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CLINICAL TRIAL STUDY

Differential Response to Three Antidepressants in Patients with Major Depressive Episode Who Suffered Covid-19-Related Trauma

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Abstract: ***Background*:** The Covid 19 pandemic might have impacted response to drug treatment in major depressive episode (MDE). We compared responses to three different antidepressant drugs, *i.e.*, vortioxetine, sertraline, and trazodone, in outpatients with MDE during Major Depressive Disorder (MDD), Bipolar Disorder (BD), or schizophrenia and related psychoses (SSOPDs) during two time periods, *i.e.*, before and after suffering Covid-19-related trauma.

***Methods*:** We conducted an observational study on clinically stabilised for at least 6 months outpatients with MDE during the course of MDD (N=58), BD (N=33), or SSOPDs (N=51). Patients, whose baseline assessments of Montgomery-Åsberg Rating Scale (MADRS), Hamilton Anxiety Rating Scale (Ham-A), Brief Psychiatric Rating Scale (BPRS), Visual Analogue Scale for Craving (VAS-crav) and World Health Organization Quality of Life, Brief version (WHOQOL-BREF) were available, were recruited at the time they suffered Covid-19-related traumas. Fifty patients, prior to the pandemic, when they were clinically stable, were treated with 15 mg/die vortioxetine, 44 with 450 mg/die trazodone, and 48 with 150 mg/die sertraline. After experiencing a major Covid-19-related personal trauma, patients showed clinical worsening which required dosage adjustment (20 mg/day vortioxetine; 600 mg/day trazodone, and 200 mg/day sertraline) and, for some of them, hospitalisation. Scores on the MADRS, Ham-A, BPRS, VAS-crav and WHOQOL-BREF were compared drug-wise and gender-wise with Student's *t* test for continuous variables and χ^2 for categorical variables.

***Results*:** The sample consisted of 142 outpatients (age, mean 39.63 ± 16.84; 70 men and 72 women); women were older than men (mean age 43.18 ± 17.61 *vs*. 35.98 ± 15.30; p=0.01). The two genders did not differ on other variables. For all treatments, worsening symptoms were observed at the time of trauma, followed by slow recovery with treatment readjustment. Trauma-related worsening in patients on vortioxetine was less intense than patients on the other two antidepressants and recovery was faster. All drugs were associated with an improvement in QoL. The vortioxetine group showed a lower hospitalisation rate (24%) than sertraline (35.4%) and trazodone (38.6%), but this was not significant (p=0.27).

***Conclusion*:** All drugs improved symptoms of Covid-19 trauma in patients with MDE, with vortioxetine showing a small advantage. No differences between vortioxetine, sertraline and trazodone were found as concerning the need for hospitalisation.

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1. INTRODUCTION

The Covid 19 pandemic has substantially altered everyday life worldwide. Due to the exceptionally high number of deaths and restrictions, the media have broadly compared it to an ongoing war. The Covid-19 pandemic is responsible for a major health crisis. Rigid health measures had to be implemented in most countries to reduce and possibly halt the spread of this viral infection [1]. Its impact on mental health is of increasing global concern [2], since it is associated with psychological distress and mental symptoms even after recovery from acute Covid-19 [3, 4].

In this global crisis, people fear about falling ill and dying for both themselves and for loved ones and suffer from being socially excluded and separated from families and caregivers. Many people are losing livelihoods and opportunities.

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People testing positive for Covid-19 must cope with anxiety, physical symptoms of increasing severity, separation, isolation and even stigma [5]. Alcohol and drug use and other addictive behaviours, such as gaming or gambling, have increased during the pandemic, similarly to domestic violence [6], which all contributing to increase in depression observed in the general population during this period. This is further enhanced by the experience of the death of a loved one due to Covid-19 or any other reason, which leaves the mourner without the opportunity to be close at that moment of the loss and to attend funerals, which may disrupt the grieving process [7].

Symptoms of anxiety and depression (16-28%) and self-reported stress (8%) are common psychological reactions to the COVID-19 pandemic in the general population and healthcare workers, and may be associated with sleep disturbance [8]. Post-traumatic stress disorder symptoms occur in about 15% in the general population [9] and more than 30% in people who recover [4].

