Apathy, or a lack of motivation, has been increasingly recognized as a distinct psychiatric syndrome. Apathy is primarily a dysfunction of the frontal-subcortical circuit and is associated with various neuropsychiatric disorders including Alzheimer’s disease. Apathy is associated with a number of adverse outcomes, including apparent cognitive impairment, decreased daily function, poor insight into one’s own functional and cognitive impairment, and poor outcome from rehabilitation treatment. Furthermore, the degree of caregiver’s burden in these patients is significant.

This article reviews the definition of apathy, prevalence and associated adverse outcomes, causation, the approach to patients with apathy, and available treatment options with particular attention to studies conducted in a nursing home setting. The purpose of this article is to increase the recognition of apathy by physicians working in the nursing home. (J Am Med Dir Assoc 2009; 10: 381–393)

Keywords: Apathy; dementia; cognition disorders; mood disorders

The term “apathy” conventionally describes a lack of interest or emotion. This usage of apathy, although it is intuitive and commonly used in clinical descriptions of patients with such traits, does not address the medical definition of apathy or its nosological status.

Marin1 proposed apathy as a syndrome defined as a lack of motivation, evidenced by diminished goal-directed overt behavior (as indicated by lack of effort, initiative, perseverance, and productivity), diminished goal-directed cognition (as indicated by diminished importance or value, lack of interest and concern about one’s personal, health, or financial problems), and diminished emotional concomitants of goal-directed behavior (as indicated by unchanging affect, lack of emotional responsivity to positive or negative events, absence of excitement). Apathy was considered a symptom of some other neurological or psychiatric syndromes if lack of motivation was attributable to intellectual impairment, emotional distress, or diminished level of consciousness. This proposed definition of apathy either as a syndrome or symptom presupposed a lack of motivation as a primary presenting feature. However, Levy and Czernecki2 noted that this definition appeared problematic because “a lack of motivation” is a psychological state corresponding to the behavioral state that may be loosely called apathy and this definition may be just verbal redundancy or tautology. In addition, it is also difficult to establish a consensus on the definition of “motivation” because it is a psychological concept encompassing several different theories from behavioral to social psychology. Levy and Czernecki,2 therefore, proposed the definition of apathy as a quantitative reduction of self-generated voluntary and purposeful behaviors. van Reekum et al3 also noted that the assessment of motivation could be controversial and suggested that apathy should be defined as an absence of responsiveness to a stimulus, with requirement that this lack of responsiveness be demonstrated by a lack of self-initiated action. These definitions proposed by Levy and Czernecki2 or van Reekum et al3 focus more on diminished self-initiated behavior rather than reduced cognitive or emotional goal-directed ability to respond to a stimulus, which was considered an equally important constituent in Marin’s initial definition.

To date, there is no clear consensus as to what definition of apathy is appropriate and clinically easy to operationalize. This lack of consensus corresponds to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV4 where apathy is not included in the glossary and mentioned merely as a nonspecific symptom of several disorders. Consensus on definition is much needed to establish appropriate gold standard diagnostic criteria for both research and clinical purposes.

DIFFERENTIAL DIAGNOSIS

Apathy may present as a syndrome, in which lack of motivation is a predominant feature and cannot be attributed to
intellectual impairment, emotional distress, or diminished level of consciousness. However, apathy can be a symptom of other neurological or psychiatric syndromes. This distinction is important since the management strategy can be different. Syndromes commonly associated with apathy are shown in Table 1.

