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REVIEW

Behavioral symptoms related to cognitive impairment

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Abstract: Neuropsychiatric symptoms (NPS) are core features of Alzheimer's disease and related dementias. On one hand, behavioral symptoms in patients with mild cognitive impairment (MCI) can indicate an increased risk of progressing to dementia. On the other hand, mild behavioral impairment (MBI) in patients who usually have normal cognition indicates an increased risk of developing dementia. Whatever the cause, all dementias carry a high rate of NPI. These symptoms can be observed at any stage of the disease, may fluctuate over its course, are a leading cause of stress and overload for caregivers, and increase rates of hospitalization and early institutionalization for patients with dementia. The clinician should be able to promptly recognize NPI through the use of instruments capable of measuring their frequency and severity to support diagnosis, and to help monitor the treatment of behavioral symptoms. The aims of this review are to describe and update the construct 'MBI' and to revise the reported NPS related to prodromal stages of dementia (MCI and MBI) and dementia stages of Alzheimer's disease and frontotemporal lobar degeneration.

Keywords: behavioral or neuropsychiatric symptoms, cognitive impairment, dementia

Introduction

Over the last several years, awareness of the importance of neuropsychiatric symptoms (NPS) in dementia has been increasing, given their universal occurrence over the course of dementia and their association with caregiver burden and early institutionalization.[1,2]

Whereas dementia is still defined as a cognitive disorder, NPS are now regarded as an intrinsic aspect of dementia, and that their underlying causes are usually neurodegenerative processes.[1,2]

NPS are almost always present in the dementia patient, and they are common hallmarks of all types of dementia, independent of etiology. Patients diagnosed with mild cognitive impairment (MCI) present with a higher rate of NPS than healthy people.[3,4] Moreover, in the MCI population, the risk of developing dementia is high when NPS are present.[5,6] Patients with a diagnosis of mild behavioral impairment (MBI)[7] show a notably increased risk of progression to degenerative dementia, even in those with normal cognition.[7]

The presence of NPS in dementia patients is associated with high caregiver burden,[8] poor prognosis, and higher rates of institutionalization and drug therapy; all of which contribute to an increased social and economic impact in people with dementia and MCI.[9] In order to be able to control these variables, NPS should be rapidly recognized and treated.

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The aims of this review are to describe and update the MBI construct[7] and to revise NPS as related to prodromal stages of dementia (MCI and MBI), and dementia stages of Alzheimer's disease (AD) and frontotemporal lobar degeneration.

Search strategy and selection criteria

We searched MEDLINE, LILACS, and AgeLine databases from 1976 to the present, using the keywords "neuropsychiatric symptoms", "behavioral and psychological symptoms", "dementia", "mild cognitive impairment", "mild behavioral impairment", and "treatment". We focused on empirical studies, meta-analyses, and authoritative reviews published since 1997, as this is when most of the progress towards understanding dementia-related NPS has occurred. We selected articles published in the English language.

We found 167 review articles in PubMed, between 1976 and 2012, with the keywords "neuropsychiatric symptoms in dementia". We analyzed 22 empirical studies related to NPS in MCI, and 30 papers related to dementia (reviews and empirical studies). We searched for the terms "behavioral symptoms in dementia", "treatment", "neuropsychiatric symptoms in dementia", "treatment", and selected 52 papers, including reviews, empirical studies, and meta-analyses; 20 of these were analyzed. Finally, we analyzed five papers found using the terms "antipsychotics" and "dementia".

Neuropsychiatric symptoms (NPS)

"Neuropsychiatric symptoms", as they are most commonly referred to in the USA (also known as "behavioral and psychological symptoms of dementia" [BPSD] according to the International Psychogeriatric Association),[10] represent a heterogeneous group of non-cognitive symptoms and behaviors occurring in subjects with dementia. BPSD constitute a major component of the dementia syndrome, irrespective of its subtype. They are as clinically relevant as cognitive symptoms, as they strongly correlate with the degree of functional and cognitive impairment.[11]

Common NPS can include agitation, anxiety, irritability, illusion and delusions, apathy, depression, disinhibition, aberrant motor and obsessive–compulsive behaviors, and sleep disorders, among others. These manifestations can be present at any stage of dementia and non-dementia–cognitive impairment.

The pathogenesis of NPS has not been clearly delineated but it is probably the result of a complex interplay of psychological, social, and biological factors. Recent studies have emphasized the role of neurochemical, neuropathological, and genetic factors underlying the clinical manifestations of BPSD.[11]

Despite being almost universally present during the course of dementia, BPSD have not been included in the defining criteria for dementia in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR)[12] or *International Statistical Classification of Diseases and Related Health Problems*, tenth revision (ICD-10)[13] classification systems. The core features of dementia according to these classifications consist of a gradual onset of multiple cognitive deficits (involving memory and at least one additional cognitive domain) not occurring exclusively during delirium and representing a decline from a previous level of functioning.[12]

However, in the DSM-5,[14] NPS are considered in some dementias such as frontotemporal dementia (FTD) (Behavioral variant Frontotemporal Neurocognitive Disorder, DSM-5), Lewy Body Dementia (Neurocognitive Disorder due to Lewy Body Dementia, DSM-5), and prodromal stages of dementia.