Since subsyndromal mental health problems are a common response to the COVID-19 pandemic in the general population, the focus needs to be shifted on the impact of the pandemic on persons with a pre-existing mental disorder. Concerns have been expressed that the population already affected by a mental disease may have an increased risk for Covid-19 infection and for worse outcomes in case of symptomatic infection [10-12]. Furthermore, people with mental disorders are more likely to suffer Covid-19 than people without [12] and some of them have an increased death risk compared to people without mental illness [13]. COVID-19 is likely to exacerbate pre-existing mental health, neurological and substance use disorders, while limiting access for those in need of services [14].

Psychiatric disorders are estimated to affect 25-32% of the adult population worldwide [15], and their incidence is likely to have increased during the pandemic [12, 16].

A link between inflammatory mechanisms and depressive symptoms has been long hypothesised [17], which led to complementing specific MDD treatment with anti-inflammatory medications, particularly in patients with increased inflammatory reactivity, so to enhance the efficacy of antidepressant treatment [18]. It is also possibility that the immune-inflammatory mechanisms may also be considered a part of antidepressant drugs mechanisms [19], such as those we used in this study. These drugs have been hypothesised to prevent the psychiatric consequences of SARS-CoV-2 infection [20].

In this study we aimed to assess in clinically stabilised patients with a diagnosing of major depressive disorder or bipolar disorder or schizophrenia spectrum and other psychotic disorders and those patients were all being treated with one of three antidepressants (vortioxetine, trazodone, and sertraline) for a major depressive episode, all of whom suffered a traumatic event during the pandemic, the impact of Covid-19-related traumatic events on their psychopathology and evaluation of the effect on clinical measures of each of the antidepressant drugs they were taking were studied. We also aimed to compare hospitalisation rates for each antidepressant.

2. MATERIALS AND METHODS

2.1. Patients

We conducted an observational study on 142 patients affected by depressive symptoms in Major Depressive Disorder (MDD), Bipolar Disorder (BD), and Schizophrenia Spectrum and Other Psychotic Disorders (SSOPDs), who were clinically stabilised for at least 6 months and treated with antidepressants, antipsychotics or mood stabilisers according to recent treatment guidelines [21, 22]. Inclusion began on 1-September 2019 (first assessment of clinical stabilisation) and ended on 30-September-2020. These patients experienced during the Covid-19 pandemic a major Covid-19-related personal trauma, defined as suffering Covid-19 infection themselves or witnessing it in a close relative, or death of a loved one (either due to Covid-19 infection or not), domestic violence, or job loss during the pandemic. Therefore, they all had experienced a disruption of clinical stability, which required adjustments in antidepressant dosage and made necessary, for some of them, hospitalisation for one month at the psychiatric ward of the Neuropsychiatric Hospital Villa Von Siebenthal, Genzano di Roma.

Patients were excluded from the study if they had acute psychosis, acute suicidal ideation, or any acute psychiatric condition that might require emergency interventions, organic, neurological, or cardiovascular disease. Other exclusion criteria were actual or planned pregnancy or breastfeeding during the study period.

After meeting inclusion criteria, patients were explained study aims and methods and provided free, informed consent. The study received approval from the local ethical committee (ASL RM2). It was conducted in accordance with the Principles of Human Rights, as adopted by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964, subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

2.2. Treatments

Before the outbreak of the Covid-19 pandemic, patients were clinically stabilised for at least 6 months and treated with antidepressants and antipsychotics and mood stabiliser according to the major guidelines for each disorder. Considering specifically antidepressant pharmacotherapy, 50 patients were treated with vortioxetine at the average daily dosage of 15 mg/die; 44 were assuming trazodone extended release at the average daily dose of 450 mg/die and 48 were treated with sertraline at the average daily dosage of 150 mg/die. They all continued on the same drug throughout the study.

With the onset of clinical worsening, as a consequence of experiencing a major Covid-19-related personal trauma, we considered an adjustment of dosage of the antidepressant therapy. Hence, people treated with vortioxetine, after the trauma were administered 20 mg/day of the same drug; those receiving trazodone were administered 600 mg/day post-trauma, and those who were receiving sertraline were put on a 200 mg/day regimen. Among patients who needed a one-month hospitalisation, besides antidepressant dose adjustment, those treated with trazodone received it intravenously

and/or intramuscularly for the first week of hospitalisation; for hospitalised patients showing psychomotor agitation, benzodiazepines were added to their pharmacotherapy.

