Drugs Aging 2007; 24 (7): 547-554
1170-229X/07/0007-0547/$44.95/0

Epidemiology and Management of Apathy in Patients with Alzheimer's Disease

Romina Mizrahi[1,2] and *Sergio E. Starkstein*[3,4]

1 PET Center, Centre for Addiction and Mental Health (CAMH), Toronto, Ontario, Canada
2 Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
3 School of Psychiatry and Clinical Neurosciences, University of Western Australia, Fremantle, Western Australia, Australia
4 Fremantle Hospital, Fremantle, Western Australia, Australia

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Abstract

Although apathy is a diagnostic term used with increasing frequency in both neurology and psychiatry, confusion still exists as to its proper definition and assessment, and whether apathy should be considered a symptom of major psychiatric diseases or an independent syndrome in its own right. Moreover, critical questions regarding the phenomenology and clinical correlates of apathy and the syndromic validity of this construct still exist. Despite these nosological concerns, there is strong evidence that apathy is a common finding in Alzheimer's disease (AD). However, the treatment of apathy is still elusive. Current data are obtained from randomised controlled trials that did not investigate apathy *per se*, but rather a number of other behavioural and psychological variables. In this context, acetylcholinesterase inhibitors and psychosocial interventions are the only available modalities for treating apathy in AD with some efficacy.

1. Definitions of Apathy

Marin[1] proposed that apathy be considered an independent psychiatric syndrome, characterised by deficits in goal-directed behaviours as manifested by simultaneous diminution in the cognitive and emotional concomitants of goal-directed behaviour. He defined 'motivation' as "the direction, intensity and persistence of goal-directed behaviour" and identified loss of motivation as the main symptom of apathy.[1] Marin structured the clinical expression of apathy around the concepts of reduced goal-directed behaviour (as manifested by lack of effort, initiative and productivity), reduced goal-directed cognition (as manifested by decreased interests, lack of plans and goals, and lack of concern about one's own health or functional status) and reduced emotional concomitants of goal-directed behaviours (as manifested by flat affect, emotional indifference and restricted responses to important life events).[1] This construct was slightly modified and organised into a standardised set of diagnostic criteria by Starkstein.[2] A similar division of apathy into emotional, cognitive and behavioural domains was more recently proposed by van Reekum and co-workers.[3] In a recent publication, Marin and Wilkosz[4] suggested that apathy should be considered the expression of diminished motivation, stating that patients with apathy "are generally able to initiate and sustain behaviour, describe their plans, goals and interests, and react emotionally to significant events and experiences". In a recent article, Levy and Dubois[5] suggested that apathy should not be defined as lack of motivation, on the basis that such a definition would be a mere psychological interpretation of a behavioural change. Instead, they defined apathy as an observable behavioural syndrome consisting of a quantitative reduction in self-generated voluntary and purposeful behaviours. They further emphasised that the extent of this behavioural change is relative to the previous behavioural pattern of the individual, that it should occur in the absence of contextual or physical changes and that it should be reversible by external stimulation.

2. Diagnostic Considerations

The Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV[6] uses the term 'apathy' to refer to a subtype of personality change due to a general medical condition, but no specific definition of apathy is provided. The International Classification of Diseases (ICD)-10[7] makes no reference to apathy. Marin[8] suggested that apathy should not be diagnosed in the context of diminished level of consciousness, moderate or severe cognitive deficits or marked emotional distress. While this strategy could help to identify a syndrome of 'pure' apathy, uncontaminated by changes in cognitive or affective domains, several empirical findings argue against this approach. First, the syndrome of apathy is most frequent among individuals with some degree of cognitive impairment, such as those with Alzheimer's disease (AD), stroke or Parkinson's disease (PD).[9-11] Several studies of patients with dementia have shown a significant association between executive dysfunction and more severe apathy, although this finding has not been consistently replicated.[3] Cognitive deficits are not sufficient to produce apathy, given that approximately half of the individuals with moderate or severe dementia in our studies did not show apathy.[12,13] Whether cognitive deficits are necessary to produce apathy has not been specifically examined, although most studies assessing apathy in a variety of neurological disorders have reported relatively low Mini-Mental State Examination scores for patients with apathy.[3] Whether the syndrome of apathy that is associated with overt dementia has a different phenomenology than the syndrome of apathy in other neurological disorders (e.g. stroke, traumatic brain injury, PD, frontal lobe lesions) or the 'pure' apathy syndrome referred to by Marin[8] has not been examined. Marin[8] also pointed out the apparent contradiction of diagnosing apathy in patients with frontal lobe lesions, who may also show concurrent violent behaviours. This suggestion implies that apathy and behavioural disinhibition are opposite expressions of a common behavioural domain, with patients being either apathetic or disinhibited. This is related to the fact that behaviours that characterise apathy

and disinhibition are very different. On the other hand, apathy and disinhibition may alternate in the same individual, an eventuality that has been demonstrated in several studies of patients with dementia.[14-16]