**APATHY IS NOT DEPRESSION**

Particular mention should be made of depression because apathy has been traditionally treated as an aspect of depression. Anhedonia, or loss of interest or pleasure can be used as a principal symptom to diagnose major depressive disorder (MDD) instead of or along with depressed mood. Because other criteria for DSM-IV diagnosis of MDD such as fatigue, hypersonnia or insomnia, loss of appetite, weight loss, and diminished ability to concentrate are prevalent among demented patients, a demented patient with apathy may be misdiagnosed as having MDD even in the absence of dysphoria. This diagnostic challenge stems from the apparent overlap between apathy and depression. Diminished interest, psychomotor retardation, fatigue/hypersonnia, and a lack of insight are common to both apathy and depression (Table 2). A number of studies have demonstrated that apathy was correlated with high scores on depression scales. However, the correlation between apathy and depression may be attributed to the correlation between apathy and negative items of rating scales quantifying depression. A study was conducted on 107 patients using the Apathy Evaluation Scale (AES), a scale devised specifically to assess apathy by Marin et al., and the Hamilton Rating Scale for depression (HamD) and it reported that convergence between AES and HamD was attributable to a subset of HamD items (diminished work/interest, psychomotor retardation, anergy, and lack of insight), which corresponds to the commonly seen symptoms in apathy syndrome. When these items were excluded from consideration, the correlation between AES and HamD was not significant. Similar convergence was also found between the Frontal System Behavior Scale (FrSBe) and the Cornell Scale for Depression (CSD). The correlation between FrSBe apathy items and negative mood items on the CSD was not significant, but the correlation between FrSBe apathy items and loss of interest and reactivity items on the CSD was significant. Thus, by carefully selecting rating scales, separate quantification of apathy and depression can be made possible.

A number of studies have reported that a certain group of patients had significant discrepancy between the levels of depression and apathy. This discrepancy made it possible to categorize patients as “pure apathy,” “pure depression,” or “apathy and depression.” A longitudinal study of 65 patients with AD and depression suggested that depression and apathy may have divergent natural histories and be distinguishable regions. A study using positron emission tomography (PET) on patients with early AD revealed that patients exhibiting apathy had significant decreases in glucose metabolism in left orbitofrontal regions, whereas depression was associated with hypometabolism in dorsolateral prefrontal regions. These findings support the notion that apathy and depression are separate disorders with anatomically distinguishable regions involved.

Another study suggested that depressive symptoms in elderly people had different clinical features along the age spectrum. Apathy may become a more prominent feature of depression in the old-old age group compared to a younger age group. These findings are congruent with the study, which confirmed that apathy would be greater in late-onset depression than in early-onset depression.

Apathy can also result from the treatment for depression. There has been a theoretical concern that serotonergic reuptake inhibitors (SSRIs) may affect the counterbalance of serotonin and dopamine, which can lead to apathy, and SSRI-induced apathy has been increasingly reported. A cross-sectional study reported that physical (fatigue, sleepiness/sedation) and cognitive (apathy, inattentiveness,

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**Table 1. Disorders Associated With Apathy**

<table>
<thead>
<tr>
<th>Neurologic Disorders</th>
<th>Psychiatric Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic brain injury</td>
<td>Depression</td>
</tr>
<tr>
<td>Stroke involving the frontal-subcortical circuit</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Alzheimer’s disease (AD)</td>
<td>Psychoses</td>
</tr>
<tr>
<td>Dementia with Lewy body (DLB)</td>
<td>Adjustment disorder</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Medical Disorders</td>
</tr>
<tr>
<td>Frontotemporal dementia (FTD)</td>
<td>Apathetic hyperthyroidism</td>
</tr>
<tr>
<td>HIV dementia</td>
<td>Drug intoxications/withdrawal</td>
</tr>
<tr>
<td>Parkinson’s disease (PD)</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Lyme disease</td>
</tr>
<tr>
<td>Anoxic encephalopathy</td>
<td>Pseudoparaphyroidism</td>
</tr>
<tr>
<td>Cerebral neoplasm</td>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>Chronic subdural hematoma</td>
<td>Testosterone deficiency</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Vitamin B12 deficiency</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>Other debilitating conditions</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>(eg, malignancy, congestive heart failure, renal or hepatic failure)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Delirium</th>
</tr>
</thead>
</table>

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MMSE scores were 20 or higher in 5 studies \cite{19,27,31,40,41} and reported in one study.\cite{34} Among the rest of the studies, the mean assessing global cognitive impairment. The MMSE score was not which is one of the most widely used clinical instruments for as-

Apathy has been reported to be common in AD outpatients. The NeuroPsychiatric Inventory (NPI), a psychiatric rating scale for assessing psychopathology in patients with neuropsychiatric disorders, was used to identify apathy in most stud-
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PREVALENCE

A number of recent studies have identified apathy as a sign-
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ASSOCIATED ADVERSE OUTCOMES

