Keeping the heart in mind: Cardiovascular determinants of neurocognitive functioning in old age

Bertens, A.S.

Chapter 2

Validity of the three apathy items of the Geriatric Depression Scale (GDS-3A) in measuring apathy in older persons

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* contributed equally.

Abstract

Objective: The Geriatric Depression Scale (GDS)-3A, a three-item subset of the GDS-15, is increasingly used as a measure for apathy in research settings to assess factors associating with this neuropsychiatric syndrome. We aimed to assess how accurately the GDS-3A discriminates between presence and absence of apathy in two populations of community-dwelling older persons, using the Apathy Scale as reference standard.

Methods: Baseline data were used from 427 participants of the Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden and 1118 participants of the PROactive Management Of Depression in the Elderly (PROMODE) Study, all ≥75 years and with available GDS-3A and Apathy Scale measurements. A cut-off score of ≥14 was used for presence of apathy according to the Apathy Scale. Areas under the receiver operating characteristic curve (AUC) were calculated. Based on the likelihood ratios for GDS-3A scores, a cut-off of ≥2 was used for presence of apathy according to the GDS-3A to calculate test characteristics.

Results: The AUC was 0.68 (95% confidence interval 0.62-0.73) in the DANTE Study and 0.72 (0.67-0.77) in the PROMODE Study. In the DANTE Study sensitivity was 29.3% (21.4-38.1) and specificity was 88.5% (84.4-91.8), whereas in the PROMODE Study sensitivity was 32.8% (24.5-41.1) and specificity 92.6% (90.9-94.2). Stratification on population characteristics did not yield more favourable test characteristics.

Conclusion: The GDS-3A has low sensitivity and high specificity as a measure of apathy in two populations of older persons. Using the GDS-3A in research might yield estimates biased towards the null in case of non-differential misclassification.

Introduction

Apathy is an important yet often overlooked neuropsychiatric behavioural syndrome that is common in older persons[1, 2]. Apathy is characterized by diminished motivation and initiative, reduced goal-directed behaviour, loss of interest and emotional indifference[3, 4]. Its presence in older persons is associated with worse cognitive functioning[5, 6], reduced therapeutic response[1], lower quality of life[7, 8], and high caregiver distress[9]. While symptoms of apathy can occur as part of depression, apathy is increasingly being recognised as a syndrome in its own right, also in the absence of a depressed mood[3, 10, 11]. No valid, easily applicable screening tool for apathy is available for use in general clinical practice[12, 13]. Because of its association with adverse health outcomes, apathy is increasingly prioritised on research agendas, with subsequent expanding knowledge on its specific prognostic[14, 15] and possibly causal factors[16-18].

Data from large observational studies could be particularly useful in identifying potentially modifiable risk factors for apathy at old age. However, only few studies have used specific instruments to prospectively collect data on symptoms of apathy, whereas symptoms of depression are often measured[15, 19]. To screen for symptoms of depression at old age, the Geriatric Depression Scale (GDS)-15 is frequently used in clinical practice as well as in research, showing a good reliability and validity[20]. In factor analyses, a subset of three GDS-15 items has repeatedly been identified as a cluster of symptoms that assesses apathy[21-23]. This GDS-3-apathy subscale (GDS-3A) comprises the items: (1) Have you dropped many of your activities and interest?; (2) Do you prefer to stay at home, rather than going out and doing new things?; and (3) Do you feel full of energy? The GDS-3A subscale is increasingly being used in research to identify participants with apathy in studying associating factors[14-16]. However, only limited evidence exists for the discriminatory value of the GDS-3A for the presence or absence of clinically relevant apathy. Van der Mast *et al*. compared the GDS-3A with the Apathy Scale in a sample of community-dwelling 90-year-olds, rendering a sensitivity of 68.6%, a specificity of 84.9%, a positive predictive value of 77.8%, and a negative predictive value of 77.8%[14]. To the best of our knowledge, this is the only study providing epidemiological test characteristics for the GDS-3A and therefore it is yet undetermined whether these discriminatory qualities of the GDS-3A also hold for other populations of older persons.

