

Apathy: A Common Psychiatric Syndrome in the Elderly

Shinya Ishii, MD, Nancy Weintraub, MD, and James R. Mervis, MD

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 ap-

peared 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 non-specific 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

GRECC, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA (S.I.); Sepulveda Campus Greater Los Angeles Veterans Affairs Health Care System, Los Angeles, CA (N.W., J.R.M.); David Geffen School of Medicine at UCLA, Los Angeles, CA (N.W., J.R.M.).

Address correspondence to Shinya Ishii, MD, GRECC, Veterans Affairs Greater Los Angeles Healthcare System, 11301 Wilshire Boulevard, Building 220, Room 302 Los Angeles, CA 90073. E-mail: sishii@mednet.ucla.edu

Copyright ©2009 American Medical Directors Association

DOI:10.1016/j.jamda.2009.03.007

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.⁵ 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 MDD⁴ such as fatigue, hypersomnia 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.⁶ This diagnostic challenge stems from the apparent overlap between apathy and depression. Diminished interest, psychomotor retardation, fatigue/hypersomnia, and a lack of insight are common to both apathy and depression⁶ (Table 2). A number of studies have demonstrated that apathy was correlated with high scores on depression scales.⁷⁻¹² 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,¹³ 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.¹¹ 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).⁸ 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.”^{5,14-17} A longitudinal study of 65 patients with AD and depression suggested that depression and apathy may have divergent natural histories and be discriminable syndromes.¹⁸ 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.¹⁹ 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.²⁰ Apathy may become a more prominent feature of depression in the old-old age group compared to a younger age group.²⁰ These findings are congruent with the study, which confirmed that apathy would be greater in late-onset depression than in early-onset depression.²¹

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.^{22,23} A cross-sectional study reported that physical (fatigue, sleepiness/sedation) and cognitive (apathy, inattentiveness,

Table 1. Disorders Associated With Apathy

<p>Neurologic Disorders</p> <ul style="list-style-type: none"> Traumatic brain injury Stroke involving the frontal-subcortical circuit Alzheimer’s disease (AD) Dementia with Lewy body (DLB) Creutzfeldt-Jakob disease Frontotemporal dementia (FTD) HIV dementia Parkinson’s disease (PD) Progressive supranuclear palsy Anoxic encephalopathy Cerebral neoplasm Chronic subdural hematoma Huntington’s disease Limbic encephalitis Multiple sclerosis Bingwanger’s encephalopathy Wernicke-Korsakoff syndrome Kluver Bucy syndrome Hydrocephalus Delirium 	<p>Psychiatric Disorders</p> <ul style="list-style-type: none"> Depression Schizophrenia Psychoses Adjustment disorder <p>Medical Disorders</p> <ul style="list-style-type: none"> Apathetic hyperthyroidism Drug intoxications/withdrawal Hypothyroidism Lyme disease Pseudoparathyroidism Chronic fatigue syndrome Testosterone deficiency Vitamin B12 deficiency Other debilitating conditions (eg, malignancy, congestive heart failure, renal or hepatic failure)
---	---

Table 2. Differences and Overlap in Clinical Symptoms of Apathy and Depression

Symptoms of Apathy	Symptoms Common to Apathy and Depression	Symptoms of Depression
Blunted emotional response Indifference Low social engagement Diminished initiation Poor persistence	Diminished interest Psychomotor retardation Fatigue/hypersomnia Lack of insight	Dysphoria Suicidal ideation Self-criticism Guilt feelings Pessimism Hopelessness

forgetfulness, word-finding difficulty, mental slowing) symptoms were frequently reported by patients with MDD after long-term successful antidepressant treatment, and the authors concluded that these symptoms were both side effects of antidepressants as well as residual symptoms of MDD.²⁴ A recent case control study on 384 MDD patients demonstrated that apathy appeared to be greater in patients treated with SSRIs than in patients with non-SSRIs with adjusted Odds Ratio (OR) of 1.90 (1.14–3.17).²⁵ It should be noted that in this study, both SSRIs and non-SSRIs appeared to be efficacious in treating apathy associated with depression in elderly patients.

Unfortunately, cognitive and physical adverse events including apathy during long-term treatment of depression have not been well studied so far and further studies are much needed, especially because late-life depression is a recurring disorder and patients often receive a prolonged course of antidepressants.²⁶

PREVALENCE

A number of recent studies have identified apathy as a significant and frequently occurring symptom in a variety of disorders.

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 studies,^{5,19,27–41} and the reported prevalence for apathy using the NPI was between 32.1%¹⁹ and 93.2%.³⁷ Most of these studies reported the mean Mini Mental Status Exam (MMSE) score, which is one of the most widely used clinical instruments for assessing global cognitive impairment. The MMSE score was not reported in one study.³⁴ Among the rest of the studies, the mean MMSE scores were 20 or higher in 5 studies^{19,27,31,40,41} and their reported point prevalence for apathy ranged from 32.1%¹⁹ to 58.7%.³¹ The largest study with 686 patients reported an apathy point prevalence of 43.0%.²⁷ The mean MMSE scores were lower than 20 in the remaining studies.^{5,28–30,32,33,35–39,41} Four studies^{35,38,39,41} had more than 100 participants and the prevalence of apathy was between 41.6%³⁸ and 75.0%.³⁵ It appears that the point prevalence of apathy was higher among the AD outpatients whose mean MMSE scores were lower than 20 than those with mean MMSE scores 20 or higher. The association between apathy and cognitive deficits will be discussed in detail later.

Seven studies using more specific instruments, such as the Apathy Evaluation Scale,⁴² the Apathy Scale,^{7,14} the Apathy Inventory,⁴³ and others^{44–47} reported that the prevalence of

apathy in AD outpatients ranged between 24%⁷ and 86%.⁴² 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%.⁴⁸ This study also reported that the incidence of apathy over an 18-month period was 21.0% among patients with dementia.⁴⁹ The other study was conducted in Brazil and reported a prevalence of 53.5%.⁵⁰ 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 paragraphs were conducted in outpatients or population based. There were several studies describing the prevalence of apathy 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 dementia,^{8,40,51} when patients would still be in the community, and persists throughout the disease.^{80,81} Another explanation is the heterogeneity of the studies. The differences in patient characteristics, diagnostic criteria for dementia and assessment 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,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.