Vortioxetine has shown effectiveness in MDEs during the course of MDD, BD or schizophrenia spectrum and other psychotic disorders in patients with or without substance use disorder (SUD) and showed few and tolerable adverse events [23]. Its mechanism of action is claimed to be related to its multimodal activity. It is a human recombinant serotonin (5-hydroxytryptamine, 5-HT) 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} partial agonist, a 5-HT_{1A} full agonist and an inhibitor of the rat 5-HT transporter with a 43% and 57% blocking activity at the doses of 5 and 10 mg/kg/day, respectively [24]. Vortioxetine behaves differently from other antidepressants, with which it shares serotonin transporter inhibition, in that it lowers thalamocortical glutamatergic transmission mediated by the 5-HT_7 receptor [25]. Some evidence suggests that effects of vortioxetine on the 5-HT receptors and SERT lead to enhanced release of 5-HT, noradrenaline (NA), dopamine, histamine, acetylcholine and glutamate. As a consequence, the efficiency of information processing in malfunctioning brain circuits would improve by facilitating long-term potentiation (LTP), neuroplasticity, and pyramidal neuron firing [26]. Along the aforementioned, other mechanisms could be at play; vortioxetine showed antioxidative and anti-inflammatory activity on human monocytes and macrophages [27], and this matches the neuroinflammation hypothesis of depression. There is a recent hypothesis describing that vortioxetine induces antidepressant effects in mice models of depression by significantly promoting the hippocampal peroxisome proliferator activated receptor a (PPARα) expression, that is known to be involved in antidepressant response [28].

Trazodone is a triazolopyridine derivative used in management of anxiety-depressive disorders. It acts inhibiting serotonin reuptake and also antagonising 5-HT_2 receptors, whose activation is considered to be responsible for insomnia, anxiety, agitation, and sexual dysfunction. Trazodone also antagonises $5HT_{2A}$, H_1, and α_1 adrenergic receptors, thus inducing and maintaining sleep, reducing psychomotor agitation, and consequently managing alcohol or other substance use withdrawal syndrome [29].

Trazodone has been studied for its action on astrocytes, which appears to be direct; it regulates signalling pathways and increases specific astrocyte-derived neurotrophic factor expression and lactate release. Hence, trazodone normalises trophic and metabolic support during neuroinflammation, which is associated with neurological diseases and major depression [30].

In Alzheimer's disease and other dementias [31], Parkinson's disease [32] and progressive supranuclear palsy (Stutzbach *et al.,* 2013) [33], *postmortem* pancreatic ER kinase (PERK) was found to be increased in various brain sites, especially in the hippocampus and substantia nigra. This molecule is part of the Unfolded Protein Response (UPR), which is a measure of cellular stress response [34]. Trazodone has been identified as a compound which attenuates UPR and overactivation of PERK signalling; thus it may have *in vitro* and *in vivo* a neuroprotective effect in neurodegenerative diseases [35].

Vortioxetine has also been suggested to be a neuroprotective agent against neuronal damage, as it was found to restrict the PERK/eIF2alpha/ATF4/CHOP stress signalling pathway, which in rats subjected to focal cerebral ischaemia-reperfusion is involved in focal cerebral ischaemia-reperfusion-related damage [36].

Sertraline, an antidepressant of the selective serotonin reuptake inhibitor (SSRI) group, is used to treat depressive, panic, obsessive-compulsive and post-traumatic stress (PTSD) disorders. It is one of the only two drugs approved by the FDA to treat PTSD [37] and is recommended as first-line in major guidelines for the prevention and treatment of acute stress disorder, PTSD, and complex PTSD [22, 38-40]. Sertraline is not only a SSRI; it binds strongly the human serotonin transporter strongly and with medium affinity the dopamine transporter [41, 42]; furthermore, despite not binding *in vivo* any biogenic monoamine receptor [43], it chronically desensitises β- [44] and α_2-adrenoceptors [45], and antagonises σ_1 receptors, differently from other similar antidepressants [46, 47]. It is not known whether its additional mechanisms have any relevance to its antidepressant-anxiolytic effects.

