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# VORTIOXETINE VERSUS SSRIs FOR THE TREATMENT OF DEPRESSION IN THE ELDERLY: A PRAGMATIC RANDOMIZED CLINICAL TRIAL

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# ABSTRACT

**Background.** Depression is among the leading causes of disability in older adults. In the elderly, selective serotonin reuptake inhibitors (SSRIs) are considered effective and generally safer compared to other classes of antidepressants, such as tricyclics. Nevertheless, older people are particularly vulnerable to adverse events. Vortioxetine is a novel antidepressant, licenced for depression in 2013. Existing data on vortioxetine suggest that it should not negatively affect cognitive performance and electrocardiogram parameters. It showed to be effective compared to placebo and as effective as SNRIs. To our knowledge randomized controlled trials comparing vortioxetine to SSRIs, the current usual care for depressed elderly, are lacking.

**Objectives.** The study assessed if, under real-world clinical circumstances, vortioxetine is better tolerated as compared with the SSRIs in elderly participants with depression.

**Methods.** We conducted a randomized, parallel-group, multicentre, open-label, pragmatic, superiority trial funded by the Italian Medicines Agency (AIFA - Agenzia Italiana del Farmaco). Twelve Italian Community Psychiatric Services consecutively enrolled elderly participants suffering from an episode of major depression over a period of 12 months. Participants were assessed at baseline and after 1, 3 and 6 months of follow-up. The primary outcome was the rate of participants withdrawing from treatment due to adverse events after six months of follow-up. At each time point, the following secondary outcomes were assessed: effectiveness, quality of life, cognitive performance, comorbidities and side effects. Outcome assessors and the statistician were masked to treatment allocation. EudraCT number: 2018-001444-66; Clinicaltrials.gov: NCT03779789. The present thesis is an interim analysis of the partial sample collected till October 2020.

**Results.** During 2019 and the first nine months of 2020 we screened 90 inpatients, of which 67 met the inclusion criteria, gave written consent and were consequently randomized to vortioxetine or SSRIs (37 and 30 respectively. By the end of 2020, the study should have included 358 participants, however the first and second pandemic waves have not allowed to recruit participants as planned, and therefore recruitment is still ongoing. This analysis is based on the first 67 enrolled participants. At endpoint three participants in the vortioxetine group discontinued medication due to AEs versus 7 in the SSRIs group (9.09 vs. 24.14%), a difference that is not statistically significant ($p = 0.17$). At one month, discontinuation rates due to AEs were significantly different,

being higher in patients receiving SSRIs than vortioxetine (20.67 vs 3.03%, p value= 0.04), with an odds ratio (OR) of 8.09 (95% confidence interval ZZ to ZZ). There were no differences in the secondary outcomes between the two groups of interventions.

**Discussion.** This innovative study will provide head-to-head comparisons for well-established antidepressant treatment options in elderly patients with depression. The preliminary analysis presented here is extremely promising, as it suggests a potentially beneficial effect of vortioxetine over the SSRIs in terms of tolerability profile. However, the pandemic period has significantly decreased the recruitment rate, making the present findings unpowered to provide firm conclusions. For this reason, recruitment is still ongoing, aiming to reach the target sample size by the end of 2021. To our knowledge this is the first study that directly compared vortioxetine with SSRIs. The results of this study will be easily generalizable, thanks to its highly pragmatic nature.

Summary

# 1. BACKGROUND

## 1.1 Epidemiology

Depression is among the most disabling conditions worldwide [1]. In half or more of the cases of depression in elderly, it may arise as a first episode in old age, representing a new condition (late onset depression), and in less than a half of cases patients experienced the first episode of depression before the old age [2].

Depression occurs in about 7% of elderly in the community [3, 4] and in up to 49% of persons admitted to nursing homes and hospitals worldwide [5, 6]. According to a report of a survey conducted between 2015 and 2017 in Italy by the Italian Institute of Statistics, it has been estimated that the prevalence of depression in the elderly population exceeds the European average, reaching almost 25% according to population-based studies [7, 8]. Rates of depression appear to be higher in older women than in older men [7, 9], however the rates of elderly committing suicide are 4 times higher in men compared to woman.

A systematic review and meta-analysis of observational studies identified the most common risk factors for depression among elderly community subjects. Disability, new medical illness, poor health status, prior depression, poor self-perceived health, and bereavement [10] were risks factors identified by multivariate analyses in at least two studies. In the quantitative meta-analysis significant risk factors were female gender, bereavement, sleep disturbance, disability and prior depression [7, 10]. The Italian survey conducted between 2015 and 2017 estimated that the prevalence of depression triples in elderly with low education compared to higher educated people [7].

As mentioned, prevalence of depression is higher among older adults are substantially higher in particular subsets of this population, including medical outpatients (5-10%, though estimates vary widely), medical inpatients (10-12%), and residents of long term care facilities (14 to 42%) [9, 11].

There is also an increased risk of morbidity among elderly with depression [2] and depression rates are markedly elevated in those individuals with other medical conditions. This translates reduced adherence to medical treatments, therefore in reduced life expectancy, poorer medical outcomes [12] and increased mortality [11].

Moreover, in elderly people, depression is associated with poor quality of life with decreased physical functioning, high risk of suicide [13] and of cognitive decline and dementia [14].

Depression is among the leading causes of disability-adjusted life years in the world and a serious public health problem among older adults [15]. Compared to people with other chronic conditions, those with depression or anxiety reported more often to have consulted the general practitioner (at least once a year 93.1% versus 85.6%) as well as the specialist (75.2 versus 64.2%) [2].

## 1.2 Clinical presentation

The diagnosis of depression is based on some criteria, regardless of the age of the patients. In table 1 are shown the diagnostic criteria according to the fifth edition of the diagnostic and Statistical Manual of Mental Disorders (DSV-V).

Table 1. Major depressive disorder criteria according to the DSM-V [16]

| **Five or more of the following A Criteria (at least one includes A1 or A2)** | |
|---|---|
| A1 | Depressed mood—indicated by subjective report or observation by others (in children and adolescents, can be irritable mood) |
| A2 | Loss of interest or pleasure in almost all activities—indicated by subjective report or observation by others |
| A3 | Significant (more than 5 percent in a month) unintentional weight loss/gain or decrease/increase in appetite (in children, failure to make expected weight gains) |
| A4 | Sleep disturbance (insomnia or hypersomnia) |
| A5 | Psychomotor changes (agitation or retardation) severe enough to be observable by others |
| A6 | Tiredness, fatigue, or low energy, or decreased efficiency with which routine tasks are completed |

| | |
|---|---|
| A7 | A sense of worthlessness or excessive, inappropriate, or delusional guilt (not merely self-reproach or guilt about being sick) |
| A8 | Impaired ability to think, concentrate, or make decisions—indicated by subjective report or observation by others |
| A9 | Recurrent thoughts of death (not just fear of dying), suicidal ideation, or suicide attempts |
| The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. | |
| The symptoms are not due to the direct physiological effects of a substance (e.g., drug abuse, a prescribed medication's side effects) or a medical condition (e.g., hypothyroidism). | |
| There has never been a manic episode or hypomanic episode. | |
| MDE is not better explained by schizophrenia spectrum or other psychotic disorders. | |
| The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation). | |

Depression in the elderly is defined by the same criteria of major depression in other age groups. However, some clinical features seem to be associated more often with older age as compared to younger patients. The most common clinical presentation of depression in the elderly is with sleep disturbance, fatigue and psychomotor retardation, loss of interest in living, and hopelessness about the future [17]. Subjects also complain about poor memory and concentration, and lower cognitive processing speed and executive dysfunction are frequent when tested [18].

## 1.3 Treatment of depression in the elderly

In the general population of individuals with depression, selective serotonin reuptake inhibitor (SSRIs) are considered effective and safe [19].

In the elderly, SSRIs are considered effective and generally safer compared to other classes of antidepressants, such as tricyclics (TCA) [20]. Therefore they are recommended by most guidelines as first-choice treatment for older adults [21-23]. However, the elderly may be particularly vulnerable to adverse events due to several reasons.

First of all, the process of aging is accompanied by a progressive reduction in the function of various organ systems, with consequent changes in pharmacokinetics, which lead to a high risk of pharmacological interactions [24, 25]. In particular, the most significant modification in pharmacokinetics comprise drug elimination, either through hepatic metabolism and/or renal excretion. The progressive decline of hepatic metabolism and renal function can reduce the elimination of several drugs, for which a dose adjustment is needed in most of the cases.

Second, modifications in the pharmacodynamics in the elderly also have a relevant effect and often lead to a reduction of the required dosage. The mechanism is not fully understood yet and studies are generally conducted on small samples [26, 27], but the hypothesis is that there are some changes in the neurotransmission systems, hormone levels, glucose metabolism and cerebrovascular circulation that may contribute to a an increased pharmacodynamic sensitivity to drugs acting in the central nervous system [28]. For these reasons older patients are likely to need a lower dose than younger patients.

Pharmacodynamic changes can partially explain why, even when prescribed with lower doses, elderly have an increased risk of AD-related adverse drug reactions (ADRs) [29].

The most common adverse events associated with SSRIs in the elderly include hyponatraemia, postural hypotension, gastrointestinal bleeding, sexual dysfunctions and cardiovascular effect specifically for citalopram [30, 31]. The risk of hyponatraemia is increased with the concomitant use of

SSRIs and diuretics [29]. The increased risk of gastrointestinal bleeding in the elderly seems to be partly related to the antiplatelet effect of SSRIs to which they may be more susceptible [29]. Moreover, adverse events may occur more often due to drug interactions in this particular group of people, in which polypharmacy is quite common [32] due to comorbidities.

Regardless of the possible safety issues in elderly, SSRIs are considered first choice agents, as alternatives are lacking in this special population, considering that tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and mirtazapine carry a higher risk for a number of adverse events, including sedation, confusion, urinary retention, cardiovascular and gastrointestinal issues [30].

### 1.4 Vortioxetine

Vortioxetine is a novel antidepressant, licensed for the treatment of depression in 2013 by FDA and EMA [33, 34]. Vortioxetine is an antagonist to 5-HT3, 5-HT1D and 5-HT7 receptors, a partial agonist to the 5-HT1B receptor and a 5-HT1A receptor agonist [35]. Its mechanism of action is not fully understood yet, but it is likely to be related with both a direct modulation of the serotoninergic receptor activity and an inhibition of the serotonin transporter. Despite similarities with SSRIs, its pharmacological profile is claimed to be novel, and it is classified among "other antidepressants" by the World Health Organization (WHO) ATC/DDD Index 2018 [36]. Vortioxetine has similar pharmacokinetic properties in young and older adults [33], the clearance of vortioxetine does not appear to be affected by age nor mild to moderate hepatic or renal impairment appears to impact the clearance of vortioxetine, that does not require dose adjustments based on these parameters [37].

Existing data on vortioxetine suggest it should not adversely affect psychomotor or cognitive performance, wakefulness, body weight, and electrocardiogram parameters [37, 38]. Further, possible, beneficial effects on cognition emerged from three randomized trials in participants with cognitive impairment [39]. A recent Cochrane systematic review, which

included 15 randomized trials (7746 participants), showed vortioxetine to be effective compared to placebo, while no significant differences emerged between vortioxetine and SNRIs as a class, in terms of both efficacy and tolerability [40]. The review did not include any study comparing vortioxetine with the SSRIs, but a recent network meta-analysis showed that vortioxetine is well tolerated and effective when indirectly compared to SSRIs [41]. Moreover, in two recent randomized trials, vortioxetine did not show significant differences on both mood and cognitive performance when compared to paroxetine [42] and escitalopram [43], respectively. The only available trial conducted in the elderly reported vortioxetine as more effective than placebo in terms of responders (301 participants, relative risk 1.49, 95% Confidence Interval (CI) 1.14 to 1.95), while no differences emerged in terms of tolerability [44].

To our knowledge randomized controlled trials comparing vortioxetine to SSRIs, the current usual care for depressed elderly, have not been conducted yet [20, 45].

## 2. OBJECTIVES

The study assessed if, under real-world clinical circumstances, vortioxetine is better tolerated as compared with the SSRIs in elderly participants with depression. In addition to tolerability, secondary outcomes the study assesses acceptability, overall mortality, self-harm and suicide, adverse events, improvement of depressive symptoms, quality of life, and cognitive performance.

## 3. METHODS AND ANALYSIS

This study has been reported accordingly to the CONSORT statements requirements. [46]. The complete CONSORT checklist (extension for pragmatic trials version) is available in appendix 2 [47]. This trial has been registered: EudraCT number: 2018-001444-66; Clinicaltrials.gov: NCT03779789 and a protocol has been published [48].

### 3.1 Study design overview

The present thesis is an interim analysis of the VESPA (Vortioxetine in the Elderly vs SSRIs: A Pragmatic Assessment) study. The VESPA study is a randomized, parallel-group, multicentre, open-label, pragmatic, superiority trial. Over a 12-month recruitment period, psychiatrists from twelve Italian Psychiatric Services were consecutively enrol in- and outpatients aged 65 or more suffering from an episode of major depression and requiring treatment with an antidepressant. Participants were randomly allocated to vortioxetine or to one of the SSRIs. Apart from treatment allocation, clinicians and patients were free of increasing or decreasing the dose according to clinical status and circumstances, as well as of stopping or continuing treatment as clinically indicated. Similarly, the use of concomitant medications during the study was allowed according to clinical status and circumstances. Routine care outside the trial continued as usual. During the study, participants were seen as often as clinically indicated with no extra visits required for the trial. The only requirement was follow-up visits at one, three, and six months of follow-up (Figure 1).