Validated scales for NPS assessment

Validated instruments, both general scales and focused scales, can be used to determine the presence, intensity, or frequency of NPS in patients with MCI and dementia. General scales allow a broad spectrum of NPS to be assessed, while focused scales are used to assess one or more behavioral symptoms (for example, scales for depression or agitation).

General scales are used to conduct multidimensional examinations, and include the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[15] the Neurobehavioral Rating Scale,[16] the Behavioral Rating Scale for Dementia,[17] and the Neuropsychiatric Inventory (NPI).[18] The NPI is the most widely used scale to measure NPS associated with cognitive disorders. It is a fully structured interview, which obtains data from an informant, usually the patient's caregiver. Recently, the NPI – Clinician (NPI-C) was developed.[19] The revised NPI-C can be used to assess single or multiple domains.[20] Unlike the NPI, each domain and potentially each sub-question within a domain, can be rated on the NPI-C. Caregivers and patients rate the frequency, severity, and distress of each item, and then the clinician provides an overall rating based on interviews and additional chart information, which brings additional strength to the measure compared with the original scale.

The NPI-C was field tested in an international validation study and compared with focused scales to determine

convergent validity. It was trimmed to 142 items (61 more than the NPI) and has been translated to several European languages.[20]

Focused scales are instruments that are used to conduct uni-dimensional evaluations, and include the Hamilton Depression Rating Scale,[21] the Cornell Scale for Depression in Dementia,[22] the Geriatric Depression Scale,[23] or the Cohen–Mansfield Agitation Inventory.[24]

NPS in pre-dementia stages of Alzheimer's disease and frontotemporal dementia

Mild behavioral impairment (MBI)

Although NPS are common in dementia, they have received less attention in prodromal dementia states. In addition, not all prodromal states involve prominent cognitive impairment. Many patients develop NPS as the first indicator of impending dementia. This is most common in patients with FTD, but is also the case in patients with AD. Taragano and Allegri[25] reported that, in 50% of a series of dementia consulting patients, NPS were the first indication of change, before the occurrence of cognitive symptoms. As a result they proposed the syndrome 'mild behavioral impairment', referring to a late-life syndrome with prominent psychiatric and related behavioral symptoms in the absence of prominent cognitive symptoms, which may also be a dementia prodrome.

In a recent study, Taragano et al[7] followed a consecutive series of 358 patients for up to 5 years. The objective was to compare MCI and MBI patients and estimate the risk of dementia development in both groups. MBI was defined as a behavioral disturbance not meeting DSM-IV or National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for dementia, psychosis, or other major psychiatric condition, and also not meeting criteria for MCI of any type. It was operationalized following the inclusion criteria shown in Table 1.

Examples of major persistent changes in patient behavior that can lead to a diagnosis of MBI are as follows: agitation, anxiety symptoms, apathy, aspontaneity, delusion symptoms, depressive symptoms, disinhibition, emotional lability, euphoria, impulsivity, indifference, irritability, lack of empathy, loss of insight, loss of personal hygiene, loss of social tact, oral/dietary changes, perseverant behavior, and sleeping disorders.

Results of this research showed that NPS were consistently and robustly associated with faster time to dementia conversion across both groups. Although this has been previously reported, this study emphasized the importance of NPS, even in the absence of cognitive symptoms, as the MBI group without cognitive complaints converted to dementia faster than the MCI group without psychiatric complaints. Rates of dementia conversion in the MBI group with cognitive complaints were comparable to those in the MCI group with NPS, suggesting that these two groups could probably be considered as one. Finally, the presence of MBI was associated with clinical and neuroimaging evidence of abnormalities in the frontal regions of the brain, and with a greater risk of conversion to FTD than to AD. Hence, MBI, specifically in the absence of cognitive symptoms, probably represents an FTD prodrome in at least half of the cases in this study.

Table 1 Mild behavioral impairment inclusion criteria[7]

a. Presence of a major change in patient behavior
b. Change occurring later in life (>60) that is persistent (>6 months)
c. No complaint of cognitive impairment by patient/informant
d. Normal occupational and social functioning
e. Normal activities of daily living
f. Absence of dementia

In a *post hoc* analysis of the study, the authors did not find any relationship between depression and a greater risk of dementia; therefore, in a new second cohort of patients (2007–2012) who were followed for up to 5 years, one focus was to study the relationship between cognitive symptoms in depression and the risk of dementia. New data emerged: the risk of dementia was higher only when the depressive syndrome was present with cognitive impairment of the cortical and not the subcortical type. The cortical cognitive profile in depression, usually uncommon, refers mainly to verbal learning memory or naming or semantic fluency impairment, while the most common subcortical profile refers mainly to attention or executive impairments. Furthermore, the great majority of depressed patients who showed no improvement in cognitive cortical impairment after remission of depression had an abnormal cerebrospinal fluid level of Abeta1-42 protein confirmed by lumbar puncture.

