Neurotox Res (2011) 19:266–278
DOI 10.1007/s12640-010-9196-9

Apathy in Neuropsychiatric Disease: Diagnosis, Pathophysiology, and Treatment

Thomas N. Chase

Received: 11 November 2009 / Revised: 28 April 2010 / Accepted: 28 April 2010 / Published online: 15 May 2010

Abstract Apathy is an increasingly recognized concomitant of a broad range of central nervous system disorders. Nevertheless, its nosology, pathogenesis and therapy remain shrouded in confusion and controversy. As yet, there is little consensus regarding methods for detecting apathy, or distinguishing it from depression, or for assessing its severity. Many now regard the apathy syndrome as primarily reflecting a lack of motivation that compromises emotional, cognitive, and overt behavioral function. Even though under-recognized and under-diagnosed, apathy hardly appears uncommon: current epidemiologic studies suggest over 10 million Americans may be affected. Its reported frequency in various neurologic and psychiatric conditions varies widely, from less than 10 to over 80%, reflecting differences in population characteristics and assessment procedures. Often apathy has been associated with such neurodegenerative disorders as Alzheimer's disease, Parkinson's disease, and fronto-temporal dementia. But it also occurs in those with psychiatric disorders such as schizophrenia and major depression. Clinical, neuropathologic, and neuroimaging observations increasingly suggest that apathy reflects dysfunction of frontal-subcortical circuits, especially those linking the ventromedial prefrontal cortex to related regions in the basal ganglia. Therapeutically, numerous small studies suggest that psychostimulants, dopaminergics, and cholinesterase inhibitors may benefit those manifesting this syndrome. However, no adequately powered, randomized controlled trials have reported success and no medication have ever been approved for this disorder. The accelerating pace of current research nevertheless promises to improve our understanding of apathy and to better address the unmet medical needs of those suffering its consequences.

Keywords Depression · Alzheimer's disease · Parkinson's disease · Schizophrenia · Depression · Prefrontal cortex · Basal ganglia · Therapeutics

T. N. Chase (✉)
Chase Pharmaceuticals Corporation, Washington, DC, USA
e-mail: tchase@chasepharmaceuticals.com

Introduction

The term apathy derives from a word for indifference or a lack of feeling, especially for exterior matters over which one has no responsibility. In more recent times, apathy came to denote behaviors involving a poverty of awareness, interest, concern, or emotion. Nevertheless, the word has remained vaguely defined and broadly applied as suggested by a few of its more common synonyms: detachment, emotionlessness, listlessness, passivity, unconcern, unawareness, submissiveness, and unresponsiveness. Sometimes, the term apathetic has been used pejoratively to imply laziness or contempt for worldly concerns. After World War I apathy assumed a more medical connotation when it was employed to describe the numbness and indifference to normal social interactions sometime associated with the combat-related stress called shell shock (Ramirez et al. 2001). But not until the last quarter of the twentieth century did apathy begin to emerge from consideration as a symptom of depression and receive independent pathophysiologic scrutiny (Robinson and Bloom 1977).

In 1990, Marin described apathy as a dysmotivational disorder occurring as a consequence of brain damage or neuropsychiatric illnesses (Marin 1990). He proposed that apathy be regarded as an illness involving a paucity of volitional, goal-directed behaviors (Marin 1996). It could

arise as a symptom of other central nervous system (CNS) disorders or as an independent syndrome in its own right (Starkstein and Leentjens 2008). According to this emerging view, apathy can occur as a clinical feature of such conditions as major depression, Alzheimer's disease or stroke that affect emotion, intellect, or level of consciousness. Apathy syndrome, on the other hand, can be diagnosed when a cluster of its clinical features—including a loss of motivation, interest and concern, goal directed and emotional responsivity, and cognitive activity—arises in the absence of emotional distress, intellectual impairment, or diminished consciousness, due to a presumed disorder of specific neuronal circuits.

As a disorder of motivation, apathy warrants consideration as one of the distinctive frontal system conditions identified during the past half-century.

According to these views, akinetic mutism can be regarded as an extreme form of apathy to the point of immobility and mutism; the term abulia can be used to emphasize a lack of spontaneity and initiative (Starkstein and Leentjens 2008). In the differential diagnosis of the apathy syndrome, akinesia, dementia, depression, anhedonia, and chronic fatigue must be considered. With these steps toward increasing definitional clarity, academic studies and research publications on the subject have climbed exponentially. Insight into the concept and pathophysiology and treatment of apathy has substantially advanced (McAllister 2000; van Reekum et al. 2005; Levy and Dubois 2006). Nevertheless, confusion lingers regarding its proper definition, nosologic position, diagnostic, and assessment procedures, and even regarding its fundamental syndromic validity (Mizrahi and Starkstein 2007). Apathy remains conceptually ill defined. The construct of a dysmotivational disorder is not simple: it cannot be directly assessed and it does not readily lead to an examination of underlying mechanisms (Derouesne 2004). The distinction from depression has proven particularly troublesome due to the overlap of symptoms and frequent comorbidities (Yeager and Hyer 2008; Tagariello et al. 2009). Officially, apathy hardly exists. Few textbooks of neurology or psychiatry dignify the term by inclusion in their index. No entry for apathy exists in the current Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) and controversy surrounds the possibility of its inclusion in the forthcoming DSM-V.