ASSOCIATED ADVERSE OUTCOMES

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

Table 3. Prevalence of Apathy Across Disorders

Disorders	Prevalence
Mild Cognitive Impairment ^{40,51,52}	14.7% ² –39.8% ⁵¹
Parkinson's disease ^{5,33,53–61}	17.0% ⁵⁶ –45.7% ⁶¹
Progressive supranuclear palsy ^{5,29,56,61,62}	22% ⁶¹ –91% ^{5,29}
Huntington's disease ^{5,62}	59% ⁵ –82% ⁶²
Corticobasal degeneration ^{61,63}	40% ^{61,63}
Frontotemporal dementia ^{61,63}	89% ⁵ –100% ⁶⁵
Dementia with Lewy body ^{5,37,64,65}	52% ⁶¹
Multiple sclerosis ^{66,67}	20% ⁶⁶ –31% ⁶⁷
Stroke ^{12,15,68–70}	15.2% ¹² –42% ⁷⁰
Vascular dementia ^{32,37,38,48,71}	22.6% ⁴⁸ –93.6% ³⁷
Traumatic brain injury ^{72,73}	20% ⁷² –70% ⁷³
Amyotrophic lateral sclerosis ⁷⁴	55.6% ⁷⁴
HIV ⁹	12% ⁹
Cardiovascular disease ⁷¹	29% ⁷¹

HIV, Human Immunodeficiency Virus.

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.^{7,14,16,27,28,33,36,42,44–46,82–84} This correlation between apathy and lower MMSE scores was also observed among patients with dementia⁸⁵ or stroke,¹⁵ 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,^{32,87–89} PD,⁵⁴ dementia,⁹⁰ and MDD.⁹¹

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 PD⁵⁴ 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,⁹² stroke,^{12,69} Mild Cognitive Impairment (MCI),⁹³ AD,⁹⁴ PD,^{58,59} and traumatic brain injury.⁹⁵

Recently 2 longitudinal studies were conducted to examine the impact of apathy.^{7,51} The first study,⁷ 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 study⁵¹ following 251 patients with amnesic 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.^{7,14,19,27,36,45,46,82,96,97} Such a relationship was also observed in patients with dementia,⁸⁵ stroke,^{15,69} vascular dementia,⁹⁸ and MDD.⁹⁹ 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.⁶⁸

Apathy also has been shown to be associated with increased caregiver burden in caregivers of AD patients^{27,30,34,42,80} and other demented patients.⁸⁵ In a study of 53 spouse caregivers of patients with dementia,¹⁰⁰ 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 AD^{14,89,101,102} 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

Table 4. Prevalence of Apathy in the Nursing Home Setting

Author, y	Country	Number of Centers in Study	Patient No.	Diagnosis	Criteria	MMSE	Assessment Instrument	Prevalence of Apathy, %
Zuidema 2007 ⁷⁵	Holland	59	1322	Dementia	DSM-IV	Not Reported	NPI-NH	34.0
Pitkala 2004 ⁷⁶	Finland	7	160	Dementia	DSM-IV	Not Reported	Nurse questionnaire	16.9
Margallo 2001 ⁷⁷	UK	3	137	Dementia	AGECAT	Mean 7.0 SD 7.0	NPI	23.0
Wood 2000 ⁷⁸	USA	1	69	Cognitively impaired	MMSE	Mean 6.7 Range (0–17)	NPI-NH	84.0
Wagner 1995 ⁷⁹	USA	70	614	Dementia	Clinical diagnosis	Mean 7.8 SD 6.1	MBPC-NH	41.0

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.

behavior was associated with low QOL.⁸⁶ In another cross-sectional study of 134 assisted living facility residents with dementia,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 authors⁸⁶ 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 ($P < .05$).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.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.¹⁰⁵

The impact of apathy on patients' attitudes toward medication adherence is somewhat inconsistent.^{9,106} One cross-sectional study on HIV patients⁹ 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 patients¹⁰⁶ 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

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 dopamine^{125,126} and serotonin,¹¹⁹ can also be a contributing factor for the pathology of apathy.

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 studies^{8,40,51} 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

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

Method	Finding	Areas involved
Autopsy CT	Neurofibrillary tangles Lesions	Anterior cingulate ¹⁰⁹ (left ¹¹⁰) Basal ganglia (bilateral, ¹¹¹ posterior internal capsule ¹⁵)
MR spectroscopy MRI	lower NAA/Cr ratios Decreased volume	Frontal lobe (right ⁷⁰) Anterior cingulate (right, ¹¹² bilateral ¹¹³) Frontal Lobe (bilateral, ¹¹⁴ left ¹¹³) Ventromedial superior frontal gyrus (right ⁹⁰) Nucleus accumbens ¹¹⁵
	Hyperintensities	Fronto-subcortical circuits (right ⁶⁹) Right hemisphere ⁶⁹ Subcortical structures ¹¹⁶
PET	Hypoperfusion	Basal ganglia (bilateral ¹¹⁷) Dorsolateral prefrontal (bilateral ¹¹⁷) Ventral striatum ¹¹⁸
	Reduced dopamine and noradrenaline transporter binding Hypometabolism (FDG)	Frontal (dorsolateral, ¹¹⁹ medial, ¹¹⁹ left orbitofrontal, ¹⁹ medial orbitofrontal ¹²⁰), bilateral anterior cingulate ¹²⁰
SPECT	Hypoperfusion	Cingulate (right, ³¹ anterior, ¹²¹ right anterior, ^{43,88} left anterior ^{122,123}) Prefrontal, ⁸⁴ Dorsolateral prefrontal (left superior ⁸⁸) Frontal (right, ⁴³ right inferior frontal gyrus, ¹²³ right medial frontal gyrus ¹²³) Orbitofrontal ¹²² (bilateral superior gyrus, ⁸⁸ left gyrus, ¹²³ right middle gyrus ⁸⁸) Temporal lobe (anterior, ⁸⁴ right inferior ⁴³) tempoparietal lobes (right posterior ¹²⁴) Putamen (bilateral ¹²⁵)
	Reduced dopamine transporter uptake	