Other important findings in this new second cohort concern the presence of a control group (n = 165) comprising psychiatric patients with neither MCI nor MBI. More patients in the MBI group converted to dementia (67/96) than in the MCI (36/87) and control (23/165) groups, showing a statistically significant difference $\chi^2 = 83.3$, df = 2; $P < 0.001$. Even when compared with subgroups of anxiety, depression, or psychosis, the difference remained significant $\chi^2 = 132$; df = 15; $P < 0.001$ (Taragano et al, unpublished data).

These findings have implications for the early detection, prevention, and treatment of patients with dementia in late life by focusing on the emergence of new behavioral symptoms.[7]

Mild cognitive impairment (MCI)

MCI represents an intermediate state of cognitive function between the changes observed in aging and the dementia diagnosis. It is currently defined as a syndrome with impairment of memory or another cognitive domain that does not interfere substantially with personal autonomy.[26] The National Institute on Aging (http://www.nia.nih.gov) and the Alzheimer's Association (http://www.alz.org) developed criteria for the symptomatic pre-dementia phase of AD, referred to here as 'MCI due to AD'. The workgroup developed the following two sets of criteria: (1) core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis, and (2) research criteria that could be used in clinical research settings, including clinical trials. The second set of criteria incorporate the use of biomarkers based on imaging and cerebrospinal fluid measures. The final set of criteria for MCI due to AD has four levels of certainty, depending on the presence and nature of the biomarker findings.[27] Moreover, in the DSM-5, MCI is classified as an entity: mild neurocognitive disorder.[14]

Concomitant to the description of MCI, NPS were better recognized.[28,29] It is important to detect NPS because (1) they assist in the early diagnosis of conversion to dementia; (2) they are markers for increased risk of progression to dementia; and (3) therapeutic management of behavioral symptoms may provide an opportunity for successful outcome.[28,29]

NPS are common in MCI patients; however, their frequency is modified when considering community or tertiary healthcare centers. A review on behavioral symptoms in MCI showed that depression, apathy, and anxiety were the most frequent.[30]

NPS in MCI

Various empirical studies have been developed to investigate NPS in MCI. Table 2 summarizes data from the last 3 years.

Depression is the most studied symptom in MCI and dementia. The most frequent depressive symptoms observed in these patients are irritability, impairment of attention and concentration, paranoid and obsessive thoughts, lack of insight, psychomotor retardation, and weight loss. The prevalence of depressive symptoms may be as high as 45%.[31] In a large prospective study, the possibility of converting to dementia during follow-up was 2.6 times greater if depression was present in MCI subjects at baseline.[6] Another longitudinal study showed an increased presence of depression, from baseline status, in patients who developed cognitive impairment and dementia versus the control population with stable cognition and healthy patients,[32] concluding that depressive symptoms are associated with cognitive decline. However, the importance of depression as a risk factor for developing dementia could not be demonstrated in other studies.[5,33]

Butters et al[34] propose that depression alters an individual's risk of cognitive dysfunction, shortening the latent period between the development of AD neuropathology and the onset of clinical dementia, thus increasing the incidence and prevalence of AD among older adults with depression.

Apathy (lack of motivation, diminished goal-directed behavior, and decreased emotional engagement) is a prevalent behavioral manifestation in MCI patients. Community and tertiary center studies[30] have found that approximately one-third of patients with a diagnosis of MCI suffers apathy.

The presence of apathy symptoms increases the likelihood of developing AD.[35] In a European study,[5] a diagnosis of apathy in amnestic-MCI (a-MCI) patients represented a 7-fold increased risk of developing AD. Similar to that observed in AD, the prevalence of apathy in MCI patients increases in relation to the decline of cognitive function.[36] Apathy was observed more frequently in multiple-domain MCI than in a-MCI, mainly in relation to executive dysfunction. In clinical practice, the presence of apathy in an MCI context allows the identification of people with potential AD.[36]

In a study about neuropsychiatric predictors of progression from a-MCI to AD, the presence of apathy, but not depression, predicted patients with a-MCI who progressed to AD. The authors found that apathy had an important impact on a-MCI and should be considered a mixed cognitive/psychiatric disturbance related to ongoing AD neurodegeneration.