The attempts to assess the association between cognitive dysfunction and apathy have been complicated by the

<table>
<thead>
<tr>
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</tr>
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<td>Low social engagement</td>
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<td>Pessimism</td>
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Table 2. Differences and Overlap in Clinical Symptoms of Apathy and Depression

Two studies reported prevalence of apathy in community-
dwelling AD patients. One was the large-scale, Cache County Study that showed point prevalence of 28.5%.\cite{41} This study also reported that the incidence of apathy over an 18-month period was 21.0% among patients with dementia.\cite{49} The other study was conducted in Brazil and reported a prevalence of 53.5%.\cite{30} Apathy appears to be common in AD patients even in population-based cohorts. The reported prevalence of apathy observed in other various disorders is summarized in Table 3.

The studies of prevalence discussed in the preceding para-
graphs were conducted in outpatients or population based. There were several studies describing the prevalence of apa-
thy in long-term care settings (Table 4). It appears that the estimates of prevalence of apathy among demented patients in nursing home settings are comparable with the estimates of prevalence of apathy among demented patients in community or outpatient settings. This finding is intriguing because the prevalence of advanced dementia is usually higher in nursing home settings compared to in the community or outpatient settings, and therefore a higher prevalence of apathy in nursing home settings would be expected. There may be several possible explanations. One of the explanations is that apathy commonly appears early in the course of demen-
tia,\cite{8,40,51} when patients would still be in the community, and persists throughout the disease.\cite{80,81} Another explanation is the heterogeneity of the studies. The differences in patient characteristics, diagnostic criteria for dementia and assess-
ment methods for apathy all contribute to the difficulties comparing the prevalence of apathy simply by its numbers.

The association between the use of antidepressants and the prevalence of apathy was examined in only one study,\cite{7} which showed that the use of antidepressants is more common in apathetic AD patients than nonapathetic AD patients. The possibility that antidepressants, especially SSRIs, may cause apathy after successful treatment of depression is a cause for concern and warrants further studies.

In summary of the reviewed data here, apathy seems to be common in various medical disorders. There is a wide range of reported prevalence of apathy, which makes comparisons across disorders very difficult or almost impossible. Nonetheless, apathy seems to be more commonly observed in disorders involving the frontal subcortical circuit, which will be reviewed later in this article.

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ASSOCIATED ADVERSE OUTCOMES

The attempts to assess the association between cognitive dysfunction and apathy have been complicated by the
possibility that apathy can cause lack of effort, which may interfere with the results of cognitive assessment. Nonetheless, the relationship between cognitive deficits and apathy has received increasing research attention. Most studies examining the relationship between apathy and cognitive dysfunction have used only the MMSE for cognitive testing. There has been accumulating evidence suggesting that a higher apathy score correlates with a lower MMSE score in patients with AD.5–15,27,28,33,36,42,44–46,82–84 This correlation between apathy and lower MMSE scores was also observed among patients with dementia16 or stroke,17 and in nursing home residents.86 On the other hand, several studies failed to replicate this correlation between apathy and cognitive deficits measured by MMSE in patients with AD,12,37–39 PD,40 dementia,41 and MDD.42

This inconsistency may be a reflection of differences in inclusion criteria, methodologies, instruments, and diagnostic criteria to diagnose apathy. The other explanation is that the inconsistency may well be related to the relative inability of the MMSE to assess the frontal lobe function with which apathy appears to be associated. A study of 89 patients with MDD showed that the correlation between MMSE and apathy was not significant, whereas there was a significant correlation between apathy and executive dysfunction.91 These findings were consistent with the previous study of 50 patients with PD92 in which apathy was not correlated with MMSE but with executive dysfunction. Levy pointed out that the MMSE does not adequately test frontal lobe function and is not a valid measurement of this cognitive domain.5

Studies have been conducted using more specific assessment tools for frontal lobe dysfunction to examine the association between apathy and cognitive deficits. Apathy was shown to be associated with frontal lobe dysfunction across various disorders including dementia,16 stroke,17–19 vascular dementia,20 and traumatic brain injury.21,22