CT, computed tomography; MR spectroscopy, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

the underlying background of abulia and apathy.¹²⁷ These seemingly contradictory characteristics may coexist or alternate in the same individual as has been demonstrated in several studies.^{5,128,129} This may not be surprising as one study using PET demonstrates that both disinhibition and apathy may be related to decreased orbitofrontal activity.¹³⁰

The diagnostic values of neuroimaging study for apathy have not been well assessed; however, as previously mentioned, an anterior cingulate circuit has been shown to be involved in motivational mechanisms and development of apathy, and imaging this area might prove useful. The importance of reviewing medications cannot be overemphasized, because adverse drug reactions are particularly common in elderly population. Dopaminergic agents, either agonists or antagonists, may be associated with motivational change. Serotonergic or cholinergic agents may interact with alterations of motivation. Antidepressants, especially SSRIs, have been implicated in the development of apathy as discussed previously.^{22,23,25}

Conditions associated with diminished motivation should be sought. Delirium, a transient state of disordered consciousness, is worth a mention. It is one of the most common psychiatric disorders in hospitalized patients and may be mistaken for apathy¹²⁷ if it presents with lethargy, anergy, and drowsiness. It is a difficult-to-treat, but potentially preventable medical condition and must not be overlooked.¹³¹ Diagnosis of delirium would require a high index of clinical suspicion for this condition and a comprehensive assessment.¹³² Bedside instruments such as the Confusion Assessment Method can be extremely useful.¹³³

Several assessment instruments are available to diagnose apathy and monitor the response to treatment in research settings. These instruments may be particularly useful for practitioners who are not accustomed to making a diagnosis of apathy. Marin developed the Apathy Evaluation Scale (AES) with 3 versions: clinician administered, informant rated, and self-rated (AES-C, AES-I, and AES-S, respectively), and he demonstrated that each version had satisfactory reliability.¹³ A subsequent study showed that AES-C was a reliable and valid tool for characterization and quantification of apathy.¹³⁴ It is an 18-item scale; response to each item is recorded on a 4-point scale and subscores are added up to generate total score. A higher score represents greater apathy. Marin reported a cutoff score of 37.5 for the AES-C, which was 2 standard deviations above the mean score for a normal healthy elderly population, but sensitivity and specificity were not reported.^{13,135} A study using Receiver Operating Curve analysis suggested a cutoff score of 40.5 for AES-C had good sensitivity and moderate specificity.¹³⁵ The Apathy Scale, an abridged 14-item version of the AES, was developed and was validated.^{14,15,54} A cutoff score of 14 was shown to have moderate sensitivity and very high specificity.^{15,54} Recently, a 10-item shorter version of the AES was developed specifically for demented nursing home residents and was demonstrated to have comparable psychometric properties for this specific setting and patient group compared with the original 18-item AES.¹³⁶

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.¹³⁷ It is based on a structured interview with a caregiver. Screening questions are asked for each domain providing an overview and triggering structured subquestions when specific abnormal behavior is noted with a screening question. The NPI has been demonstrated to have good reliability and validity.^{83,138} The NPI apathy subcategory was submitted to internationally known experts and deemed to have high content validity.¹³⁸ However, correlational analysis between the NPI and AES revealed that the strength of relationships was, although statistically significant, not very high.¹³⁵ It should also be noted that there is no clear cutoff score established for the NPI to diagnose apathy. The nursing home version of the NPI administered by nursing staffs is also reported to be useful.¹³⁸

A number of assessment tools, including the Frontal Systems Behavior Scale,¹³⁹ formerly referred to as the Frontal Lobe Personality Scale,¹⁴⁰ the Dementia Apathy Interview and Rating,⁸² the Lille Apathy Rating Scale,⁵⁵ the Apathy Inventory,⁸⁹ the Behavior Rating Scale for Dementia,¹⁴¹ and the Scale for the Assessment of Negative Symptoms in Alzheimer's Disease¹⁴² 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.¹³⁶

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.¹⁴³

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.¹⁴⁴

Unfortunately, the nonpharmacological treatment of apathy has not been a subject of systematic research. Behavioral therapy seems to be effective at improving apathy.¹⁴⁵ Live interactive music may have positive engagement effects.¹⁴⁶ The combination of cognitive stimulation activities with donepezil treatment is also more effective in patients with mild to moderate AD compared with donepezil alone.¹⁴⁷ 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.¹⁴⁸ 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.^{3,149–152} 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.¹⁵³ 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 patients¹⁵⁴; 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.¹⁵⁵ 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.¹⁵⁶ 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.¹⁵⁷ In another RCT, which was the first RCT conducted for patients with AD in the nursing home setting,¹⁵⁸ 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,¹⁵⁹ 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 (n = 2033),¹⁶⁰ mean changes in the NPI apathy item were not significant, although significant improvement was observed in clusters containing apathy. In an open-label trial,¹⁶¹ 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.¹⁶²

In an RCT of rivastigmine in the nursing home setting,¹⁶³ 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^{151,164} and bromocriptine,¹⁵¹ 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,¹⁶⁵ 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,^{109,166} whereas the results of the effect of deep brain stimulation on apathy were conflicting.^{166–172} All dopaminergic agents predispose to behavioral side effects including psychosis and should be used with caution. Antidepressants with stimulating properties such as bupropion¹⁷³ 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,¹⁷⁴ 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.¹⁷⁵ 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.¹⁷⁶ 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.¹⁷⁷

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, because such a lack of consensus contributes to the heterogeneity of the current studies and also impedes the wide recognition of this disorder by clinicians. Apparent overlap between apathy and depression is still a cause for concern. Progress in identifying apathy, depression, and their overlap depends on standardizing the diagnostic criteria and further research on assessment tools. Many assessment methods are now available and appear promising. A more concise, clinically usable bedside screening instrument would be invaluable. Functional neuroimaging techniques in diagnosing apathy need to be investigated. Better understanding of pathophysiology and risk factors contributing to apathy is necessary. Identification of modifiable factors may lead to effective treatment, or even prevention, of apathy. The impact of apathy, especially on cognitive function, needs

further attention. Last, further investigation on treatment of apathy is needed. Current evidence is largely limited to observational studies, and RCT-level evidence is required.