Diagnosis and Psychometrics

There is no formal consensus on diagnostic criteria for apathy as a syndrome. Thus, questions regarding the phenomenology and clinical correlates of apathy as well as the syndromic validity of this construct persist (Mizrahi and Starkstein 2007). Based on views introduced by Marin and subsequently elaborated by others, apathy is now generally regarded as a disorder of motivation and operationalized as diminished goal oriented behavior and cognition (Marin 1990; Starkstein and Leentjens 2008). Carefully considered and evaluated diagnostic criteria for apathy in dementia and in Parkinson's disease have been proposed (Starkstein and Leentjens 2008; Starkstein et al. 2009). Nevertheless, the lack of broadly recognized diagnostic standards constitutes a significant barrier to research in the field, complicating not only the development of validated assessment instruments but also the conduct of therapeutic studies and the registration of successful interventions. Indeed, regulatory authorities generally prefer that diagnostic criteria and severity scales not be conflated. In an attempt to address the need for fully validated diagnostic tools for apathy, a taskforce has recently proposed that the syndrome be defined as a disorder of motivation that persists over time and meets the following requirements: (1) the core feature of apathy, diminished motivation, must be present for at least 4 weeks; (2) two of the three dimensions of apathy (reduced goal-directed behavior, goal-directed cognitive activity, and emotions) must also be present; (3) there should be identifiable functional impairments attributable to the apathy; and (4) criteria are given to exclude symptoms and states that mimic apathy (Robert et al. 2009). Completion of this work should help meet a crucial scientific need as well as an increasing regulatory imperative.

Several scales are currently available to evaluate the severity of apathy in patients with psychiatric and neurological disease. Unfortunately, all suffer from the inability to be fully validated against external criteria, due to the lack of generally accepted diagnostic standards. Most have versions based on information provided by the patient, a caregiver or other informant, or the interviewers' opinion; although, the frequently marginal agreement between these versions is a source of concern. General measures of attention and cognition, such as MiniMental State Examination or full scale IQ scores, lack sensitivity for detecting frontal cognitive impairment and typically show little change in apathetic individuals (Feil et al. 2003). In current practice, both multi-item scales focused on characterizing and quantifying apathy as well as more limited single item apathy measures occurring as one element of larger disease or behavior-oriented scales are in general use.

- *The Apathy Evaluation Scale* is the most frequently utilized instrument for detailing and grading apathy (Marin et al. 1991). Three versions (clinician, informant, and self-rated) of the 18-item scale are available. An abbreviated version has also been constructed (Lueken et al. 2007). Although administration and

scoring have yet to be fully standardized, the reliability and validity of this scale in different patient groups have been extensively evaluated (Clarke et al. 2007). The scale has been found useful in discriminating apathy from standard measures of depression and anxiety, in assessing first episode psychosis patients, and in estimating the effects of pharmaceutical interventions (Padala et al. 2007, 2010; Faerden et al. 2008).

- *The Apathy Scale*, a widely used measure resembling the Apathy Evaluation Scale, is composed of 14 items scored by the patient's relative or caregiver (Starkstein et al. 1992). It is regarded as a generally reliable and valid instrument, especially for use in patients with Parkinson's or Alzheimer's disease (Starkstein et al. 2001).
- *The Apathy Inventory* provides a global assessment of apathy as well as separate assessments of emotional blunting, lack of initiative, and lack of interest. It has been judged to have high internal consistency, item reliability, and inter-rater reliability in patients with mild cognitive impairment, Parkinson's disease, Alzheimer's disease, and in healthy elderly subjects (Robert et al. 2002). Both patient- and informant-based versions are available for this brief scale, which as yet has found only limited usage.
- *The Lille Apathy Rating Scale* is a relatively lengthy, 33 item, semistructured patient interview that yields a global score as well as composite subscores for different domains of apathy (cognitive, behavioral, affective, self awareness) (Sockeel et al. 2006). It was developed for use in Parkinson's disease, where it shows acceptable psychometric properties and the ability to distinguish apathy from depression. The first assessment of an English language version of the Lille scale by a group other than its original developers found it to be a coherent instrument demonstrating both convergent and divergent validity as compared to the Apathy Scale (Zahodne et al. 2009). A recently developed caregiver-based version reportedly has excellent psychometric properties and to be valid for use in Parkinson's disease as compared to the informant- and interviewer-rated versions of the Apathy Evaluation Scale (Dujardin et al. 2008).
- *The Frontal Systems Behavior Scale* is a 46-item instrument intended to measure the behavioral effects of frontal brain damage (Stout et al. 2003). It includes a total score as well as scores on three subscales: apathy (14 items), disinhibition (15 items), and executive dysfunction (17 items). Versions are available for self-rating and for rating by a caregiver. The scale is considered to have good reliability and validity in the assessment of psychological deficits associated with frontal-subcortical circuit dysfunction and has found relatively wide usage in patients with neurologic and psychiatric disease (Malloy and Grace 2005).

