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Effectiveness of the Open Screening Programs in Recruiting Subjects to Prodromal and Mild Alzheimer's Disease Clinical Trials

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Abstract

BACKGROUND AND OBJECTIVES: Due to the lack of scientific data comparing the success and cost-effectiveness of trial recruiting strategies, the main goal of this paper is to present our results and experiences in recruiting participants to prodromal and mild AD clinical trials from an open-access screening program.

DESIGN: The screening procedure includes the interview, and combined tests administration conducted by experienced neuropsychologist: Mini-Mental State Examination (MMSE) and Auditory-Verbal Learning Test (AVLT). The clinical evaluation was based on test scores, patient and/or caregiver interview, and the health questionnaire.

SETTINGS AND PARTICIPANTS: The open-access screening program was conducted in Wroclaw Alzheimer's Center for 18 months (2018-2019). We invited individuals age 50 or older with the caregivers. The total number of subjects was 730 (N=730).

MEASUREMENTS AND RESULTS: Due to our research, the detection rates in the screened population were 0,7% for severe dementia, 4,1% for moderate dementia, 18,6% for mild dementia, and 28,9% for mild cognitive impairment (MCI). From 347 individuals classified in our open-access screening programs as MCI or mild dementia patients, as many as 248 patients were screened in Alzheimer's disease clinical trials, which is 71,47%. Moreover, 63 from 347 individuals selected from our program as MCI or mild dementia patients were randomized into the clinical trials, which is 18,16%. Furthermore, 63 from total 730 (8,6%) patients were randomized in clinical trials.

CONCLUSIONS: Open-access screening programs can improve detection of MCI and dementia in society, help to distinguish demented from non-demented elderly, and improve recruitment of prodromal AD patients who would probably not have come to the memory clinic otherwise.

Key words: Alzheimer's disease, mild cognitive impairment, dementia, screening, randomized controlled trial.

Introduction

Due to worldwide elderly population growth and lifespan extension, the number of patients with dementia, most often caused by Alzheimer's disease (AD), will probably increase exponentially. The 2016 World Alzheimer Report estimates that the number of people with dementia worldwide (46.8 million) will almost double every 20 years, and it is expected to rise to 131,5 million by 2050. Furthermore, the total estimated worldwide cost of dementia in 2016 was US$818 billion, and it was predicted to rise to a trillion-dollar disease by 2018 (1).

It is well known that pathophysiological changes in Alzheimer's disease begin many years prior to clinical manifestations of the disease. Therefore, in 2011 the National Institute of Aging and Alzheimer's Association (NIA-AA) created separate diagnostic guidelines for the clinical stages of AD including mild cognitive impairment (MCI) and dementia (2). The definition of MCI provided by NIA-AA characterized mild cognitive impairment (MCI) as a cognitive performance below the expected range for that individual based on all available information, including clinical judgment and/or on cognitive test performance (with or without adjustments for age, education, occupation, sex, etc.). In the diagnostic procedure, the evidence of decline in cognitive performance from baseline must also be present (reported by the individual, study partner, or observed by change on longitudinal cognitive testing/behavioral assessments or by a combination of these). It is noteworthy that cognitive presentations that are not primarily amnestic can also occur, and the subject performs daily life activities independently, but cognitive problems can impact more complex activities of daily life (2). On the other hand, dementia is defined as a substantial progressive cognitive impairment that affects several domains and/or neurobehavioral symptoms. The problems may be reported by an individual, observer (study partner) or observed by change on longitudinal cognitive testing. The primary feature differentiating dementia from MCI is clearly evident functional impact on daily life, the patient needs assistance with daily living activities. Dementia can be divided into mild, moderate, and severe (2).

Furthermore, the latest research framework (2018) from the NIA-AA points to the importance of early detection of the disease and the clinical trial enrollment of participants in prodromal (MCI) or preclinical ("asymptomatic") stages of AD, when the treatment

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could be more effective (2). Interestingly, subjective experience of cognitive decline in the elderly, without objective impairment on cognitive assessment, called subjective cognitive decline (SCD), has been suggested to be a possible first symptom of preclinical AD (3). Compared to healthy individuals, the elderly with SCD have an increased risk of progression to MCI and dementia (4). Therefore, focusing on AD as a continuum, the crucial need is to recognize the disease as soon as possible, based on both clinical and biomarker findings.