REFERENCES

1. Marin RS. Apathy: A neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci* 1991;3:243–254.
2. Levy R, Czernecki V. Apathy and the basal ganglia. *J Neurol* 2006;253:VII54–VII61.
3. van Reekum R, Stuss DT, Ostrander L. Apathy: Why care? *J Neuropsychiatry Clin Neurosci* 2005;17:7–19.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition ed.; Arlington, VA: American Psychiatric Publishing, Inc.; 2004.
5. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci* 1998;10:314–319.
6. Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer's disease. *J Am Geriatr Soc* 2001;49:1700–1707.
7. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2006;77:8–11.
8. Ready RE, Ott BR, Grace J, Cahn-Weiner DA. Apathy and executive dysfunction in mild cognitive impairment and Alzheimer disease. *Am J Geriatr Psychiatry* 2003;11:222–228.
9. Rabkin JG, Ferrando SJ, van Gorp W, et al. Relationships among apathy, depression, and cognitive impairment in HIV/AIDS. *J Neuropsychiatry Clin Neurosci* 2000;12:451–457.
10. Lavretsky H, Lesser IM, Wohl M, et al. Clinical and neuroradiologic features associated with chronicity in late-life depression. *Am J Geriatr Psychiatry* 1999;7:309–316.
11. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord* 1993;28:117–124.
12. Piamarta F, Iurlaro S, Isella V, et al. Unconventional affective symptoms and executive functions after stroke in the elderly. *Arch Gerontol Geriatr Suppl* 2004;315–323.
13. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991;38:143–162.
14. Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry* 2001;158:872–877.
15. Starkstein SE, Fedoroff JP, Price TR, et al. Apathy following cerebrovascular lesions. *Stroke* 1993;24:1625–1630.
16. Starkstein SE, Ingram L, Garau ML, Mizrahi R. On the overlap between apathy and depression in dementia. *J Neurol Neurosurg Psychiatry* 2005;76:1070–1074.
17. Andersson S, Krogstad JM, Finset A. Apathy and depressed mood in acquired brain damage: Relationship to lesion localization and psychophysiological reactivity. *Psychol Med* 1999;29:447–456.
18. Starkstein SE, Mizrahi R, Garau L. Specificity of symptoms of depression in Alzheimer disease: A longitudinal analysis. *Am J Geriatr Psychiatry* 2005;13:802–807.
19. Holthoff VA, Beuthien-Baumann B, Kalbe E, et al. Regional cerebral metabolism in early Alzheimer's disease with clinically significant apathy or depression. *Biol Psychiatry* 2005;57:412–421.
20. Mehta M, Whyte E, Lenze E, et al. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *Int J Geriatr Psychiatry* 2008;23:238–243.
21. Krishnan KR, Hays JC, Tupler LA, et al. Clinical and phenomenological comparisons of late-onset and early-onset depression. *Am J Psychiatry* 1995;152:785–788.
22. Hoehn-Saric R, Lipsey JR, McLeod DR. Apathy and indifference in patients on fluvoxamine and fluoxetine. *J Clin Psychopharmacol* 1990;10:343–345.
23. Settle EC Jr.. Antidepressant drugs: Disturbing and potentially dangerous adverse effects. *J Clin Psychiatry* 1998;59:25–30. discussion 40–22.