Recently 2 longitudinal studies were conducted to examine the impact of apathy.23 The first study,24 following 354 subjects with AD for 1 to 4 years, showed that apathy was significantly associated with older age and a higher frequency of minor and major depression. In addition, the frequency of apathy increased from 14% in the very mild stage of AD to 61% in the severe stage of AD. AD patients who developed apathy during the follow-up period had a significantly greater cognitive and functional decline than AD patients without apathy. The authors suggested that apathy is a behavioral marker of a more “malignant” type of AD with more severe behavioral problems and faster progression of cognitive, functional, and emotional deficits. Whether the successful treatment of apathy may reduce the progression of these deficits remains to be seen with further research. Another study,25 following 251 patients with amnestic MCI for 1 year demonstrated that after a 1-year follow-up, 15.1% of the patients with apathy at baseline developed AD in comparison with 6.9% of the nonapathetic patients. This difference was not statistically significant (P = .10) after controlling for age, sex, education level, anxiety, and depression levels. At the 1-year follow-up, patients developing AD had a significantly higher frequency of apathetic symptoms (91.7%) than patients without AD (26.9%). In summary, apathy seems to be correlated with cognitive deficits, especially frontal lobe dysfunction. Limited evidence from longitudinal studies suggests that apathy may precede or occur concomitantly with a faster progression of cognitive, functional, and emotional deficits in a subgroup of AD patients and could be a marker to predict such decline.

There are several studies that suggested an association between apathy and impaired activity of daily living (ADL) among patients with AD.26,27,28,33,36,42,44–46,82,96,97 Such a relationship was also observed in patients with dementia28 stroke,29,30,31 vascular dementia,32 and MDD.33 Additionally, in a prospective study of 237 poststroke patients conducted in a rehabilitation hospital, cognitive impairment and apathy, but not depression, were correlated negatively with functional improvement after rehabilitation.34

Apathy also has been shown to be associated with increased caregiver burden in caregivers of AD patients27,30,34,42,82,85 and other demented patients.85 In a study of 53 spouse caregivers of patients with dementia,96 deterioration of relationship quality was specifically associated with the presence of behavioral problems, notably apathy, but not with cognitive status or functional impairment.

Although apathy is a significant source of distress to a caregiver, it does not seem to concern patients themselves as much. Apathy was shown to be associated with poor insight into cognitive and behavioral changes in patients with AD14,89,101,102 and patients with traumatic brain injury.73 Most patients with mild AD were aware of their cognitive deficits but failed to appraise their severity and their consequences.101

Apathy may also affect patient perception of quality of life (QOL). In a multicenter cross-sectional study investigating the relationship between apathy and subjective QOL in 92 nursing home residents, the relationship between apathy and QOL appeared to vary with the cognitive functioning of the residents. In residents with a low level of cognitive functioning measured by MMSE, apathetic behavior was associated with high subjectively perceived QOL; in residents with a higher level of cognitive functioning, apathetic

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**Table 3. Prevalence of Apathy Across Disorders**

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Cognitive Impairment</td>
<td>14.7% − 39.8%</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>17.0% − 45.7%</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>22% − 91%</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>59% − 82%</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>40% − 61%</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>89% − 100%</td>
</tr>
<tr>
<td>Dementia with Lewy body</td>
<td>52% − 61%</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>20% − 31%</td>
</tr>
<tr>
<td>Stroke</td>
<td>15.2% − 42%</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>22.6% − 93.6%</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>20% − 70%</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>55.6% − 74%</td>
</tr>
<tr>
<td>HIV</td>
<td>12%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>29%</td>
</tr>
</tbody>
</table>

HIV, Human Immunodeficiency Virus.
behavior was associated with low QOL.\textsuperscript{86} In another cross-sectional study of 134 assisted living facility residents with dementia,\textsuperscript{103} apathy was the third strongest predictor, after agitation and depression, of QOL perceived by caregivers. These results suggest that apathy may affect both subjective and objective QOL but the relationship between subjective QOL and apathy may depend on the patient’s level of cognitive function. The authors\textsuperscript{86} proposed that a positive relationship between apathy and subjective QOL in patients with severely impaired cognition may suggest that apathy could be an adaptive behavior to cope with their own cognitive, functional, and emotional deficits. Apathy could have a protective effect by causing disengagement and withdrawal from stimulating activities, which can potentially make patients aware of their deficits. Another possible explanation is that frontal lobe dysfunction, commonly observed in patients with apathy, may influence emotional functioning and be related to this positive finding. Whether therapy aimed at apathy may improve or worsen subjective QOL remains to be seen with further research.