Two frequently used instruments make use of single items to assess apathy:

- *The Neuropsychiatric Inventory*, a well-established and widely used structured interview developed to evaluate behavioral dysfunction including apathy in dementia patients (Cummings et al. 1994). A single item measures both the frequency and the severity of apathy. Assessment involves a screening question plus follow-up questions in the case of a positive answer. The apathy item has been found to have good interrater agreement, but has not been further evaluated with respect to reliability. The scale is used mainly in patients with neurodegenerative disorders including those participating in therapeutic studies.
- *The Unified Parkinson's Disease Rating Scale*, the standard assessment instrument for Parkinson's disease, contains an item to evaluate motivation/initiative on a five-point scale (Goetz et al. 2008; Leentjens et al. 2008). Unfortunately, the apathy item focuses on motivation and goal-directed activities and does not evaluate the emotional aspects of apathy; it has acceptable specificity but lacks sensitivity when compared to the Apathy Scale (Starkstein and Merello 2007; Pedersen et al. 2008; Kirsch-Darrow et al. 2009). Like the Neuropsychiatric Inventory, the Parkinson Scale collects little information about apathy and best serves as a rough screening measure.

Prevalence and Clinical Characteristics

Apathy may be the most frequent psychobehavioral alteration occurring in patients with brain disease, although there are no authoritative estimates of its frequency in the general population. A rough approximation of this number—obtained by multiplying the modal frequency of apathy reported in PubMed-cited studies of the major disorders with which it is associated times the U.S. prevalence of these disorders—suggests apathy may afflict some 10 million individuals living in the United States. It generally arises in association with a broad array of CNS disorders including psychiatric conditions such as depression and schizophrenia, neurodegenerative diseases such as Alzheimer's and Parkinson's, vascular insults such as stroke and traumatic brain injury, and some cerebral infections and tumors. Although most often diagnosed in patients with concomitant depression or dementia, apathy is now widely considered as a distinct neuropsychiatry syndrome that can occur in the absence of either of these

comorbidities (Levy et al. 1998; Starkstein et al. 2001; Dujardin et al. 2007; Tagariello et al. 2009). In any single disorder, the prevalence of apathy in the published literature varies widely, reflecting differences in such factors as population characteristics, diagnostic and severity criteria, and the assessment procedures employed.

In relation to psychiatric disease, apathy has been reported to affect 19–88% of those suffering from major depression, especially older individuals with poor executive function (Feil et al. 2003; Marin et al. 2003). Indeed, due to the overlap of key symptoms the frequent conflation of apathy with depression has proven to be a major diagnostic challenge, notwithstanding the widely accepted distinction that apathy is primarily a motivational disorder while depression is a disorder of mood (Marin et al. 1991; Starkstein et al. 2001; Tagariello et al. 2009). In demented individuals, a significant relationship between apathy and depression has been observed in those with the greatest cognitive deficits, but apathy in the absence of depression is not infrequent (Fava et al. 2006; Kirsch-Darrow et al. 2006). In some depressed individuals, treatment with selective serotonin reuptake inhibitors has been implicated as a causal or exacerbating factor, while in others apathy may have been uncovered by, rather than result from, antidepressant therapy (Wongpakaran et al. 2007). Apathy is also a common negative symptom of schizophrenia, affecting about half of these individuals (Kiang et al. 2003; Roth et al. 2004; Faerden et al. 2009). Even though not closely related to the severity of positive symptoms, apathy appears more highly associated with functional outcome than other symptom measures. In patients with chronic schizophrenia as well as those with first episode psychosis, apathy has been found to relate more directly to indices of executive dysfunction than to measures of other neurocognitive domains (Craig et al. 2005).