24. Fava M, Graves LM, Benazzi F, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term anti-depressant treatment. *J Clin Psychiatry* 2006;67:1754–1759.
25. Wongpakaran N, van Reekum R, Wongpakaran T, Clarke D. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: A case-control study. *Ann Gen Psychiatry* 2007;6:7.
26. Alexopoulos GS. Depression in the elderly. *Lancet* 2005;365:1961–1970.
27. Benoit M, Andrieu S, Lechowski L, et al. Apathy and depression in Alzheimer's disease are associated with functional deficit and psychotropic prescription. *Int J Geriatr Psychiatry* 2008;23:409–414.
28. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology* 1996;46:130–135.
29. Litvan I, Mega MS, Cummings JL, Fairbanks L. Neuropsychiatric aspects of progressive supranuclear palsy. *Neurology* 1996;47:1184–1189.
30. Kaufer DI, Cummings JL, Christine D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: The Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc* 1998;46:210–215.
31. Benoit M, Dygai I, Migneco O, et al. Behavioral and psychological symptoms in Alzheimer's disease. Relation between apathy and regional cerebral perfusion. *Dement Geriatr Cogn Disord* 1999;10:511–517.
32. Aharon-Peretz J, Kliot D, Tomer R. Behavioral differences between white matter lacunar dementia and Alzheimer's disease: A comparison on the neuropsychiatric inventory. *Dement Geriatr Cogn Disord* 2000;11:294–298.
33. Aarsland D, Cummings JL, Larsen JP. Neuropsychiatric differences between Parkinson's disease with dementia and Alzheimer's disease. *Int J Geriatr Psychiatry* 2001;16:184–191.
34. Pang FC, Chow TW, Cummings JL, et al. Effect of neuropsychiatric symptoms of Alzheimer's disease on Chinese and American caregivers. *Int J Geriatr Psychiatry* 2002;17:29–34.
35. Mirakhor A, Craig D, Hart DJ, et al. Behavioural and psychological syndromes in Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19:1035–1039.
36. Senanarong V, Pongvarin N, Jamjumras P, et al. Neuropsychiatric symptoms, functional impairment and executive ability in Thai patients with Alzheimer's disease. *Int Psychogeriatr* 2005;17:81–90.
37. Srikanth S, Nagaraja AV, Ratnavalli E. Neuropsychiatric symptoms in dementia—frequency, relationship to dementia severity and comparison in Alzheimer's disease, vascular dementia and frontotemporal dementia. *J Neurol Sci* 2005;236:43–48.
38. Fuh JL, Wang SJ, Cummings JL. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. *J Neurol Neurosurg Psychiatry* 2005;76:1337–1341.
39. Monastero R, Mariani E, Camarda C, et al. Association between apolipoprotein E epsilon4 allele and apathy in probable Alzheimer's disease. *Acta Psychiatr Scand* 2006;113:59–63.
40. Hwang TJ, Masterman DL, Ortiz F, et al. Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. *Alzheimer Dis Assoc Disord* 2004;18:17–21.
41. Benoit M, Robert PH, Staccini P, et al. One-year longitudinal evaluation of neuropsychiatric symptoms in Alzheimer's disease. The REAL.FR Study. *J Nutr Health Aging* 2005;9:95–99.
42. Thomas P, Clement JP, Hazif-Thomas C, Leger JM. Family, Alzheimer's disease and negative symptoms. *Int J Geriatr Psychiatry* 2001;16:192–202.
43. Robert PH, Darcourt G, Koulibaly MP, et al. Lack of initiative and interest in Alzheimer's disease: A single photon emission computed tomography study. *Eur J Neurol* 2006;13:729–735.
44. Devanand DP, Brockington CD, Moody BJ, et al. Behavioral syndromes in Alzheimer's disease. *Int Psychogeriatr* 1992;4:161–184.
45. Landes AM, Sperry SD, Strauss ME. Prevalence of apathy, dysphoria, and depression in relation to dementia severity in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 2005;17:342–349.
46. Stout JC, Wyman MF, Johnson SA, et al. Frontal behavioral syndromes and functional status in probable Alzheimer disease. *Am J Geriatr Psychiatry* 2003;11:683–686.
47. Bozzola FG, Gorelick PB, Freels S. Personality changes in Alzheimer's disease. *Arch Neurol* 1992;49:297–300.
48. Lyketsos CG, Steinberg M, Tschanz JT, et al. Mental and behavioral disturbances in dementia: Findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 2000;157:708–714.
49. Steinberg M, Sheppard JM, Tschanz JT, et al. The incidence of mental and behavioral disturbances in dementia: The cache county study. *J Neuropsychiatry Clin Neurosci* 2003;15:340–345.
50. Tatsch MF, Bottino CM, Azevedo D, et al. Neuropsychiatric symptoms in Alzheimer disease and cognitively impaired, nondemented elderly from a community-based sample in Brazil: Prevalence and relationship with dementia severity. *Am J Geriatr Psychiatry* 2006;14:438–445.
51. Robert PH, Berr C, Volteau M, et al. Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: A one-year follow-up study. *Clin Neurol Neurosurg* 2006;108:733–736.
52. Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA* 2002;288:1475–1483.
53. Zgaljardic DJ, Borod JC, Foldi NS, et al. Relationship between self-reported apathy and executive dysfunction in nondemented patients with Parkinson disease. *Cogn Behav Neurol* 2007;20:184–192.
54. Starkstein SE, Mayberg HS, Preziosi TJ, et al. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1992;4:134–139.
55. Sockeel P, Dujardin K, Devos D, et al. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: Validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2006;77:579–584.
56. Aarsland D, Litvan I, Larsen JP. Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2001;13:42–49.
57. Dujardin K, Sockeel P, Devos D, et al. Characteristics of apathy in Parkinson's disease. *Mov Disord* 2007;22:778–784.
58. Pluck GC, Brown RG. Apathy in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2002;73:636–642.
59. Isella V, Melzi P, Grimaldi M, et al. Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. *Mov Disord* 2002;17:366–371.
60. Aarsland D, Larsen JP, Lim NG, et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999;67:492–496.
61. Borroni B, Turla M, Bertasi V, et al. Cognitive and behavioral assessment in the early stages of neurodegenerative extrapyramidal syndromes. *Arch Gerontol Geriatr* 2008;47:53–61.
62. Litvan I, Paulsen JS, Mega MS, Cummings JL. Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. *Arch Neurol* 1998;55:1313–1319.
63. Litvan I, Cummings JL, Mega M. Neuropsychiatric features of corticobasal degeneration. *J Neurol Neurosurg Psychiatry* 1998;65:717–721.
64. Pasquier F, Lebert F, Lavenu I, Guillaume B. The clinical picture of frontotemporal dementia: Diagnosis and follow-up. *Dement Geriatr Cogn Disord* 1999;10:10–14.
65. Diehl-Schmid J, Pohl C, Pernecky R, et al. Behavioral disturbances in the course of frontotemporal dementia. *Dement Geriatr Cogn Disord* 2006;22:352–357.
66. Diaz-Olavarrieta C, Cummings JL, Velazquez J, Garcia de la Cadena C. Neuropsychiatric manifestations of multiple sclerosis. *J Neuropsychiatry Clin Neurosci* 1999;11:51–57.
67. Figved N, Klevan G, Myhr KM, et al. Neuropsychiatric symptoms in patients with multiple sclerosis. *Acta Psychiatr Scand* 2005;112:463–468.
68. Hama S, Yamashita H, Shigenobu M, et al. Depression or apathy and functional recovery after stroke. *Int J Geriatr Psychiatry* 2007;22:1046–1051.
69. Brodaty H, Sachdev PS, Withall A, et al. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke—the Sydney Stroke Study. *Psychol Med* 2005;35:1707–1716.