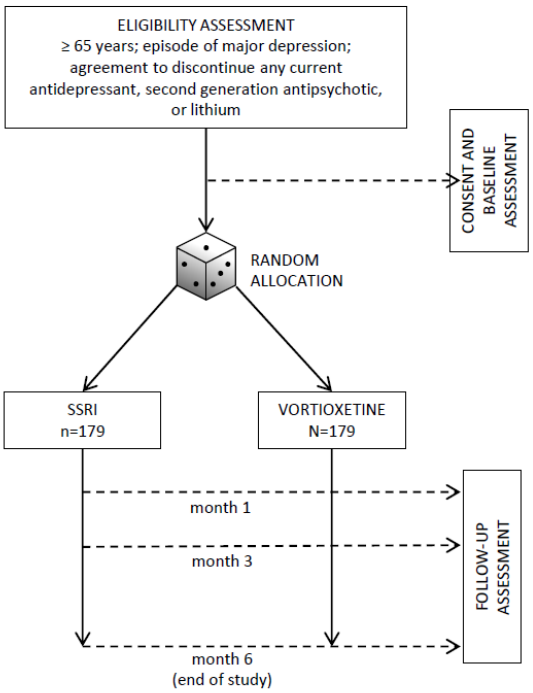


Figure 1. Study flow-chart.

Legend: RF=recruitment form; FUF=follow-up form; MADRS=Montgomery–Åsberg Depression Rating Scale; UKU=Udvalg for Kliniske Undersogelser Side Effect Rating Scale; EQ-5D=EuroQual 5 Dimensions

As a consequence of these pragmatic characteristics oriented to resemble clinical practice as much as possible, both patients and clinicians were not blind to pharmacological treatments provided during the trial. Blinding was applied to outcome assessors and statisticians performing the analyses. The study has been designed according to the principles described in the CONSORT statement (extended version for pragmatic trials) [47] (see Appendix 1). The study was financially supported by the Italian Medicines Agency (AIFA - *Agenzia Italiana del Farmaco*) and has already been approved by the Ethics Committee for Clinical Research of Verona and Rovigo (*Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo*) (prot. n. 61211 of the 19/09/2018; Protocol version n. 1.5 of the 09/06/2018).

### 3.2 Assessment of pragmatism

To quantify the level of pragmatism of our study, we employed the pragmatic–explanatory continuum indicator summary-2 (PRECIS-2) [49]. This is a validated tool, developed to help investigators make design decisions consistent with the intended purpose of their trial. It explores nine domains (eligibility criteria, recruitment, setting, organisation, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis), for each of which a score from 1 (very explanatory) to 5 (very pragmatic) is provided. The result is graphically summarized in Figure 2.

| | |
|---|---|
| Eligibility | 4 |
| Recruitment | 5 |
| Setting | 4 |
| Organization | 4 |
| Flexibility Delivery | 5 |
| Flexibility Adherence | 4 |
| Follow-Up | 4 |
| Primary Outcome | 5 |
| Primary Analysis | 5 |

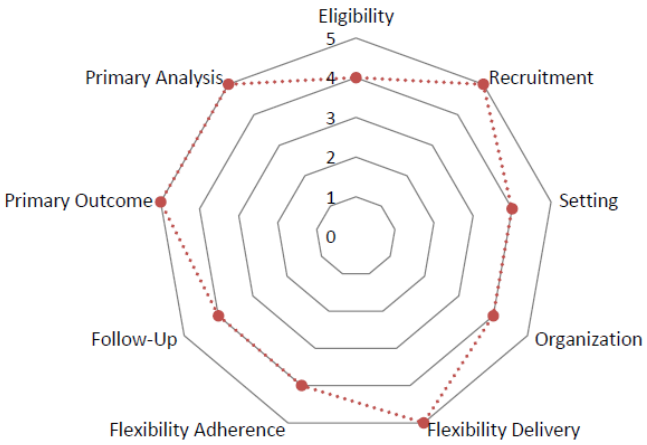


Figure 2. Pragmatism wheel according to the PRECIS-2 tool

Reasons for the scoring are reported in Table 2. A routine use of the PRECIS-2 tool when submitting RCT protocols to funders, research ethics committees and peer-reviewed journals, has been growingly recommended, considering that not all RCTs self-labelled as "pragmatic" or "naturalistic" are actually pragmatic. This process can also help understand the extent to which trial results may be relevant to real-world practice [50].

Table 2. Scoring of PRECIS-2 tool.

| Items | Score | Rationale |
|---|---|---|
| **Eligibility -** to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care | 4 | Target population: Elderly with depression. Inclusion criteria are wide. No exclusion criteria were applied in terms of setting of recruitment, severity of depression, past use of psychotropic drugs, current use of benzodiazepines, number and severity of medical comorbidities, and multiple pharmacotherapy. Diagnosis are based on clinical judgment (guided by DSM-5 criteria), as it is in usual practice. Nevertheless, investigator and patient have to agree to discontinue any current antidepressant, second generation antipsychotic, or lithium. |
| **Recruitment** - how much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients? | 5 | Participants were recruited without extra efforts. They will be recruited during usual appointments and/or visits. |
| **Setting -** how different is the setting of the trial and the usual care setting? | 4 | The study is multicenter, based in more than 10 psychiatric centers of the National Health System in Italy with a University center. |
| **Organisation** - how different are the resources, provider expertise and the organisation of care delivery in the intervention arm of the trial and those available in usual care? | 4 | We used usual staff and resources, but some extra resources were necessary to hire researchers for the study. |
| **Flexibility (delivery) -** how different is the flexibility in how the intervention is delivered and the flexibility likely in usual care? | 5 | The intervention is flexible, similar to usual care. |
| **Flexibility (adherence) -** how different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care? | 4 | No extra measures. Participants were free to assume the intervention or drop it, but drugs were prescribed and given to the participants during visits. This was different from usual care (patients have a prescription and go to the pharmacy to buy drugs). |

| | | |
|---|---|---|
| **Follow-up** - how different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care? | 4 | The primary outcome was assessed after 1, 3 and 6 months, as it is usually done in everyday practice. Six months represent a clinically sound time frame for assessing the overall tolerability of medications, including both acute, short-term and medium-long-term effects. Nevertheless, visits could be longer than usual to assess all the scales and long-term effects and adverse events could occur after 6 months. |
| **Primary outcome** - to what extent is the trial's primary outcome relevant to participants? | 5 | Primary outcome is relevant to participants and policy makers. |
| **Primary analysis** - to what extent are all data included in the analysis of the primary outcome? | 5 | The Intention to Treat (ITT) population will consist of all randomized patients. This ITT population will be used for the analysis of both primary and secondary outcomes. Missing values in rating scales will be imputed using the Last Observation Carried forward (LOCF) approach. |

PRECIS 5-point Likert Scale score: (1) Very Explanatory; (2) Rather Explanatory; (3) Equally Pragmatic/Explanatory; (4) Rather Pragmatic; (5) Very Pragmatic

## 3.3 Participants

The following inclusion criteria were applied:

a. The participant is 65 years old or above;
b. The participant is willing to participate by signing an informed consent form;
c. The participant is suffering from an episode of major depression, based on clinical judgment (guided by DSM-5 criteria);
d. Treatment with an antidepressant is appropriate, based on clinical judgment;
e. There is agreement between investigator and participant to discontinue any of the following concomitant drugs: antidepressant, second generation antipsychotic, or lithium. All other concomitant medications are allowed;
f. Uncertainty about which trial treatment would be best for the participant.

Participants were be excluded in case of:

a. Dementia, of any type and stage, as formally diagnosed by a specialist (geriatrician, neurologist, or others);
b. Diagnosis of schizophrenia or bipolar disorder;
c. Clinical conditions or treatments that contraindicate the use of oral vortioxetine or SSRIs, according to clinical/medical judgment (for example conditions or treatments that increase risk of bleeding, seizures, serotoninergic syndrome, hyponatraemia, etc.).

All medications were prescribed according to routine clinical practice, in compliance with the Summary of Product Characteristics (SPC) registered in the AIFA databank (https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/home).

No exclusion criteria were applied in terms of setting of recruitment, severity of depression, past use of psychotropic drugs, current use of benzodiazepines (as long as SPC indications are respected), number and severity of medical comorbidities, and multiple pharmacotherapy. Such criteria selected participants similar to those who require antidepressant treatment under usual care, including patients with multiple medical comorbidities. The recruitment was pragmatic, as participants were selected among people attending inpatient and outpatient community services. There was no overt recruitment effort. Also, allowing different recruitment settings, having multiple sites of recruitment, and selecting patients similar to those who are treated in every day clinical practice, increases the generalizability of trial results. To control for a potential risk of excessive heterogeneity between centres, the randomization was stratified by centre. According to these features, the PRECIS-2 “setting” domain has been evaluated as pragmatic.

### 3.4 Interventions

Patients were randomized to either vortioxetine or one of the SSRIs. Doctors were free to choose which SSRIs is more appropriate among those marketed in Italy and commonly used in clinical practice in the elderly

(sertraline, citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine). A flexible dosing schedule, within the licensed dose range and in line with the summary of product characteristics (SPC), was suggested (Table 3) in order to resemble clinical practice as much as possible.

Table 3. Treatments and dosing schedule

| **Medication** | **Licensed dose range in the elderly** | **Notes from the registered Summary of Product Characteristics** |
|---|---|---|
| vortioxetine | 5 – 20 mg/day | The minimum effective dose of 5 mg vortioxetine once daily should always be used as an initial dose for participants aged ≥ 65 years. Caution should be exerted when prescribing to elderly participants at doses above 10 mg vortioxetine once daily. |
| sertraline | 50 – 200 mg/day | Caution is required in the elderly, because these patients may be at greater risk of hyponatraemia. |
| paroxetine | 20 – 40 mg/day | In the elderly, increased plasma concentrations of paroxetine have been reported, however within the range observed in younger subjects. The treatment should start at the same doses used in adults. |
| citalopram | 10 – 20 mg/day | In the elderly, half of the dose range prescribed in adults is required. |
| escitalopram | 5 – 10 mg/day | In the elderly, half of the dose range prescribed in adults is required. |
| fluoxetine | 20 – 60 mg/day | Caution is required when the dose is increased in the elderly, and generally the daily dose should not be above 40 mg/day. The maximum recommended dose is 60 mg/day. |
| fluvoxamine | 100 – 300 mg/day | In elderly participants, titration should be slower, and the dosage should always be established with caution. |

Formulation choice (tablets versus drops) were made by clinicians and participants following everyday practice, and no measures will be implemented to optimise treatment adherence.

According to the PRECIS-2 "flexibility-delivery" and "flexibility-adherence" domains, treatment delivery has been rated as pragmatic,

although a full score of 5 could not be reached as we were formally required to follow the EU pharmacovigilance regulation [51, 52].

### 3.5 Outcome measures

The primary outcome of this study was the number of participants withdrawing from allocated treatment due to adverse events at the end of the study (6 months). This measure may be considered a pragmatic proxy of tolerability [53] as it occurs when adverse events actually reach an unbearable burden, as perceived by patients and/or relatives and/or carers and/or clinicians. Antidepressant treatment were considered withdrawn due to adverse effects when the drug is stopped for more than two consecutive weeks following the occurrence of any adverse event, based on clinical judgment and/or as reported by participants. Participants were additionally evaluated after also one and three months from randomization, collecting relevant clinical information and assessing scales, as showed in table 3. Side effects responsible for treatment withdrawal, and their severity, were recorded the follow-up form and an *ad hoc* form for Severe Adverse Events (SAE).

Secondary outcomes included:

1. acceptability: withdrawals from allocated treatment due to any cause (this outcome measure included withdrawals for side-effects plus withdrawals for any other issues);
2. overall mortality;
3. any episode of deliberate self-harm;
4. suicide mortality;
5. adverse events, measured as the mean change in scores at the Antidepressant Side-Effect Checklist (ASEC) [54] at each time point. ASEC is a validated rating scale measuring the occurrence and severity of 21 antidepressant adverse events;
6. response to treatment, defined as a reduction of at least 50% of the baseline score of the Montgomery–Åsberg Depression Rating Scale

(MADRS) [55] at each time point. MADRS is a validated, ten-item questionnaire for assessing the severity of depression;

7. efficacy, measured as mean change scores at MADRS at each time point;
8. quality of life, measured as mean change scores of the self-administered scale EQ-5D,[56], at each time point. EQ-5D explores five areas, including mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and assesses the overall subjective perception of health with an analogic scale;
9. cognitive performance, measured as mean change scores of the Short Blessed Scale (SBT) [57],at each time point. SBT is a validated, six-item weighted instrument, originally designed to identify dementia, which assesses orientation, registration, and attention.

Rating scales to assess the secondary outcomes were administered by blind assessors at one, two and three months after randomization. In addition, the Charlson Age-Comorbidity Index (CACI) [58] was employed. This is a validated rating scale used to evaluate the degree of medical comorbidity, and to predict the 10-year survival in participants with multiple comorbidities. All study tools and phases are shown in Table 3.

