Dementia: Advances and Treatment

Chapter 2

Adding Methylphenidate to Address Apathy in Dementia- Insights from Case Reports

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1. Introduction

Dementia is increasingly becoming a critical issue in countries with ageing populations. In some, the rate is relatively lower as the age of the 'elderly' population is relatively young, the mortality rate among dementia patients is high and there may be an underestimation of the extent of the problem due to the difficulty of the diagnosis of dementia. The most frequently observed neuropsychiatric symptoms in Alzheimers' Dementia (AD) are night-time behavior and apathy as measured by the neuropsychiatric Inventory (NPI). These symptoms interfere with the quality of life (QoL) for both patients and caregivers and may be an important factor in the decision-making on how to manage an elderly person's disease.

Apathy is a symptom defined as a lack of motivation, not attributable to diminished level of consciousness, cognitive impairment or emotional distress related to daily function. It is frequently reported in patients with Parkinson's Disease, AD, Vascular Dementia and psychosis. Apathy in AD has been consistently associated with relatively more severe cognitive deficits, more severe impairments in activities of daily living (ADL), higher levels of burden and distress in caregivers, and increased use of economic and medical resources [1]. It is also associated with reduced functional level, decreased response to treatment and poor illness outcome [2]. Apathy in patients with AD is associated with poor insight into their apathy syndrome and the low self-ratings of AD patients is related to their difficulty in remembering

changes from the time before disease onset [3]. Screening and early detection of these symptoms are important to facilitate differential diagnosis and embark on treatment endeavours.

Psychostimulants have been employed in the treatment for cognitive and behavioural symptoms in dementia for some time now; but when used as a treatment for cognitive deficits in older persons, the results have been varied. Methylphenidate is a stimulant drug used mainly to treat attention deficit hyperactivity disorder (ADHD) in children. It acts by augmenting the activity of dopamine in the brain and an understanding of 'inverted-U' effects in the prefrontal cortex (PFC) alerts the clinician as to why some children show improvement and some others experience adverse effects at similar doses administered [4]. Dopamine also influences many cognitive processes, including executive function but most studies employing Ritalin for that purpose produced little or no effect on cognition.

Methylphenidate has been tried in older persons with advanced physical disease and as a form of palliative care to treat fatigue, depressive symptoms and apathy. While there is a lack of studies that ascertain the usefulness of psychostimulants in the treatment of excessive daytime sedation in dementia, Methylphenidate has also been reported to have helped people with 'vascular depression', i.e. depressive illness that arises from vascular pathology afflicting the brain, and who had not responded to regular antidepressants. However, emotional blunting (lack of responsivity) which is frequently a sign of depression should not be mistaken for apathy (lack of motivation).

The limited literature available have consistently reported improvements in apathy with Methylphenidate and that it is a possible treatment modality to that end in dementia [5]. Supporting this are related findings of reduced activity in parts of the brain responsible for the dopaminergic reward system [6]. Furthermore, recent results on the use of Ritalin have been more promising and it has even been shown to improve mobility and gait stability, in addition to executive function [7].

Despite the physical side-effects of Methylphenidate which can increase blood pressure and elevate heart rate, as well as behavioural effects which can lead to irritability, agitation and psychosis, the benefits of its use nonetheless seem to outweigh its drawbacks [8]. It is hoped that the final results from the currently on-going Apathy in Dementia Methylphenidate Trial 2 (ADMET2) examining its efficacy and safety as treatment for clinically significant apathy in Alzheimer's Disease participants will serve to guide us in our future decision-making.

In the meantime, we describe two cases of Mixed Dementia where executive function benefitted from Methylphenidate as add-on therapy by improving apathy as measured by the Apathy Evaluation Scale (AES) [9]. There are 3 versions of this scale: the self-rated (AES-S), the informant-rated (AES-I) and the clinician-administered (AES-C)-the latter has been reported to have fairly good psychometric traits and measures indicators of apathy in the previ-

ous four weeks [10]. Our patients were selected based on their similarities in presentation, severity of dementia, pharmacological treatments given and the presence of apathy.

2.1. Case 1

Mr. KJ, an 86 year old male, a former pastor, began to show early mild and gradual signs of cognitive decline from the age of 75. He has had a long-standing history of hypertension and diabetes mellitus, under good control with medication. There was no family history of dementia. 2 years ago in December 2015, he experienced psychological decompensation when his wife had a heart attack. He was violent and delusional and coupled with confusion, it was believed that he suffered recent cerebral infarcts, visualized on brain scanning with multiple older deep white matter infarcts, against a background of generalized atrophy. A diagnosis of Mixed AD and Multi-infarct Dementia was made. He settled after admission for Behavioural and Psychological Symptoms of Dementia (BPSD) but was later noted to become withdrawn, in spite of optimal doses of Memantine, Donepezil and Escitalopram. He refused to leave the bed or meet people.