70. Glodzik-Sobanska L, Slowik A, Kieltyka A, et al. Reduced prefrontal N-acetylaspartate in stroke patients with apathy. *J Neurol Sci* 2005; 238:19–24.
71. van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-plus Study. *Int J Geriatr Psychiatry* 2008;23:266–271.
72. Al-Adawi S, Dorvlo AS, Burke DT, et al. Apathy and depression in cross-cultural survivors of traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 2004;16:435–442.
73. Kant R, Duffy JD, Pivovarnik A. Prevalence of apathy following head injury. *Brain Inj* 1998;12:87–92.
74. Grossman AB, Woolley-Levine S, Bradley WG, Miller RG. Detecting neurobehavioral changes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2007;8:56–61.
75. Zuidema SU, Derksen E, Verhey FR, Koopmans RT. Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. *Int J Geriatr Psychiatry* 2007;22:632–638.
76. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Behavioral symptoms and the administration of psychotropic drugs to aged patients with dementia in nursing homes and in acute geriatric wards. *Int Psychogeriatr* 2004;16:61–74.
77. Margallo-Lana M, Swann A, O'Brien J, et al. Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. *Int J Geriatr Psychiatry* 2001;16:39–44.
78. Wood S, Cummings JL, Hsu MA, et al. The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. *Am J Geriatr Psychiatry* 2000;8:75–83.
79. Wagner AW, Teri L, Orr-Rainey N. Behavior problems of residents with dementia in special care units. *Alzheimer Dis Assoc Disord* 1995;9:121–127.
80. Hart DJ, Craig D, Compton SA, et al. A retrospective study of the behavioural and psychological symptoms of mid and late phase Alzheimer's disease. *Int J Geriatr Psychiatry* 2003;18:1037–1042.
81. Steinberg M, Tschanz JT, Corcoran C, et al. The persistence of neuropsychiatric symptoms in dementia: The Cache County Study. *Int J Geriatr Psychiatry* 2004;19:19–26.
82. Strauss ME, Sperry SD. An informant-based assessment of apathy in Alzheimer disease. *Neuropsychiatry Neuropsychol Behav Neurol* 2002;15:176–183.
83. Binetti G, Mega MS, Magni E, et al. Behavioral disorders in Alzheimer disease: A transcultural perspective. *Arch Neurol* 1998;55:539–544.
84. Craig AH, Cummings JL, Fairbanks L, et al. Cerebral blood flow correlates of apathy in Alzheimer disease. *Arch Neurol* 1996;53:1116–1120.
85. Onyike CU, Sheppard JM, Tschanz JT, et al. Epidemiology of apathy in older adults: The Cache County Study. *Am J Geriatr Psychiatry* 2007; 15:365–375.
86. Gerritsen DL, Jongenelis K, Steverink N, et al. Down and drowsy? Do apathetic nursing home residents experience low quality of life? *Aging Ment Health* 2005;9:135–141.
87. Craig D, Mirakhor A, Hart DJ, et al. A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. *Am J Geriatr Psychiatry* 2005;13:460–468.
88. Benoit M, Claret S, Koulibaly PM, et al. Brain perfusion correlates of the apathy inventory dimensions of Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19:864–869.
89. Robert PH, Claret S, Benoit M, et al. The apathy inventory: Assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int J Geriatr Psychiatry* 2002; 17:1099–1105.
90. Rosen HJ, Allison SC, Schauer GF, et al. Neuroanatomical correlates of behavioural disorders in dementia. *Brain* 2005;128:2612–2625.
91. Feil D, Razani J, Boone K, Lesser I. Apathy and cognitive performance in older adults with depression. *Int J Geriatr Psychiatry* 2003;18: 479–485.
92. Janzing JG, Naarding P, Eling PA. Depressive symptom quality and neuropsychological performance in dementia. *Int J Geriatr Psychiatry* 2005;20:479–484.
93. Robert PH, Berr C, Volteau M, et al. Neuropsychological performance in mild cognitive impairment with and without apathy. *Dement Geriatr Cogn Disord* 2006;21:192–197.
94. McPherson S, Fairbanks L, Tiken S, et al. Apathy and executive function in Alzheimer's disease. *J Int Neuropsychol Soc* 2002;8:373–381.
95. Andersson S, Bergedalen AM. Cognitive correlates of apathy in traumatic brain injury. *Neuropsychiatry Neuropsychol Behav Neurol* 2002;15:184–191.
96. Freels S, Cohen D, Eisdorfer C, et al. Functional status and clinical findings in patients with Alzheimer's disease. *J Gerontol* 1992;47: M177–M182.
97. Boyle PA, Malloy PF, Salloway S, et al. Executive dysfunction and apathy predict functional impairment in Alzheimer disease. *Am J Geriatr Psychiatry* 2003;11:214–221.
98. Zawacki TM, Grace J, Paul R, et al. Behavioral problems as predictors of functional abilities of vascular dementia patients. *J Neuropsychiatry Clin Neurosci* 2002;14:296–302.
99. Steffens DC, Hays JC, Krishnan KR. Disability in geriatric depression. *Am J Geriatr Psychiatry* 1999;7:34–40.
100. de Vugt ME, Stevens F, Aalten P, et al. Behavioural disturbances in dementia patients and quality of the marital relationship. *Int J Geriatr Psychiatry* 2003;18:149–154.
101. Derouesne C, Thibault S, Lagha-Pierucci S, et al. Decreased awareness of cognitive deficits in patients with mild dementia of the Alzheimer type. *Int J Geriatr Psychiatry* 1999;14:1019–1030.
102. Starkstein SE, Sabe L, Chemerinski E, et al. Two domains of anosognosia in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1996;61: 485–490.
103. Samus QM, Rosenblatt A, Steele C, et al. The association of neuropsychiatric symptoms and environment with quality of life in assisted living residents with dementia. *Gerontologist* 2005;45:19–26.
104. van Dijk PT, Dippel DW, Habbema JD. A behavioral rating scale as a predictor for survival of demented nursing home patients. *Arch Gerontol Geriatr* 1994;18:101–113.
105. Chaturvedi SK, Sarmukaddam SB. Prediction of outcome in depression by negative symptoms. *Acta Psychiatr Scand* 1986;74:183–186.
106. Padala PR, Desouza CV, Almeida S, et al. The impact of apathy on glycemic control in diabetes: A cross-sectional study. *Diabetes Res Clin Pract* 2008;79:37–41.
107. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: An update. *J Psychosom Res* 2002;53:647–654.
108. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. *Dialogues Clin Neurosci* 2007;9:141–151.
109. Marshall GA, Fairbanks LA, Tekin S, et al. Neuropathologic correlates of apathy in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2006;21: 144–147.
110. Tekin S, Mega MS, Masterman DM, et al. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. *Ann Neurol* 2001;49:355–361.
111. Hama S, Yamashita H, Shigenobu M, et al. Post-stroke affective or apathetic depression and lesion location: Left frontal lobe and bilateral basal ganglia. *Eur Arch Psychiatry Clin Neurosci* 2007;257:149–152.
112. Lavretsky H, Ballmaier M, Pham D, et al. Neuroanatomical characteristics of geriatric apathy and depression: A magnetic resonance imaging study. *Am J Geriatr Psychiatry* 2007;15:386–394.
113. Apostolova LG, Akopyan GG, Partiali N, et al. Structural correlates of apathy in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;24: 91–97.
114. Roth RM, Flashman LA, Saykin AJ, et al. Apathy in schizophrenia: Reduced frontal lobe volume and neuropsychological deficits. *Am J Psychiatry* 2004;161:157–159.
115. Paul RH, Brickman AM, Navia B, et al. Apathy is associated with volume of the nucleus accumbens in patients infected with HIV. *J Neuropsychiatry Clin Neurosci* 2005;17:167–171.
116. Starkstein SE, Sabe L, Vazquez S, et al. Neuropsychological, psychiatric, and cerebral perfusion correlates of leukoaraiosis in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1997;63:66–73.