The third most common NPS is anxiety. The literature on the prevalence of anxiety is conflicting, perhaps due to differences in diagnostic criteria. Anxiety is defined as an excessive apprehension and feeling of foreboding,[36] and its diagnostic frequency varies from 10%[28] to 45%.[31] Demey et al[4] found that 37% of MCI patients had anxiety versus 5% of a control group. In a study with 3 years of follow-up, people with a diagnosis of MCI and the presence of anxiety symptoms had a higher risk of progressing to AD than individuals with MCI without anxiety.[33]

A recent study of NPS in MCI subtypes,[37] including 1,779 participants, concluded that, while there were few

Table 2 Neuropsychiatric symptoms in mild cognitive impairment. Data reviewed from 2010 to 2012

Study	Patients	Objective	Conclusions
Somme et al[87]	132	To identify NPS that predict the progression from a-MCI to dementia using an easy-to-administer screening tool for NPS	Faster progression to dementia was observed in patients with either night-time behavioral disturbance, apathy, or anxiety as well as in those with a higher number of items affected
Peters et al[88]	230	To examine the association of NPS severity with risk of transition to all-cause dementia, AD and VaD	The presence of at least one NPS was a risk factor for all-cause dementia, as was the presence of NPS with mild severity. Night-time behaviors were a risk factor for all-cause dementia and of AD, whereas hallucinations were a risk factor for VaD
Shahnawaz et al[89]	767	To study the prevalence and characteristics of depressive symptoms in MCI	Individuals with MCI symptoms, when compared especially with a-MCI, express more depressive symptoms than cognitively intact individuals. These findings highlight the importance of assessing and treating depressive symptoms in MCI
Richard et al[90]	397	To investigate if apathy predicts the progression from MCI to AD	Symptoms of apathy, but not of depressive affect, increase the risk of progression from MCI to AD. Apathy in the context of symptoms of depressive affect does not increase this risk. Symptoms of apathy and depression have differential effects on cognitive decline
Lee et al[91]	243	To examine the neuroanatomical changes associated with depressive symptoms in MCI	Depressive symptoms were associated with greater atrophy in AD-affected regions, increased cognitive decline, and higher rates of conversion to AD. Depression in individuals with MCI may be associated with underlying neuropathological changes, including prodromal AD, and may be a potentially useful clinical marker in identifying MCI patients who are most likely to progress to AD
Gallagher et al[92]	161	To determine whether NPS track existing measures of declining cognitive and functional status or may be considered distinct and sensitive biomarkers of evolving Alzheimer's pathology	NPS and, in particular, anxiety symptoms are common in patients with MCI. In this sample, anxiety for upcoming events and purposeless activity frequently co-occurred and were significant clinical predictors of earlier conversion to AD. However, these findings were not independent of cognitive status at baseline and therefore may be markers of severity rather than independent predictors of disease progression
Chan et al[93]	321	To explore the association between NPS and risk of cognitive decline in Chinese older persons residing in the community	Depression in non-demented older patients may represent an independent dimension reflecting early neuronal degeneration. Further studies should be conducted to assess whether effective management of NPS exerts beneficial effects on cognitive function
Ryu et al[94]	220	To determine the persistence of NPS over 6 months in participants with MCI	NPS were highly persistent overall in older people with MCI. Persistence was predicted by having more severe symptoms at baseline. Clinically significant levels of NPS were associated with decreased quality of life. We conclude that clinicians should be aware that NPS symptoms in MCI usually persist
Palmer et al[5]	131	To evaluate whether depression or apathy in patients with a-MCI increases the risk of progressing to AD	Apathy, but not depression, predicts which patients with a-MCI will progress to AD. Thus, apathy has an important impact on a-MCI and should be considered a mixed cognitive/psychiatric disturbance related to ongoing AD neurodegeneration
Ramarkers et al[95]	263	To investigate the predictive accuracy of affective symptoms for AD during a follow-up study in subjects with MCI, and whether the predictive accuracy was modified by age, the presence of a-MCI or the length of follow-up	Affective symptoms are associated with a decreased risk for AD. The risk may be dependent on MCI subtype or length of follow-up, but it does not depend on age

Abbreviations: AD, Alzheimer's disease; a-MCI, amnestic mild cognitive impairment; NPS, neuropsychiatric symptoms; VaD, vascular dementia.

associations between a-MCI and NPS, the presence of executive dysfunction in MCI was associated with greater severity of symptoms, and specifically with depression (evidenced by the Geriatric Depression Scale [GDS] score)[23] and anxiety.[37]

Other symptoms, such as agitation (physical or verbal outbursts, general emotional distress, restlessness, pacing, shredding paper or tissues, yelling) and irritability (abnormally excitable or sensitive to stimulation, readily excited to impatience or anger), show lower prevalence in MCI patients compared with depression, apathy, and anxiety. Irritability was observed in almost 20% of MCI patients in a large community-based study.[3] The presence of irritability reached 55% in a tertiary referral center-based study.[4] Agitation symptoms have a lower prevalence but may be a marker of rapid cognitive impairment.[30]

Psychotic symptoms such as delusions, hallucinations, and illusions are rare in MCI patients.[3] However, presence of these behavioral disturbances may reflect a major risk of developing dementia.