In the Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden and the Proactive Management of Depression in the Elderly (PROMODE) Study both the GDS-3A and the Apathy Scale were assessed as part of a neuropsychological evaluation, providing the unique opportunity to compare these questionnaires in two large cohorts of older persons. Therefore, the aim of conducting the current study was to assess how accurately the GDS-3A discriminates

between presence and absence of apathy in two populations of community-dwelling older persons, compared to the Apathy Scale.

Methods

Study populations

We used baseline data of two Dutch randomised controlled trials, the DANTE Study and the PROMODE Study.

Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden

The primary aim of the DANTE trial was to assess whether discontinuation of antihypertensive treatment in older persons with mild cognitive deficits improves cognitive, psychological and general daily functioning[24] . Participants aged ≥75 years, using antihypertensive medication, with a current systolic blood pressure ≤160 mmHg, without serious cardiovascular disease, and without a diagnosis of dementia were recruited from primary care practices between May 2011 and July 2013. Of the 5537 selected older persons, 2002 consented to participate in a Mini Mental State Examination screening. A total of 1301 persons did not meet the MMSE selection criterion (MMSE score of 21-27), 67 did not meet other selection criteria, 204 declined to participate, and 3 had missing data on the Apathy Scale and/or the GDS-15, leaving 427 participants for further analyses.

PROactive Management Of Depression in the Elderly (PROMODE) Study

The primary aim of the PROMODE trial was to investigate the (cost-) effectiveness of a stepped-care intervention programme among older persons with depressive symptoms[25]. A total of 2759 participants aged 75 years and above were recruited from primary care practices between April 2007 and July 2008. A total of 366 persons were excluded because of a MMSE score of less than 19 points, a limited life expectancy, recent loss of partner, a diagnosis of dementia or a current treatment for depression. Of the remaining 2393 persons invited to participate, 1054 were non-responders, 101 did not meet selection criteria and 120 persons had inadequate assessment or missing data of the Apathy Scale, leaving 1118 participants for analyses[8].

The medical ethics committee of the Leiden University Medical Center approved both the DANTE and PROMODE Study, and informed consent was obtained from all participants. In the DANTE Study all participants had mild cognitive deficits and therefore gave informed consent after written and verbal description of the study was given in the presence of a close relative serving as a proxy decision maker[26].

Measurements

Geriatric Depression Scale (GDS)

In both studies, the GDS-15[27] was administered at baseline by trained research personnel to assess presence of depressive symptoms within the last few weeks. The GDS-15 is a short version of the GDS-30[27], and shows a good reliability and validity[20]. The scale consists of 15 items that can be scored as present or absent (range 0-15 point, with higher scores indicating more symptoms of depression). A score of five or higher is indicative of clinically relevant depressive symptoms[20]. The apathy subscale (GDS-3A) of the GDS-15 consists of the following 3 items (score range 0-3 points): (1)Have you dropped many of your activities and interest?; (2)Do you prefer to stay at home, rather than going out and doing new things?; and (3)Do you feel full of energy?

Apathy Scale

In both studies trained research personnel assessed the Apathy Scale to record presence of symptoms of apathy. The Apathy Scale, a semi-structured interview combining input from participants, proxy and clinical impression, is an abbreviated version of the Apathy Evaluation Scale[3], and has a good one-week test-retest reliability, inter-rater reliability and internal validity[28]. The Apathy Scale consists of 14 items that are scored on a four-point Likert scale (range 0-42 points, with higher scores indicating more symptoms of apathy). A score of at least 14 points is considered to be indicative for the presence of clinically relevant apathy[28]. The research personnel was not blinded for the GDS-15 scores.

Additional measurements

In both studies socio-demographic characteristics were assessed at baseline using standardized interviews. Level of education was dichotomized at primary education (six years of schooling) and use of alcohol was dichotomized at 14 consumptions per week. Global cognitive functioning was assessed with the MMSE (score range 0-30 points, with higher scores indicating better cognitive function)[29]. In the DANTE Study, presence of cardiovascular disease was obtained from the general practitioners using structured questionnaires, and defined as myocardial infarction or coronary reperfusion procedure longer than three years ago, and/or peripheral arterial disease, as persons with serious or recent cardiovascular disease (such as a history of stroke, transient ischemic attack or heart failure and/or a myocardial infarction/coronary reperfusion procedure within the last three years) were excluded from participation. No information regarding presence of cardiovascular disease was available in the PROMODE Study.