Apathy is also common in patients with neurodegenerative disorders affecting the cerebral cortex and basal ganglia. Some 25–88% of individuals with Alzheimer's disease reportedly manifest apathy (Landes et al. 2001, 2005). It generally tends to afflict those with the greatest cognitive impairment and global disease severity (Starkstein et al. 2006). Apathy is also significantly associated with depression in these individuals, although depression is neither necessary nor sufficient to produce apathy (Lechowski et al. 2009). Alzheimer patients who develop apathy reportedly decline faster cognitively than those who do not manifest apathy (Lechowski et al. 2009). In other dementias (including frontotemporal, Lewy body and vascular) as well as in mild cognitive impairment (MCI), the reported prevalence of apathy ranges from 38 to 95% (Robert et al. 2006; Galvin et al. 2007). In frontotemporal dementia, apathy is the most common presenting symptom and with disease progression apathy appears in 62–89% of patients (Mendez et al. 2008). There is evidence to suggest that apathy and depression have a differential role in the development of dementia in those diagnosed with MCI: a recent study classified 40% of 124 pts as MCI depressed, 17% as MCI depressed-apathetic, and 12% as MCI apathetic (Vicini Chilovi et al. 2009). The rates of conversion were 7.9% for depressed, 19% for depressed-apathetic, and 60% for apathetic subjects. The presence of apathy was a positive risk factor for conversion apart from age, or functional, or cognitive status at baseline; in contrast, MCI-depressed subjects had a reduced risk of conversion. Apathy, a core-feature of dementia with Lewy-bodies that may help distinguish it from Alzheimer's disease, reportedly presents in 58% of these patients and worsens with disease progression (Borroni et al. 2008).

Neurodegenerative disorders primarily affecting the basal ganglia are also frequently associated with apathy. It occurs in 20–70% of patients with Parkinson's disease (Barbas 2006; Kirsch-Darrow et al. 2006; Aarsland et al. 2007; Dujardin et al. 2007). Apathetic symptoms cluster within the subtype characterized by hypokinesia, rigidity, postural instability, and gait disorder (Reijnders et al. 2009). However, apathy levels do not always correlate with the severity of motor dysfunction and thus some regard it as an independent construct (Dujardin et al. 2007; Kulisevsky et al. 2008). Parkinsonian patients with apathy often manifest comorbid depression and/or dementia (Starkstein et al. 2009). In general, apathy has been found to be associated with higher depression scores and lower cognitive functioning (Pedersen et al. 2009). Apathy is also a frequent concomitant of other degenerative diseases that prominently involve the basal ganglia including progressive supranuclear palsy, corticobasal degeneration, and Huntington's disease (Hamilton et al. 2003; Lauterbach 2004). In the latter disorder, apathy has been reported to occur in 34–76% of patients depending on the disease stage and assessment methods used (Thompson et al. 2002). Both its presence and its severity relate to motor and cognitive impairments (van Duijn et al. 2007). Carriers of the Huntington's disease mutation, including presymptomatic individuals, evidenced more apathy than noncarriers (Kingma et al. 2008). A comparison of corticobasal degeneration with progressive supranuclear palsy indicates that apathy is more frequent in the latter (58 vs. 34%) disorder, but correlates with neither age nor motor dysfunction (Borroni et al. 2009). Apathy, along with other cognitive and behavioral impairments, frequently presents in patients with amyotrophic lateral sclerosis, especially in those with the sporadic form linked to frontotemporal dementia, where it arises independent of mood or deficits in such cognitive domains as memory, receptive language, and visuospatial perception (Wicks et al. 2009).

Individuals suffering from stroke or brain trauma also commonly manifest apathy. Recent studies in post-stroke patients yield an average apathy prevalence of about 35% (Angelelli et al. 2004; Brodaty et al. 2005). Apathy tends to occur more frequently in first time stroke patients who are older and more cognitively impaired (Santa et al. 2008). Apathy is also common in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), where it appears to be associated with greater depression, cognitive deterioration, global functional disability, and an inability to carry out the independent activities of daily living. A recent study found that apathy, affecting 41% of 132 CADASIL patients, can occur separately from depression and has an independent impact on the overall quality of life; multiple regression modeling indicated a significant and independent association between apathy and a higher load of white matter and lacunar lesions (Reyes et al. 2009). Apathy reportedly affects some 50% of adults suffering from traumatic brain injury (Marin and Wilkosz 2005). Severity correlates most closely with cognitive deficits linked to frontal dysfunction; specifically, apathy scores related closely with reduced performance on tests of acquisition and memory, psychomotor speed, and executive function (Andersson and Bergedalen 2002). A study of postanoxic encephalopathy suggested that apathy manifests in nearly 80% of these individuals (von Cramon and Matthes-von Cramon 1994). Apathy may also complicate idiopathic normal pressure hydrocephalus, multiple sclerosis, certain brain infections such as HIV and progressive multifocal leukoencephalopathy, and be occasionally associated with brain tumors and Wilson's disease (Figved et al. 2005; DeVito et al. 2007; Svetel et al. 2009).