Table 4. Study phases and tools

| **Procedures and tools** | **T0 Enrolment phase (duration: 12 months)** | **T1 (1 month)** | **T2 (3 months)** | **T3 (6 months)** |
|---|---|---|---|---|
| Review of criteria for inclusion in the study | X | | | |
| Informed consent document signed | X | | | |
| Randomization (allocation to treatment and number assigned) | X | | | |
| Recruitment Form | X | | | |

| | | | | |
|---|---|---|---|---|
| ASEC | | X | X | X |
| MADRS | X | X | X | X |
| EQ-5D | X | X | X | X |
| CACI | X | X | X | X |
| SBT | X | X | X | X |
| Follow-up form | | X | X | X |
| Severe Adverse Event (SAE) Form | | any time | | |

### 3.6 Safety

The VESPA study operatively employed the definitions endorsed by the EC Directive 2001/20/EC,[59]. As soon as a severe adverse event occurs, an *ad hoc* form for Severe Adverse Events (SAE) was filled in and forwarded to the coordinating centre (University of Verona), in accordance with the EU regulation about pharmacovigilance in clinical research [51]. If, for any reasons, the disadvantages of participation appeared to be significantly greater than foreseen, the Principal Investigator of the site informed trial participants and the bodies providing ethical oversight.

Considering that the study medications were already in the Italian market and considering that they were prescribed for licensed indications without altering clinical practice, the VESPA study did not appoint an ad hoc data safety and monitoring committee.

### 3.7 Sample size calculation

Considering the differential rate of withdrawals due to adverse events between SSRIs and vortioxetine on the basis of a meta-analysis of antidepressants for older people [20] and of three clinical trials of vortioxetine in older patients with depression [42, 43, 45] we expected the vortioxetine group to show a clinically significant advantage by reducing this rate from about 17% [20] to about 5% [42, 43, 45]. A sample size of 276 participants (138 in each group) achieves 90% power to detect a difference of 12% between the two withdrawal proportions in favour of

vortioxetine. The test statistics was the two-sided Z test with pooled variance. The significance level of the test is targeted at 5%. Based on the above-mentioned studies, we assumed that about 23% of the participants could be lost within 6 months (the mean of the total dropout rates of vortioxetine and SSRI studies in the elderly). Therefore 358 participants (179 in each group) will be enrolled in order to obtain at least 276 evaluable subjects. The sample size calculation was performed according to the methodology described by Pocock [60]. For the purpose of this thesis we performed an interim analysis with the sample of participants recruited till the 1st of October 2020.

### 3.8 Randomization

Participants were randomly assigned to vortioxetine or SSRIs with an allocation ratio of 1:1. A centralized web-based randomization procedure was employed to guarantee the concealment of allocation. The trial biostatistician prepared the sequence of treatments randomly permuted in blocks of constant size. The site investigators did not know the block size. Allocation was stratified by recruiting centre. By using the web-based application RedCap [61], investigators were able to screen participants for inclusion, administer instruments maintaining the blindness to treatment allocation, and randomize them.

### 3.9 Data management

At baseline, before randomization, and after one, three and six months, a number of socio-demographic and clinical information were collected, along with the administration of the above-mentioned validated rating scales (MADRS, EQ-5D, CACI, SBT, ASEC). All data on other medications were registered at every visit. The ASEC scale was administered only during follow-up.

All study data are collected with RedCap and digitally stored by the *Istituto di Ricerche Farmacologiche Mario Negri IRCCS*, a not-for-profit biomedical research organization based in Milan (Italy), where also the

statistical analysis will be performed on the final sample. Analyses of the partial sample were performed by the PhD candidate and discussed with the supervisor.

RedCap allows an immediate data validation at the moment of data collection. Moreover, a set of electronic and manual edit checks is performed. The local coordinator of each recruiting centre will store and safely preserve hard copy documents (signed informed consent and self-administered questionnaires) for at least 7 years after the end of the study, according to the Italian law. At the end of the study the full dataset will be made available upon motivated request as a spreadsheet file in an online repository (e.g. Dryad Digital Repository). This is in line with FAIR principles [62], aimed at enhancing the accessibility and reutilization of novel research data.

The accuracy and completeness of data collection is monitored by site visits. At least one visit for each recruiting centre is planned. Furthermore, auditing is be also carried out remotely, as the data manager of the study is able to regularly check the trial dataset through the web application RedCap.

### 3.10 Statistical Analysis

As this thesis is an interim analysis of a partial sample of the VESPA study some adjustments to the statistical analyses were made, as compared to the ones that will be performed on the total sample described in the protocol of the study [48].

According to the pragmatic principle of intention-to-treat (ITT), efforts were made to follow each participant until the end of the study. The ITT population consists of all randomized participants and is used for the analysis of both primary and secondary outcomes. The odd ratio (OR) of the primary outcome is calculated on the ITT population. Subjects with missing primary outcome data were allocated to the worst outcome. When possible, in addition to the primary analysis, appropriate statistical methods were planned to adjust for the potential confounding effect of prognostic factors (sex, age, living condition, severity of comorbid medical conditions,

MADRS score at baseline). Missing rating scales scores were imputed using the Last Observation Carried forward (LOCF) approach: ratings were carried forward from the last available assessment to the 6-month follow-up assessment.

As previously mentioned, this work analysed a partial sample of the VESPA study, which is still ongoing. At each time point we included all participants that were recruited and reached that time point.

The primary outcome was, consequently, analysed based on the endpoint data for each participant, meaning the latest assessment available when statistical analyses were performed (October 1st 2020). Secondary analyses were performed at one, three and six months.

The proportion of participants withdrawing from the study due to adverse events within 6 months of follow-up were compared between the two groups of treatment using a logistic regression with centre (random variable) as a covariate in the whole sample. For the partial sample Fisher exact test was used, as the frequency of the event was lower than 5. Subjects withdrawing for reasons not related to adverse effects will be excluded from the analysis.

For dichotomous secondary outcomes, the proportion of participants withdrawing from the study due to adverse events within 6 months were compared between the two groups of treatment using a Fisher exact test. For continuous secondary outcomes, the 6-month estimate were compared between the two groups of treatment with a Wilcox test or a Welch t-test, according to the variable's distribution (normally or not normally distributed).

Adverse events were tabulated and descripted. Nominal value for statistical significance was be set at 0.05, two-tailed. All analyses were performed using Rstudio version 1.3.1056 (© 2009-2020 RStudio, PBC)

### 3.11 Ethics and dissemination

This study was conducted according to globally accepted standards of good clinical practice, as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996, in agreement with the Declaration of Helsinki [63] and in keeping with local regulations. The recruiting investigators obtained informed consent. All participants were informed about the study procedures and aims, both verbally and by written documentation. The subject's consent was confirmed by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussion. Participants could withdraw from the study at any time without further explanation or any negative consequences. Participants' data were managed and safeguarded in accordance with the European Data Protection Regulation 2016/679 [64]. The highly pragmatic design minimized the time deduction to ordinary clinical practice. An Ethics Advisory Board (EAB) indirectly supervised the processes of recruitment, informed consent procedures, and data management (protection and privacy), taking into due account the vulnerability of the population. Once the final report will be available, the study results will be extensively disseminated to the international scientific community in the form of peer-reviewed journal articles, giving preference to open-access journals.

The study was financially supported by the AIFA and has already been approved by the Ethics Committee for Clinical Research of Verona and Rovigo (*Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo*) (prot. n. 61211 of the 19/09/2018; Protocol version n. 1.5 of the 09/06/2018).

# 4. RESULTS

## 4.1 Recruitment

Recruitment started on February 2019 at the coordinating center of Verona. To date (October 2020), study recruitment is ongoing in Verona, Catanzaro, Milano Bicocca, Rome, L'Aquila and Ferrara.

The COVID-19 pandemic over the past few months introduced several challenges for all clinical trials, including our study, mainly with regard to trial enrollment. In February 2020, following the Government and hospital guidance at the time of the first lockdown, study recruitment was temporarily paused. Additionally, public health measures related to COVID-19, including quarantine and lockdown, had a tangible impact on the study flow for the already enrolled patients at different study sites. Hereafter, we explored options to efficiently minimize the COVID-19 impact on our study. The implementation of feasible alternatives for follow-up assessments, such as telehealth-based practices, was accelerated and allowed for clinical visits to resume fairly soon. Remote data collection rapidly took over for those participants who were already enrolled in the study, to minimize the impact of the pandemic. However, recruitment had to stop and wait till the lockdown ended, therefore we acknowledged such modifications in the study protocol, as agreed with AIFA. Further, some of our participants got COVID-19 infection, and one of them (in the vortioxetine group) was admitted to a dedicated ward in severe conditions, and this made it impossible to gather data on the main and secondary outcomes. After the recruitment halt was lifted in June, we were allowed to recruit anew, although in-person visits were reduced in many centers and substituted with remote visits when possible. Moreover, evidence from study sites worldwide suggest the COVID-19 outbreak substantially affected the willingness of patients to continue study participation, but also the willingness of new patients to enroll in the study [65]. Likewise, this trend slowed the pace of our study recruitment requiring adjustments of study timeline. Despite delays for study enrolment and challenges regarding

patient retention, our continuous efforts to avoid study disruption without compromising safety and health of study participants and investigators at all study sites were successful.

As of October 1st 2020 we had recruited 67 patients; 34, 11, 11, 6, 4 and one patient had been recruited in Verona, Catanzaro, Rome, Milano Bicocca, Ferrara and L'Aquila respectively, as shown in figure 4.

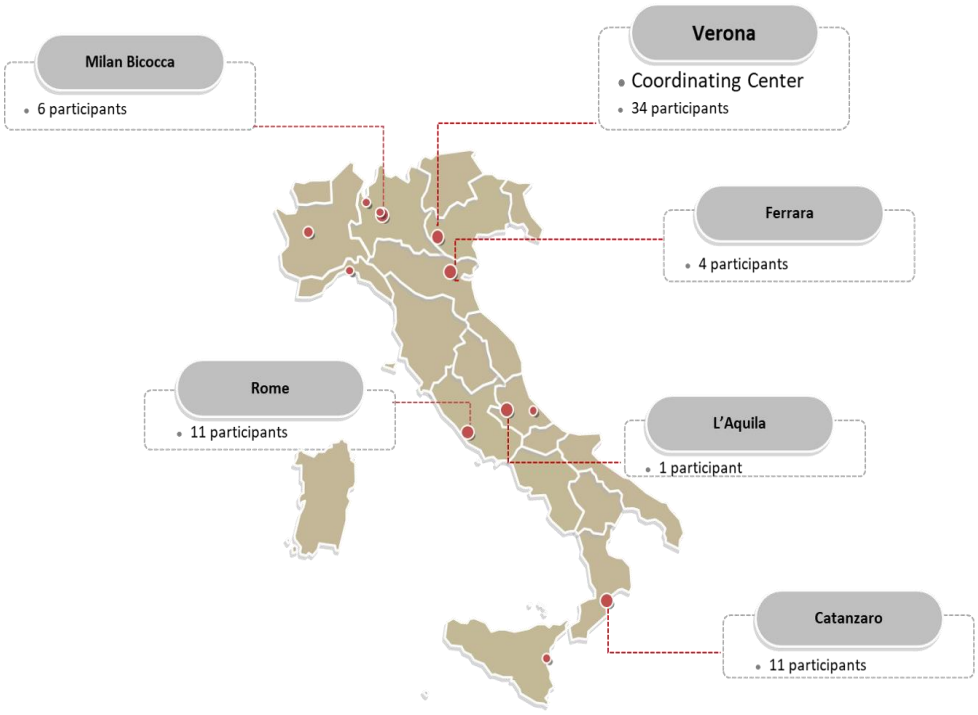


Figure 3. Map of the VESPA centres, recruitment status.

### 4.2 Participant flow and number analysed

During 2019 and the first nine months of 2020 we screened 90 inpatients, of which 67 met the inclusion criteria, gave written consent and were consequently randomized to vortioxetine or SSRIs (37 and 30 respectively). Figure 3 provides the flow diagram of the recruitment process.