Apathy also appears to be associated with poor nutritional status. In a prospective multicenter study of 686 AD outpatients, apathy was associated with more pronounced deficits in nutritional status ($P < .05$).\textsuperscript{27}

Apathy may have prognostic value for demented patients in the nursing home. In a prospective cohort study of 569 patients with dementia residing in the nursing home, items of the Rating Scale for Elderly Patients, a nurse-administered, 35-item scale evaluating behavioral and cognitive impairment developed in the Netherlands, found that physical impairment, dependency, and apathy had the most prognostic value to predict the 2-year survival rate. Items measuring aggressive or depressive behavior and cognitive impairment were less predictive. The 2-year survival rate for the entire cohort was 56%, and the presence of apathy was associated with increased 2-year mortality.\textsuperscript{104}

Apathy seems to be associated with poor treatment response among depressed patients when they were treated according to clinical practice, mainly with antidepressants for 1 year.\textsuperscript{105}

The impact of apathy on patients’ attitudes toward medication adherence is somewhat inconsistent.\textsuperscript{9,106} One cross-sectional study on HIV patients\textsuperscript{9} showed apathy was not related to patient expectancies toward medication adherence as measured by a questionnaire. The association between apathy and actual medication adherence rate was not examined in this study. Another cross-sectional study on diabetic patients\textsuperscript{106} demonstrated apathetic patients were less likely to adhere to exercise plan or insulin regimen, as shown by an inventory, and had higher BMI and HgbA1c. It seems likely that apathy has negative impact on the medication compliance, which in turn may lead to increased medical and psychiatric morbidity. Furthermore, a lack of concern about one’s personal, health, or financial problems is an important aspect of apathy and may have direct adverse impact on self-care, leading to failure to recognize early symptoms of impending medical and psychosocial problems.

In summary, apathy has been shown to be associated with a variety of adverse outcomes. However, most studies were

### Table 4. Prevalence of Apathy in the Nursing Home Setting

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Number of Centers in Study</th>
<th>Patient No.</th>
<th>Diagnosis Criteria</th>
<th>MMSE Assessment</th>
<th>Prevalence of Apathy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuidema 2007\textsuperscript{75}</td>
<td>Holland</td>
<td>59</td>
<td>1322</td>
<td>Dementia</td>
<td>DSM-IV</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Pitkala 2004\textsuperscript{76}</td>
<td>Finland</td>
<td>7</td>
<td>160</td>
<td>Dementia</td>
<td>DSM-IV</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Margallo 2001\textsuperscript{77}</td>
<td>UK</td>
<td>3</td>
<td>137</td>
<td>Dementia</td>
<td>AGECAT</td>
<td>Mean 7.0</td>
</tr>
<tr>
<td>Wood 2000\textsuperscript{78}</td>
<td>USA</td>
<td>1</td>
<td>69</td>
<td>Cognitively impaired</td>
<td>MMSE</td>
<td>Mean 6.7</td>
</tr>
<tr>
<td>Wagner 1995\textsuperscript{79}</td>
<td>USA</td>
<td>70</td>
<td>614</td>
<td>Dementia</td>
<td>Clinical diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; AGECAT, Automated Geriatric Examination for Computer Assisted Taxonomy; MMSE, Mini-Mental State Exam; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory-Nursing Home Version; MBPC-NH, Memory and Behavior Problems Checklist-Nursing Home Version.
designed as cross-sectional studies and they did not provide insight into temporal causality between apathy and its associated outcomes. Apathy may well cause adverse outcomes or adverse outcomes may well cause apathy, or even an inconspicuous confounding factor may play a role. Further studies are needed to assess the impact, causation, and mechanisms of apathy on outcomes.