Clinical Course and Functional Consequences

As expected of a condition that can reflect various underlying pathophysiologies, the clinical course of apathy varies widely. Although few studies have addressed this issue directly, the available information suggests that symptoms can be a chronic when associated with a non-remitting or steadily progressive disorder. For example, apathy scores have been observed to generally worsen in Parkinson's disease patients as well as in those with Lewy body dementia (Funkiewiez et al. 2004; Borroni et al. 2008). Similarly, a longitudinal study found apathy to increase over a 33-month follow-up period in individuals with Alzheimer's disease (Aalten et al. 2005). In a sample of 155 Alzheimer subjects, the prevalence of apathy was 19%; after 12 months, persistence was 52%, remission was 48%, and emergence was 21%. Apathy thus increases with the severity of Alzheimer's disease, especially along with the loss of executive cognition, and appears to be an independent contributor to a rapid decline in global function (Lechowski et al. 2009; Turro-Garriga et al. 2009). In Huntington's disease, apathy progresses along with the motor and the cognitive abnormalities that characterize this disorder (van Duijn et al. 2007). Long-lasting apathy is also believed to occur in those with chronic schizophrenia, although with a relatively high degree of instability due especially to environmental influences (Malla et al. 1993). In contrast, apathy can subside when associated with spontaneously remitting conditions. For example, observations in post-stroke patients suggest that apathy tends to improve along with motor disability over a period of months. However, persisting apathy in stroke survivors is predicted by older age, greater cognitive loss, and low functional status (Mayo et al. 2009). A tendency for apathy to abate might also be expected in certain other potentially remitting conditions such as CNS infectious and metabolic disorders, although data on this matter remains scant (Ghobrial and Ruby 2002).

Numerous studies document the deleterious consequences that apathy can have on interpersonal relationships, occupational functioning, and general health (Velligan et al. 2002; Mayo et al. 2009). Apathy has the potential to impair activities of daily living, diminish the quality of life, increase caregiver burden, and complicate the therapy of comorbidities. In Parkinson's disease, apathy has been reported to limit the effective treatment of motor abnormalities and lead to increased disability and a diminished quality of life (Pluck and Brown 2002; Weintraub et al. 2004; Barbas 2006). Apathy can thus be an important source of caregiver stress, even when not of concern to the patient themselves (Aalten et al. 2006; Aarsland et al. 2007). Studies in Alzheimer patients also point to an association between apathy and a loss of function as measured by activities of daily living and quality of life scales (Samus et al. 2005). Persisting apathy has been found to have a significant negative impact on physical function, participation, health perception, and general health over the first 12 months after stroke (Starkstein et al. 1993; Mayo et al. 2009). Apathy has also been observed to contribute to the unsatisfactory integration of patients with traumatic brain injury into home and community activities (Cattelani et al. 2008). Apathy has been identified in schizophrenic individuals as independently related to functional outcome above and beyond other negative symptoms and related to poor compliance with as well as low benefit from treatment (Kiang et al. 2003). Apathy has also been reported to be an independent contributor to functional disability in Huntington's disease (Hamilton et al. 2003). When present, apathy can impair all six basic activities of daily living: dressing, bathing, walking, eating, transferring, and toileting (Freels et al.

1992). To the extent that apathy predisposes to both a poor outcome of illness and a poor response to treatment, it exacerbates the societal burden of any associated disorder.

Pathophysiology

Clinical observations as well as studies in animal models of motivated behavior support the view that frontal-subcortical system dysfunction contributes to the appearance of apathy (van Reekum et al. 2005; Levy and Dubois 2006; Dellu et al. 1996; Peters et al. 2006; Farrar et al. 2007; Filali et al. 2009). Focal lesions (such as stroke) as well as diffuse neurodegenerative processes (such as Alzheimer's disease) or predominantly white matter disorders (including multiple sclerosis) or generalized encephalopathies can give rise to abnormalities in goal-directed behavior, if critical components of this frontal lobe–basal ganglia system are affected. The location and extent of neuronal dysfunction, not its etiology, are the crucial determinants. Most neuropathologic and neuroimaging evaluations link apathy to abnormalities in specific regions of frontal lobe, cingulate gyrus, and basal ganglia. In five studies, an average of 61% of those with focal lesions involving the frontal lobe manifested apathy; individuals with lesions involving the basal ganglia have a lower prevalence of apathy, averaging about 40% (Levy and Dubois 2006; Peters et al. 2006; Rushworth et al. 2007). In this subcortical group, damage to the caudate nucleus, internal segment of globus pallidus and the medial dorsal thalamic nuclei that disrupt associative and limbic pathways from and to the prefrontal cortex were most frequently correlated with alterations in motivated behavior. While not perfectly consistent, the results of apathy localization studies have provided a remarkably coherent pattern in spite of differences in such factors as patient selection criteria, coexisting brain disorders, and data acquisition and analysis procedures.