Statistical analyses

Characteristics of the study populations are presented as mean (standard deviation (SD)), number (%) or median (interquartile range (IQR)) when appropriate. In a receiver operating characteristic (ROC) curve the true positive rate (sensitivity) was plotted against the false positive rate (100-specificity) for different cut-off points of the GDS-3A, and the area under the curve was calculated. For each score on the GDS-3A, likelihood ratios were calculated: the proportion of participants with a specific test score in the presence of apathy was divided by the proportion of participants without apathy with that same test score. A two by two contingency table was created to determine the discriminatory accuracy of the GDS-3A using a cut-off of two or more points in assessing presence of apathy (according to ≥14 on the Apathy Scale). Sensitivity and specificity were calculated, as well as likelihood ratios for a positive (LR+) and negative (LR-) test using the following formulas: LR+ = sensitivity/(1-specificity) and LR- = (1-sensitivity)/specificity).

Spearman's correlation coefficients were computed for the GDS-3A and the Apathy Scale. To assess the influence of each item on the correlation of the GDS-3A with the Apathy Scale, these analyses were repeated after omitting either the first, second or third item of the GDS-3A. Furthermore, to assess whether discriminatory accuracy of the GDS-3A depended on population characteristics, we performed analyses in strata of age (of 5 years from 75 years onwards), gender, cognitive function (dichotomised at the median MMSE score), level of education (dichotomised at 6 years), and presence of cardiovascular disease (yes or no; only in the DANTE Study). Data were analysed using SPSS, version 22.0 and, Stata, version 12.0.

Results

In Table 2.1 the characteristics are shown of the 427 participants of the DANTE Study (mean age 81.3 (SD 4.6)) and the 1118 participants of the PROMODE Study (mean age 81.8 (SD 4.9)), with mean Apathy Scale scores of 11.3 (SD 4.7) and 7.5 (SD 4.6), respectively. Presence of apathy according to a score of ≥14 points on the Apathy Scale was 28.8% in the DANTE Study and 10.9% in the PROMODE Study.

Figure 2.1 presents the ROC curves, with areas under the ROC curves of 0.68 (95% confidence interval 0.62–0.73) in the DANTE Study and 0.72 (0.67–0.77) in the PROMODE Study.

In Table 2.2 the likelihood ratios for the individual GDS-3A scores are shown. In the DANTE Study, the likelihood ratio was 1.96 (1.18–3.25) for a score of two and 5.36 (2.08–13.8) for a score of three on the GDS-3A, while this was 4.32 (3.02–6.18) and 5.44 (1.56–19.0) respectively in the PROMODE Study.

Table 2.1 Characteristics of the DANTE Study and the PROMODE Study

	DANTE	PROMODE
Number of participants	427	1118
Age, years (mean, SD)	81.3 (4.6)	81.8 (4.9)
Female gender (n, %)	257 (60.2%)	684 (61.1)
Presence of CVD (n, %)[a]	48 (11.2%)	-[b]
MMSE score (median, IQR)	26 (25 - 27)	28 (27 - 29)
Lower level of education (n, %)[c]	142 (33.3%)	333 (29.8%)
Apathy Scale (mean, SD)	11.3 (4.7)	7.5 (4.6)
Apathy according to Apathy Scale (n, %)[d]	123 (28.8%)	122 (10.9%)
Apathy Scale score in those with apathy (mean, SD)	17.2 (3.3)	16.6 (2.8)
Scores on the GDS-3A (n, %)		
0	225 (52.8%)	718 (64.2%)
1	131 (30.7%)	286 (25.6%)
2	52 (12.2%)	104 (9.3%)
3	19 (4.4%)	10 (0.89%)
Depressive symptoms present (n, %)[e]	45 (10.5%)	64 (5.7%)