Marin and Wilkosz[4] suggested that apathy should be diagnosed only after a comprehensive neuropsychiatric evaluation, including an assessment of the individual's social and physical environment. They further emphasised the importance of taking into consideration the great variability in each individual's goals, interests, emotional displays and activities, all of which are strongly influenced by general experience, education, social status, age cohort and a host of other cultural factors. All of these considerations are certainly relevant and should be explicitly considered in relation to any clinical assessment of apathy. The dilemma is how to diagnose apathy in neuropsychiatric disorders, given the paucity of diagnostic criteria and standardised instruments to detect and measure the severity of this syndrome.

Several instruments are currently used to measure the severity of apathy in neuropsychiatric disorders. Marin and co-workers[17,18] developed the Apathy Evaluation Scale, an 18-item scale that can be administered as a self-rated scale, caregiver paper-and-pencil test or clinician administered test. Our group[11] developed the Apathy Scale as an abridged version of Marin's scale. The Children's Motivation Scale is also based on the Apathy Evaluation Scale, and rates the severity of apathy in children and adolescents.[1] The Neuropsychiatric Inventory (NPI), a multidimensional instrument that is administered to caregivers, assesses apathy together with nine other behavioural and emotional domains.[19] Strauss and Sperry[20] developed the Dementia Apathy Interview and Rating scale to assess dementia-related changes in motivation, emotional responsiveness and engagement. The interviewer scores the frequency of specific behaviours over the past month on the basis of responses provided by the primary caregiver, with further clarifications as to whether the given behaviour has changed from the time prior to dementia onset. Robert and co-workers[21] designed the Apathy Inventory as a rating scale for the global assessment of apathy, with separate assessments for emotional blunting, lack of initiative and loss of interest. The authors have demonstrated the reliability of this instrument in patients with either AD or PD.

Our group has recently published the validation of a structured interview to diagnose apathy in dementia.[22] We designed the Structured Clinical Interview for Diagnosis of Apathy (SCIDA) to screen for symptoms of apathy and apply clinical diagnostic criteria. The SCIDA includes questions that assess the domains of lack of motivation relative to the individual's previous level of functioning, lack of interest in performing everyday activities, dependency on others to structure activity, lack of interest in learning new things or in new experiences, lack of concern about one's personal problems, unchanging or flat affect and lack of emotional response to positive or negative personal events. Based on answers to specific questions and similar to the Structured Clinical Interview for DSM-III-R (SCID)[23] scoring system (a clinical instrument for assessing psychiatric disorders), symptoms are scored as either absent, subclinical or definitely present.

In conclusion, the nosological position of apathy is still in a state of flux. Apathy is not listed in either the DSM-IV or in the ICD-10. This may rapidly change, as apathy is among the most frequent and disabling behavioural problems in neuropsychiatry. Standardised diagnostic criteria have been recently proposed, and there is preliminary evidence of the reliability and validity of a structured interview to diagnose apathy in dementia. The presence of cognitive deficits, impulsivity or marked emotional distress should not exclude the diagnosis of apathy, but should be documented as qualifiers. A series of scales have been published that assess the severity of apathy in a variety of neuropsychiatric disorders, including stroke, traumatic brain injury, AD and PD.

3. Prevalence of Apathy in Alzheimer's Disease (AD)

Our group examined the prevalence of apathy in a study that included a consecutive series of 319

patients with AD, 117 patients with depression but no dementia and 36 age-comparable healthy individuals.[13] Based on Apathy Scale scores, apathy was diagnosed in 37% of the AD patients, 32% of the depressed patients without dementia and none of the healthy controls. About two-thirds of the AD patients with apathy were also depressed (mostly major depression). Among patients with dementia, apathy was significantly associated with more severe impairments in activities of daily living and cognitive functions, older age and poor awareness of behavioural and cognitive changes. Among depressed patients without dementia, apathy was significantly associated with the severity of depression (37% of patients with major depression had apathy compared with 9% of patients with minor depression). We also found that patients with dementia and apathy but no depression had similar depression scores to patients with dementia but neither apathy nor depression, demonstrating that apathy may not artificially increase the ratings of depression in dementia.