CAUSATION

Recently literature has increasingly made it clear that apathy may be associated with a disruption of the frontal-subcortical circuit. This circuit starts from the anterior cingulate cortex, then proceeds to the ventral striatum, globus pallidus, and thalamus, with a final loop back to the anterior cingulate cortex. It has been considered to be involved in generation of motivation as a loop, and a lesion anywhere in this circuit may result in similar picture, apathy.107,108 Numerous neuroanatomical, neuropsychological, and functional imaging studies have provided evidence to support the role of the anterior cingulate circuit in the development of apathy (Table 5). Regional chemistry, especially dopamine125,126 and serotonin119 can also be a contributing factor for the pathology of apathy.

Table 5. Neuroanatomical and Functional Imaging of Areas Associated with Apathy

<table>
<thead>
<tr>
<th>Method</th>
<th>Finding</th>
<th>Areas involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsy CT</td>
<td>Neurofibrillary tangles, Lesions</td>
<td>Anterior cingulate (left110) Basal ganglia (bilateral, posterior internal capsule15)</td>
</tr>
<tr>
<td>MR spectroscopy</td>
<td>lower NAA/Cr ratios, Decreased volume</td>
<td>Frontal lobe (right70) Anterior cingulate (right, bilateral112) Frontal Lobe (bilateral, left115) Ventromedial superior frontal gyrus (right96) Nucleus accumbens115 Fronto-subcortical circuits (right69) Right hemisphere69 Subcortical structures116 Basal ganglia (bilateral117) Dorsolateral prefrontal (bilateral117) Ventral striatum118</td>
</tr>
<tr>
<td>PET</td>
<td>Hypoperfusion</td>
<td>Frontal (dorsolateral,119 medial,119 left orbitofrontal19, medial orbitofrontal120), bilateral anterior cingulate120</td>
</tr>
<tr>
<td>SPECT</td>
<td>Hypoperfusion</td>
<td>Cingulate (right,31 anterior,121 right anterior,43,88 left anterior122,123) Prefrontal,184 Dorsolateral prefrontal (left superior88) Frontal (right,43 right inferior frontal gyrus,12 right medial frontal gyrus123) Orbitofrontal122 (bilateral superior gyrus,88 left gyrus,123 right middle gyrus88) Temporal lobe (anterior,184 right inferior,43) tempoparietal lobes (right posterior24)</td>
</tr>
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CT, computed tomography; MR spectroscopy, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

EVALUATION

Making a reliable diagnosis of apathy is essential before treatment for apathy is initiated. The medical, neurological, and psychosocial history is important. The psychosocial history will indicate the patient’s baseline level of motivation and facets of adult personality. New-onset apathy in later life should be alarming. Several recent studies8,40,51 have shown that MCI patients can exhibit apathy as well as other neuropsychiatric symptoms. Therefore, it has been suggested that in some patients, these symptoms can precede the onset of overt dementia. Patients with MCI and apathy should be carefully monitored.

Apathy is prevalent in patients with neurodegenerative disorders including AD, PD, and stroke. Historical clues suggesting these neurodegenerative disorders should be considered. Comprehensive neuropsychological assessment to clarify cognitive function with particular attention to frontal lobe function is necessary.

Caution should be exercised when evaluating a patient with the so-called frontal lobe syndrome. They may show marked signs of disinhibition such as loss of social grace, impulsive anger, violence, and inappropriate sexual behavior in
The Neuropsychiatric Inventory (NPI) is also increasingly used as a valid and an efficient method of identifying psychological and behavioral disturbances in patients with neurodegenerative disorders. A number of assessment tools, including the Frontal Systems Behavior Scale, formerly referred to as the Frontal Lobe Personality Scale, the Dementia Apathy Interview and Rating, the Lille Apathy Rating Scale, the Apathy Inventory, the Behavior Rating Scale for Dementia, and the Scale for the Assessment of Negative Symptoms in Alzheimer’s Disease were developed and validated, although they were less commonly used to measure apathy. Among these assessment instruments, AES may be the most practical in clinical setting, especially the nursing home. It is the most studied and frequently used in research settings and has been demonstrated to be a reliable and validated measure as discussed above. The clinician-administered version is a 10- to 20-minute semi-structured interview, but a shorter version, which is validated in the nursing home, is also available.