NPS in dementia stages of Alzheimer's disease and frontotemporal dementia

Alzheimer's disease

AD is a progressive neurodegenerative disease that is characterized by impairment of cognitive and functional abilities as well as by NPS. Cognitive impairment can include impairment of memory, visuospatial functions, language, and executive functions. In addition, NPS such as depression, apathy, and agitation seem to already be common in early stages of AD and can have an impact on the well-being of both patients and caregivers. Cognitive performance has been consistently associated with functional ability.[38] In cognitive impairment and dementia, both functional ability and behavior are significantly correlated with caregiver burden, although the strength of association is more than two times higher for behavioral changes.[39]

The neuroanatomic involvement of prefrontal subcortical limbic regions is an early feature of AD.[40] Reflecting this is the early, often prodromal, appearance of neuropsychiatric and behavioral alterations that become more fulminate and problematic as AD progresses. Depression, anxiety, irritability, aggressiveness, apathy, euphoria, sleep and appetite disturbances, motor restlessness, hallucinations, delusions, and paranoia are typical features of fulminate AD.[18] These features can be the presenting signs of an impending dementia years before cognitive decline becomes apparent, and are often the most difficult to deal with from the perspective of the caregiver, friends, family, and clinicians of individuals with AD at any stage.[41]

The NPS often get worse over the course of the disease and may fluctuate in presentation.[36] Depression and apathy are the symptoms most frequently observed in the evolution of AD, and usually occur in early stages and in MCI.[20]

NPS in Alzheimer's disease: neuroanatomical correlations

Most reports in the literature indicate that behavioral symptoms and cognition are not related,[42,43] or that the relationship is weak.[44,45] There is also evidence that any change in behavioral symptoms is independent from changes occurring in cognitive measures.[46] Instead, Harwood et al[47] described a relationship between psychological and behavioral disturbances and Mini-Mental State Examination (MMSE) scores. Hallikainen et al found that NPS were not correlated with cognitive performance, showing that cognitive and behavioral disturbances are instead distinct entities in AD, at least in the mild stage of the disease.

Apathy is the most prevalent symptom in AD patients and its frequency increases in relation to illness progression. In early AD, 42% of patients showed apathy, increasing to 90% in severe AD.[48] This progression reflects the frontosubcortical dysfunction and the impairment in communication between the anterior cingulate cortex and other cortical areas that accompanies the progression of AD. Proposed diagnosis criteria for apathy in AD have recently been published.[49]

Post-mortem and in vivo studies suggest that AD is associated with a dysfunctional dopaminergic system, since reduced levels of dopamine and homovanillic acid, as well as altered dopamine-receptor density, have been described in discrete brain regions coinciding with the mesocorticolimbic pathway system,[50] including atrophy,[51] hypoperfusion, and hypometabolism in the anterior cingulate gyrus and orbitofrontal areas.[52] It is also possible that dysfunction in these areas underlies the reported relationship between increased changes in frontal white matter and apathy,[53] together with disruption of deep white matter afferents and efferents to the basal ganglia and/or by decrement of metabolic activity in frontal subcortical regions.

Depression is another common symptom in AD, and proposed diagnosis criteria have just been published.[54] Mega et al[48] found that the prevalence of depression was up to 60% in patients with advanced AD. A recent study of different subtypes of geriatric depression (major

depression disorder [MDD], dysthymia disorder [DD], subsyndromal depression disorder [SsD], and depression due to dementia of Alzheimer type [DdD]) reported that the DdD group presented moderate depressive symptoms associated with anxiety, similar to MDD group, they had the greatest cognitive impairment with a cortical profile, and showed the highest scores in daily life activities and caregiver burden scales than the other three groups (MDD, DD, SsD).[55]

Apathy and depression may occur together, but one must be differentiated from the other.[35] Lyketsos and Lee[56] reported that the presence of depression was related to increased institutionalization, caregiver burden and caregiver depression.

In AD patients, psychotic symptoms can present with hallucinations and delusion and are associated with high caregiver burden.[8] These symptoms are more frequently present in moderate and advanced stages, and could be drug or delirium induced.[36] Hallucinations and delusions observed in AD have been proposed as a distinct syndrome, in order to differentiate it from other psychoses.[57]

In the Cardiovascular Health study,[58] where the trajectory of cognitive decline as a predictor of psychosis in early AD was evaluated, the working group found that individuals who ultimately develop psychosis have more rapid cognitive deterioration during the earliest phases of AD than individuals with AD who do not develop psychosis. The genetic and other neurobiological factors leading to the expression of AD plus psychosis may exert their effects by acceleration of the neurodegenerative process. Two studies found an association between psychosis and increased severity of beta-amyloid senile plaques in the presubiculum,[59] and across cortical regions.[60] Förstl et al[61] reported changes in neuronal counts in the CA1 hippocampus and parahippocampal gyrus, while Zubenko et al[59] described increased density of neurofibrillary tangles (NFTs) in the middle frontal cortex. Furthermore, Farber et al[62] reported that AD patients with psychosis had a 2.3-fold greater density of neocortical NFTs than AD subjects devoid of psychotic symptoms.