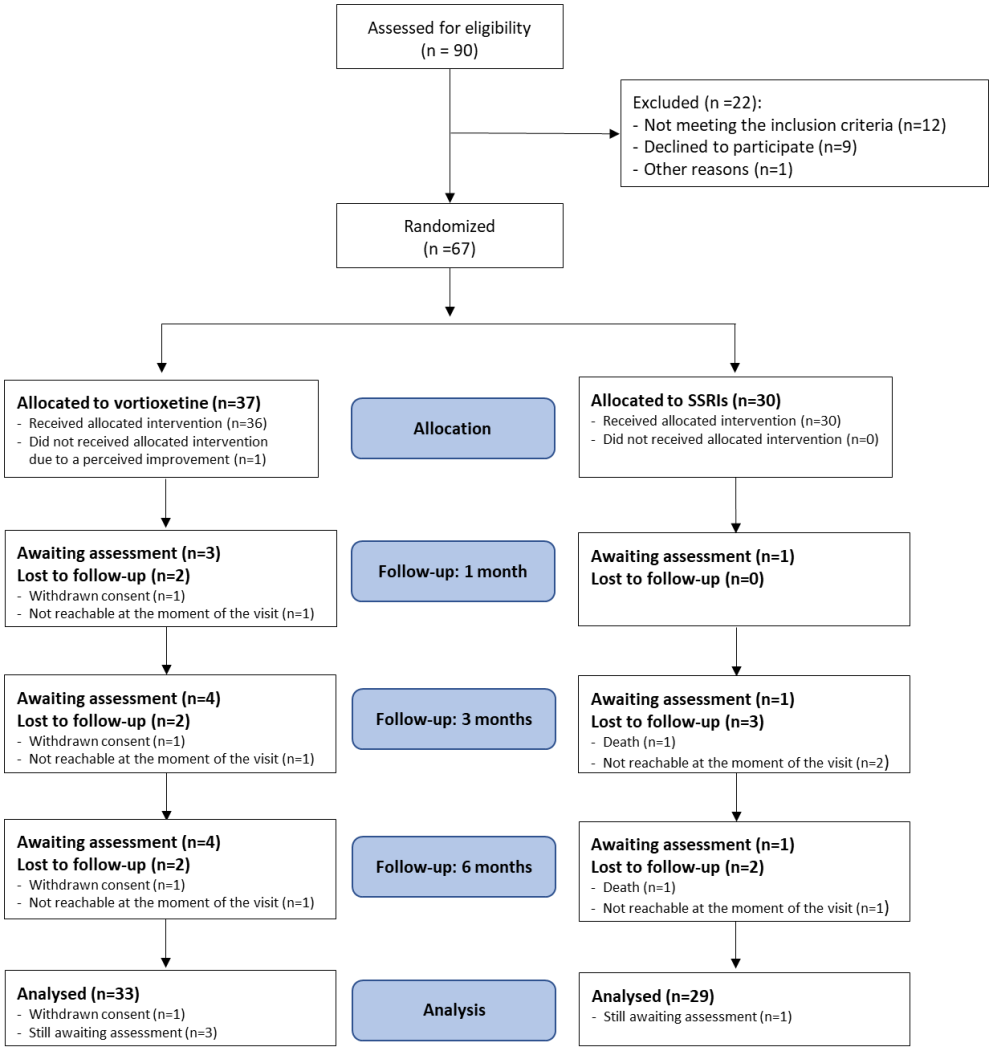


Figure 4. CONSORT flow diagram

Footnote 1: the study is still ongoing, so some patients did not have completed due assessments, but they are not missing.

The primary analysis was conducted on the basis of the intention-to-treat (ITT) principle. As the study is still ongoing and some participants did not complete all the three follow-ups yet (at one, three and six months). We, consequently, performed the analysis on the ITT population with the currently available data. The ITT population was therefore different at each time-point. As shown in figure 3, 62 participants reached the one month assessment of the study (33 for vortioxetine and 29 for SSRIs), 54 the three months one (27 each) and 52 the six months (26 each). One patient assigned to vortioxetine withdrawn consent at the first follow-up, therefore he was

excluded from the analyses, all other participants that reached each time point were included, without any other exclusion.

Details on each time point are described below. At one month one participant (assigned to vortioxetine) refused to complete the assessment, but we were able to retrospectively retrieve data on the main outcome (discontinuation) and some secondary outcomes (comorbidities, CACI), but not on MADRS, SBT and ASEC, as this patient accepted to complete the three and six months assessments afterwards.

At three months one participant assigned to SSRIs committed suicide, but we retrieved information on the main outcome. Moreover, one patient assigned to vortioxetine and two assigned to SSRIs did not completed the assessment. For two of them we retrieved information on the main outcome (1 SSRIs, 1 vortioxetine), but for one (SSRIs assigned) it was impossible to retrieve data as -due to COVID-19 disease- he was admitted with a severe respiratory condition to a specialized ward. Another patient (SSRI allocated) withdrawn consent at three months but gave consent to use data collected till that moment.

At six months, one patient assigned to SSRIs died for the progression of a pre-existing disease and did no completed the assessment, but data on the main outcome were retrieved trough the family doctor and the relatives.

### 4.3 Baseline data

The mean age of the sample was 73.85 years old (standard deviation, sd= 5.28) and 73.1% of the participants were females. Table 5 shows the baseline characteristics of the participants in the two groups. There were no differences between the two study groups with regard to any of the demographic characteristics.

Table 5. Baseline characteristics of study groups

| | **Vortioxetine** (n=37) | **SSRIs** (n=30) | p-value |
|---|---|---|---|
| Age (mean ± sd) | 73.19 ± 5.43 | 74.67 ± 5.07 | 0.25 |
| Female (n, %) | 26, 70.3% | 23, 76.7% | 0.59 |
| Married status (n married, %) | 20, 54.05% | 14, 46.67% | 0.80 |
| Living with: (n, %) | | | 0.42 |
| Alone | 13, 35.1% | 8, 26.7% | |
| With family | 24, 64.9% | 21, 70% | |
| With an assistant | 0, 0% | 1, 3.3% | |
| Working: (n, %) | | | 0.43 |
| Employed | 2, 5.4% | 1, 3.3% | |
| Unemployed | 3, 8.1% | 0, 0% | |
| Retired | 32, 86.5% | 29, 96.7% | |
| Years of school education (mean, sd) | 8.56± 4.31 | 6.93 ± 3.12 | 0.098 |
| MADRS total score (mean ± sd) | 28.19 ± 6.47 | 29.93 ± 6.93 | 0.3 |
| EQ5D total score (mean ± sd) | 49.14 ± 18.5 | 46.33 ± 22.82 | 0.86 |
| CACI total score (mean ± sd) | 4.24 ± 1.61 | 4.5 ± 1.94 | 0.44 |
| CACI diabetes (n, %) | 6, 16.22% | 7, 23.3% | 0.7 |
| CACI epatopatia (n, %) | 2, 5.4% | 3, 10% | 0.65 |
| CACI neoplasia (n, %) | 1, 2.7% | 2, 6.7% | 0.58 |
| CACI infarto (n, %) | 2, 5.4% | 2, 6.7% | 1.00 |
| SBT total score (mean ± sd) | 3.78 ± 5.57 | 4.67 ± 5.55 | 0.26 |

CACI: Charlson Age-Comorbidity Index; EQ5D: EuroQol – 5 Dimension; MADRS: Montgomery–Åsberg Depression Rating Scale; SBT: Short Blessed Scale; SD: standard deviation; SSRI: Selective Serotonin Reuptake Inhibitor.

Mean baseline MADRS scores were 28.19 (sd=6.47) and 29.93 (sd= 6.93) for patients assigned to vortioxetine and SSRIs, respectively. The baseline

total SBT scores were 3.78 (sd=5.57) and 4.67 (sd=5.55) for the vortioxetine and SSRIs group, respectively.

Table 6 shows the mean target doses and mean titration time for each antidepressant that was prescribed at baseline. The mean target dose prescribed of vortioxetine at baseline was 6.53 mg (sd=2.34), ranging from 5 mg to 10 and the mean titration duration was 4.52 days (sd=4.75). Participants assigned to SSRIs were prescribed sertraline in 22 patients with a mean target dose of 50 mg and a mean titration duration of 7.78 days (sd=4.06), citalopram in 4 patients with a mean target dose of 20 mg and a mean titration duration of titration of 7.75 days (sd=1.5), paroxetine and escitalopram in two patients each with a mean target dose of 20 and 7.5 mg respectively and a mean duration time of titration of 3.5 (sd= 4.95) and 10.5 (sd=4.95) days respectively.

Table 6. Mean daily doses and mean time to titrate for each antidepressant prescribed at baseline.

| **Drug** | **N, %** | **Mean target dose ± sd (mg)** | **Mean time to titrate ± sd (days)** |
|---|---|---|---|
| **Vortioxetine** | **37, 100%** | 6.53 ± 2.34 | 4.52 ± 4.75 |
| **SSRIs** | **30, 100%** | - | - |
| Sertraline | 22, 73.3% | 50 ± 0 | 7.78 ± 4.06 |
| Citalopram | 4, 13.3% | 20 ± 0 | 7.75 ± 1.5 |
| Paroxetine | 2, 6.7% | 20 ± 0 | 3.5 ± 4.95 |
| Escitalopram | 2, 6.7% | 7.5 ± 3.54 | 10.5 ± 4.95 |

sd: standard deviation; SSRI: Selective Serotonin Reuptake Inhibitor.

As shown in table 7, at one month the mean dose of vortioxetine was 7.05 (sd=2.46), at three months 9.17 (2.89) and at six 10 (2.67). at one, three and six months respectively the mean dose (and sd) for sertraline was 58.33 (15.43), 67 (20.58) and 60.56 (23.11). For citalopram it was 20 (sd=0), for paroxetine 20mg (0) and for escitalopram 10 mg (0) at all three time points.

Table 7. Daily dose characteristics

| | **At one month** | | **At three months** | | **At six months** | |
|---|---|---|---|---|---|---|
| **Drug** | **N** | **mean dose ± sd (mg)** | **N** | **mean dose ± sd (mg)** | **N** | **mean dose ± sd (mg)** |
| **Vortioxetine** | 28 | 7.05 ± 2.46 | 21 | 9.17 ± 2.89 | 15 | 10 ± 2.67 |
| **SSRI** | | | | | | |
| Sertraline | 15 | 58.33 ± 15.43 | 10 | 67 + 20.58 | 9 | 60.56 + 23.11 |
| Citalopram | 3 | 20 ± 0 | 2 | 20 ± 0 | 2 | 20 ± 0 |
| Paroxetine | 2 | 20 ± 0 | 1 | 20 | 1 | 20 |
| Escitalopram | 1 | 10 | 1 | 10 | 1 | 10 |

sd: standard deviation; SSRI: Selective Serotonin Reuptake Inhibitor.

### 4.4 Outcomes and estimation

Primary outcome

Survival rates at baseline, one, three and six months are provided in figure 5.

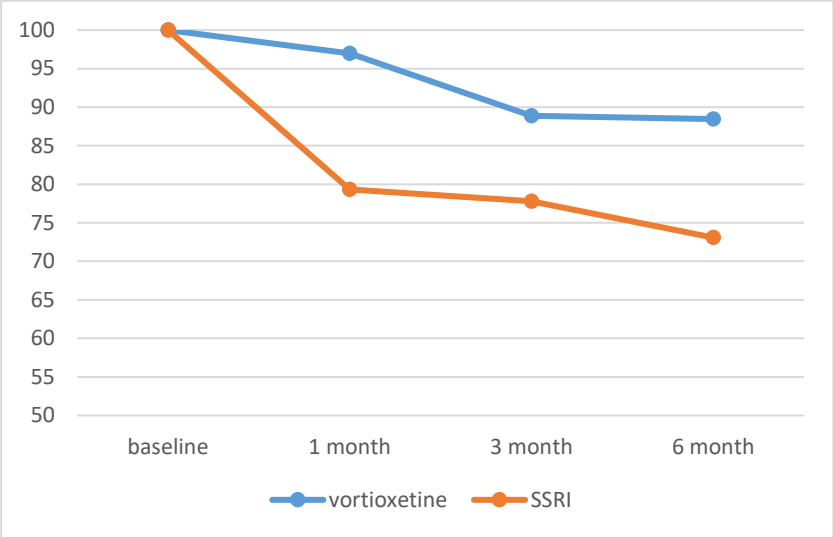


Figure 5. Survival rate of the probability of continuing antidepressants from baseline to six months in the vortioxetine and SSRI groups.

The main outcome, dropouts due to AEs was measured at endpoint, meaning at six months for patients who already completed the study or the at latest observation available for patients still awaiting six months assessment. At endpoint three participants in the vortioxetine group discontinued medication due to AEs versus seven in the SSRIs group (9.09 vs. 24.14%, p=0.17 for Fisher's exact test). We estimated an OR of 3.12 (95% CI 0.63 to 20.82) of discontinuing medication due to AEs in the SSRIs group compared to the vortioxetine group (table 8).

The AEs that caused discontinuation were confusion, vertigo and glaucoma for vortioxetine, and constipation, vertigo, fatigue, nausea/vomit, confusion, hypertension for the SSRIs. Other AEs reported by at least one patient without leading to discontinuation were hypertension, diarrhoea, nausea, chest pain, anxiety, sweating, constipation, xerostomia and headache for vortioxetine and nausea, sweating, vertigo, tremor, insomnia and itch for

SSRIs. With the exception of nausea, which was reported by two patients in the vortioxetine group and two in the SSRIs group, each AE was reported by one patient.

As secondary outcomes we assessed the number of participants withdrawing due to inefficacy or any other reason (acceptability). At endpoint six participants in the vortioxetine group and four in the SSRIs group (18.18% vs 13.79%) discontinued the drug due to inefficacy (OR 0.64, 95% CI 0.11 to 3.19, p-value=0.73 for Fisher's exact test) or for the rates of drop-outs due to any reason (total drop-out) (OR 1.4, 95% CI 0.43 to 4.61, p-value=0.6 for Fisher's exact test). Table 8 shows the number of participants that discontinued for any reason in the two groups and in total.