Unfortunately, despite the science and industry efforts, there is still no cure for Alzheimer's disease, and the available treatment strategies bring only symptomatic benefits. Therefore, Alzheimer's disease remains the leading cause of death with no effective treatment available (5). During the last decades, considerable effort has been focused on research and clinical trials of new drugs and promising therapies in AD. The NIA-AA counted more than 150 open studies calling for more than 70 000 patients which could require screening of more than 700 000 potential participants (6). Moreover, following the data, a combination of restrictive inclusion and exclusion criteria determine a small proportion of AD patients who are eligible for trials, 27% of patients from the research, and 10-13% from the clinical settings (1, 6).

The key challenge in AD research is low participation in clinical trials (7). A review of 24. phase II and III AD clinical trials reveals that only a third recruited a sufficient number of participants within a year (1). Scientific data indicates that the majority of all AD patients are older than 75 years, which increases the risk of exclusion for age-related reasons such as comorbidities and use of prohibited drugs (1). Clement et al. (2019) distinguished several barriers and facilitators of AD trials recruitment related to three themes: systemic factors (AD diagnostic pathway, patient records, embedding research in patient care, and the national research database), healthcare professionals, and patients and their companions. Authors showed that current diagnostic pathways and data systems made screening process difficult. Moreover, they indicate that challenges such as gatekeeping and restricted access for potentially eligible patients are often caused by, preferred by clinicians, recruiting subjects only from their own clinics, and recommended the use of a wide range of the new approaches to identify and recruit patients (7). The open-access screening programs are one of the most effective methods to improve trial recruitment. Increasing the pool of potential participants by enhancing awareness and facilitates attitudes towards research via advertising, education, and community outreach campaigns are also one of the remedial strategies in AD research suggested by Boada et al. (2018) (6).

Due to the challenges faced by Alzheimer's disease research to enroll the specified number of participants and the problems with slow recruitment to AD clinical trials, it is noteworthy that open-access screening programs could be an effective method to improve AD trial recruitment. It is especially valuable in recruiting prodromal AD patients who would probably not have come to the doctor or to the memory clinic otherwise. People with MCI belong to the group of the high risk of developing dementia or AD when compared with similarly aged individuals in the general population. The data mentioned by Diniz et al. showed that patients with MCI convert to dementia at rates of approximately 10% per year and that subjects with MCI had a 6.7 higher risk to progress to dementia (8). Therefore, creating screening programs for the elderly including early diagnosis of MCI and dementia is highly recommended. There is a pressing demand for testing new treatments and interventions which can slow or halt the progression of AD, and increase the pool of potential participants.

Our program was aimed at citizens of Wroclaw (the Lower Silesia province, Poland). Due to the data collected by the Central Statistical Office (Poland), the 60+ population was 21,9% of the number of Lower Silesia province citizens. In Wroclaw, in 2017 the number of people aged 60+ was about 152 thousand, including 15,2 thousand dementia patients, and approximately 23 – 45,7 thousand people with MCI which was a large group of individuals potentially interested in participating in the open-access screening program targeting cognitive decline (9).

Methods

In this report, we will focus on the open-access screening program conducted in Wroclaw Alzheimer's Center for 18 months (2018-2019) as a valuable trial recruitment strategy. The program was implemented to increase awareness in the local society of early diagnosis of cognitive disorders and memory problems, and to improve the prevention of cognitive decline and dementia. The interest in screening tests of individuals with memory problems was gained due to the advertising campaign and frequent appearance in the local media (newspapers, television, and radio interviews), as well as on the internet (social media and websites targeting the elderly and their families). The main goal of our program was to create an efficient, cost-effective, and relatively quick method of screening for cognitive impairment, and recruiting for Alzheimer's disease clinical trials. It is noteworthy that the applied screening process as a part of the evaluation for dementia and cognitive impairment was quickly administered and relatively cheap – approximately 30 USD per individual, which includes site personnel time and advertising. The screening procedures were conducted during the site working time, so it does not cause additional costs. The internet-based advertisement, e.g. social media, the website was for free. Due to the importance and meaning of the initiative of the open-access screening program for the elderly, the local media (newspapers and television)

were willing to provide the information and invite our health care specialists for the interviews free of expense, which increased the number of people who received information about our program