Neuroimaging studies have similarly confirmed severe abnormalities in grey matter volume, cerebral blood flow, and metabolism in the above-mentioned cortical regions of AD subjects with psychotic symptoms.[63] Anatomically, these changes partially coincide with cholinergic and dopaminergic pathways, supporting (together with neurochemical and pharmacological evidence) the role of acetylcholine and dopamine imbalance in the pathogenesis of AD psychosis.[64] Psychosis has also been associated with the relative preservation of norepinephrine in the substantia nigra and a significant serotonin reduction in the presubiculum.[65]

Delusions have been associated with an increase in muscarinic receptors in the orbitofrontal cortex,[20] as revealed in a study where fluorodeoxyglucose positron emission tomography (PET) analysis correlated delusions with reduced glucose metabolism in the right frontal region.

Agitation and irritability are common behavioral symptoms. Recently, an Asian study found a prevalence of irritability/aggression greater than 70%.[66] Altered glucose metabolism (measured by PET) has also been associated with anxiety, apathy, agitation, and disinhibition in AD involving multiple regions: anxiety was related to the bilateral entorhinal cortex, anterior parahippocampal gyrus, left superior temporal gyrus, and insula; apathy was related to the bilateral anterior cingulated gyrus, medial orbitofrontal cortex, and medial thalamus; agitation/disinhibition was related to frontal and temporal lobes.[20]

The diagnosis of anosognosia is frequent in patients with mild AD but not in those with MCI. In the latter case, a true anosognosia was not able to be identified, but rather only a decreased awareness of illness.[67] Furthermore, reduced awareness of cognitive difficulties is linked with verbal memory performances in patients with MCI but not in those with AD, suggesting the involvement of factors other than neuropsychological ones in AD. Thus, neuropsychiatric dimensions commonly present in patients with AD should be investigated along with anosognosia.[57]

Frontotemporal dementia

In 1998, Neary and colleagues[68] established diagnostic criteria for frontotemporal lobar degeneration (FTLD) and defined three major subtypes: FTD, semantic dementia (SD), and progressive non-fluent aphasia.

Spectrum manifestations of FTLD include two principal presentations: gradual behavioral impairment and language dysfunction pattern.

DSM-5 classification describes this entity as frontotemporal neurocognitive disorder with a behavioral or a language variant ('Behavioral Variant of Frontotemporal Neurocognitive Disorder' [bv-FTD], 'Language Variant of Frontotemporal Neurocognitive Disorder').

FTLD is a degenerative disorder associated with presentation in younger patients,[69] and high prevalence of affected relatives (40% of positive family history).[49]

NPS in behavioral variant of frontotemporal dementia: neuroanatomical correlations

bv-FTD begins with atrophy of the orbitofrontal, anterior cingulated, and anterior insular cortex and quickly involves the basal ganglia.[70] Clinically, bv-FTD is characterized by a cluster of behavioral symptoms in association with executive dysfunction. Changes in personality and social behavior that include apathy and disinhibition can occur. Patients lose their initiative, set aside their personal responsibilities, and experience impairment of their professional activities. They lose empathy for others and are not interested in what may occur in their environment. Patients are not aware of their changes in behavior (anosognosia).[71,72]

Disinhibition presents as inappropriate social behavior, loss of decorum, and inappropriate vocabulary. Other clinical features include lack of insight, denial of illness, dramatic changes in personal hygiene and dressing, repetitive motor acts, modifications in eating habits, hyperorality, and hypersexuality; Klüver-Bucy syndrome can even develop.[71,72] These patients can have affective disorders, gluttony, hypermetamorphosis, and visual and auditory agnosia.

In FTD subjects, apathy has been associated with atrophy in the anterior cingulated cortex, right dorso-lateral prefrontal cortex, and adjacent medial frontal cortex. This suggests that dysfunction in the frontosubcortical cingulate pathways is implicated in apathy regardless of the subtype of dementia.[11]

Patients can develop depression, with exaggerated or unmotivated emotional lability, but with an absolute indifference to their surroundings. Anxiety, suicidal ideation, amimia, and hypochondriac behavior can occur.[73]

Patients with bv-FTD exhibit impairment in their self-criticism, self-perception, and social skills. Clinically, they are socially uninhibited and lack emotional recognition and empathy. They fail in the recognition of social behavior, and are not able to appropriately evaluate the severity of moral and social transgressions. In relation to social functioning, laboratory tests indicate that physiological and behavioral responses are intact in certain emotional contexts. For example, they do not differ from control groups in their emotional response to loud noises, or to films and scenes with sadness, happiness, or fear. Therefore, evidence exists that the physiological and behavioral infrastructure that is necessary for some aspects and responses to simple emotions is preserved in early stages of bv-FTD.[73] However, FTD emotional impairment clearly occurs in areas of socio-emotional functioning that require high-order processing of the social world.