Table 8. Number of withdrawal participants in each group due to AEs, inefficacy and other reasons (n, %) at endpoint.

| | **SSRIs (29, 100%)** | **Vortioxetine (33, 100%)** | **OR (95% CI)** | **p value** | **Total (62, 100%)** |
|---|---|---|---|---|---|
| **AEs** | 7 (24.14) | 3 (9.09) | 3.12 (0.63 to 20.82) | 0.17 | 10 (16.13) |
| **Inefficacy** | 4 (13.79) | 6 (18.18) | 0.64 (0.11 to 3.19) | 0.73 | 10 (16.13) |
| **Other reason** | 0 (0.0) | 1 (3.03) | na | na | 1 (1.61) |
| **For any reason** | 11 (37.93) | 10 (30.30) | 1.4 (0.43 to 4.61) | 0.6 | 21 (33.87) |

AE: adverse event; CI: confidence interval; na: not assessed; OR: odds ratio; SSRI: Selective Serotonin Reuptake Inhibitor.

Analyses were repeated at all three time points: at one, three and six months.

- Dropouts at one month

As shown in table 9, at one month the number of participants withdrawing from allocated treatment due to AEs was 1 and 6 in the vortioxetine and SSRIs group respectively (3.03 vs 20.67%) (OR 8.09, 95% CI 0.89 to 394.85, p-value= 0.04 for Fisher's exact test). At one-month participant who discontinued vortioxetine reported having confusion, vertigo and worsening of the glaucoma. The six participants discontinuing SSRIs reported having, constipation (n=1), vertigo (n=1), nausea (n=2), fatigue (n=2), hypertension (n=1).

Other reported AEs in the vortioxetine group were: nausea (n=3), hypertension (n=2), sweating (n=2), anxiety (n=1) diarrhoea (n=1), constipation (n=1) hypertension and chest pain (n=1), xerostomia and headache (n=1). In the SSRIs group: vertigo (n=2), insomnia (n=2) nausea (n=1), sweating (n=1), itching (n=1), tremor (n=1).

No patients discontinued due to inefficacy in the first month of follow-up and one patient assigned to vortioxetine never received the drug, reporting a clinical improvement of the depressive symptoms.

Table 9. Number of withdrawal participants in each group due to adverse events, inefficacy and other reasons (n, %) at one month.

| | **SSRIs (29, 100%)** | **Vortioxetine (33, 100%)** | **OR (95% CI)** | **p value** | **Total (62, 100%)** |
|---|---|---|---|---|---|
| **AEs** | 6 (20.67) | 1 (3.03) | 8.09 (0.89 to 394.85) | 0.04 | 7 (11.29) |
| **Inefficacy** | 0 (0.0) | 0 (0.0) | na | na | 0 (0.0) |
| **Other reasons** | 0 (0.0) | 1 (3.03) | na | na | 1 (1.61) |
| **For any reason** | 6 (20.67) | 2 (6.06) | 2.48 (0.63 to 10.95) | 0.22 | 8 (12.90) |

AE: adverse event; CI: confidence interval; na: not assessed; OR: odds ratio; SSRI: Selective Serotonin Reuptake Inhibitor

- Dropouts at three months

At three months the number of participants withdrawing from allocated treatment due to adverse events was 3 and 6 respectively in the vortioxetine and SSRIs group (11.11 vs 22.22%). This difference was not statistically significant (OR 2.25, 95% CI 0.41 to 15.66, p-value= 0.46 for Fisher's exact test). AEs that led to discontinuation were increased restlessness (n=1) and weight loss (n=1) for vortioxetine, whereas for SSRIs they did not differ from the one-month ones.

Other reported AEs were: somnolence (n=1), sweating (n=1), headache (n=1) in the vortioxetine group and itching (n=1), neck pain (n=1), sedation (n=1), hyperglycaemia (n=1) in the SSRIs group.

There were one and three patients in the Vortioxetine and the SSRIs group respectively discontinuing due to inefficacy at three months (3.70 vs 11.11%) (OR 1.28, 95% CI 0.23 to 176.87, p-value 0.61 46 for Fisher's exact test). The difference between the two groups in the total dropouts was not statistically significant (OR 2.48, 95% CI 0.63 to 10.95, p-value= 0.22 46 for Fisher's exact test).

Data on three months discontinuation rates are reported in table 10.

Table 10. Number of withdrawal participants in each group due to AEs, inefficacy and other reasons (n, %) at three months.

| | **SSRIs (27, 100%)** | **Vortioxetine (27, 100%)** | **OR (95% CI)** | **p value** | **Total (54, 100%)** |
|---|---|---|---|---|---|
| **AEs** | 6 (22.22) | 3 (11.11) | 2.25 (0.41 to 15.66) | 0.46 | 9 (16.67) |
| **Inefficacy** | 3 (11.11) | 1 (3.70) | 3.18 (0.24 to 176.87) | 0.6 | 4 (7.41) |
| **Other reasons** | 0 (0.0) | 1 (3.70) | Na | na | 1 (18.52) |
| **For any reason** | 9 (33.33) | 5 (18.52) | 2.48 (0.63 to 10.95) | 0.22 | 14 (25.93) |

AE: adverse event; CI: confidence interval; na: not assessed; OR: odds ratio; SSRI: Selective Serotonin Reuptake Inhibitor

- Dropouts at six months

At 6 months (table 11) three participants in the vortioxetine group and 7 the SSRIs group discontinued due to AEs (11.54% vs 26.92%, OR 2.77, 95% CI 0.53 to 18.88, p-value=0.29 for Fisher's exact test). AEs leading to discontinuations were the same reported in the other time-points. Other reported AEs were somnolence, epigastralgia, dysuria, vertigo, worsening of the chronic bronchitis symptoms, sweating each reported by one patient in the vortioxetine group and fatigue, headache, somnolence for SSRIs.

Six people discontinued due to inefficacy in the vortioxetine group and four in the SSRIs (23.08% vs 15.38%, OR 0.64, 95% CI 0.11 to 3.19, p-value=0.73 for Fisher's exact test). The total number of dropouts was 10 vs 11 (38.46% vs 42.31%) respectively for vortioxetine and SSRIs (OR 1.2, 95% CI 0.43 to 4.61, p-value= 0.6 for Fisher's exact test).

Table 11. Number of withdrawal participants in each group due to AEs, inefficacy and other reasons (n, %) at six months.

| | **SSRIs (26, 100%)** | **Vortioxetine (26, 100%)** | **OR (95% CI)** | **p value** | **Total (51, 100%)** |
|---|---|---|---|---|---|
| **AEs** | 7 (26.92) | 3 (11.54) | 2.77 (0.53 to 18.88) | 0.29 | 10 (19.61) |
| **Inefficacy** | 4 (15.38) | 6 (23.08) | 0.64 (0.11 to 3.19) | 0.73 | 10 (19.61) |
| **Other reasons** | 0 (0.0) | 1 (3.84) | na | Na | 1 (2.0) |
| **For any reason** | 11 (42.31) | 10 (38.46) | 1.2 (0.43 to 4.61) | 0.60 | 21 (41.18) |

AE: adverse event; CI: confidence interval; na: not assessed; OR: odds ratio; SSRI: Selective Serotonin Reuptake Inhibitor

Other secondary outcomes

- Overall mortality, suicide and episodes of self-harm

One participant allocated to SSRIs committed suicide before the second follow-up. Compliance to the prescribed medication (paroxetine) in the last month was not clear, and the psychiatrist following her reported that she was concerned about the husband, who was developing symptoms of dementia.

One patient allocated to SSRIs died because of a progression of pre-existent disease (haematological cancer) 5 months after randomization.

There were no self-harm behaviours in any of the two groups.

- Adverse events -ASEC checklist

Adverse events measured as the mean change in scores at the Antidepressant Side-Effect Checklist (ASEC) by a blind assessor confirmed the findings of the main outcome. Table 12 shows that at all three time points the mean score at ASEC was higher for the SSRIs group, with a significant difference at one month (p value=0.01).

Table 12. ASEC score at each time point

| | SSRIs (mean and sd) | Vortioxetine (mean and sd) | p-value |
|---|---|---|---|
| At one month | 9.9 + 5.79 | 6.64 $\pm$ 4.26 | 0.01 |
| At three months | 7.76 + 6.65 | 6.85 $\pm$ 3.72 | 0.98 |
| At six months | 6.35 +5.27 | 5.11 $\pm$ 3.68 | 0.55 |

- MADRS response

Responders were defined as participants having a reduction of at least 50% of the baseline score at each point measured at MADRS. At one month there

were 5 responders in each group, at three months 13 for vortioxetine and 10 for SSRIs and at six months 17 for vortioxetine and 12 for SSRIs (table 13).

There were no statistical differences between groups in terms of responders at any timepoint.

Table 13. Responders at MADRS

| | SSRIs | Vortioxetine | OR (95% CI) | p-value |
|---|---|---|---|---|
| Responders at one month | 5 | 5 | 1.19 (0.23 to 6.31) | 1 |
| Responders at 3 months | 10 | 13 | 0.77 (0.19 to 3.01) | 0.76 |
| Responders at 6 months | 12 | 17 | 0.54 (0.12 to 2.31) | 0.52 |

AE: adverse event; CI: confidence interval; OR: odds ratio; SSRI: Selective Serotonin Reuptake Inhibitor.

- Efficacy- MADRS

We found no difference between groups in terms of efficacy at any endpoint, using the mean MADRS scores at MADRS at six months, showed an improvement in both groups, with a mean of 13.0 (sd=9.12) in the vortioxetine group and of 14.19 (sd=6.78) and this difference was found to be not statistically significant (Welch Two Sample t-test p-value=0.63),a s shown in table 14.

Table 14. Efficacy measured with MADRS mean scores

| | SSRI (mean and SD) | Vortioxetine (mean and SD) | p-value |
|---|---|---|---|
| MADRS at baseline | 29.93 $\pm$ 6.93 | 28.19 $\pm$ 6.47 | 0.3 |
| MADRS at one month | 21.71 $\pm$ 10.9 | 19.45 $\pm$ 9.14 | 0.41 |

| | | | |
|---|---|---|---|
| MADRS at three months | 14.86 ± 7.33 | 14.73 ± 9.42 | 0.85 |
| MADRS at six months | 14.19 ± 6.87 | 13.0 ± 9.12 | 0.63 |

MADRS: SSRI: Selective Serotonin Reuptake Inhibitor.

At one and three months, the mean scores at MADRS were respectively 19.45 (SD 9.14) and 14.73 (SD 9.42) for vortioxetine and 21.71 (sd=10.9) and 14.86 (SD 7.33). No statistically significant differences between groups were detected at each time point (table 14).

Both groups showed an improvement of around 15 points at the MADRS, with baseline MADRS scores indicating moderate depression and follow-up MADRS indicating mild or no depression.

- Quality of life

Quality of life, measured as mean change scores of the self-administered scale EQ-5D at each time point, showed an improvement of 10.68 points for the vortioxetine group and of 8.67 in the SSRIs group, although this difference was found to be not significant (Wilcox test).

Table 15 shows the EQ5D total scores for both groups, which did not differ at any timepoint.

Table 15. Quality of life measured with EQ5D

| | SSRIs (mean and SD) | Vortioxetine (mean and SD) | p-value |
|---|---|---|---|
| EQ5D at baseline | 46.33 ± 22.82 | 49.14 ± 18.5 | 0.86 |
| EQ5D at one month | 48.36 ± 23.50 | 53.0 ± 21.37 | 0.51 |
| EQ5D at three months | 57.00 ± 19.88 | 55.50 ± 22.20 | 0.83 |
| EQ5D at six months | 55.00 ± 16.81 | 60.00 ± 19.79 | 0.42 |

EQ5D: EuroQol 5 Dimension total scores; SSRI: Selective Serotonin Reuptake Inhibitor.

- Cognitive performance (SBT)

The Short-Blessed Scale (SBT) was used to measure the cognitive performance in the participants (table 16). We did not find any difference in the two groups in terms of improvement on cognitive performance (Wilcox test).

Table 16. Cognitive performance at each time point for study groups

| | SSRIs (mean and SD) | Vortioxetine (mean and SD) | p-value |
|---|---|---|---|
| SBT total score baseline | 4.67 $\pm$ 5.55 | 3.78 $\pm$ 5.57 | 0.26 |
| SBT total score at one month | 5.9 $\pm$ 6.64 | 4.13 $\pm$ 6.77 | 0.15 |
| SBT total score at three months | 4.31 $\pm$ 5.56 | 4.26 $\pm$ 7.21 | 0.61 |
| SBT total score at 6 months | 4.58 $\pm$ 6.48 | 3.95 $\pm$ 7.67 | 0.33 |

SBT: Short Blessed Scales; SSRI: Selective Serotonin Reuptake Inhibitor.

# 5. DISCUSSION

## 5.1 Main findings

Here we presented the results of the interim analysis in a subsample of the VESPA study [48]. This is an innovative study that provided head-to-head comparisons for well-established antidepressant treatment options [20]; specifically, elderly patients with depression were assigned to SSRIs or to a new antidepressant, vortioxetine. To our knowledge this is the first study that directly compares vortioxetine with SSRIs [41, 45].

As previously mentioned in detail, the Covid-19 pandemic over the past months introduced a relevant challenge for this clinical trial, reducing our possibility of screening and recruiting participants for the study. The recruitment stopped for several months and therefore at the time this thesis was written the sample and the number of events were smaller than expected. These preliminary results are based on the subsample collected till October 2020.