117. Lopez OL, Zivkovic S, Smith G, et al. Psychiatric symptoms associated with cortical-subcortical dysfunction in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 2001;13:56–60.
118. Remy P, Doder M, Lees A, et al. Depression in Parkinson's disease: Loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 2005;128:1314–1322.
119. Franceschi M, Anchisi D, Pelati O, et al. Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. *Ann Neurol* 2005;57:216–225.
120. Marshall GA, Monseratt L, Harwood D, et al. Positron emission tomography metabolic correlates of apathy in Alzheimer disease. *Arch Neurol* 2007;64:1015–1020.
121. Migneco O, Benoit M, Koulibaly PM, et al. Perfusion brain SPECT and statistical parametric mapping analysis indicate that apathy is a cingulate syndrome: A study in Alzheimer's disease and nondemented patients. *Neuroimage* 2001;13:896–902.
122. Lanctot KL, Moosa S, Herrmann N, et al. A SPECT study of apathy in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;24:65–72.
123. Benoit M, Koulibaly PM, Migneco O, et al. Brain perfusion in Alzheimer's disease with and without apathy: A SPECT study with statistical parametric mapping analysis. *Psychiatry Res* 2002;114:103–111.
124. Ott BR, Noto RB, Fogel BS. Apathy and loss of insight in Alzheimer's disease: A SPECT imaging study. *J Neuropsychiatry Clin Neurosci* 1996;8:41–46.
125. David R, Koulibaly M, Benoit M, et al. Striatal dopamine transporter levels correlate with apathy in neurodegenerative diseases. A SPECT study with partial volume effect correction. *Clin Neurol Neurosurg* 2008;110:19–24.
126. Czernecki V, Pillon B, Houeto JL, et al. Motivation, reward, and Parkinson's disease: Influence of dopatherapy. *Neuropsychologia* 2002;40:2257–2267.
127. Marin RS. Differential diagnosis and classification of apathy. *Am J Psychiatry* 1990;147:22–30.
128. Starkstein SE, Garau ML, Cao A. Prevalence and clinical correlates of disinhibition in dementia. *Cogn Behav Neurol* 2004;17:139–147.
129. Buettner L, Fitzsimmons S. Mixed behaviors in dementia: The need for a paradigm shift. *J Gerontol Nurs* 2006;32:15–22.
130. Peters F, Perani D, Herholz K, et al. Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal dementia. *Dement Geriatr Cogn Disord* 2006;21:373–379.
131. Inouye SK, Bogardus ST Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340:669–676.
132. Shapiro B, Mervis JR. Distinguishing delirium and dementia. *Aging Health* 2007;3:33–48.
133. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941–948.
134. Clarke DE, Van Reekum R, Patel J, et al. An appraisal of the psychometric properties of the Clinician version of the Apathy Evaluation Scale (AES-C). *Int J Methods Psychiatr Res* 2007;16:97–110.
135. Clarke DE, Reekum R, Simard M, et al. Apathy in dementia: An examination of the psychometric properties of the apathy evaluation scale. *J Neuropsychiatry Clin Neurosci* 2007;19:57–64.
136. Lueken U, Seidl U, Volker L, et al. Development of a short version of the Apathy Evaluation Scale specifically adapted for demented nursing home residents. *Am J Geriatr Psychiatry* 2007;15:376–385.
137. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44:2308–2314.
138. Cummings JL. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology* 1997;48:S10–S16.
139. Stout JC, Ready RE, Grace J, et al. Factor analysis of the frontal systems behavior scale (FrSBe). *Assessment* 2003;10:79–85.
140. Grace J, Stout JC, Malloy PF. Assessing frontal lobe behavioral syndromes with the frontal lobe personality scale. *Assessment* 1999;6:269–284.
141. Tariot PN, Mack JL, Patterson MB, et al. The Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease. The Behavioral Pathology Committee of the Consortium to Establish a Registry for Alzheimer's Disease. *Am J Psychiatry* 1995;152:1349–1357.
142. Reichman WE, Coyne AC, Amirneni S, et al. Negative symptoms in Alzheimer's disease. *Am J Psychiatry* 1996;153:424–426.
143. Smith MM, Buckwalter KP. Behaviors associated with dementia: Whether resisting care or exhibiting apathy, an older adult with dementia is attempting communication. Nurses and other caregivers must learn to 'hear' this language. *Am J Nurs* 2005;105:40–52.
144. Marin RS, Wilkosz PA. Disorders of diminished motivation. *J Head Trauma Rehabil* 2005;20:377–388.
145. Politis AM, Vozzella S, Mayer LS, et al. A randomized, controlled, clinical trial of activity therapy for apathy in patients with dementia residing in long-term care. *Int J Geriatr Psychiatry* 2004;19:1087–1094.
146. Holmes C, Knights A, Dean C, et al. Keep music live: Music and the alleviation of apathy in dementia subjects. *Int Psychogeriatr* 2006;18:623–630.
147. Chapman SB, Weiner MF, Rackley A, et al. Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. *J Speech Lang Hear Res* 2004;47:1149–1163.
148. Verkaik R, van Weert JC, Francke AL. The effects of psychosocial methods on depressed, aggressive and apathetic behaviors of people with dementia: A systematic review. *Int J Geriatr Psychiatry* 2005;20:301–314.
149. Chatterjee A, Fahn S. Methylphenidate treats apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2002;14:461–462.
150. Keenan S, Mavaddat N, Iddon J, et al. Effects of methylphenidate on cognition and apathy in normal pressure hydrocephalus: A case study and review. *Br J Neurosurg* 2005;19:46–50.
151. Campbell JJ, Duff JD. Treatment strategies in amotivated patients. *Psychiatr Ann* 1997;27:44–49.
152. Padala PR, Petty F, Bhatia SC. Methylphenidate may treat apathy independent of depression. *Ann Pharmacother* 2005;39:1947–1949.
153. Jansen IH, Olde Rikkert MG, Hulsbos HA, Hoefnagels WH. Toward individualized evidence-based medicine: Five "N of 1" trials of methylphenidate in geriatric patients. *J Am Geriatr Soc* 2001;49:474–476.
154. Whitehouse PJ, Price DL, Struble RG, et al. Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. *Science* 1982;215:1237–1239.
155. Kaufer DI, Cummings JL, Christine D. Effect of tacrine on behavioral symptoms in Alzheimer's disease: An open-label study. *J Geriatr Psychiatry Neurol* 1996;9:1–6.
156. Cummings JL, Nadel A, Masterman D, Cyrus PA. Efficacy of metrifonate in improving the psychiatric and behavioral disturbances of patients with Alzheimer's disease. *J Geriatr Psychiatry Neurol* 2001;14:101–108.
157. Gauthier S, Feldman H, Hecker J, et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *Int Psychogeriatr* 2002;14:389–404.
158. Tariot PN, Cummings JL, Katz IR, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J Am Geriatr Soc* 2001;49:1590–1599.
159. Seltzer B, Zolnouni P, Nunez M, et al. Efficacy of donepezil in early-stage Alzheimer disease: A randomized placebo-controlled trial. *Arch Neurol* 2004;61:1852–1856.
160. Herrmann N, Rabheru K, Wang J, Binder C. Galantamine treatment of problematic behavior in Alzheimer disease: Post-hoc analysis of pooled data from three large trials. *Am J Geriatr Psychiatry* 2005;13:527–534.
161. Edwards KR, Hershey L, Wray L, et al. Efficacy and safety of galantamine in patients with dementia with Lewy bodies: A 12-week interim analysis. *Dement Geriatr Cogn Disord* 2004;17:40–48.
162. McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. *Lancet* 2000;356:2031–2036.
163. Cummings JL, Koumaras B, Chen M, Mirski D. Effects of rivastigmine treatment on the neuropsychiatric and behavioral disturbances of nursing home residents with moderate to severe probable Alzheimer's

