RESEARCH ARTICLE

Could verbal fluency predict the response or remission to anti-depressants in geriatric depression? Rat onale and protocol of the predict age study

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Aims: Geriatric depression is a heterogeneous disorder that is characterized by altered emotional and language processing, due to deficits in frontal lobe functioning. Verbal fluency (VF) is associated with dorsolateral prefrontal cortex functioning and related to executive processes, semantic memory, speed of information processing, and initiation. A few studies suggested that VF score may predict antidepressant response or remission, but the results are limited, especially in geriatric population. The PREDICT age project is an exploratory pilot study that aims to determinate if VF score may be a potential predictive factor of response or remission in geriatric depression.

Methods: Forty-two patients of 60 years of age and older, with a diagnostic of unipolar depression, will receive an antidepressant medication, undergo neuropsychological battery and will be followed-up during ten weeks.

Results: Primary outcome measure will be the capacity of the VF score to predict response or remission to antidepressant. The secondary aim will be to determinate whether other factors (depression severity, age of onset of depression, number of previous episodes, inflammatory level, and other cognitive abilities) could be potential predictive factors of response or remission to antidepressants.

Key Words: *Cognition; Depression; Geriatric psychiatry; Prediction; Treatment outcome*

INTRODUCTION

Major Depressive Disorder (MDD) is a widespread psychiatric disorder associated with high rates of morbidity and mortality and may lead to impaired quality of life [1]. In older adults, the prevalence of MDD is estimated to be between 2% and 10%, while mild form is found to be present in 20% to 30% [2]. To manage major depressive episode, a large variety of psychotropic medications is available but raises issues about the most appropriate therapy for each patient. This point is crucial in geriatric population because response or remission rates decrease with each line of treatment and increase the risk of exacerbation of pre-existing somatic comorbidities, loss of autonomy, and suicide. Choosing an appropriate therapy for an older adult with MDD could be facilitated by the identification of predictive factors of response or remission to antidepressants. A recent systematic review of the potential predictive factors of response or remission to antidepressants in geriatric population has identified sociodemographic, clinical, neurobiological, neurocognitive and genetic parameters [3]. Poor social network, poor level of functioning, and poorly self-rated health have been proposed as possible predictors of poor response or poor remission. Among the clinical characteristics, a higher intensity of depression at baseline and a comorbid anxiety were found to be the best predictors of nonresponse or non-remission, and an early change in symptom severity during the first 4 weeks was associated with higher rates of response or remission. Morphological studies suggested an important predictive role of white matter hyper intensities (WMH) in antidepressant response. Some researchers reported that WMH in the Anterior Cingular Cortex (ACC), in the region of the basal ganglia and the pontine reticular formation, or a global burden of WMH predicted nonresponse or non-remission. However, results are conflicting because other investigators have found no significant correlations between WMH burden and response to antidepressants. The pathophysiology of depression implicates the functioning of different cerebral structures such as the prefrontal cortex, the ACC or the basal ganglia. These structures are involved in emotion regulation and cognitive control, and it is assumed that WMH could impair connectivity between cortical and subcortical regions [4]. In depressed older adults, decreased metabolic activity at rest has been observed in the dorsal ACC and in the dorsolateral prefrontal cortex (DLPFC) during episodes of depression.4 Moreover, the higher prevalence of executive dysfunction and impaired processing speed were assumed to be linked to front striatal abnormalities [4]. These two neurocognitive factors seem to be particularly relevant in the course of depression in older adults and many authors found that they were predictors of poor remission to antidepressants [5]. Some studies have suggested that patients presenting these symptoms were part of a subgroup that is less likely to respond to antidepressants and particularly to serotonin-selective reuptake inhibitors. In older populations, a reduced processing speed was found to be a predictor of non-remission after 12 weeks of sertraline [6].

Verbal Fluency (VF) is a common short neuropsychological test and is widely used to assess cognitive functioning in psychiatric disorders.11 VF tasks (i.e., semantic and phonemic fluency) involves generating as many words as possible in a limited amount of time. It requires verbal ability, semantic memory, attention, processing speed and executive functioning as this task relies on efficient organization of verbal retrieval and recall, effortful-self-initiation, inhibition of responses already given or inappropriate responses [7]. This task is associated to DLPFC functioning and involves the left inferior frontal gyrus since it is associated with both phonologic and semantic operations in functional neuroimaging studies. Many authors observed that depressed patients showed significantly attenuated activations in the left prefrontal cortex or in cingulate regions during a verbal fluency task when compared to control subjects [8]. Another study found that verbal fluency task was correlated with decreased dopaminergic activity within the striatum and was the strongest predictor of fluoxetine response [9,10].

In the current study, the main aim is to assess pre-treatment VF score as a predictor of response to antidepressant in geriatric unipolar depression. The secondary aim will be to determinate whether other factors (depression

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severity, age of onset of depression, number of previous episodes, inflammatory level, and other cognitive abilities) could be potential predictive factors of response or remission to antidepressants.