Program eligibility criteria

The main reasons for creating the program were that the majority of patients with early dementia and MCI are undiagnosed in primary care practices and the memory complaints or other cognitive symptoms are often minimized by the patients and/or their families, as well as there are underestimated by health professionals. We assume that a brief combined screen can detect mild cognitive impairment (MCI) and dementia with reasonable accuracy. We invited to cognitive screening the citizens of Wroclaw, age 50 or older who have memory complaints with their caregivers (family members or friends). The patient's motivation to participate in the program varies from the concerns about own cognitive health to the family worries due to the cognitive problems of the subject. The participation in the program was free for the patients which was an important factor influencing the decision to get tested.

Screening procedure

The clinical evaluation conducted by the experienced neuropsychologist was based on test scores, patient and informant interviews, and the health questionnaire - self-reported health information such as age, family history, medical history, and medication information. The caregiver interview was crucial for diagnosing the functional impairment, and cognitive decline. The screening program was created to diagnose cognitive functioning of the screened subjects. Therefore, the experienced geriatric neuropsychologist evaluated only cognitive functions and the diagnosis includes normal cognitive functioning, MCI or dementia. Obviously, it is impossible to find the cause of dementia or MCI only due to cognitive tests and interview. Moreover, the important aspect of the screening process was to differentiate between MCI, dementia and depression which was based on clinical evaluation, observation during the tests, and interview with the patient and informant, conducted by the experienced neuropsychologist. The screening procedure includes combined tests administration: Mini-Mental State Examination (MMSE) and Rey Auditory-Verbal Learning Test (AVLT) which were the first step in the screening process.

The MMSE is the most widely used, quick (10 minutes), and valuable instrument for grading cognitive impairment in the elderly. It measures several cognitive domains such as orientation to time and place, immediate recall, short-term memory, calculation, language, and constructive ability. The items of the MMSE include tests of orientation, registration, recall, calculation and attention, naming, repetition, comprehension, reading, writing and drawing (10). The scores of MMSE are reliable between tests and raters. Moreover, the MMSE correlates significantly with other mental tests and batteries (such as the cognitive subscale of the Alzheimer's Disease Assessment Scale - ADAS-Cog), electroencephalography, computerized tomography, magnetic resonance imaging, single photon emission computed tomography scan, cerebrospinal fluid proteins and enzymes, and brain biopsy synapse numbers (11). The maximum MMSE score is 30 and the following cut-off levels classify the severity of cognitive impairment: no cognitive impairment 27-30, mild cognitive impairment (MCI) 24-26, mild dementia 19-23, moderate dementia 11-18; and severe dementia $\leq$10. Cognitive performance as measured by the MMSE varies within the population by age and education level, therefore we used Mungases et al. (12) scoring system to evaluate the cognitive performance of patients. The correction of the raw score was made by adding specific numerical value due to the age and educational level of the subject.

It is noteworthy, due to the data provided by Benson et al. (13), that the MMSE is a crucial and effective instrument in screening dementia, but it is relatively ineffective in separating the MCI patients from those with depression. The authors recommended the use of other than the MMSE or additional method to evaluate mental status more effectively. Furthermore, Mitchell (14) shows a very limited value of MMSE in making diagnosis of MCI against healthy controls and modest rule-out accuracy. He also pointed at the necessity of combining MMSE with other methods to diagnose MCI. On the other hand, Diniz et al. highlight that the qualitative analysis of the cognitive performance of MCI patients in the subitems of the MMSE may help distinguish the MCI subtypes in clinical practice. Accordingly, the subjects with MCI presented worse performance than controls on the verbal memory task and "pentagon drawing" task. Moreover, amnestic MCI patients performed worse only on the "three-word recall" task; non-amnestic MCI subjects performed worse on the "three-stage command" task, and multiple-domain MCI patients performed worse on the "drawing a pentagon" task (15).