Clinical–pathological investigations in Alzheimer's disease have found that apathy correlates with neurofibrillary tangle density in the anterior cingulate gyrus (Marshall et al. 2006). Magnetic resonance imaging (MRI) studies show a significant association between apathy severity and cortical gray matter atrophy in the anterior cingulate bilaterally [Brodmann area 24] and in the left medial frontal cortex [Brodmann areas 8 and 9] (Apostolova et al. 2007). A voxel-based morphometric study of MRI images from Alzheimer patients yielded similar results, with apathy correlating with gray matter loss in the anterior cingulate and frontal cortex bilaterally, the head of the left caudate nucleus and in the putamen bilaterally (Bruen et al. 2008). Similar findings derive from most single photon emission computerized tomography (SPECT) and positron emission tomography (PET) studies suggesting bilateral involvement of the orbito- and middle-frontal and anterior cingulate regions, along with less consistent changes in temporal cortical and medial thalamic areas (Migneco et al. 2001; Benoit et al. 2004; Lanctot et al. 2007; Marshall et al. 2007). In frontotemporal dementia, MRI, SPECT, and PET studies have linked apathy to orbitofrontal abnormalities, extending from Brodmann area 10 to the anterior cingulate cortex, especially on the right (Peters et al. 2006; Mendez et al. 2008; Zamboni et al. 2008). Some studies also indicate caudate head/ventral striatal involvement (Rosen et al. 2005). In frontotemporal lobar degeneration, apathy was found to be associated with volume loss on MRI in the dorsal anterior cingulate and dorsolateral prefrontal cortex (Massimo et al. 2009).

Imaging studies of other brain disorders provide general support for these localization results. Parkinson's disease patients, studied with a PET marker for dopamine and noradrenaline transporters, evidenced an inverse correlation between apathy severity and binding density in the ventral striatum (Remy et al. 2005). A SPECT evaluation of individuals with apathy due to subcortical stroke revealed cerebral blood flow reductions in frontal and anterior temporal regions (Okada et al. 1997). Patients with right hemisphere damage as a result of acquired brain damage, such as traumatic or hypoxic brain injury or stroke, had greater apathy than those with left-sided lesions (Andersson and Krogstad 1999). An MRI study of geriatric patients with major depression linked apathy to gray matter loss in the right anterior cingulate (Lavretsky et al. 2007). MRI, SPECT, and PET scans in schizophrenic individuals suggest that apathy most closely relates to left lateral as well as bilateral frontal and striatal abnormalities (Joseph 1999; Roth et al. 2004). Although there are few systematic evaluations of apathy in relation to the integrity of white matter connections between frontal cortex and basal ganglia, one MRI study found apathy to be especially common in elderly individuals with prominent vascular white matter lesions (Alves et al. 2009).

The parallel organization of functionally segregated circuits linking basal ganglia and frontal cortex was first described by Alexander and coworkers and subsequently shown to be intimately involved in human behaviors including apathy (Alexander et al. 1986; Levy and Czernecki 2006). Three major, behaviorally relevant frontal-subcortical systems are now recognized: the dorsolateral prefrontal circuit (implicated in the organization of information to facilitate a response and executive dysfunction); the orbitofrontal circuit (implicated in the integration of limbic and emotional information into behavioral responses, disinhibition, and social conduct); and the medial frontal and anterior cingulate circuit (implicated in motivational states and apathy) (Tekin and Cummings 2002;

Bonelli and Cummings 2007). Since there are multiple prefrontal-basal ganglia circuits, apathy may differ in accordance with the mix of circuits involved. It may thus be best to regard apathy not as a single entity but rather as a heterogeneous disorder, usefully divided into multiple subtypes. An understanding of these systems provides a comprehensive framework for advancing our ability to master the chemistry and pharmacology of human behavior.

A variety of pharmacologic agents reportedly influence apathy. These drug-induced behavioral changes can best be recognized in humans, even if the clinical situation often complicates rigorous data interpretation. Although pharmacologic studies in animal models of apathy have also lent insight into mechanisms contributing to the regulation of motivated behaviors, the lack of full model validation constrains use of the results. Drugs claimed to benefit apathy in humans include serotonergic antidepressants (Siddique et al. 2009), antipsychotics (Marangell et al. 2002), catecholaminergic psychostimulants (Padala et al. 2010), antidementia cholinomimetics, and antiglutamatergics (Swanberg 2007; Rodda et al. 2009), and antiparkinsonian dopaminergics (Leentjens et al. 2009). All presumably act through effects on neurotransmitters mediating frontal-subcortical circuit function. These neural systems include glutamatergic efferents from the frontal cortex as well as monoaminergic and cholinergic projections from the basal ganglia back to the anterior frontal lobes.