We did not detect any baseline differences between the two groups with regard to clinical or demographic characteristics.

In terms of tolerability, overall results showed a trend in favour of vortioxetine compared to SSRIs. At endpoint the difference between vortioxetine and SSRIs for the dropout rates due to AEs was not statistically significant; however, this is likely to be related to the small number of participants that were recruited at the time of the analysis. As recruitment is currently ongoing, we expect to reach the target sample size that will provide adequate statistical power. Estimating ORs provided measures of comparisons that were less affected by sample size (ref). Specifically, we estimated that 9.09% in the vortioxetine group versus 24.14 % in the SSRIs group discontinued the medications due to AEs at endpoint. In other words, patients prescribed SSRIs who discontinued medication due to AEs were more than twice as much than patients prescribed with vortioxetine. According to the OR estimated of 3.12 (95% CI 0.63 to 20.82) patients

prescribed SSRIs were threefold more likely to discontinue medication due to AEs compared to patients prescribed vortioxetine.

This result is in line with previous findings from indirect comparisons (network meta-analysis) showing that vortioxetine was better tolerated than other antidepressants, including SSRIs [41]. This result will need to be confirmed in the whole sample, at the end of the VESPA study, which will provide an appropriate power to the analysis.

Of note is also that, intergroup differences for discontinuation rates due to AEs, at one month were statistically significant, being higher in patients receiving SSRIs than vortioxetine (20.67 vs 3.03%, p value= 0.04), with an OR of 8.09 (95%CI 0.89 to 394.85). According to the summary of product characteristics, patients prescribed SSRIs may experience AEs during the first month, and more likely in the first days of treatment (ref- package insert). This result confirms the hypothesis that vortioxetine could have a different pharmacological profile as compared to SSRIs and be better tolerated than them [25, 33, 35, 36, 41]. For the SSRIs as a group the rate of dropouts due to AEs was higher in the first month and then slightly increased in the following months (20.67->22.22->26.92%), whereas for vortioxetine it was lower in the first months and the increase was observed later (3.03-> 11.11->11.54%).

In terms of the type of AEs reported, previous randomized short-term trials (6-8 weeks) [66] addressing the incidence of specific AEs in people with major depression found nausea, diarrhoea, dry month, constipation, vomiting, dizziness and pruritus among the most reported AEs for vortioxetine. The frequency of these AEs was dose-dependent, increasing with higher doses. The most common adverse event was nausea: in 21% of participants at 5 mg/day, 32% at 15 mg and 20 mg/day [66]. Although it was not possible to calculate frequencies, considered the size of our sample and the few number of AEs reported, it is possible to note that the type of AEs reported in our study was in line with previous studies.

No severe AEs were reported nor self-harming behaviours. One completed suicide occurred, but it did not seem to be related to the drug (paroxetine), as the patient was probably not compliant to the medication in the month before suicide.

Another finding was that, in terms of effectiveness, vortioxetine showed no differences as compared to SSRIs. There were no differences in effectiveness between groups both when measured as the difference in the response rate (17 responders for vortioxetine and 12 for SSRIs, OR=0.54, 95%CI 0.12 to 2.31) and when measured with mean score at endpoint. Both groups showed an improvement in the mean score from baseline to endpoint of around 15 points, which is considered clinically highly significant [67, 68].

Same applies to the quality of life, that improved in both groups, without relevant differences between them.

One of our secondary hypotheses was that vortioxetine could have some benefits in terms of cognition, as reported by other studies [38, 39, 69]. The change in the SBT did not show any difference between groups, but rather an overall improvement in the score for both groups. This could be related to the fact that treating depression could indirectly bring a benefit in cognition regardless of the antidepressant class. However, it needs to be noted that SBT might not be a scale sensitive enough to measure such fine differences in cognitive improvements. Therefore it was not possible to confirm or contradict previous findings on the benefit of vortioxetine for cognitive performances [39].

## 5.2 Limitations

Some limitations need to be outlined. First, the COVID pandemic has forced us to stop and slow the screening and recruiting phases. Consequently, these results should be considered preliminary, as recruitment is currently ongoing. These preliminary results are underpowered because of the limited

sample size. Therefore, due to the low frequency of events and the small sample, we planned different analyses as compared to the ones that will be performed in the final sample of the VESPA study. For this thesis, we adapted our analyses to the size of the sample, estimating ORs, which are not affected by the sample size.

Second, according to the current pharmacovigilance regulation of the European Union, medication boxes must be labelled and dispensed by the hospital pharmacy. This deviates from ordinary practice and may have an impact on adherence to medications, reducing or increasing it depending on the organization and location of the hospital pharmacy. In big psychiatric services, in which the hospital is quite far from the residence of the patients, reaching it to collect medication can be hardly feasible. On the other hand, in other centres, in which local pharmacies are not available on the territory, dispensing the medication directly to the patient after the visit, can increase the availability of them, and therefore the adherence. Considering that our study involved five different centres all over the Italian peninsula with different characteristics, we did not observed any specific impact in one or the other direction.

Third, at enrolment the included participants had to discontinue any other antidepressant or second generation antipsychotic before random allocation. We employed this strategy to avoid the potential confounding effect of other psychotropic drugs. Nevertheless, after random allocation any concomitant medication was allowed. This choice aimed at resembling everyday practice, as elderly patients are sometimes prescribed low doses of second generation antipsychotics or antidepressants (e.g. mirtazapine, amitriptyline, trazodone) for insomnia or for other symptoms (e.g. cachexia, cephalalgia, etc.).

Fourth, it can be argued that this study may suffer from performance bias [70]. As the main outcome was not assessed by a blinded clinician, it could have been influenced by personal subjective judgments of the investigators, who, being aware of the treatments received by participants, could have performed differently according to the allocated treatment arms. Although it

is known that open-label design might be associated with the risk of detecting and performance bias, we adopted some strategies to minimize it. First, to minimize detection bias, blinded assessors independently assessed the presence and severity of adverse events, using the ASEC. This internal quality check confirmed the results of the main outcome, drop-outs due to AEs. Second, the decision to discontinue the medication was never an independent choice of the investigator, but it was suggested by the patients' general practitioners, by other specialists (not involved in the study) or by patients themselves without discussing it with the investigator. Therefore, investigators could not have affected this decision and consequently the main outcome, but they rather noted at each time-point visit a decision that was taken by someone else. As far as concern the risk of performance bias, it can be objected that investigators may have provided vortioxetine, or the control SSRI, at excessively low or high doses, altering this way the likelihood of dropping out from treatment because of side-effects or lack of efficacy. Nevertheless, the mean prescribed doses at each time point, both vortioxetine and SSRIs, were within the range of the average suggested doses for elderly, according to guidelines and summary of product characteristics (table 7) [21, 33, 71].

## 5.3 Generalizability

As the design of the study is highly pragmatic [72], it minimizes the risk of selection bias, which is particularly relevant when assessing a population often excluded from experimental research, due to its fragility, such as older people. Resembling everyday clinical practice as much as possible, the results of this study can be easily generalized [72]. Participants were enrolled in five Italian psychiatric services on the basis of the need for an antidepressant prescription because of a depressive episode, without limitations to the recruitment setting. Rating scales were easy to administer and of relatively short duration, in order not to substantially alter clinical practice. The web-based application RedCap allowed to simplify the process

of recruitment, randomization, and collection of socio-demographic and clinical data, minimizing the time deducted from ordinary clinical practice. Thirdly, the comparison group consisted of participants receiving any of the SSRIs. This choice minimized the possibility of selection bias, avoiding the systematic exclusion of participants who did not benefit from a specific SSRI in the past. Moreover, the choice of such comparator resembles the everyday clinical practice, as SSRIs are currently the antidepressants suggested for elderly by guidelines. These results suggest that vortioxetine might be better tolerated than SSRIs and as effective as them.

## 6. CONCLUSIONS

Considering the overall psychological, medical and economic burden of depression in the elderly, and the few available pharmacological alternatives for treating this population group, if the result of this thesis are confirmed also in the final sample, it is likely that it will have a positive impact on everyday clinical practice. Furthermore, considering the pragmatic nature of the study, we expect that results will be immediately applicable to ordinary practice without requiring any specific training or implementation strategies. If the hypothesis of a better tolerability and equivalent efficacy of vortioxetine compared to SSRIs will be confirmed in the whole sample, this drug may become a reference first-line drug for the treatment of depression in the elderly. This, besides improving the overall psychological well-being and quality of life of elderly people with depression, might at the same time reduce hospitalizations for medical adverse events (such as falls, bleeding, hyponatraemia, QTc alterations), poor medical outcomes, and related health care costs.

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## APPENDIX 1

# SCHEDA DI RECLUTAMENTO

Nome del medico _____

Data di reclutamento _____

Nome del centro di reclutamento _____

**VERIFICA DEI CRITERI DI INCLUSIONE/ESCLUSIONE**

Per poter essere incluso nello studio il paziente dovrà soddisfare tutti i seguenti criteri:

☐Età maggiore o uguale a 65 anni

☐Firma del consenso informato

☐Presenza di un episodio depressivo maggiore sulla base della valutazione clinica (guidata dai criteri del DSM-5)

☐Il trattamento con antidepressivi è considerato appropriato sulla base del giudizio clinico, tenendo in considerazione sia il quadro psichiatrico, sia quello medico generale (eventuali comorbidità o terapie che controindichino l'uso di antidepressivi)

☐Qualora il paziente stesse assumendo attualmente altri antidepressivi, antipsicotici di seconda generazione, o litio, appare clinicamente appropriato sospendere tali terapie, con modalità in linea con la comune pratica clinica, e il paziente acconsente a tale procedura

☐Il paziente non ha una diagnosi di demenza prodotta da uno specialista (es. neurologo o geriatra)

☐Il paziente non ha una diagnosi di schizofrenia o disturbo bipolare

☐Vi è incertezza rispetto a quale trattamento possa essere più appropriato per il paziente (vortioxetina o antidepressivi SSRI)

**DATI SOCIO-DEMOGRAFICI E CLINICI**

Età _____

Sesso ☐ maschio ☐ femmina

Nazionalità ☐ italiano ☐non italiano

Con chi vive ☐ vive solo ☐vive con familiari ☐vive con assistente domestico (con o senza familiari) ☐vive in una struttura residenziale (casa di riposto o altro)

Stato civile ☐ sposato ☐non sposato o vedovo

Situazione lavorativa ☐ occupato ☐ disoccupato ☐ pensionato

Anni di educazione scolastica _____

Luogo di reclutamento ☐ reparto ospedaliero medico/chirurgico ☐ reparto ospedaliero psichiatrico ☐ambulatorio di psichiatria

Anno della prima diagnosi psichiatrica _____

**Comorbidità psichiatriche.** Riportare le 3 principali (inclusi abuso/dipendenza da alcool o sostanze)

| Diagnosi | Codice ICD-10 |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

**Terapie psicofarmacologiche assunte in passato**

| | | | |
|---|---|---|---|
| ☐ SERTRALINA | ☐ VORTIOXETINA | ☐ ANTIPSICOTICI DI PRIMA GEN. | ☐ LITIO |
| ☐ CITALOPRAM | ☐ SNRI | ☐ QUETIAPINA | ☐ ALTRI STABILIZZATORI DEL TONO DELL'UMORE |
| ☐ ESCITALOPRAM | ☐ MIRTAZAPINA | ☐ OLANZAPINA | ☐ ASENAPINA |
| | | | ☐ altro ap: _____ |
| ☐ FLUOXETINA | ☐ AD TRICICLICI | ☐ RISPERIDONE | ☐ NON NOTO |
| ☐ FLUVOXAMINA | ☐ altri AD | ☐ PALIPERIDONE | |
| ☐ PAROXETINA | ☐ BENZODIAZEPINE | ☐ CLOZAPINA | |

Numero di ricoveri ospedalieri in Psichiatria negli ultimi 5 anni _____

Durata complessiva (in settimane) _____

Numero di episodi autolesivi negli ultimi 5 anni _____

Quanti di tali episodi autolesivi hanno avuto serie conseguenze (ad es. hanno richiesto un intervento medico o un ricovero, o hanno provocato grave danno fisico, ecc.)? _____

**Attuale terapia farmacologica medica**

| Nome generico | Dose |
|---|---|
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |

**Attuale terapia psicofarmacologica (prima della randomizzazione)**

| Nome generico | Dose | Verrà sospesa? | |
|---|---|---|---|
| _____ | _____ mg/die | ☐ SI | ☐ NO |
| _____ | _____ mg/die | ☐ SI | ☐ NO |
| _____ | _____ mg/die | ☐ SI | ☐ NO |
| _____ | _____ mg/die | ☐ SI | ☐ NO |
| _____ | _____ mg/die | ☐ SI | ☐ NO |
| _____ | _____ mg/die | ☐ SI | ☐ NO |
| _____ | _____ mg/die | ☐ SI | ☐ NO |

**Somministrazione dei questionari da parte del medico:** (a) MADRS; (b) EQ-5D; (c) CACI; (d) SBT

**ORA IL PAZIENTE PUÒ ESSERE RANDOMIZZATO**

**CODICE UNIVOCO ASSEGNATO AL PAZIENTE** _____

**Esito randomizzazione**

Riportare il dosaggio obiettivo e il tempo stimato per la titolazione graduale:

