] vs. 27.5 [24.2, 29]; r = 0.178, $P = 0.351$; Table 2).

Discussion

In the present study, we aimed to investigate the role of MBI in elderly subjects referred to a tertiary psychiatric outpatient clinic and treated for a major depressive episode. Particularly, we examined the impact of MBI on the long-term outcome of psychiatric symptom severity, global functioning and cognition. According to results from our exploratory analyses, the presence of MBI had no impact on the severity and course of general psychopathology and depressive symptoms; patients with and without MBI had the same severity in psychiatric symptoms at baseline, including depressive ones, and displayed the same reduction in symptoms severity during

Table 1 Characteristics of the whole sample and differences between patients with and without mild behavioral impairment (MBI)

	Whole sample (N = 29)	Without MBI (N = 18)	With MBI (N = 11)		
Demographic variables	N (%)/mean ± SD/median [IQR]	N (%)/mean (SD)/median [IQR]	N (%)/mean (SD)/median [IQR]	SMD	*P*-value
Gender (male)	11 (37.9)	5 (27.8)	6 (54.5)	0.565	0.240
Age (years)	74.21 ± 7.93	74.14 ± 9.06	74.32 ± 6.04	0.023	0.954
School years	10.00 [5.00–13.00]	8.00 [5.00–12.75]	13.00 [10.50–15.00]	0.703	0.085
Marital status				1.320	0.029
Single	2 (6.9)	2 (11.1)	0 (0.0)		
Divorced	2 (6.9)	1 (5.6)	1 (9.1)		
Married	15 (51.7)	6 (33.3)	9 (81.8)		
Widowed	10 (34.5)	9 (50.0)	1 (9.1)		
Follow-up duration (weeks)	32.00 [28.00–35.00]	32.00 [27.25–36.50]	31.00 [28.00–33.50]	0.041	0.946
Psychiatric diagnosis					
Mood disorders				0.783	0.634
Major depressive disorder (single episode)	4 (13.8)	2 (11.1)	2 (18.2)		
Major depressive disorder (recurrent)	7 (24.1)	3 (16.7)	4 (36.4)		
Bipolar disorder type 1	7 (24.1)	5 (27.8)	2 (18.2)		
Bipolar disorder type 2	7 (24.1)	6 (33.3)	1 (9.1)		
Cyclothymic disorder	2 (6.9)	1 (5.6)	1 (9.1)		
Specified bipolar disorder	2 (6.9)	1 (5.6)	1 (9.1)		
Any bipolar or related disorder	18 (62.1)	13 (72.2)	5 (45.5)	0.565	0.240
Any anxiety disorder	17 (58.6)	11 (61.1)	6 (54.5)	0.133	1.000
Panic disorder	10 (34.5)	7 (38.9)	3 (27.3)	0.249	0.694
Agoraphobia	4 (13.8)	4 (22.2)	0 (0.0)	0.756	0.268
Generalized anxiety disorder	11 (37.9)	7 (38.9)	4 (36.4)	0.052	1.000
Social anxiety disorder	1 (3.4)	1 (5.6)	0 (0.0)	0.343	1.000
Medical comorbidity					
Thyroid diseases	3 (10.3)	2 (11.1)	1 (9.1)	0.067	1.000
Hypertension	14 (48.3)	7 (38.9)	7 (63.6)	0.511	0.362
Diabetes mellitus type 2	4 (13.8)	1 (5.6)	3 (27.3)	0.613	0.139
Dyslipidemia	6 (20.7)	2 (11.1)	4 (36.4)	0.622	0.164
Obesity	1 (3.4)	0 (0.0)	1 (9.1)	0.447	0.379
Mild cognitive impairment (MCI)	5 (17.2)	2 (11.1)	3 (27.3)	0.419	0.339
First-degree family history					
Any psychiatric disorder	22 (75.9)	16 (88.9)	6 (54.5)	0.825	0.071
Any mood disorder	18 (62.1)	13 (72.2)	5 (45.5)	0.565	0.240
Any anxiety disorder	6 (20.7)	5 (27.8)	1 (9.1)	0.497	0.362