Considerable data link dysfunction of dopaminergic transmission in the mesocorticolimbic reward pathway to the pathophysiology of apathy (Bressan and Crippa 2005). In rats, blockade of D1 dopamine receptor-mediated transmission inhibits the motivational properties of rewarding as well as aversive stimuli (Acquas et al. 1989). In dementia patients, apathy severity was found to relate to striatal dopamine uptake, as assessed by a SPECT ligand; specifically, a lack of initiative correlated with right and left putamen dopamine transporter uptake (David et al. 2008). Another cerebral imaging study found an inverse correlation between apathy and dopamine transporter levels in the caudate nucleus of Lewy body dementia patients (Roselli et al. 2009). Further evidence suggesting that dopaminergic pathways contribute to the pathogenesis of apathy derives from the results of deep brain stimulation studies in individuals with Parkinson's disease. Electrical excitation of the subthalamic nucleus, which functions in a cortico-basal ganglia-thalamo-cortical circuit and has been anatomically linked to the mesolimbic dopaminergic pathway, can induce or exacerbate apathy in some parkinsonian patients (Drapier et al. 2008; Haegelen et al. 2009). Dopamine agonist treatment reportedly attenuates apathy in these individuals (Czernecki et al. 2008).

Pharmacologic probes have also helped inform our views of the role of other transmitter systems in the pathogenesis of apathy. For example, links between apathy and gamma-aminobutyric acid (GABA) system function arise from both clinical and animal model observations. In patients with seizure disorders, adverse effects such as apathy primarily complicate the use of antiepileptics (barbiturates, benzodiazepines, valproate, gabapentin, and vigabatrin) that act centrally to potentiate GABA-mediated inhibitory neurotransmission (Ketter et al. 1999). Studies in rodents suggest a partial explanation for these clinical observations by indicating that stimulation of GABA(A) receptors in the ventral pallidum produces behavioral changes such as apathy that are also associated with dopamine depletion in the nucleus accumbens (Farrar et al. 2008). The ventral pallidum receives substantial GABAergic input from the nucleus accumbens and serves as a component of pathways regulating response allocation and effort-related choice behavior by conveying information from the accumbens to other parts of these forebrain circuits. Evidence favoring the participation of cholinergic, serotonergic, and glutamatergic systems in the pathogenesis of apathy derives primarily from observations made during the clinical evaluation of pharmaceuticals that selectively act upon these transmitters (Swanberg 2007; Rodda et al. 2009; Siddique et al. 2009). Taken together, the foregoing observations suggest that the successful treatment of apathy will probably involve drugs affecting one or more of these frontal-subcortical systems.

Current Therapeutic Approaches

At present, there are no approved medications for the treatment of apathy and no proof of efficacy exists for any drug in current use. Apathy is often left undiagnosed and thus untreated, not only because it is confused with depression and other similar behavioral disorders but also because it not uncommonly occurs in a mild and transient form in the general population. On the other hand, a mounting body of preclinical and clinical evidence now indicates that apathy reflects dysfunction of fronto-subcortical projection systems, including monoaminergic, cholinergic, glutamatergic, and GABAergic pathways, and thus should be potentially amenable to pharmacotherapeutic interventions targeting these systems (Bressan and Crippa 2005; Gauthier et al. 2007; Swanberg 2007; Farrar et al. 2008; Leentjens et al. 2009; Siddique et al. 2009; Padala et al. 2010). Current data further raise the possibility that more than one type of apathy exists, reflecting involvement of more than one cortical-subcortical system, and that therapies directed toward more than one pharmacologic target might prove most efficacious. Unfortunately, it is difficult to gauge how successful the pursuit of this therapeutic strategy has been. Few clinical trials singled

out apathy as the primary therapeutic target. Most pharmaceutical data on apathy derive from studies designed to evaluate effects on other behavioral or physical parameters. Moreover, few investigations involving apathy have employed adequately powered, randomized, well-controlled designs, and rigorous statistical analyses of the results (Marin and Wilkosz 2005; Roth et al. 2007; Lane-Brown and Tate 2009). An evaluation of the various claims of success thus presents a daunting challenge.