☐**VORTIOXETINA** _____ mg/die tempo titolazione (giorni) _____

☐**SERTRALINA** _____ mg/die tempo titolazione (giorni) _____

☐**CITALOPRAM** _____ mg/die tempo titolazione (giorni) _____

☐**ESCITALOPRAM** _____ mg/die tempo titolazione (giorni) _____

☐**PAROXETINA** _____ mg/die tempo titolazione (giorni) _____

☐**FLUXETINA** _____ mg/die tempo titolazione (giorni) _____

☐**FLUVOXAMINA** _____ mg/die tempo titolazione (giorni) _____

**Attuale terapia psicofarmacologica (dopo la randomizzazione).** Riportare i farmaci prescritti in concomitanza con vortioxetina o SSRI (e.g. benzodiazepine)

| Nome generico | Dose |
|---|---|
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |

## SCHEDA DI FOLLOW-UP A ☐ 1 ☐ 3 ☐ 6 MESI

Nome del medico _____

Data di reclutamento _____

Nome del centro di reclutamento _____

Codice univoco del paziente _____

**NOTA IMPORTANTE!** Fare sempre riferimento alle seguenti definizioni (per ulteriori dettagli consultare la SOP#1):

- **Evento Avverso (Adverse Event - AE).** Un AE è definito come qualsiasi evento medico indesiderato che si verifica dalla prima dose del farmaco in studio fino a 30 giorni dopo la dose finale, indipendentemente dal fatto che sia considerato correlato al farmaco in studio. Inoltre, qualsiasi evento indesiderato noto che si verifica dopo il periodo di segnalazione di eventi avversi, e che lo sperimentatore valuta come potenzialmente correlato al farmaco in studio, deve essere considerato un AE.
- **Evento Avverso Grave (Serious Adverse Event - SAE).** Un SAE è definito in generale come qualsiasi evento medico indesiderato o esperienza indesiderata che si verifica durante il trattamento in studio (a qualsiasi dose) o entro 30 giorni dall'interruzione dello stesso. Tale evento o esperienza comporta almeno una delle seguenti conseguenze:
  - È letale (per qualsiasi causa);
  - Comporta un pericolo per la vita;
  - Richiede o prolunga il ricovero ospedaliero;
  - Comporta invalidità o menomazione persistente e/o significativa;
  - Comporta un'anomalia congenita o un difetto alla nascita;
  - Comporta l'insorgenza di un tumore maligno secondario;
  - Richiede un intervento medico significativo.

  Per SAE si intende anche qualsiasi altro evento giudicato particolarmente "serio" dal medico o definito grave dall'Agenzia Italiana del Farmaco (AIFA) (http://www.aifa.gov.it/en/content/reporting-adverse-reaction). Non sono considerati SAE quei ricoveri ospedalieri che si verificano nelle seguenti circostanze:
  - chirurgia elettiva;
  - ospedalizzazione di durata inferiore a 24 ore;
  - il ricovero é normale parte del trattamento o del monitoraggio del trattamento in studio;
  - il ricovero é associato ad una progressione della malattia di base.

Allo stato attuale il paziente:

☐ha ritirato il consenso allo studio → in questo caso non compilare la scheda

☐è deceduto → in questo caso compilare la scheda riportando le informazioni fino al momento del decesso
Data decesso _____
Causa decesso _____

☐non è più rintracciabile → in questo caso compilare la scheda riportando le informazioni fino a quando il paziente è stato rintracciabile

☐prosegue la presa in carico → in questo caso compilare la scheda

Il paziente ha interrotto il trattamento assegnato alla randomizzazione per 2 o più settimane consecutive?

☐NO, l'ha assunto continuativamente Dosaggio attuale _____mg/die

☐NO, l'ha interrotto per meno di 2 settimane consecutive Dosaggio attuale _____mg/die
☐SI, l'ha interrotto per più di 2 settimane consecutive Data sospensione _____

→ in questo caso, riportare il motivo della sospensione:

☐ comparsa di condizioni mediche e/o introduzione di terapie mediche non più compatibili con l'uso di vortioxetina o SSRIs

☐ comparsa di condizioni psichiatriche e/o introduzione di terapie psichiatriche non più compatibili con l'uso di vortioxetina o SSRIs

☐ inefficacia sulla sintomatologia depressiva

☐ eventi avversi imputabili a vortioxetina o SSRIs. In questo caso riportare l'evento avverso più rilevante, responsabile della sospensione:

☐Nausea/vomito ☐Stipsi ☐Diarrea ☐ Dolore addominale ☐Anoressia ☐Calo ponderale ☐Aumento ponderale
☐Astenia, affaticabilità ☐Sedazione diurna ☐Disturbi del sonno ☐Sogni anomali
☐Apatia, indifferenza emotiva ☐Aumento dell'ansia, tensione, irrequietezza ☐Difficoltà mensico-attentive ☐Confusione mentale
☐Alterazioni ECG ☐Ipertensione ☐Ipotensione ☐Ipotensione ortostatica ☐Edema
☐Sanguinamento ☐ Caduta a terra ☐Fratture ☐Iponatremia
☐Rash cutaneo ☐Prurito ☐Fotosensibilità ☐Artralgia, mialgia
☐Cefalea ☐Parestesie ☐ Vertigini ☐ Effetti extrapiramidali ☐Crisi epilettiche
☐Disturbi dell'accomodamento, visione offuscata ☐Arrossamento ☐Disfunzioni urinarie
☐Disfunzioni sessuali ☐Iperidrosi ☐Xerostomia
☐Altro _____

Quali eventi avversi (AE) si sono verificati dall'ultima valutazione clinica? Utilizzare la terminologia CTCAE, consultabile al link:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

| Eventi avversi | Livello di gravità |
|---|---|
| _____ | ☐Grado 1 ☐Grado 2 ☐Grado 3 ☐Grado 4 ☐Grado 5 |
| _____ | ☐Grado 1 ☐Grado 2 ☐Grado 3 ☐Grado 4 ☐Grado 5 |
| _____ | ☐Grado 1 ☐Grado 2 ☐Grado 3 ☐Grado 4 ☐Grado 5 |
| _____ | ☐Grado 1 ☐Grado 2 ☐Grado 3 ☐Grado 4 ☐Grado 5 |
| _____ | ☐Grado 1 ☐Grado 2 ☐Grado 3 ☐Grado 4 ☐Grado 5 |

**Grado 1 =** Lieve. Asintomatico o lieve sintomi; sole osservazioni cliniche o diagnostiche; intervento medico non indicato.
**Grado 2 =** Moderato. Minimo; locale; indicato un intervento non invasivo; comporta limitazione delle attività quotidiane "strumentali" (Instrumental Activities of Daily Living - ADL*) appropriate per l'età.
**Grado 3 =** Grave o clinicamente significativo, ma non immediatamente pericoloso per la vita; ospedalizzazione o prolungamento di ospedalizzazione; invalidante; limitante la cura di sé (Self-care ADL **).
**Grado 4 =** Conseguenze pericolose per la vita; urgente intervento indicato.
**Grado 5 =** Morte correlata a AE.
[* Instrumental ADL = preparare i pasti, fare compere, usare il telefono, gestire il denaro, ecc.]
[**Self-care ADL = fare il bagno, vestirsi e svestirsi, alimentarsi, usare i servizi igienici, assumere le terapie]

Per ciascun evento avverso di grado pari o maggiore a 3:

a. compilare l'apposita SCHEDA EVENTI AVVERSI GRAVI;
b. inviare la scheda al Servizio di Farmacologia della AOUI Verona, contattando i seguenti recapiti: tel. 045 8124706 o 045 8124904, e-mail: segreteria.farmacologia@aovr.veneto.it;
c. allertare il Centro Coordinatore (045 8124063; email: giovanni.ostuzzi@univr.it; corrado.barbui@univr.it)

È stata formulata una nuova diagnosi psichiatrica (inclusi abuso/dipendenza da alcool/sostanze) dall'ultima valutazione clinica? ☐ SI ☐ NO
Se SI, riportare le diagnosi:

| Diagnosi | Codice ICD-10 |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

È stato praticato un intervento psichiatrico non farmacologico (psicoterapia, ECT, altro) dall'ultima valutazione clinica? ☐ SI ☐ NO
Se SI, riportare l'intervento:

| Nome dell'intervento | Periodo |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

Numero dei ricoveri in Psichiatria dalla precedente valutazione _____
Durata complessiva dei ricoveri (in settimane) _____
Numero di episodi autolesivi dalla precedente valutazione _____
Quanti di tali episodi autolesivi hanno avuto serie conseguenze (ad es. hanno richiesto un intervento medico o un ricovero, o hanno provocato grave danno fisico, ecc.)? _____

**Attuale terapia medica**

| Nome generico | Dose |
|---|---|
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |

**Attuale terapia psicofarmacologica**
**(incluso il farmaco assegnato alla randomizzazione)**

| Nome generico | Dose |
|---|---|
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |
| _____ | _____ mg/die |

## The Montgomery-Asberg Depression Rating Scale (MADRS)

**ISTRUZIONI GENERALI**

La valutazione dovrebbe essere basata su un colloquio clinico che va da domande generali sui sintomi, a domande più specifiche, per consentire una precisa valutazione della gravità. L'esaminatore deve decidere se la risposta si colloca esattamente in uno dei punti definiti dalla scala (0, 2, 4, 6) o in un punto intermedio (1, 3, 5).

È eccezionale che un paziente depresso non possa essere valutato sugli item della scala. Se non è possibile ottenere dal paziente risposte chiare, si devono utilizzare, come base per la valutazione, tutte le indicazioni pertinenti e le informazioni ottenute da altre fonti, come generalmente si fa nella pratica clinica.

*La scala può essere usata per valutazioni ripetute dopo intervalli di tempo a scelta del valutatore, settimanali o altro, ma è necessario specificare sempre il periodo esplorato.*

| | | | | |
|---|---|---|---|---|
| **1 - TRISTEZZA MANIFESTA**<br>Scoraggiamento, depressione e disperazione (qualcosa di più di un semplice abbassamento del tono dell'umore) che traspaiono dal linguaggio, dalla mimica e dalla postura.<br>*Valutare in base alla profondità e all'incapacità a reagire positivamente.* | ❑ 0 | Assenza di tristezza. | ❑ 1 |
| | ❑ 2 | Sembra scoraggiato, ma può rallegrarsi senza difficoltà. | ❑ 3 |
| | ❑ 4 | Appare triste ed infelice per la maggior parte del tempo. | ❑ 5 |
| | ❑ 6 | Appare infelice per tutto il tempo. Estremamente scoraggiato. | |
| **2 - TRISTEZZA RIFERITA**<br>Verbalizzazione di umore depresso, indipendentemente dal fatto che sia o meno anche manifesto. Comprende la malinconia, lo scoraggiamento o il sentimento di non poter essere aiutati, di essere senza speranza.<br>*Valutare in base all'intensità, alla durata ed al grado in cui l'umore, da quanto riferito, viene influenzato dagli eventi.* | ❑ 0 | Tristezza occasionale in rapporto con le circostanze. | ❑ 1 |
| | ❑ 2 | Triste o malinconico, ma può rallegrarsi senza difficoltà. | ❑ 3 |
| | ❑ 4 | Sentimenti pervasivi di tristezza o melanconia. L'umore è ancora influenzato dalle circostanze esterne. | ❑ 5 |
| | ❑ 6 | Tristezza, disperazione o scoraggiamento permanenti o senza fluttuazioni. | |
| **3 -TENSIONE INTERNA**<br>Sentimenti di malessere mal definito, irritabilità, agitazione interiore, tensione nervosa crescente fino al panico, al terrore o all'angoscia.<br>*Valutare in base ad intensità, frequenza, durata e grado di rassicurazione richiesta.* | ❑ 0 | Calmo. Tensione interna solo passeggera. | ❑ 1 |
| | ❑ 2 | Sensazioni occasionali d'irritabilità e di malessere mal definito. | ❑ 3 |
| | ❑ 4 | Sensazioni continue di tensione interna o panico intermittente che il paziente può controllare con difficoltà. | ❑ 5 |
| | ❑ 6 | Continuo stato di terrore o angoscia. Panico opprimente. | |
| **4 - RIDUZIONE DEL SONNO**<br>Riduzione della durata o della profondità del sonno rispetto al tipo di sonno del paziente quando stava bene. | ❑ 0 | Dorme come al solito. | ❑ 1 |
| | ❑ 2 | Lieve difficoltà ad addormentarsi o sonno leggermente diminuito, superficiale o agitato. | ❑ 3 |
| | ❑ 4 | Sonno diminuito o interrotto per almeno 2 ore. | ❑ 5 |
| | ❑ 6 | Meno di 2 o 3 ore di sonno. | |