2.2. Case 2

Mrs. RC, an 80 year old female, a retired teacher, showed early and barely noticeable signs of irritability and targeted suspiciousness towards family members from the age of 70. There were no medical problems, other than a kinked coronary artery, and no family history of dementia too. 5 years ago, in April 2012, she suffered a stroke when under extreme mental stress but there was full neurological recovery. There was only clear deterioration in memory after her husband underwent heart surgery-she was also easily overwhelmed and would then appear ‘confused’. Depressive Pseudodementia considered until she began to have falls (Holter negative). Brain scan showed that the previous right thalamic infarct was no more observable but deep white matter ischaemia seemed widespread, with surrounding cerebral atrophy. She was diagnosed to have Mixed AD and Binswanger’s Disease. Her memory deteriorated and she became very depressed, in spite of being on Escitalopram. A rash over the patch site necessitated a change to oral Rivastigmine, to which she also did not tolerate. Memantine was then started, optimized and Donepezil later added. Nevertheless, she became withdrawn, unwilling to speak much and had little interest to interact with others.

3. Method

Being possible candidates to determine the effectiveness of Methylphenidate augmentation to their existing drug regime, we first confirmed their cognitive impairment by administering the Mini Mental State Examination (MMSE), with them scoring 19/30 and 13/30 respectively that confirmed dementia, wherein a score of 23 or less indicated cognitive impairment [11]. Thereafter, we used the Clinical Dementia Rating (CDR) Scale to evaluate the severity

of dementia, with CDR-2 obtained for both subjects, indicating moderate stage [12]. We then obtained AES scores before introduction of Ritalin therapy (AES-Ia/AES-Ca) [13], and eight months respectively after treatment (AESb/AES-Cb) and finally four weeks after reducing the dose (AESc/AES-Cc) (**Table 1**).

4. Progress

Mr. KJ was described to have become "bright as a spark" and highly motivated after Methylphenidate was added, up to a dose of 20mg daily. There was excitability and a decision was made to reduce the dose. However, he became almost bed-ridden, so it was re-started at 10mg 4 times a week and he returned close to the level he was at when taking the drug daily. He even went out with family to visit friends and would be tired by nighttime, but was content. Thus, the regime was continued as it was.

Mrs. RC began to show interest in calling up friends upon introduction of Methylphenidate at 5mg daily but it was short-lived, hence dose was increased in stages to 15mg OD. When it was later decreased to 10mg daily, she was observed to have regressed into being disinterested, whilst claiming everything was "okay". Therefore the dose was escalated, and this time further to 20mg daily, in response to which she cheered up tremendously and had spontaneous speech.

5. Discussion

Apathy and related disorders of diminished motivation (ADDM) can be non-specific and a vague aspect of psychiatric disorders but have profound clinical consequences. Apathy is not a 'depressive equivalent' - apathy and depression are clinically and conceptually different states. Apathy has validity in its description as a symptom, a syndrome or even a dimension of behaviour. The diagnosis depends on detecting simultaneous dimunition in goal-related actions, thought and emotional responses. Detecting apathy depends on specific changes in patients' observable, or overt, activity, thought content and emotional responsivity. Diagnosis is by detecting simultaneous decrease in goal-directed activity, thought content and emotional responses. Decrements in overt behavior may entail subtle inefficiencies in the way people get their work done at home or at work, or the entailment of severe impairments in initiating and sustaining goal-directed behavior such that patients require prompting to perform personal and instrumental ADL. When impaired to the point that initiation of behavior is nearly or completely absent, patients are better characterized not as having apathy but having abulia or akinetic mutism respectively. The cognition of patients with apathy reveals a decrease in goal-related thought content, reporting verbatims like "I have little desire to do anything today", "I have no plans" or "I'm just not interested in much anymore" [13].

Apathy is, in essence, lack of motivation and Marin et al (1991) defined it as "lack

of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress. It is often associated with impaired insight because of its association with frontal lobe injury or dementing disease. Right hemisphere stroke patients would have higher mean levels of apathy than left hemisphere affected ones. For prognostic purposes, a measure of motivation may be a valid predictor of recovery from stroke, fractures causing loss of mobility and other illnesses. The correlation coefficients for test-retest reliability suggest that the AES can be used to evaluate the stability of apathy over time - it evaluates the extent to which apathy changes in concert with, or independently of, other clinical variables such as mood, cognition, functional impairment, environmental manipulation or pharmacological intervention. The convergent validity coefficients suggest that under some circumstances, one version of the AES might be used as an alternative to the other, such as when severe impairment precludes self-ratings. Normals tended to rate themselves as slightly apathetic while apathetic subjects tended to underestimate the severity of their apathy.10 Our two subjects had a lack of insight and were hence, unsuitable to rate themselves using the AES-S and therefore the AES-I and AES-C were used.