Pharmacologic agents most frequently administered (off-label) to apathetic patients include dopaminergic antiparkinson agents, acetylcholinesterase inhibitors for Alzheimer's disease, atypical antipsychotics for schizophrenia and psychostimulants. In Parkinson's disease, treatment of coexisting apathy with dopaminergic agonists or the weak glutamateric antagonist amantadine has reportedly met with some success (Ferreri et al. 2006; Borek et al. 2007; Czernecki et al. 2008; Leentjens et al. 2009). Clinical observations also suggest that apathy in Alzheimer's disease benefits, albeit modestly, from cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, as well as from the low-affinity glutamate antagonist memantine (Gauthier et al. 2007; Swanberg 2007; Rodda et al. 2009). Some aver that apathy responds better to cholinesterase inhibitors, while a reduction in irritability and agitation may be more closely associated with memantine treatment (Cummings et al. 2008). The successful use of methylphenidate to treat stroke-induced apathy has been reported (Spiegel et al. 2009). Atypical antipsychotics given to patients with schizophrenia (clozapine alone or with mirtazapine, respiradone, olanzapine) as well as certain antidepressants (buproprion) and psychostimulants (amphetamine, methylphenidate, and modafinil) used in the treatment of various brain disorders are also said to have benefited apathy (Marangell et al. 2002; Corcoran et al. 2004; Daiello 2007; Padala et al. 2007, 2010). Thus, although recent therapeutic studies have identified approaches worthy of further evaluation, as yet there is insufficient evidence to indicate that any pharmacological treatment actually ameliorates apathy (Drijgers et al. 2009).

Experimental Therapeutic Intervention

The development of safe and effective therapies for apathy constitutes a pressing unmet medical need. A rational approach to this goal is informed by the study of the components, circuitry, and pharmacology of motivated behavior in animals and humans. While no preclinical model has yet been shown to mimic clinical apathy nor to forecast its clinical course or response to therapy, several rodent models involving frontal lobe injury and goal-directed behavior do evidence some construct as well as face validity (Dellu et al. 1996; Hasegawa et al. 1996; DeFord et al. 2001; Takeo et al. 2003a, b; Farrar et al. 2007). Drugs found active in such models should thus be considered as potential candidates for clinical evaluation in patients suffering from apathy. Similarly, drugs known to affect one or more transmitters systems comprising the frontal-subcortical circuits implicated in the pathogenesis of apathy also warrant consideration for clinical trials, alone or in combination, within or across comorbidities.

A novel cyclic GABA derivative, nefiracetam, may illustrate pharmaceuticals of this type (Gouliaev and Senning 1994; Crespi 2002). A variety of preclinical evidence suggests that nefiracetam, which differs from other racetams both in chemical structure and in pharmacologic activity, enhances cholinergic, GABAergic, and monoaminergic function within the CNS (Luthman et al. 1994; Sakurai et al. 1998). Its mechanism of action appears to involve an inhibitory interaction at a subunit of certain G-proteins leading to the activation of specific N- and L-type calcium channels and adenylate cyclase signaling cascades (Yoshii et al. 2000; Takeo et al. 2003a, b; Moriguchi et al. 2007). Nefiracetam reportedly reverses the catecholamine and serotonin deficits induced in rat frontal brain by unilateral embolic infarction (Watabe et al. 1994). The administration of nefiracetam to these animals has also been found to restore regional neuronal function, as evidenced by increased cerebral blood flow and glucose utilization, in affected brain areas (Jin et al. 2002). In the same dose range, nefiracetam has been observed in animal models to positively influence behavioral activity that has a motivational component or involves interactive behaviors (Hasegawa et al. 1996; DeFord et al. 2001; Takeo et al. 2003). Clinically, a controlled study involving over 200 post-stroke patients suggested that the drug safely improves apathy and related functional measures (Ohtomo 1994). A follow-up evaluation, conducted in 70 post-stroke patients with major depression who also met diagnostic criteria for apathy, suggested a significant dose and time-related improvement in Apathy Scale scores, a secondary outcome measure, after several weeks of treatment (Robinson et al. 2009). Concomitant improvement in a functional scale was also observed, but no clinically significant, drug-related adverse events. These findings, if confirmed, would support the view that apathy may be due, at least in part, to dysfunction of frontal-subcortical cholinergic, monoaminergic, and GABAergic projection systems and thus be benefited by pharmaceutical interventions that act in this brain region to enhance the activity of one or more of these neuronal circuits.

Conclusions

Apathy is becoming increasingly recognized as a common source of significant medical disability. Nevertheless, no adequate trials have reported success and no medication has ever been approved for this disorder. Additional studies of innovative pharmacologic approaches are thus urgently needed to advance our understanding and treatment of apathy. The accelerating pace of current basic and clinical neurosciences research does, however, promise to improve our understanding of apathy and address the urgent needs of those suffering its consequences.

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