Due to the increasing number of prodromal AD clinical trials and the global efforts to slow\stop the progression of the disease in the early stages, one of the main goals of our program was to improve the detection of MCI and recruitment of prodromal AD patients. According to the scientific data showing that the use of only one neuropsychological test often over-estimates abnormality, resulting in sub-optimal specificity, we utilized the combination of the MMSE and the AVLT supported by the interview with patient and informant as an effective method of detecting Alzheimer's dementia and MCI due to AD. The data collected by Lachner and Engel [16] reveal that memory task that uses delayed retrieval with distraction may differentiate best the demented

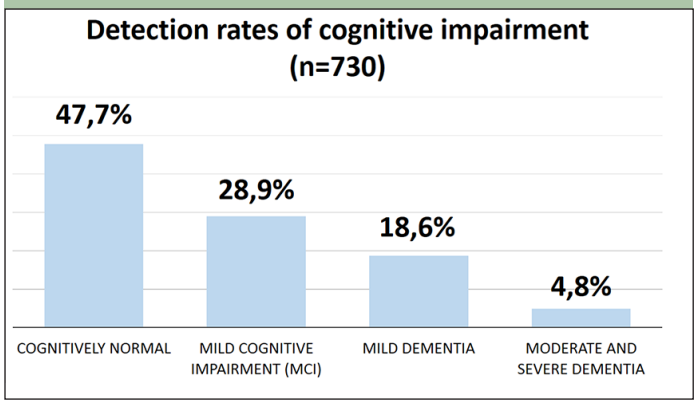
from depressed patients. Moreover, also Vuoksimaa et al. (16) pointed at there is a potential for improving the detection of MCI by requiring more than one episodic memory measure and AVLT seems to be quite practical and cost-effective in both clinical and research settings. Interestingly, the results of their study in prodromal AD patients show a significantly higher risk of conversion to AD of AVLT- individuals at the 3-year follow-up than AVLT+ individuals. Accordingly, conversion rates were 50.9% for the AVLT- group, but only 16.5% for the AVLT+ group (17). The AVLT is a useful tool in detection of MCI and prediction of its progression to dementia. It is also optimal in balancing sensitivity and specificity in clinical settings (18).

The Rey's AVLT is widely spread, brief and easy to use tool for evaluating verbal learning and memory, including proactive inhibition, retroactive inhibition, retention, encoding versus retrieval, and subjective organization (18). It requires the subject to learn a 15-item word list which an examiner reads aloud at the rate of one per second over five trials (List A, Trials 1-5), then to recall that list after a short period (Trial 6) during which another 15-item word list (List B) is presented once for recall; again recall List A after 20-30 minutes of additional testing (Delayed Recall). Eventually, the patient identifies as many of the 15 words as possible when presented with them in the context of a longer list of words (Recognition) (19, 20). It is approximately 10 to 15 minutes required for the test procedure (not including 30 minutes interval). The AVLT has been proven helpful and effective neuropsychological marker of AD dementia and MCI due to AD, and valuable tool for differentiating between the preclinical phase of Alzheimer's disease, mild cognitive impairment and normal aging (21). Furthermore, it is noteworthy that patients with probable AD and probable subcortical ischemic vascular dementia (SIVD) can be also distinguished with a high degree of accuracy by recognition memory subtest of the Rey's AVLT (21). Unfortunately, there is a lack of population-based norms for AVLT. In our program we use norms created by Ivnic et al. (20) as support for qualitative evaluation of the patient's performance conducted by our experienced geriatric neuropsychologist, focusing especially on the recognition subtest of the AVLT as a crucial factor in cognitive decline due to the AD. We are aware of the limitations of this method but we are also certain that it could be a very useful tool for the psychologist specialized in neurodegenerative diseases in clinical evaluation of cognitive function.