Although many apathy scales have been developed, the AES has several advantages over the others and has greatly facilitated and promoted research into apathy. It is also the most widely used one to characterize and quantify symptoms [14]. Higher scores indicate higher levels of apathy, reflecting a lower level of motivation to get things done during the day. Although originally used in people with stroke, AD and depression, Kant et al (1998) used the AES to study those with traumatic brain injury (TBI) and found 85% of those who were apathetic according to AES also met the criteria for depression using the Beck Inventory-II. Because that study implied that the AES may not distinguish the apathy of depression from neurologically-based apathy, Glenn et al (2002) modified Marins' definition of apathy, deleting the exclusion due to 'emotional distress' and adding some other clarifications as well: "lack of motivation not attributable to diminished level of consciousness, cognitive impairment or motor dysfunction, and manifested by decreased initiative, akinesia, emotional indifference and flat affect" [15]. In both our subjects, we found AES-I scores to be more representative of the beneficial effect of Methylphenidate in alleviating apathy in dementia (as opposed to the AES-C scores obtained) and possible reasons for this are discussed later under the heading 'Limitations'.

Although no cut-off score on the AES-S and EAS-I was found to have reasonable sensitivity and specificity with respect to the ability to predict the clinician's designation of a subject as apathetic when dealing with TBIs [15], it is widely accepted that a range of 34-37.5 and above has been considered as the cut-off range whereby a non-TBI subject would be considered as apathetic and this is what we adopted in analysing the scores obtained. Multiple variables interact in some disorders to produce apathetic states, eg. a depressed individual

might show apathy as a result of neurogenic impairment in primary motivational systems, neuropsychological deficits, low subjective expectancy of success or negative perceptions of potential sources of reward, and maladaptive affective or behavioural responses that elicit reduction in environmental rewards. The AES treats apathy as a psychological dimension defined by simultaneous deficits in the overt behavioural, cognitive and emotional concomitants of goal-directed behavior. Clinician-rated and self-rated versions of the AES discriminated apathy from depression and the AES-S did this almost as well as the AES-C [10].

Patients with poor cognitive function would experience the most severe apathy symptoms and AES-C had significant inverse correlation ($p<0.05$) with MMSE scores [16], indicating more severe apathy is significantly correlated with more severe cognitive deficits [3], We, however, could not replicate this with our findings but there was no concurrent repeat cognitive testing as we were more concerned about the effect of Methylphenidate on apathy - we thus merely relied on the initial CDR and MMSE scores and did not incorporate depression scales either, a problem we later came to realise and is duly given a mention later. Apathy is more evident than depression in AD patients and may be more common among patients with a later age of dementia onset [17]. Point prevalences for severe apathy symptoms, ranging from 60.3% 2 and 61.7%,1 indicate that AD patients have poor awareness of their emotions, blunting and lack of initiative [18], and that apathy is the most frequent neuropsychiatric syndrome in AD [19]. We found this observation applicable to both our subjects.

Diminished emotional responsivity is shallow, abbreviated or unchanging emotion in response to goal-directed events like if confronted with personal losses, health problems or financial misfortune, patients with apathy will be described as emotionally indifferent, placid, euphoric, affectively shallow or flat. Although diminished activity, diminished interests and attenuated emotional responses occur in many psychiatric and medical conditions, what distinguishes apathy is that all three aspects are simultaneously affected. Loss of motivation sometimes occurs as a result of developmental transitions such as retirement and psychotherapy then facilitates appropriate mourning and the acquisition of new goals; on the other hand, more serious cases of motivational loss may benefit from specific medical interventions and pharmacotherapy [13]. Loss of interest contributes significantly to predicting AD over time, hence the need to discriminate the treatment effects on apathy versus depression carefully [20]. Padala, Petty and Bhatia (2005) described a case of major depression with apathy and over the course of a four-week treatment regimen with Methylphenidate, apathy (measured by the AES) improved while depression (measured by the Hamilton Rating Scale) remained unchanged [21]. This was something we encountered, more especially in Case 2 (Mrs. RC) and highlights the importance of differentiating apathy from depression. Variations in the required dosing of Methylphenidate was also something we found to be of interest between our subjects and we wonder if the ‘inverted-U’ phenomenon [4] influenced our decision on their respective

dosages so as to strike a balance between efficacy and perceived side-effects.