- disease: A 26-week, multicenter, open-label study. *Am J Geriatr Pharmacother* 2005;3:137–148.
164. Van Reekum R, Bayley M, Garner S, et al. N of 1 study: Amantadine for the amotivational syndrome in a patient with traumatic brain injury. *Brain Inj* 1995;9:49–53.
165. Guttman M, Jaskolka J. The use of pramipexole in Parkinson's disease: Are its actions D(3) mediated? *Parkinsonism Relat Disord* 2001;7:231–234.
166. Funkiewiez A, Ardouin C, Cools R, et al. Effects of levodopa and subthalamic nucleus stimulation on cognitive and affective functioning in Parkinson's disease. *Mov Disord* 2006;21:1656–1662.
167. Drapier D, Drapier S, Sauleau P, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? *J Neurol* 2006;253:1083–1091.
168. Schupbach WM, Chastan N, Welter ML, et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5-year follow-up. *J Neurol Neurosurg Psychiatry* 2005;76:1640–1644.
169. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004;75:834–839.
170. Castelli L, Lanotte M, Zibetti M, et al. Apathy and verbal fluency in STN-stimulated PD patients: An observational follow-up study. *J Neurol* 2007;254:1238–1243.
171. Contarino MF, Daniele A, Sibilio AH, et al. Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78:248–252.
172. Castelli L, Perozzo P, Zibetti M, et al. Chronic deep brain stimulation of the subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and personality traits. *Eur Neurol* 2006;55:136–144.
173. Corcoran C, Wong ML, O'Keane V. Bupropion in the management of apathy. *J Psychopharmacol* 2004;18:133–135.
174. Marangell LB, Johnson CR, Kertz B, et al. Olanzapine in the treatment of apathy in previously depressed participants maintained with selective serotonin reuptake inhibitors: An open-label, flexible-dose study. *J Clin Psychiatry* 2002;63:391–395.
175. Padala PR, Burke WJ, Bhatia SC. Modafinil therapy for apathy in an elderly patient. *Ann Pharmacother* 2007;41:346–349.
176. Newburn G, Newburn D. Selegiline in the management of apathy following traumatic brain injury. *Brain Inj* 2005;19:149–154.
177. Cummings JL, Schneider E, Tariot PN, Graham SM. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology* 2006;67:57–63.