| | | | | |
|---|---|---|---|---|
| **5 - RIDUZIONE DELL'APPETITO**<br>Perdita dell'appetito rispetto a quello abituale.<br>*Valutare in base alla perdita del desiderio di mangiare o al bisogno di sforzarsi a mangiare.* | ❑ 0 | Appetito normale o aumentato. | ❑ 1 |
| | ❑ 2 | Appetito leggermente ridotto. | ❑ 3 |
| | ❑ 4 | Mancanza di appetito. Il cibo non ha sapore. | ❑ 5 |
| | ❑ 6 | Bisogna insistere perché mangi qualcosa. | |
| **6 - DIFFICOLTÀ DI CONCENTRAZIONE**<br>Difficoltà a raccogliere le idee che può giungere fino all'incapacità a concentrarsi.<br>*Valutare in base all'intensità, alla frequenza ed al grado di compromissione.* | ❑ 0 | Nessuna difficoltà di concentrazione. | ❑ 1 |
| | ❑ 2 | Occasionale difficoltà a raccogliere le idee. | ❑ 3 |
| | ❑ 4 | Difficoltà a concentrarsi ed a mantenere l'attenzione con riduzione della capacità di leggere o di sostenere una conversazione. | ❑ 5 |
| | ❑ 6 | Incapace di leggere o di conversare se non con grande difficoltà. | |
| **7 - STANCHEZZA**<br>Difficoltà a cominciare la giornata o lentezza ad iniziare ed a compiere le attività quotidiane. | ❑ 0 | Praticamente nessuna difficoltà ad iniziare la giornata. Assenza di lentezza. | ❑ 1 |
| | ❑ 2 | Difficoltà ad iniziare un'attività. | ❑ 3 |
| | ❑ 4 | Difficoltà ad iniziare attività abituali che vengono eseguite con fatica. | ❑ 5 |
| | ❑ 6 | Estrema stanchezza. Incapace di fare alcunché senza aiuto. | |
| **8 - INCAPACITÀ DI PROVARE SENSAZIONI**<br>Esperienza soggettiva di una diminuzione di interesse per l'ambiente circostante o per le attività che normalmente procurano piacere. La capacità di reagire in maniera emotivamente appropriata alle circostanze o alla gente è ridotta. | ❑ 0 | Normale interesse per l'ambiente circostante e per le persone. | ❑ 1 |
| | ❑ 2 | Ridotta capacità di provare piacere per gli interessi abituali. | ❑ 3 |
| | ❑ 4 | Perdita d'interesse per l'ambiente circostante. Riduzione dei sentimenti verso amici e conoscenti. | ❑ 5 |
| | ❑ 6 | Sentimento di paralisi emotiva, incapacità di provare collera, dispiacere o piacere, completa incapacità, vissuta anche con dolore, di sentire qualcosa per i parenti e per gli amici più stretti. | |
| **9 - PENSIERI PESSIMISTICI**<br>Idee di colpa, d'inferiorità, di autoaccusa, di peccato, di rimorso e di rovina. | ❑ 0 | Assenza di idee pessimistiche. | ❑ 1 |
| | ❑ 2 | Idee fluttuanti di insuccesso, di autoaccusa o di autosvalutazione. | ❑ 3 |
| | ❑ 4 | Persistenti idee di autoaccusa o chiare idee di colpa o di peccato, ma su basi razionali. Pessimismo circa il futuro. | ❑ 5 |
| | ❑ 6 | Idee deliranti di rovina, di rimorso o di colpe imperdonabili. Autoaccuse assurde e irremovibili. | |
| **10 - IDEE DI SUICIDIO**<br>Sentimento che la vita non vale la pena di essere vissuta; che la morte naturale sarebbe benvenuta; idee di suicidio e preparativi di suicidio.<br>*I tentativi di suicidio non devono, di per sé, influenzare la valutazione.* | ❑ 0 | Si gode la vita o la prende come viene. | ❑ 1 |
| | ❑ 2 | Stanco della vita. Fugaci idee di suicidio. | ❑ 3 |
| | ❑ 4 | Sarebbe meglio essere morto. Ricorrenti idee di suicidio ed il suicidio è considerato come una soluzione possibile, mancano tuttavia progetti o intenzioni precise. | ❑ 5 |
| | ❑ 6 | Progetti espliciti di suicidio se si presentasse l'occasione. Preparativi di suicidio. | |

Short Blessed Test (SBT)

Ora le farò alcune domande per valutare la sua memoria e concentrazione. Alcune potranno essere più semplici e altre più complicate.

| | | |
|---|---|---|
| 1. In che anno siamo? | ☐ Risposta corretta (0) | ☐Risposta errata (1) |
| 2. In che mese siamo? | ☐ Risposta corretta (0) | ☐Risposta errata (1) |

Ripeta dopo di me il seguente nome e indirizzo: **Francesco Bianchi, Viale della Repubblica 10, Milano** (ripetere 3 volte). Bene, ora cerchi di tenere a mente questo nome e indirizzo per alcuni minuti.

| | | |
|---|---|---|
| 3. Senza guardare l'orologio, che ore sono adesso? (considerare corretta la risposta con un'ora di margine) | ☐ Risposta corretta (0) | ☐Risposta errata (1) |

4. Conti a ritroso da 20 a 1
(se il soggetto inizia a contare in avanti o se dimentica il compito, ripetere l'istruzione e segnare un errore)

Numero errori: ☐ 0 ☐ 1 ☐ 2 o più

5. Nomini i mesi dell'anno a ritroso
(se é necessario suggerire il primo nome per iniziare, dev'essere conteggiato un errore)

Numero errori: ☐ 0 ☐ 1 ☐ 2 o più

6. Ripeta il nome e l'indirizzo che le ho chiesto di ricordare

Numero errori: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

**Calcolo del punteggio**

| Item # | Errori (0 - 5) | Coefficiente di ponderazione | Punteggio finale per ciascun item |
|---|---|---|---|
| 1 | ☐ 0 ☐ 1 | x4 | |
| 2 | ☐ 0 ☐ 1 | x3 | |
| 3 | ☐ 0 ☐ 1 | x3 | |
| 4 | ☐ 0 ☐ 1 ☐ 2 | x2 | |
| 5 | ☐ 0 ☐ 1 ☐ 2 | x2 | |
| 6 | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 | x2 | |
| | | | **Punteggio tot. _____** *(range 0-28)* |
| Considerare i seguenti cut-off: **0-4:** congitività nella norma; **5-9:** possibile compromissione cognitiva (possibile approfondire la valutazione per possibile decadimento cognitivo in fase iniziale); **10 o più:** compromissione cognitiva compatibile con demenza (inviare per valutazioni più dettagliate per decadimento cognitivo) | | | |

## The EQ-5D

Valutare ciascuna delle seguenti aree considerando lo stato di salute come percepito da lei oggi.

1. Mobilità
☐ Non ho problemi a camminare
☐ Ho qualche problema a camminare
☐ Sono confinato a letto

2. Cura di sé
☐ Non ho problemi ad accudire a me stesso
☐Ho qualche problema a vestirmi e lavarmi
☐Sono incapace a vestirmi e lavarmi da solo

3. Attività usuali
☐Non ho problemi a compiere le mie abituali attività
☐Ho qualche problema a compiere le mie abituali attività
☐Non sono in grado di compiere le mie abituali attività

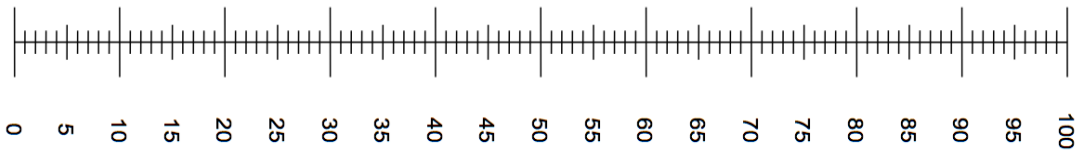
4. Dolore/disagio
☐Non ho dolore o disagio
☐Sento un modesto dolore o disagio
☐Ho un estremo dolore o disagio

5. Ansia/depressione
☐Non sono ansioso o depresso
☐Sono moderatamente ansioso o depresso
☐Sono altamente ansioso o depresso

Segni una X sulla scala per indicare come è il suo stato di salute oggi:

Stato di salute peggiore possibile

Stato di salute migliore possibile



## Charlson Age-Comorbidity Index (CACI)

| | | |
|---|---|---|
| Età | ☐60-69 | +2 |
| | ☐70-79 | +3 |
| | ☐ >= 80 | +4 |
| Diabete mellito | ☐NO | 0 |
| | ☐non complicato | +1 |
| | ☐con danno d'organo avanzato | +2 |
| Epatopatia | ☐NO | 0 |
| | ☐lieve | +1 |
| | ☐moderato-severa | +3 |
| Neoplasie | ☐NO | 0 |
| | ☐leucemia, linfoma, o tumori solidi localizzati | +2 |
| | ☐tumori solidi metastatizzati | +6 |
| AIDS | ☐NO | 0 |
| | ☐SI | +6 |
| Patologie renali croniche | ☐NO | 0 |
| | ☐SI | +2 |
| Insufficienza cardiaca congestizia | ☐NO | 0 |
| | ☐SI | +1 |
| Infarto miocardico | ☐NO | 0 |
| | ☐SI | +1 |
| BPCO | ☐NO | 0 |
| | ☐SI | +1 |
| Patologie vascolari periferiche | ☐NO | 0 |
| | ☐SI | +1 |
| Eventi cerebrovascolari o TIA | ☐NO | 0 |
| | ☐SI | +1 |
| Demenza | ☐NO | 0 |
| | ☐SI | +1 |
| Emiplegia | ☐NO | 0 |
| | ☐SI | +2 |
| Patologie del tessuto connettivo | ☐NO | 0 |
| | ☐SI | +1 |
| Ulcera peptica | ☐NO | 0 |
| | ☐SI | +1 |

Punteggio totale _____

# The Antidepressants Side-Effects Checklist (ASEC)

Valutare l'intensità di ciascuno dei seguenti sintomi nel periodo intercorso dalla precedente valutazione.
Punteggio: 0 = assente; 1 = lieve; 2 = moderata; 3 = severa.
Indicare poi se il sintomo è verosimilmente un effetto collaterale del farmaco antidepressivo.
Riportare un commento con le informazioni più rilevanti qualora non si trattasse di un effetto collaterale.

| Sintomo | Punteggio (0-3) | | | | È un effetto dell'antidepressivo? | | Commento |
|---|---|---|---|---|---|---|---|
| Bocca secca | 0 | 1 | 2 | 3 | SI | NO | |
| Sonnolenza | 0 | 1 | 2 | 3 | SI | NO | |
| Insonnia, sonno disturbato | 0 | 1 | 2 | 3 | SI | NO | |
| Visione offuscata | 0 | 1 | 2 | 3 | SI | NO | |
| Cefalea (mal di testa) | 0 | 1 | 2 | 3 | SI | NO | |
| Stipsi (stitichezza) | 0 | 1 | 2 | 3 | SI | NO | |
| Diarrea | 0 | 1 | 2 | 3 | SI | NO | |
| Aumento appetito | 0 | 1 | 2 | 3 | SI | NO | |
| Diminuzione appetito | 0 | 1 | 2 | 3 | SI | NO | |
| Nausea o vomito (1=leggera nausea; 2=nausea più severa; 3=nausea con vomito) | 0 | 1 | 2 | 3 | SI | NO | |
| Disfunzioni urinarie | 0 | 1 | 2 | 3 | SI | NO | |
| Disfunzioni sessuali | 0 | 1 | 2 | 3 | SI | NO | |
| Palpitazioni | 0 | 1 | 2 | 3 | SI | NO | |
| Senso di "testa leggera" in posizione eretta | 0 | 1 | 2 | 3 | SI | NO | |
| Sensazione che la stanza stia girando | 0 | 1 | 2 | 3 | SI | NO | |
| Sudorazione | 0 | 1 | 2 | 3 | SI | NO | |
| Aumento della temperatura corporea | 0 | 1 | 2 | 3 | SI | NO | |
| Tremore | 0 | 1 | 2 | 3 | SI | NO | |
| Disorientamento | 0 | 1 | 2 | 3 | SI | NO | |
| Sbadigli | 0 | 1 | 2 | 3 | SI | NO | |
| Aumento di peso | 0 | 1 | 2 | 3 | SI | NO | |

Quali altri sintomi ha avuto dall'introduzione del trattamento antidepressivo (o dalla precedente valutazione) che pensa potrebbero essere effetti collaterali dell'antidepressivo?

_____

Quali interventi sono stati messi in atto per trattare l'effetto collaterale?

_____

**APPENDIX 2**

**CONSORT checklist**


# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2-3 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 6-11 |
| | 2b | Specific objectives or hypotheses | 12 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 13-14 |

| | | | |
|---|---|---|---|
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | -- |
| Participants | 4a | Eligibility criteria for participants | 17-18 |
| | 4b | Settings and locations where the data were collected | 13-14; 17-18 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 20-22 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 16-18 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | 24-25 |
| Sample size | 7a | How sample size was determined | 22 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | 18 |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 23 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 23 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 23-24 |

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| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 23-24 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | 23-24 |
| | 11b | If relevant, description of the similarity of interventions | |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 24-26 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 24-26 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | 28-30 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | 28-30 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 27 |
| | 14b | Why the trial ended or was stopped | 27 |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | 31 |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | 28-30 |

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| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | 34-43 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | 34-43 |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | 34-43 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | 34 |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 46-48 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 48 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 44-46; 50 |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 13 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | 13 |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 14 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.