**MANAGEMENT**

**Nonpharmacologic**

Successful treatment of apathy requires multidisciplinary approaches. Caregivers need to understand that apathy is not just a physiologic change associated with dementia or other neurodegenerative disorders, but it is a pathological state that may become a source of significant morbidities to the patients and also a source of distress to their caregivers. They should be encouraged to introduce new sources of pleasure, interest, and stimulation. Increasing opportunity for socialization is helpful. Nursing care to promote comfort and functional autonomy may be facilitated by focusing on the person rather than on the disease.

The patient’s general medical conditions (eg, seizures, pain, orthostatic hypotension) should be aggressively treated. Sensory deficits, if present, should be corrected (eg, eye glasses, magnifying lenses, large-print books, hearing aids, cerumen removal). Daily exercise protocol may be implemented to increase a patient’s mobility. Environmental modification (eg, adaptive devices such as wheelchair, visible clocks and calendars, adequate lighting, familiar faces such as family, orientation interventions) may be beneficial. These elementary steps may increase the reward potential of the environment and thereby enhance motivation.
Unfortunately, the nonpharmacological treatment of apathy has not been a subject of systematic research. Behavioral therapy seems to be effective at improving apathy. Live interactive music may have positive engagement effects. The combination of cognitive stimulation activities with donepezil treatment is also more effective in patients with mild to moderate AD compared with donepezil alone. A recent systematic review concluded that some evidence showed that multisensory stimulation in a multisensory room reduces apathy in people in the latter phases of dementia. Although no studies have been published, it is likely that other interventions, such as pet therapy, art therapy, or physical therapies will clearly prove useful as well.

**Pharmacologic**

Methylphenidate and dextroamphetamine are psychostimulants widely used for narcolepsy, attention deficit hyperactive disorder, and depression. They are also used for apathy, but most of the studies of methylphenidate in treating apathy have been limited to case reports or case series. These reports are considerably different in associated conditions, dose of the medication used, methodologies, and assessment tools used to monitor response. Two individual crossover, double-blinded, randomized trials, known as “N of 1” trials, were conducted to investigate the efficacy of methylphenidate in apathetic geriatric patients with AD. One patient’s apathy showed significant improvement on the AES whereas the other apathetic patient’s trial was stopped because the AES could not be completed.

At present, the literature provides a limited evidence that methylphenidate is beneficial in treating apathy. These psychostimulants can cause adverse reactions including insomnia, loss of appetite, and elevated blood pressure and should be used with discretion in the frail elderly population.

Acetylcholinesterase inhibitors were initially developed for potential cognitive benefits by therapeutically augmenting cholinergic activity after the early discovery of a marked cholinergic deficit in the brains of AD patients; however, their effect on other neuropsychiatric symptoms associated with dementia has attracted increased interest. Tacrine was the first acetylcholinesterase inhibitor and was shown to reduce apathy in an open-label study in AD patients. Tacrine was later withdrawn from the market owing to hepatotoxicity. A retrospective analysis of pooled data from 2 randomized controlled trials (RCTs) showed metrifonate, another acetylcholinesterase inhibitor, improved apathy in patients with AD. Metrifonate is not approved in the United States. Currently, 3 acetylcholinesterase inhibitors, donepezil, galantamine, and rivastigmine, are available in the United States.

In an RCT, donepezil was found to decrease the NPI apathy scores in AD patients. In another RCT, which was the first RCT conducted for patients with AD in the nursing home setting, both donepezil and placebo improved behavioral and psychological symptoms measured by the NPI with no differences between the groups. The authors attributed the lack of differences in the groups to the frequent use of concomitant psychotropics in both groups and concluded that the impact of donepezil on behavior in the nursing home setting was unresolved and merited further investigation. In another RCT, donepezil tended to improve apathy measured by the Apathy Scale in AD patients compared to placebo, but the difference did not reach statistical significance. However, the participants in the trial had only mild apathy at the baseline, which may explain the absence of drug-placebo difference.

In a post hoc analysis of pooled data from 3 large RCTs of galantamine in AD patients, mean changes in the NPI apathy item were not significant, although significant improvement was observed in clusters containing apathy. In an open-label trial, galantamine was shown to reduce apathy in patients with dementia with Lewy body (DLB). In an RCT, treatment with rivastigmine produced a significant reduction in apathy and anxiety in patients with DLB.