Results

The total number of subjects examined in the open screening program conducted in 2018-2019 in Wroclaw Alzheimer's Center was 730 (N=730). The data were collected from January 1, 2018, to May 20, 2019. The mean age of the participants was 71,7 years. Due to our research, the detection rates in the screened population were 0,7% for severe dementia, 4,1% for moderate dementia, 18,6% for mild dementia, and 28,9% for MCI. Less than half of the screened population – 47,7% - were evaluated as cognitively normal. We investigated the proportion of people with MCI and dementia who were eligible for clinical trials. The number of individuals with mild dementia and MCI screened in prodromal and mild AD clinical trials was 248 (34% of all individuals). Furthermore, 63 from 730 (8,6%) patients were randomized in clinical trials, which includes 4,9% MCI and 3,7% mild dementia cases screened in our program, with a 74,6% screen failure (SF) rate, which is typical result for AD clinical trials. Moreover, 19,9% of patients with mild dementia, and 17,1 % of individuals with MCI detected during the program were randomized in prodromal and mild AD clinical trials.

Figure 1. The detection rates of cognitive impairment in the studied population (n=730)



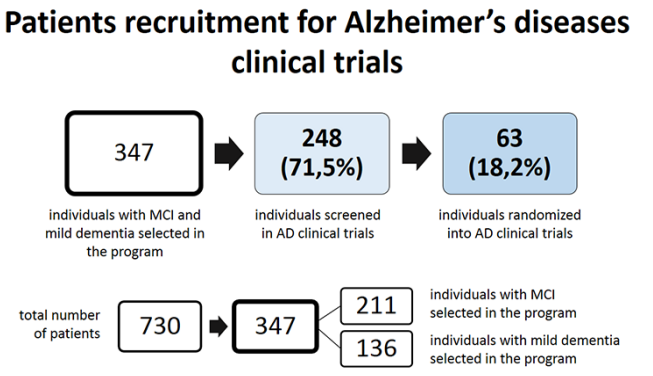
More interestingly, from 347 patients classified in our open-access screening programs as those with MCI or mild dementia, as many as 248 individuals were screened in AD clinical trials, which is 71,47%. Moreover, 63 from 347 individuals selected from our program as MCI or mild dementia patients were randomized into the clinical trials, which is 18,16% of the selected group which means that as much as over 18% individuals selected in open-access screening program as cognitively impaired (MCI or mild dementia) were randomized into prodromal and mild AD clinical trials, and as much as 71,47% were eligible for screening for clinical trials. This numbers shows how important and effective in improving recruitment of the participants to AD clinical trial the open screening programs could be.

Discussion

Summarizing, open-access screening programs can improve detection of MCI and dementia in society, help to distinguish demented from non-demented elderly, and improve recruitment of prodromal AD patients who would probably not have come to the memory clinic otherwise. The weakness of the study is the lack

of measure collecting the functional impairment of the patient. The information gathred were based on the caregiver interview which were our choice because of the cost and time reasons. Likewise, we tried to limit the number of tools used in our open screening program to create a cost-effective and relatively quick method of screening patients which prevented us from using more complex and valuable methods such as CDR (Clinical Dementia Rating), FAQ (Functional Activities Questionnaire), ADCS-ADL (Alzheimer's Disease Cooperative Study Activities of Daily Living), ADAS-Cog (Alzheimer's Disease Assessment Scale–Cognitive Subscale), and RBANS (Repeatable Battery for the Assessment of Neuropsychological Status). Moreover, it is important to point at the lack of the population-based norms for AVLT. Nonetheless, it still can be usefull tool for experienced geriatric neuropsychologist in qualitative evaluation. Our findings may help elucidate the role and importance of the screening process in detecting cognitive impairment in the elderly as an effective and relatively cheap recruitment method in AD clinical trials. There is an urgent need for research focusing on the cost-effectiveness, applicability, and barriers of different recruitment strategies. It is noteworthy that the improvement of clinical trial recruitment strategies, including open screening programs can result in more rapid drug development.

Figure 2. The number and percentage of patients screened and randomized into prodromal and mild Alzheimer's disease clinical trials selected from the open-access screening program



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Conflicts of interest: There are no conflict of interest.

Ethical standards: This work was conducted in accordance with the principles set fourth by the Declaration of Helsinki. All volunteers gave written iformed consent before participating.

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