Patients with bv-FTD have deficits in the recognition of negative emotions in other people, and in activating more complex emotions such as feeling ashamed. Feeling ashamed is a member of the 'self-conscious' family of emotions; others are guilt, pride, and embarrassment. All of them are cognitively complex and require an appreciation of the person and its social context. It is believed that these self-conscious emotions emerge relatively late in the phylogeny and ontogeny, and are related to different cerebral regions (for example, medial prefrontal cortex, anterior cingular, and insula) that are vulnerable in FTD. Feeling ashamed occurs when a person's behavior infringes social norms. The emotional result indicates that a social transgression has occurred and helps to motivate attempts to correct and repair the situation.[73]

In bv-FTD, the estimated prevalence of delusions is 0%–23%.[74,75] Omar et al[76] found that patients with bv-FTD presented with delusions in an early stage of the disease, occurring as an important symptom found in the first year since the beginning of the disease. In some patients, delusions appeared before cognitive impairment.

NPS in semantic dementia and non-fluent aphasia: neuroanatomical correlations

Presentations with language dysfunction are less frequent than bv-FTD. Two subtypes are recognized: SD and non-fluent progressive aphasia (NFA). SD, also known as a temporal variant of FTD, begins with asymmetric atrophy of the anterior temporal lobes and anterior insulae,[77] with later involvement of the orbitofrontal cortex and basal ganglia.[78] Clinical features of SD include speech that is fluent but poor; the meaning of words is notably altered and anomalies are present. NFA patients show agrammatism and effortful speech, and single-word comprehension and meanings are sparse.[79]

Behavioral symptoms, particularly depression, anxiety, and apathy, are present in SD and NFA.[80,81] Rosen et al[81] found characteristic disinhibition, aberrant motor behavior, and eating disorders in patients with a diagnosis of SD.

NPS management

The evaluation of a patient with NPS and cognitive impairment should begin with a complete history of cognitive and functional status, co-morbidities, family history, prescribed and non-prescribed medications, sleep patterns, and concerns regarding social and environmental changes. Detailed neuropsychiatric and medical examinations should be conducted to evaluate concomitant or triggering clinical intercurrences.

Table 3 Recent pharmacological research on neuropsychiatric symptom management (2012)

Study	Patients	Objective	Conclusions
Azermai et al[96]	40	To study the effects of abrupt antipsychotic discontinuation in cognitively impaired older persons	Abrupt antipsychotic discontinuation appears to be feasible in older individuals with BPSD Systematically performed discontinuation efforts in clinical practice are needed to differentiate between patients where antipsychotics have no added value and patients where the benefits outweigh the risks of their use
Mori et al[97]	140	To investigate the effects of a cholinesterase inhibitor, donepezil, in patients with DLB in a randomized, double-blind, placebo-controlled exploratory phase II trial	Donepezil at 5 and 10 mg/day produces significant cognitive, behavioral, and global improvements that last at least 12 weeks in DLB patients, reducing caregiver burden at the highest dose. Donepezil is safe and well tolerated
Dominguez-Alonzo et al[98]	Adult rats	To explore whether melatonin stimulates dendrite formation and complexity in the adult rat hippocampus in organotypic slice cultures, which is a model that preserves the hippocampal circuitry and their tridimensional organizations of connectivity	Evidence strongly suggests that melatonin may be useful in the treatment of neuropsychiatric diseases to repair the loss of dendrites and re-establish lost synaptic connections
Li et al[99]	84	To evaluate the efficacy and safety of donepezil plus natural hirudin in patients with mild-to-moderate AD	Compared with the donepezil treatment in the patients with mild-to-moderate AD, the results suggest that donepezil combined with natural hirudin may improve the treatment effects in the ADL, BPSD, and cognition of the patients. Furthermore, this joint treatment is safe
Bidzan et al[100]	71	To determine the effect of pharmacological treatment of aggressive behavior, while taking into account the dynamics of disease progression during observation	Acetylcholinesterase inhibitors may have beneficial effects on aggressive behavior in the course of AD, similar to that seen with the use of valproic acid and antipsychotics
Chatterjee et al[101]		To evaluate the risk of cerebrovascular events associated with use of risperidone, olanzapine, and quetiapine in community-dwelling older adults in the USA	The study suggested that quetiapine use may be associated with a moderately lower risk of cerebrovascular events than olanzapine in older adults. Prescribers should closely monitor the patients treated with atypical agents for the incidence of cerebrovascular adverse events
Gardette et al[102]	534	To determine the all-cause mortality risk associated with antipsychotic use among AD patients	Antipsychotic use may be associated with an increased risk of mortality, but to a lesser extent than several other factors that were found to be significant predictors of mortality (age, male gender, cognitive score, recent hospitalization, medical aid). To date, antipsychotic risks outweigh their benefits in BPSD for which non-pharmacological approaches remain the first-line strategy and should be privileged

Abbreviations: AD, Alzheimer's disease; ADL, activities of daily living; BPSD, behavioral and psychological symptoms; DLB, dementia with Lewy bodies.