6. Limitations

The AES-C, although requiring a semi-structured interview with verbal and non-verbal observations, would not have been expected to yield accurate assessment scores as it was carried out by different assessors (while the AES-I used the same raters in all three assessments).

It was also possible that poor familiarity with the AES could have led to inter-rater inconsistencies, especially among the clinicians, as there was no formal training given on its use.

Depression scales and periodic cognitive assessments should have been carried out to have been satisfied of the absence of co-morbidity and take into account cognitive deterioration over time respectively that could have affected the clinician-derived scores.

7. Conclusion

Methylphenidate may help improve apathy in dementia and appears to be dose-related.

Table 1: Comparative Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR) Scale and Apathy Evaluation Scale (AES) Scores.

	Case 1	**Case 2**
Years with dementia	9	5
MMSE	19/30	13/30
CDR	2	2
AES-I[a]	31	41
AES-I[b]	22	29
AES-I[c]	24	41
AES-C[a]	28	23
AES-C[b]	35	40
AES-C[c]	41	29

8. References

1. Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer's Disease. J Am Geriatr Soc. 2001; 49: 1700-1707.

2. Reekum RV, Stuss DT, Ostrander L. Apathy: Why Care? J. Neuropsychiatr Clin Neurosci. 2005; 17: 7-19.

3. Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndrome Validity of Apathy in Alzheimer's Disease. Am J Psychiatry. 2001; 158: 572-577.

4. Levy F. Stimulant Side Effects and Inverted-U: Implications for ADHD Guidelines. Aust NZ Psychiatr. 2013; 47(3): 217-221.

5. Dolder CR, Davis LN, McKinsey J. Use of Psychostimulants in Patients with Dementia. Ann Pharmacother. 2010;

44(10): 1624-1632.

6. Lanctot KL, Herrman N, Black SE, Ryan M, Rothenburg LS, Liu BA, Busto UE. Apathy Associated with Alzheimer's Disease: Use of Dextroamphetamine Challenge. Am J Geriatr Psychiatr. 2008; 16(7): 551-557.

7. Ben Itzhak R, Giladi N, Greundlinger L, Hausdorff JM. Can Methylphenidate Reduce Fall Risk in Community-living Older Adults? A Double-blind, Single-dose Cross-over Study. J Am Geriatr Soc. 2008; 56(4): 695-700.

8. Rosenberg PB, Lanctot KL, Drye LT, Herrman N, Scherer W, Bachman DL, Mintzer JE. Safety and Efficacy of Methylphenidate for Apathy in Alzheimer's Disease: A Randomized, Placebo-controlled Trial. J Clin Psychiatr. 2013; 74(8): 810-816.

9. Marin RS. Apathy: Concept Syndrome Neural Mechanisms and Treatment. Seminars Clin Neuropsychiatr. 1996; 1: 304-314.

10. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and Validity of the Apathy Evaluation Scale. Psychiatr Res. 1991; 38: 143-162.

11. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental State' a Practical Method for Grading the Cognitive State of Patients for the Clinicians. J Psychiatr Res. 1975; 12: 189-98.

12. Morris JC. The Clinical Dementia Rating (CDR): Current Version and Scoring Rules. Neurology. 1993; 43: 2412-14.

13. Marin RS. Apathy – Who Cares? An Introduction to Apathy and Related Disorders of Diminished Motivation. Psychiatr Ann. 1997; 27(1): 18-23.

14. Clarke DE. Apathy in Dementia: An Examination of the Psychometric Properties of the Apathy Evaluation Scale. J Neuropsychiatry Clin Neurosci. 2007; 19: 57-64.

15. Glenn MB, Burke DT, O'Neil-Pirozzi T, Goldstein R, Jacob L, Kettell J. Cut-off Score on the Apathy Evaluation Scale Subjects with Traumatic Brain Injury. Brain Injury. 2002; 16(6): 509-16.

16. Hsieh C-J, Chu H, Cheng J-S J, Shen WW, Lin C-C. Validation of Apathy Evaluation Scale and Assessment of Severity of Apathy in Alzheimer's Disease. Psychiatr and Clin Neurosci. 2012; 66: 227-34.

17. Marin RS, Firinciogullari S, Biedrzycki RC. The Sources of Convergence Between Measures of Apathy and Depression. J Affect Disord. 1993; 28: 7-14.

18. Robert PH, Clairet 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 Psychiatr. 2002; 17: 1099-1105.

19. Levy ML, Cummings JL, Fairbanks LA et al. Apathy is Not Depression. J Neuropsychiatry Clin Neurosci. 1998; 10: 314-319.

20. 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.

21. Padala PR, Petty F, Bhatia SC. Methylphenidate May Treat Apathy Independent of Depression. Ann Phamacother. 2005; 39(11): 1947-1949.