SD, standard deviation; CVD, cardiovascular disease; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale

a: Cardiovascular diseases comprise myocardial infarction or coronary intervention > 3 years ago, or presence of peripheral artery disease

b: No data on cardiovascular morbidity available in the PROMODE Study

c: Level of education is dichotomized at 6 years

d: Apathy according to the Apathy Scale: score of ≥14

e: Depressive symptoms present according to the GDS-15: score of ≥5

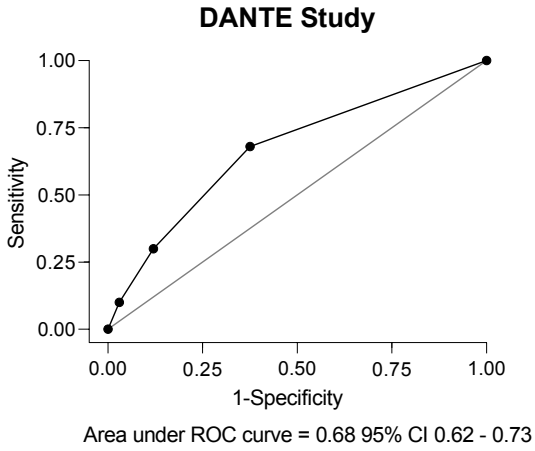
Table 2.2 Performance of the GDS-3A in the DANTE Study and the PROMODE Study

		DANTE Study (n=427)		
GDS-3A score	N	Apathy present[a]	Apathy absent	Likelihood ratio for GDS-3A score
3	19	13	6	5.36 (2.08 - 13.8)
2	52	23	29	1.96 (1.18 - 3.25)
1	131	50	81	1.53 (1.15 - 2.03)
0	225	37	188	0.49 (0.37 - 0.65)
Total	427	123	304	
		PROMODE Study (n=1118)		
GDS-3A score	N	Apathy present[a]	Apathy absent	Likelihood ratio for GDS-3A score
3	10	4	6	5.44 (1.56 - 19.0)
2	104	36	68	4.32 (3.02 - 6.18)
1	286	46	240	1.56 (1.21 - 2.02)
0	718	36	682	0.43 (0.33 - 0.57)
Total	1118	122	996	

Data are presented as numbers, or as likelihood ratios with 95% confidence intervals.

GDS, Geriatric Depression Scale

a: Apathy present: Apathy Scale score ≥14



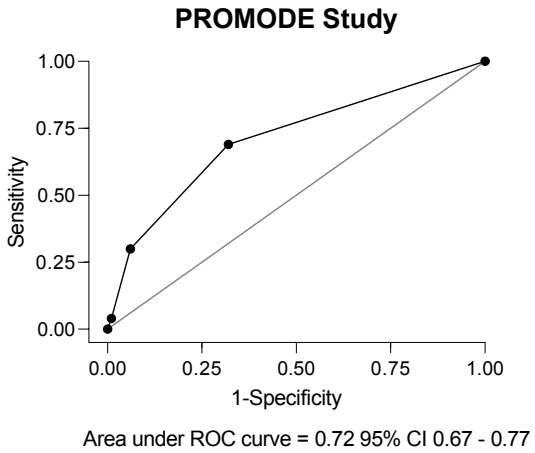


Figure 2.1 Receiver Operating Characteristic (ROC) curve for GDS-3A compared to the Apathy Scale in the DANTE Study and PROMODE Study

Since the percentage of participants scoring three points on the GDS-3A was low in both studies (n=19 for the DANTE Study and n=10 for the PROMODE Study), a cut-off score of ≥2 was used for the calculation of sensitivity and specificity (Table 2.3). The GDS-3A had a sensitivity of 29.3% (21.4–38.1) and a specificity of 88.5% (84.4–91.8) in the DANTE Study, and 32.8% (24.5–41.1) and 92.6% (90.9–94.2), respectively, in the PROMODE Study. Correlation coefficients between the GDS-3A and the Apathy Scale were 0.42 in the DANTE Study and 0.39 in the PROMODE Study (both p-values<0.001). Coefficients remained largely similar after omitting either the first,

second or third item of the GDS-3A. Stratified analyses according to age, gender, cognitive function, presence of cardiovascular disease, and level of education rendered largely similar test characteristics in both studies (data not shown).