Neurodegenerative disorders				0.647	1.000
Unspecified dementia or cognitive decline	4 (13.8)	2 (11.1)	2 (18.2)		
Frontotemporal dementia	1 (3.4)	1 (5.6)	0 (0.0)		
Alzheimer disease	1 (3.4)	1 (5.6)	0 (0.0)		
Multiple sclerosis	1 (3.4)	1 (5.6)	0 (0.0)		
Any neurodegenerative disorder	7 (24.1)	5 (27.8)	2 (18.2)	0.230	0.677
Course of mood disorder					
Age at onset of psychiatric symptoms (years)	30.00 [18.50–53.50]	24.00 [18.00–51.00]	30.00 [20.00–61.50]	0.255	0.533
Age at onset of mood disorder (years)	45.00 [28.00–64.00]	49.00 [25.50–65.00]	30.00 [28.50–61.50]	0.172	0.702
Age at onset of depression (years)	44.00 ± 22.00	40.64 ± 23.47	50.17 ± 19.41	0.443	0.411
Number of previous depressive episodes	3.00 [2.00–5.00]	3.00 [2.00–5.75]	3.00 [2.00–3.00]	0.550	0.423
Index episode features					
Psychotic symptoms	1 (3.4)	1 (5.6)	0 (0.0)	0.343	1.000
Mixed features	7 (24.1)	4 (22.2)	3 (27.3)	0.117	1.000
Anxious distress	8 (27.6)	4 (22.2)	4 (36.4)	0.315	0.433
Atypical features	4 (13.8)	3 (16.7)	1 (9.1)	0.228	1.000
Melancholic features	3 (10.3)	2 (11.1)	1 (9.1)	0.067	1.000
Psychometric assessment					
CGI - Severity of illness	4.00 [4.00–5.00]	4.00 [4.00–4.00]	4.00 [4.00–5.00]	0.212	0.648
MMSE total score	28.00 [24.00–29.00]	27.50 [23.50–29.00]	28.00 [24.50–29.50]	0.200	0.716
Global Assessment of Functioning (GAF)	53.10 ± 15.55	55.83 ± 15.55	48.64 ± 15.18	0.468	0.233
BPRS total score	40.41 ± 6.85	39.22 ± 5.90	42.36 ± 8.09	0.444	0.237
BPRS Depression/Anxiety	15.76 ± 3.36	15.61 ± 2.89	16.00 ± 4.15	0.109	0.768
BPRS Activation	11.00 [10.00–14.00]	10.50 [10.00–13.75]	11.00 [10.00–15.00]	0.455	0.386
BPRS Negative Symptoms/Retardation	9.00 [6.00–10.00]	8.50 [5.25–9.75]	9.00 [6.50–10.00]	0.233	0.439
BPRS Psychosis	6.00 [6.00–7.00]	6.00 [6.00–7.00]	7.00 [6.00–9.00]	0.537	0.317
MBI-C total score	0.00 [0.00–12.00]	0.00 [0.00–0.00]	13.00 [11.00–22.50]		
MBI-C drive	0.00 [0.00–4.00]	0.00 [0.00–0.00]	8.00 [3.00–13.50]		
MBI-C affect	0.00 [0.00–2.00]	0.00 [0.00–0.00]	5.00 [1.50–14.00]		
MBI-C impulse	0.00 [0.00–2.00]	0.00 [0.00–0.00]	3.00 [0.50–3.50]		
MBI-C social	0.00 [0.00–0.00]	0.00 [0.00–0.00]	0.00 [0.00–0.00]		
MBI-C perception	0.00 [0.00–0.00]	0.00 [0.00–0.00]	0.00 [0.00–0.00]		
Duration of MBI (months)			27.00 [19.00–39.00]		

Mean and SD were reported for continuous variables with normal distribution; median and interquartile range (IQR) were reported for continuous variables with non-normal distribution. Comparative analyses were conducted using Student's *t*-test for continuous variables with normal distribution and Mann–Whitney-Wilcoxon test for continuous variables with non-normal distribution. Pearson's chi-squared test or, when appropriate, Fisher's exact test was used for comparison of categorical variables. The standardized mean difference (SMD) was reported for each comparison.

BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; IQR, interquartile range; MBI, Mild Behavioral Impairment; MBI-C, Mild Behavioral Impairment - Checklist; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; SMD, standardized mean difference.

Table 2 Differences between baseline and follow-up in the whole sample and in patients with and without mild behavioral impairment (MBI)

	Whole sample (N = 29)		Time		Without MBI (N = 18)		With MBI (N = 11)		Time × MBI	
	N (%)/mean ± SD/median [IQR]				N (%)/mean (SD)/median [IQR]		N (%)/mean (SD)/median [IQR]			
	Baseline	Follow-up	F	*P*-value	Baseline	Follow-up	Baseline	Follow-up	F	*P*-value
BPRS total score	40.2 ± 6.9	31.6 ± 5.7	43.71	< 0.001	39.2 ± 5.9	30.4 ± 5.4	42.1 ± 8.5	33.6 ± 6.0	0.01	0.916
BPRS Depression/Anxiety scale	15.8 ± 3.4	11.5 ± 4.2	25.15	< 0.001	15.6 ± 2.9	10.4 ± 3.1	16.0 ± 4.2	13.3 ± 5.2	2.48	0.127
GAF score	53.1 ± 15.6	65.2 ± 18.7	12.99	0.001	55.8 ± 15.	71.9 ± 16.5	48.6 ± 15.2	54.1 ± 17.3	3.17	0.086
MMSE total score	28.00 [24.00–29.00]	28.00 [25.00–29.00]			27.50 [23.50–29.00]	27.5 [24.2–29]	28.00 [24.50–29.50]	28 [27–30]		

Mean and SD were reported for continuous variables with normal distribution; median and interquartile range (IQR) were reported for continuous variables with non-normal distribution. Two-way mixed ANOVA was used to compare group changes in BPRS total score, BPRS Depression/Anxiety subscale, and GAF score from baseline to follow-up, including MBI diagnosis as a between-subjects factor and time (i.e. baseline vs. follow-up) as a within-subjects factor.

BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; IQR, interquartile range; MBI, Mild Behavioral Impairment; MMSE, Mini-Mental State Examination; SMD, standardized mean difference.

the follow-up. This result suggests that, notwithstanding previous reports of a limited response of LLD to antidepressants (Morimoto *et al*., 2015), an improvement in severity of psychiatric symptoms is observable in the long-term even in patients with NPS. Conversely, in our sample, MBI had a negative impact on global functioning over time. A negative association between the presence of MBI and overall functioning over time had already been found in a short-term prospective observational investigation from our group (Elefante *et al*., 2022). This study confirms the same outcome in the long-term. Indeed, though patients with and without MBI had a similar level of functioning at baseline, those with MBI showed a significantly lower improvement at the end of the follow-up.

Although a 1-year follow-up study previously showed an association between the presence of NPS and a greater residual cognitive impairment in patients with LLD (Zhang *et al*., 2021), we did not observe differences in MMSE total score between patients with or without MBI both at baseline and at follow-up (on average after 8 months). It is worth noting that MMSE is a screening tool and is probably inadequate to register subtle cognitive changes, especially those affecting frontal/executive and visuospatial functions (Woodford and George, 2007). Additionally, the fact that some MMSE score were missing may further restrict the validity of this result. The GAF scale, instead, can estimate everyday independent activities, integrated abilities, and the corresponding level of care required (Jones *et al*., 1995). We hypothesize that in LLD patients with MBI, the absence of functional improvements in everyday activities involving a wide range of skills over time may reflect an underlying neurodegenerative process.