A recent study from Latin America that examined 60 AD patients using the NPI reported that the most frequent neuropsychiatric symptoms in AD were apathy (53%), depression (38%), sleep disturbance (38%) and anxiety (25%).[24] A study from the US reported that 59% of a series of 131 AD patients had apathy occurring at least 4–8 days per month.[25] In a larger study that included 435 patients with AD, Craig and co-workers[26] reported that apathy/indifference was the most common behavioural symptom (76%), followed by aberrant motor behaviour (65%), appetite/eating changes (64%), irritability/lability (63%) and agitation/aggression (63%). Depressive and apathetic symptoms were the earliest to appear; hallucinations, elation/euphoria and aberrant motor behaviour were later symptoms. Another important finding was that the apathy/indifference factor was 'moderately' distressing to caregivers. Similar findings were earlier reported by Thomas and colleagues.[27]

4. Longitudinal Studies of Apathy in AD

In a recent study, Starkstein and co-workers[28] examined the clinical correlates and predictive validity of apathy in AD in a consecutive series of 354 patients with AD who received a follow-up assessment 1–4 years after baseline. Apathy was significantly associated with older age and both major and minor depression, and the frequency of apathy increased from 14% in the stage of very mild AD to 61% in the stage of severe AD. An important finding was that apathy was a significant predictor of depression at follow-up, and those patients who developed apathy during the follow-up period had a significantly greater cognitive and functional decline than AD patients without apathy. Of note, depression was neither necessary nor sufficient to produce apathy (23% of non-depressed patients had apathy, whereas 45% of patients with major depression and 49% of patients with minor depression had no apathy). The study also demonstrated that patients who became depressed during the follow-up period did not develop more severe apathy at follow-up than patients without depression, supporting the nosological separation of apathy and depression in AD. We suggested that apathy may be a behavioural marker of a more 'malignant' type of AD, with more severe behavioural problems and a faster cognitive and functional decline. Our findings provide partial support for the suggestion by Levy and co-workers[14] that apathy should not be construed as a mere symptom of depression in dementia. Our finding of greater cognitive and functional decline in AD patients with apathy is consistent with the findings of Boyle and co-workers,[29] who reported that after adjustment for both depression and cognitive deficits, apathy was significantly correlated with more severe functional deficits.

In a recent longitudinal study that examined whether apathy is a significant predictor of dementia in patients with amnestic mild cognitive impairment (MCI), Robert and co-workers,[30] found that after a 1-year follow-up, 13 (15%) MCI individuals with apathy at baseline converted to AD compared with 9 (7%) MCI individuals without apathy. In addition, at the 1-year follow-up, those individuals that had con-

verted to AD had a significantly higher frequency of symptoms of apathy (92%) compared with MCI individuals who did not convert to AD (27%). These observations are consistent with the finding that apathy is one of the most frequent neuropsychiatric symptoms in mild AD.[31] Finally, among individuals with MCI, apathy was significantly associated with lower performances on free recall but not on cued recall.[30,32] Taken together, these studies strongly suggest that apathy is one of the earliest and most frequent behavioural changes in AD.

5. Treatment of Apathy in AD

5.1 Pharmacological Treatment

Given the high frequency of apathy in dementia, it is quite surprising that pharmacological strategies to treat this condition are rarely implemented. In this section, we review the most useful pharmacological options.

5.1.1 Acetylcholinesterase Inhibitors

It has been proposed that acetylcholinesterase inhibitors may exert beneficial psychotropic effects in patients with AD, based on the suggestion that limbic and paralimbic cortices, which are associated with emotion processing, have cholinergic deficits in AD. Restoration of potential dysfunction in these brain regions may be critical to the processing of emotion and may underlie the behavioural response to acetylcholinesterase inhibitors observed in some studies.[33]

Despite the relatively high prevalence of apathy in dementia, few randomised controlled trials (RCTs) have evaluated treatment of the condition. Cummings and co-workers[34] reported a retrospective analysis of pooled NPI data from two double-blind, placebo-controlled, multicentre, 26-week studies of metrifonate in mild-to-moderate probable AD. Patients received placebo (n = 222) or metrifonate (n = 450), and after 26 weeks, metrifonate-treated patients had significantly reduced NPI total scores ($p = 0.001$) and some decrease in apathy scores ($p = 0.019$). Cummings and co-workers[35] also reported a beneficial effect of rivastigmine on apathy in nursing home residents with moderate-to-severe AD in a 26-week, open-label, multicentre study. One limitation of this trial was that it was not restricted to patients with behavioural disturbances at baseline. More recently, a Canadian study[36] pooled data from three randomised, double-blind, placebo-controlled trials of 3, 5 and 6 months' duration that included >2000 subjects with mild-to-moderate AD. Galantamine-treated subjects showed a significant decrease in mean NPI scores on the domains of delusions, hallucinations, anxiety, apathy/indifference and aberrant motor behaviour. The authors considered these symptoms to represent a specific group of cholinergic-responsive behavioural symptoms in AD. These findings are consistent with those of Mega and co-workers,[37] who conducted an open-label, 8-week study of galantamine in 22 patients (19 finishers) with probable AD. Responders to galantamine showed a significant reduction in the apathy score. Kaufer and colleagues[38] reported a significant reduction in apathy scores with tacrine in an open-label study that included 50 patients with possible or probable AD. Together with delusions, apathy was the only symptom cluster that decreased at all dementia severity stages.