METHODOLOGY

Study population

This study will be conducted in a context of an open, prospective comparison of cognitive performances of responders versus non-responders to ten weeks of antidepressant treatment.

The inclusion criteria will be:

- Men or women aged 60 years or older
- Meeting DSM-5 criteria for Major Depressive Episode (as part of unipolar disorder), as determined by a structured clinical interview.

Patients will be recruited from three psychiatric departments in the Franche-Comté Region (France).

Subjects will be excluded if they met diagnostic criteria for dementia, primary psychotic or schizoaffective disorder, bipolar disorder, current non-stabilized medical illness and drug or alcohol disorder within the last three months.

After participants have been provided with a complete description of the study, written informed consent will be obtained from each participant.

Follow-up measures

We will follow the participants during ten weeks after inclusion. Depression severity will be assessed by MADRS score at 1 (visit 2), 2 (visit 3), 4 (visit 4), 6 (visit 5) and 10 weeks (visit 6) after inclusion (Figure 1).

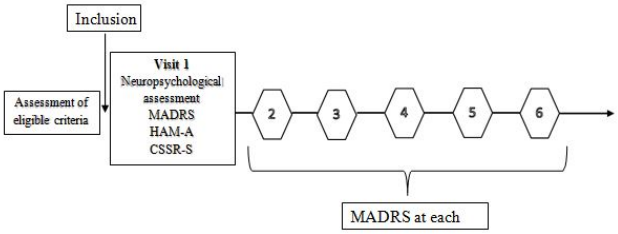

Figure 1) *Study flow diagram*

Statistical analyses

Patients will be considered as responders to antidepressant if their MADRS score decreases by 50% or more between baseline and the end of treatment.

Primary outcome will be the capacity of the VF score (semantic, phonologic, simple or alternated VF) to predict antidepressant response or remission. To determine this capacity, we will use Receiver Operating Characteristic (ROC) curves analysis (with two target variables: response/remission to antidepressants versus no response/remission to antidepressants) to determine the area under the curve (AUC) and the relationship between sensitivity and 1-minus specificity for each possible cutoff of VF. In case we find an AUC>0.8 for the VF score, the test will be considered as a good predictor of response/remission. The null hypothesis will be an AUC=0.5.

Secondary outcomes will be analyzed with the same statistical method as for the primary outcome. The predictive or non-predictive value of each of the secondary criteria will be studied independently on the response to treatment.

A descriptive analysis of all variables (clinical, biological, and neuropsychological) at each time will be performed. The analysis of the qualitative and ordinal variables will include the size and frequency of each modality. Quantitative variables will include the mean, standard deviation, median and extreme values.

Depending on the statistical power of the study, a multivariate analysis (logistic regression analysis) of the treatment response will be performed in order to study the weight of each factor relative to the others. The model will be adjusted for age, sex and level of education. In addition to the first statistical indicators, the logistic regression will provide the Odds Ratio (OR) of the verbal fluency score depending on whether it will be coded as a quantitative or qualitative variable associated with the response.

All analyses will be performed by the clinical investigation center of the University Hospital of Besancon. The software SAS for Windows version 9.4 and MedCalc version 15 will be used.

Safety and ethical considerations

The investigators will collect and report all serious adverse events to the trial sponsor and to the pharmacovigilance department of our institution.

The study protocol was approved by an independent ethic committee.

RESULTS

Primary outcome measure will be the capacity of the VF score to predict response or remission to antidepressant. The secondary aim will be to determinate whether other factors (depression severity, age of onset of depression, number of previous episodes, inflammatory level, and other cognitive abilities) could be potential predictive factors of response or remission to antidepressants.

DISCUSSION

Depending on the statistical power of the study, a multivariate analysis (logistic regression analysis) of the treatment response will be performed in order to study the weight of each factor relative to the others. The model will be adjusted for age, sex and level of education. In addition to the first statistical indicators, the logistic regression will provide the Odds Ratio (OR) of the verbal fluency score depending on whether it will be coded as a quantitative or qualitative variable associated with the response.

All analyses will be performed by the clinical investigation center of the University Hospital of Besancon. The software SAS for Windows version 9.4 and MedCalc version 15 will be used.

CONCLUSION

In light of the high burden of depression and the increased morbi-mortality in geriatric population, the need to prescribe an efficacious antidepressant from the first-line treatment is evident. Very few studies have examined the correlation between VF score at baseline and response to antidepressants, and these results are therefore limited. The present trial is innovative since it aims to determine whether VF scores may be a potential predictive factor of response or remission to antidepressants in a poorly studied population.

We expect the present study to contribute to research in the geriatric depression field. In case of positive results, a study with a larger sample size would be conducted in order to confirm the outcomes. If many potential predictive factors are highlighted, combining these factors to predict the response/remission to antidepressants would also be considered, which might help clinicians identify the treatment that leads to remission.

TRIAL STATUS

At the time of manuscript submission, participant recruitment was not completed. The inclusion started on March 2017 and the trial is ongoing.

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AUTHOR CONTRIBUTIONS

All the authors contributed to the conception and design of this article.

DISCLOSURE STATEMENT

None declared.

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