MBI has already been associated with preclinical markers of neurodegeneration, especially (AD)-related. In particular, low plasma level of $A\beta_{42}/A\beta_{40}$ (Miao *et al*., 2021a), Aβ-PET positive status (Lussier *et al*., 2020), atrophy in the entorhinal cortex and hippocampus (Matuskova *et al*., 2021), AD genetic loci as well as increased neurofilament light chain plasma level have been found in patients with MBI (Andrews *et al*., 2018; Naude *et al*., 2020; Creese *et al*., 2021). The neurodegenerative nature of MBI has been supported in the present research as well; in fact, the impact on global functioning appears to be mediated by the occurrence of NPS belonging to MBI rather than LLD. Based on recent research investigating the behavioral manifestations of neurodegenerative diseases, the detection of NPS, including mood alterations, in aged people should raise suspicion of subsequent neurodegeneration (Brodaty *et al*., 2012; Geda *et al*., 2014; Masters *et al*., 2015). Particularly, persistent NPS of affective dysregulation and emotional dysregulation representing a clear qualitative change from patient's previous behavior should be investigated, according to previous findings (Ebrahim *et al*., 2022). Similarly, specific symptoms, such as apathy, have been previously found to confer a higher

risk for cognitive decline compared to less specific depressive symptoms and MBI-apathy may confer even greater risk than conventionally measured apathy (Robert *et al.*, 2008; Palmer *et al.*, 2010; Martin and Velayudhan, 2020; Vellone *et al.*, 2022).

Both NPS and LLD have been associated with a high risk of neurodegeneration in several studies and a solid body of evidence supported the role of LLD as a risk factor for progression of cognitive decline (Modrego and Ferrández, 2004; Geda *et al.*, 2006; Donovan *et al.*, 2014; Riddle *et al.*, 2017). It is likely that a subgroup of subjects having NPS with LLD may be at higher risk of having functional deterioration and possibly a neurodegenerative course.

Several limitations of our study should be acknowledged. First, the clinical setting (a tertiary psychiatric unit) could not have been representative of all patients with LLD, but rather of a subpopulation at high risk for developing complicated course. Moreover, the small sample size and the attrition rate of 34.1% limited the generalizability of the results. Finally, the relatively short length of follow-up period did not allow to determine with certainty if the patients with MBI have a lack of functional recovery or a considerably slower improvement of functioning when compared to patients without MBI, nor if an increased risk of major cognitive impairment could be observed in patients with MBI. Future studies are required to corroborate our preliminary findings with larger sample numbers and longer follow-up. Moreover, it would be particularly interesting to find out whether biomarkers of neurodegeneration and neuroimaging findings differ between patients with MBI and LLD, since both have been considered risk factors for neurodegenerative diseases.

In conclusion, MBI symptoms can be observed in subjects without MCI and in patients with major psychiatric disorders. In our sample, in fact, high level of MBI were observed in over one-third of the cases, suggesting that these symptoms are relatively frequent in LLD. Moreover, at the end of the follow-up period, the presence of MBI was associated with a lack of improvement in global functioning. These findings support the view that MBI may be a prodrome of a neurodegenerative condition and that the identification of this syndrome may have relevant clinical implications. Further research on larger sample are necessary to confirm our preliminary observations.

Acknowledgements

Conflicts of interest

G.P. acted as consultant to Janssen Angelini, Sanofi Aventis, and Neuraxpharm. He received a scholarship/research support from Angelini. He is a member of the speaker/advisory board of Sanofi-Aventis, Lundbeck, Angelini, and Janssen. Z.I. has received grants funding from NIA, CIHR, CCNA, Brain Canada, ADDF, Weston Foundation and honoraria/consulting fees from Lundbeck, Otsuka, Roche and Biogen. He is a member of the advisory board of OCEANS study at Johns Hopkins DSMB. For the remaining authors, there are no conflicts of interest.

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