In summary, there is limited evidence from RCTs for the efficacy of acetylcholinesterase inhibitors to treat apathy in AD. However, recent results from several open-label studies have been promising.

5.1.2 Psychostimulants

There are no controlled studies of the efficacy of psychostimulants to treat apathy in AD. Galynker et al.[39] reported a reduction in negative symptoms, as measured on the Scale for the Assessment of Negative Symptoms (SANS)[40] in patients with AD (n = 12) treated with methylphenidate. However, no apathy instrument was used and some patients were also depressed. Interestingly, depression scores did not diminish after methylphenidate treatment. To date, the limited data available on the effectiveness of psychostimulants in AD derive from heterogeneous samples,[3] such as patients with traumatic brain injury (see review[41]), subcortical infarcts[42] and other neuropsychiatric disorders.[43]

5.1.3 Dopaminergic Agonists

The efficacy of dopaminergic agents (i.e. bromocriptine, amantadine) for the treatment of apathy and negative symptoms has rarely been examined.[3] Most studies reported in the literature were not controlled, and no study to our knowledge was carried out in AD patients exclusively. There is a case report of three patients with confirmed AD at autopsy that showed a significant improvement of negative symptoms after treatment with amantadine.[44]

5.2 Non-Pharmacological Treatments

In a study that included 54 patients with mild-to-moderate AD, Chapman and co-workers[45] evaluated the combined effect of a cognitive-communication programme plus the acetylcholinesterase inhibitor donepezil (n = 26), compared with donepezil alone (n = 28). The stimulation programme consisted of 12 hours of intervention over an 8-week period and involved participant-led discussions requiring homework, interactive sessions and discussions using salient life stories. Evaluation of change scores from baseline to 12 months revealed a positive effect for the donepezil-plus-stimulation group on discourse and functional abilities, and a trend toward improvement of apathy, irritability and patient-reported quality of life.

More recently, a randomised, placebo-controlled trial[46] (n = 32) with blinded observer raters explored whether music, live or pre-recorded, was effective in the treatment of apathy in subjects with moderate-to-severe dementia. This interesting study showed that live interactive music has immediate and positive engagement effects in dementia subjects with apathy, regardless of the severity of their dementia. Pre-recorded music was non-harmful but less clearly beneficial. Concordant with these findings, a systematic review of the effectiveness of 13 psychosocial methods (behavioural, emotional, cognition and stimulation oriented) for reducing depressed, aggressive or apathetic behaviours in people with dementia suggested that there is some evidence that multi-sensory stimulation reduces apathy in late stages of dementia.[47] Politis and co-workers[48] also reported a significant improvement in apathy in a randomised, controlled, partially masked, clinical trial in patients with dementia residing in a long-term care facility.

6. Conclusion

RCT-level evidence for the treatment of apathy in AD is very limited. Current data are drawn from RCTs that investigated a number of other behavioural and psychological variables in addition to apathy, and systematic RCT-level data are still lacking. Interestingly, only acetylcholinesterase inhibitors have shown some positive effect in the treatment of apathy in dementia. One limitation is that few other psychoactive compounds have been formally tested. Several methodological issues may limit the feasibility of conducting research on pharmacological treatments for apathy in AD. First, methods of diagnosing apathy in AD are not well established, and standardised criteria have only recently been published.[22] Secondly, no psychoactive compounds have been specifically designed to treat apathy in dementia. Whilst there is currently a strong interest in treating negative symptoms of schizophrenia (which has several phenomenological commonalities with the syndrome of apathy in dementia), less attention has been given to evaluating treatments for apathy in AD. Thirdly, given that psychosocial interventions in apathy have been reported to be effective, the placebo effect in pharmacological studies may be high. In conclusion, acetylcholinesterase inhibitors and psychosocial interventions are the only currently available modalities with some efficacy in the treatment of apathy in AD.[49,50]

Acknowledgements

This study was partially supported with grants from the Raine Medical Research Foundation, and the National Health and Medical Research Council. The authors have no conflicts of interest that are directly relevant to the content of this article.

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Correspondence: Prof. *Sergio E. Starkstein*, Education Building T-7, Fremantle Hospital, Fremantle, WA 6959, Australia.
E-mail: ses@cyllene.uwa.edu.au