Standard laboratory studies and structural (computerized axial tomography [CAT] scan, magnetic resonance imaging [MRI]) or functional (single photon emission computed tomography [SPECT], PET) images of the brain could be necessary. New technologies based on neuroimaging (such as intracerebral amyloid molecular imaging with PET) and biochemical analyses of cerebrospinal fluid (such as measurement of amyloid-beta peptide and hyperphosphorylated tau protein), may reveal correlates between intracerebral pathology and pre-dementia symptoms.

Information from family members and caregivers is important in the presence of both cognitive and behavioral impairment, in patients with pre-dementia and dementia stages of AD, and FTD. Anxiety, irritability, and agitation in patients with dementia can be relieved with environmental modifications (avoidance of dark and noisy environments), recreation, and music and light therapies.

A wide variety of pharmacologic agents are used in the management of psychiatric and behavioral symptoms in dementia; for example, cholinesterase inhibitors, N-methyl-

D-aspartate (NMDA) antagonists, antipsychotics, antidepressants, and other drugs (benzodiazepines, mood stabilizers, non-benzodiazepine hypnotics). Despite this, pharmacologic therapies are not particularly effective.

A systematic review found that the atypical antipsychotics risperidone and olanzapine currently have the best evidence for efficacy. However, care is needed to avoid the side effects associated with these drugs.[82]

Each pharmacologic or non-pharmacologic intervention should be tailored to the specific symptoms of an individual patient, and decisions about the type and duration of treatment should be based on its efficacy and the patient's tolerance.

Pharmacological treatment of NPS

Specific considerations about each symptom and its pharmacological treatment are outside the scope of this review, and previous publications have covered this issue.[36,83,84] However, Table 3 summarizes some reports from the last year on pharmacotherapy of NPS in AD and FTD.

Pharmacotherapy of NPS in Alzheimer's disease

Pharmacotherapy of NPS in AD has been studied in numerous randomized and controlled trials. The largest number of studies has focused on antipsychotics. Data are of reasonably high quality and indicate that risperidone and olanzapine are more effective than placebo for institutionalized patients with severe agitation, aggression, and psychosis. The efficacy of antipsychotics is counterbalanced by safety concerns that include cerebrovascular adverse events and mortality. Cholinesterase inhibitors and NMDA antagonists appear to have modest benefits for patients with mild to moderate–severe symptoms. Antidepressants are effective for treating depression in AD, but more data are required to determine the efficacy of trazodone and citalopram for agitation and aggression. Carbamazepine appears to be efficacious, although side effects and concerns about drug–drug interactions limit its use. The data do not support the use of valproate. Benzodiazepines should only be considered for short-term, as-needed use. Data regarding other pharmacologic interventions, such as beta blockers, buspirone, and estrogen preparations, are insufficient.[85]

Pharmacotherapy of NPS in frontotemporal dementia

To date, there are no approved and established pharmacologic treatment options for FTD. Available treatment strategies are based mainly on small clinical trials, miscellaneous case reports, or small case-controlled studies. The results of these studies, and conclusions about the efficacy of the medications used are often contradictory. Approved therapeutic agents for AD, such as acetylcholinesterase inhibitors and NMDA antagonists, have been used off-label to treat cognitive and behavioral symptoms in FTD, but outcomes have not been consistent. For behavioral or psychopathological symptoms, treatment with antidepressants, especially selective serotonin reuptake inhibitors, could be helpful. Antipsychotics are often not well tolerated because of their adverse effects; these drugs should be given very carefully because of an increased risk of cerebrovascular events. In addition to pharmacologic options, physical, occupational, or speech therapy can be applied to improve functional abilities. Currently, no effective treatment is available that targets the cause of FTD.[86]

Conclusion

It has already been demonstrated that the presence of NPS in MCI patients is an indicator of increased risk of progression to dementia. However, the topic is vast, since doctors have only very recently begun to recognize the existence of patients with behavioral disorders without cognitive impairment as another population at risk of developing degenerative dementia. Therefore, the focus has been placed on the need to learn about these NPS in pre-dementia stages of AD and FTD.

Psychiatric and behavioral symptoms are present universally in patients with dementia. Diagnosis, characterization, and management are essential in clinical practice in order to ameliorate caregiver burden as well as to avoid frequent hospitalizations and early institutionalization.

Pharmacologic and non-pharmacologic interventions should be tailored to the specific symptoms of each individual patient, and decisions about the type and duration of treatments should be based on their efficacy and patients' tolerance.

A multidisciplinary health team is fundamental to the optimal management of patients with NPS and cognitive impairment.

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