Table 2.3 Presence of apathy according to the GDS-3A and the Apathy Scale in the DANTE Study and the PROMODE Study

DANTE		**Apathy Scale ≥14**		
		Positive	Negative	
GDS-3A ≥2	Positive	36	35	71
	Negative	87	269	356
		123	304	427
Sensitivity	29.3% (21.4 - 38.1)			
Specificity	88.5% (84.4 - 91.8)			
LR+	2.54 (1.68 - 3.85)			
LR-	0.80 (0.71 - 0.90)			
PROMODE		**Apathy Scale ≥14**		
		Positive	Negative	
GDS-3A ≥2	Positive	40	74	114
	Negative	82	922	1004
		122	996	1118
Sensitivity	32.8% (24.5 - 41.1)			
Specificity	92.6% (90.9 - 94.2)			
LR+	4.41 (3.15 - 6.17)			
LR-	0.73 (0.64 - 0.82)			

Data are presented as numbers, percentages with 95% confidence intervals, or likelihood ratios with 95% confidence intervals.

GDS, Geriatric Depression Scale; LR, likelihood ratio

Discussion

In our study investigating the applicability of the GDS-3A in research settings, the GDS-3A only moderately discriminated between presence and absence of clinically relevant apathy in two populations of older persons, when using the Apathy Scale as reference standard. Using a cut-off of ≥2 for presence of apathy according to the GDS-3A, sensitivity compared to the Apathy Scale was 29.3% in the DANTE Study and 32.8% in the PROMODE study, whereas in both studies specificity was high (88.5% and 92.6%, respectively).

To the best of our knowledge, our study is the second to report epidemiological test characteristics for the GDS-3A, and the first to do so in two large cohorts of older persons with a wider age range. The likelihood ratios for the GDS-3A scores increased with increasing test scores in both studies, but poorly discriminated for

scores of one or two (1.53 and 1.96 in the DANTE Study, respectively, and 1.56 and 4.32 in the PROMODE Study). Although a score of three had a moderately high likelihood ratio in both studies (5.36 in the DANTE Study and 5.44 in the PROMODE Study), the number of participants in this category was very low in both studies, limiting power for analyses. Therefore we decided to use a cut-off of ≥2 for calculations of test characteristics in these populations, with modest corresponding likelihood ratios because of a low sensitivity and high specificity. In both the DANTE Study and the PROMODE Study the GDS-3A scores moderately but significantly correlated with Apathy Scale scores and the correlation did not depend on the performance of a single item.

A possible explanation for the moderate performance of the GDS-3A is that, although interviewer-administered, it records self-reported symptoms. The Apathy Scale however, is a semi-structured interview allowing the interviewer to incorporate his or her own clinical judgement and information obtained from proxies. Since disease awareness might be low in apathy [1], this difference might explain the low sensitivity of the GDS-3A. Although lack of self-awareness might at least partly explain the low sensitivity of the GDS-3A, our findings in the DANTE Study and the PROMODE Study contrasts with findings of Van der Mast *et al*. Using data from the Leiden 85-plus Study, they reported a sensitivity of 68.6% using the same cut-off values for both the GDS-3A and the Apathy Scale[14]. The difference in test characteristics might be explained by a higher prevalence of apathy according to the Apathy Scale in the Leiden 85-plus study, which was present in 51 out of 117 participants (43.6%) and might be due to the much higher age in the Leiden 85-plus Study. It is increasingly recognized that also sensitivity and specificity may vary across patient populations[30, 31]. For example with a lower disease prevalence, there may be more patients with less severe symptoms, and sensitivity can be lower[32].

In contrast to the population-based Leiden 85-plus Study, participants from both our studies were selected for participation in clinical trials, were on average younger, had better cognitive function, higher level of education and better cardiovascular health (the latter information only available in the DANTE Leiden Study). However, stratified analyses showed that aforementioned characteristics did not explain the differences in findings between our current study and the Leiden 85-plus Study.