In an RCT of rivastigmine in the nursing home setting, apathy was one of the 8 symptoms that improved significantly from the baseline.

The evidence suggests that acetylcholinesterase inhibitors may be effective for the treatment of apathy, although test subjects have not been selected on the basis of the presence of apathy. Whether the effect of acetylcholinesterase inhibitors on apathy is a class effect needs to be answered with further studies. It is possible that each agent has different effects on different behaviors at different points in the illness. Also, acetylcholinesterase inhibitors have not been extensively studied for patients with apathy and neurodegenerative disorders other than AD and further trials are awaited.

Other agents have been used for the treatment of apathy, although controlled trials are mostly lacking. Dopaminergic drugs, such as amantadine and bromocriptine, have been used successfully to treat apathy in case reports. Pramipexole may be used in apathetic patients with PD because it has preferential affinity for D3 dopamine receptor, which is considered to be related to mood and apathy, although its theoretical advantage has not yet been translated into superiority in clinical efficacy for apathy. Levodopa/carbidopa appears to improve motivation in apathetic patients with PD, whereas the results of the effect of deep brain stimulation on apathy were conflicting. All dopaminergic agents predispose to behavioral side effects including psychosis and should be used with caution. Antidepressants with stimulating properties such as bupropion may be used if concomitant depression is present. SSRIs should be used with extra caution if necessary. Atypical antipsychotics have been widely used in the treatment of negative symptoms in schizophrenia. In a case series, olanzapine was used successfully in the treatment of apathy in the absence of depression in patients on long-term treatment with SSRIs for nonpsychotic MDD. Modafinil has stimulating or arousing effects and was used with a satisfactory result in a case series. Selegiline is a selective inhibitor of monoamine oxidase (MAO) type B, which plays a major role in the metabolism of dopamine, and it appears to be effective for apathy in a case series. A post hoc analysis of RCT on add-on memantine treatment to donepezil in patients with AD failed to show the effectiveness of memantine on apathy.
The treatment of apathy is often complicated and difficult. Evidence to guide clinicians treating apathy is limited and all those involved including family members should be made aware of the risks and benefits of each management plan. Optimization of medical care and treatment of any other medical conditions that can contribute to development of apathy should be pursued. Any unnecessary psychotropics or other medications, especially if they can be associated with diminished motivation, should be discontinued or tapered down. Nonpharmacologic treatment should be used first and aggressively. Use of pharmacologic treatment may be considered if above measures are not successful. The choice of agent is often guided by the comorbidities patients experience so that the agent used can be targeted at underlying comorbidity as well as apathy. Acetylcholinesterase inhibitors are preferred agents used for AD patients with apathy, dopaminergic agents for PD, and stimulating antidepressants for depression with apathetic traits. Treatment of DLB is difficult but anticholinesterase inhibitors have favorable effects on apathy as well as other disruptive behaviors. The potential benefits of medications should be carefully weighed against risks, including drug interactions and tolerability.

CONCLUSION AND FUTURE DIRECTIONS

In summary, apathy is a common disorder, but easily overlooked. It is primarily a deficit in motivation and should be distinguished from depression. Apathy is associated with various disorders of the brain that involve the frontal lobes and their associated subcortical structures. Accumulating evidence suggests that apathy is associated with various adverse outcomes, but seems to be treatable. Treatment of apathy requires multidisciplinary approaches based on the understanding of apathy from the biomedical, psychological, and socioenvironmental aspects. Acetylcholinesterase inhibitors appear to be gaining support as pharmacologic treatment from the growing body of evidence, whereas only very limited evidence exists for other agents.

Apathy has been receiving growing research interest along with our deepening understanding of the frontal subcortical circuits over the past 2 decades; however, our understanding of apathy remains far from adequate. A consensus on definition is much needed to establish appropriate gold standard diagnostic criteria for both research and clinical purposes. Further investigation and research on assessment tools. Many assessment methods are used for AD patients with apathy, dopaminergic agents for PD, and stimulating antidepressants for depression with apathetic traits. Treatment of DLB is difficult but anticholinesterase inhibitors have favorable effects on apathy as well as other disruptive behaviors. The potential benefits of medications should be carefully weighed against risks, including drug interactions and tolerability.

REFERENCES