Besides other, currently unmeasured, patient characteristics, differences in diagnostic accuracy might also be artificially caused by our use of the Apathy Scale, an imperfect reference standard[12, 33]. The Apathy Scale was developed in patients with Parkinson's disease[28] and showed good interrater reliability (r=0.81), test-retest reliability (r=0.90), and good internal consistency (Cronbach's α=0.76). Test characteristics for a cut-off of ≥14 compared to a clinical diagnosis of apathy were calculated in 12 patients (sensitivity 66%, specificity 100%). The only other study on psychometric properties of the Apathy Scale reported fair internal consistency

(Cronbach's α=0.69)[34]. Although data on the performance of the Apathy Scale in other populations is scarce, the questionnaire is derived from the well-validated Apathy Evaluation Scale (AES)[12, 35]. The Apathy Scale is shorter and has the possibility to combine information from the patient, informant and clinician, making it a more favourable instrument. Even so, these imperfect characteristics of our reference standard may underlie the moderate performance of the GDS-3A in our study. However, it must be emphasized that the same reference standard was used in the Leiden 85-plus Study, making results comparable for the purpose of this study. Moreover, if reference standard misclassification would explain differences in sensitivity and specificity, a pattern of higher sensitivity and lower specificity with increasing disease prevalence would be observed[33]. As this was not consistently found for the DANTE Study, PROMODE Study and Leiden 85-plus Study, it is less likely that reference standard misclassification explains the variation in sensitivity and specificity across the different studies.

Strengths of this study include the use of two relatively large sized, well-defined samples of older persons and very few missing data on the GDS-3A and Apathy Scale, implying a low risk of validation bias. Furthermore, the research protocols for the DANTE Study and the PROMODE Study were designed similarly with regard to administering the questionnaires, which contributes to comparability of results. However, there are several limitations of this study that need to be taken into account when interpreting the results. First, it is important to state that the current study was not designed to assess added diagnostic value, but is a test accuracy study aiming to investigate the applicability of the GDS-3A in research settings. Second, only 19 (4.4%, DANTE Study) and 10 (0.89%, PROMODE Study) of the participants had GDS-3A scores of three. Although numbers were too low to calculate valid diagnostic test characteristics for this cut-off in our study populations, increasing the cut-off for apathy might yield higher specificity but even lower sensitivity. This may be favoured in certain research settings, depending on the aim of the study. Third, the interviewers administering the Apathy Scale were not formally blinded for the GDS-3A scores, which could have led to information bias. Nonetheless, since the GDS-3A questions were incorporated in the GDS-15 questionnaire and our current aim was not the primary aim of the studies, we do not expect different results with a blinded study design. Furthermore, apathy can occur as a symptom of depression and as a syndrome in its own right[10]. As no formal diagnosis of depression was available in either study, we were not able to differentiate between apathy and depression. However, the GDS-3A items were identified as measuring apathy by several studies on construct validity[21-23] as well as an expert panel installed by Van der Mast *et al*.[14]. We therefore deem it justified using these items as a measure for apathy. Last, both the DANTE and PROMODE participants were selected for clinical trials, limiting generalizability of the study results.

The main premise of this study was to assess the applicability of the GDS-3A in research settings. Given the moderate likelihood ratios in both the DANTE and PROMODE Study, our results suggest that the GDS-3A is not a useful tool in clinical practice to screen for presence of apathy. However, the GDS-3A may still be a useful scale in research, depending on the aim of the study. Because of its low sensitivity regardless of the cut-off used, the GDS-3A will not be suitable to determine the prevalence of apathy in specific populations. In studies focussing on potential risk and prognostic factors however, it can still be a useful instrument as long as it can be assumed that the misclassification is non-differential. If so, effect sizes will be biased towards the null, both when the GDS-3A is used as a measure of outcome and determinant[36]. Furthermore, the higher the prevalence of apathy in a population, the smaller the bias will be[36], making the GDS-3A better suited for research in older populations.

In conclusion, our results from two large study cohorts show that the GDS-3A is only very moderately accurate in discriminating between presence and absence of clinically relevant apathy in older persons. Although we think it is therefore a less favourable screening tool for clinical practice, the GDS-3A can still be useful in research if no other measurement of apathy is available. Because of the non-differential misclassification, and thus dilution of effect, the GDS-3A is preferably used in large studies. Especially for studies among older people, with long follow-up, the GDS-3A might be attractive to study risk factors and prognostic factors for apathy, since it is unlikely that these earlier studies used a validated questionnaire. However, since it becomes increasingly clear that apathy is an important and useful endpoint in studies among older people, future studies should use a more valid instrument. In all instances, caution has to be taken in interpreting negative findings as evidence for absence of an association.

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