2.3. Study Assessments

We considered the clinical course of our stabilised outpatients, up to 6 months post-trauma, while facing with major Covid-19-related traumas.

Outpatients were evaluated at baseline, when in a stable clinical picture, before the pandemic outburst (T0), and then at the moment of suffering Covid-19-related personal trauma (T1).

Clinical assessment was performed after one month of treatment after pharmacotherapy adjustments (T2), for both outpatients and inpatients, and the after 2 months (T3), 3 months (T4) and 6 months (T5) of continued treatment.

To rate psychopathology, we used the validated clinician-rating scales Montgomery-Åsberg Depression Rating Scale (MADRS) [48], the 24-item Brief Psychiatric Rating Scale (BPRS) [49] to assess psychopathological status (mainly its psychotic side), and the Hamilton Anxiety Rating Scale (HAM-A) [50]. The Visual Analogue Scale (VAS-crav) [51] was used to evaluate craving in patients with a SUD and the World Health Organization Quality of Life, Brief version (WHOQOL-BREF) [52] was used to evaluate quality of life (QoL).

2.4. Statistical Analysis

Frequency distributions and descriptive statistics were performed to analyse the sample. We used univariate analysis of variance (ANOVA) for continuous variables and the chi-squared test (χ^2) for nominal variables after ensuring normal distribution with the Shapiro and Wilk [53] test and sphericity with the Mauchly *W*-test [54]. Data were analysed using the IBM Statistical Package for the Social Sciences (SPSS) Version 23 (IBM, Armonk, New York, 2016). Significance was set at $p<0.05$.

3. RESULTS

The final sample consisted of 142 white outpatients, 70 males (49.3%) and 72 (50.7%) females, diagnosed with

MDD (N=58; 40.8%), BD (N=33; 23.2%) and SSOPDs (N=51; 35.92%). Patients' age ranged from 13 to 79 years, mean 39.63, standard deviation (SD)=16.84.

Of the entire 142 outpatient sample, 50 (35.2%) patients were treated with vortioxetine (15 mg/day at baseline and 20 mg/day after Covid-19 pandemic-related stressful life event, which we will heretofore call Covid-19-related trauma for simplicity, although its traumatic impact and nature have not been assessed through a dedicated specific scale like the Clinician-Administered PTSD Scale for DSM-5-CAPS-5), 44 (30.99%) patients with trazodone (450 mg/day at baseline and 600 mg/day after Covid-19-related trauma), and 48 (33.8%) with sertraline (150 mg/day at baseline and 200 mg/day post- Covid-19-related trauma). There were no significant differences in antidepressant use across diagnoses.

Patients were assessed for alcohol and/or substance-use disorder; 35.2% reported no alcohol or illicit/recreational substance use, while 64.8 % had a diagnosis of SUD and/or AUD.

There were no significant gender differences in baseline sociodemographic characteristics, except that female patients were older, and more male patients were diagnosed with a SSOPD.

Descriptive statistics are shown in Table **1**.

All measures worsened from T0 (prior to Covid-19-related stressful life event) to T1 (time of Covid-19-related trauma); we will report on results between T1 and T5 (6 months after Covid-19-related trauma).

3.1. Effects of Antidepressant Treatment on Depressive, Anxious and General Symptoms

We implemented mixed model ANOVAs involving three independent variables, *i.e.*, SUD (presence/absence), Gender and Treatment (vortioxetine, sertraline or trazodone) as between-subjects variables, and Time (Pre-Covid-19, Covid-19, and 1 month, 2 months, 3 months and 6 months after Covid-19) as within-subjects variable, and MADRS, HAM-A, BPRS, VAS-crav, and WHOQOL-BREF scores as dependent variables.

3.1.1. MADRS Scores

Comparing pre-Covid-19 and Covid-19 periods, results indicate a main effect of time ($F_{(1.000,130.000)}$=147.292, p<0.001, η^2=0.531; from 13.75±4.60 at T0 to 20.38±7.06 at T1) and an interaction effect, *i.e.*, a Time × Treatment effect ($F_{(2.000,130.000)}$=10.376, p<0.001, η^2=0.138), with less impairment for the vortioxetine group (from 14.20±3.60 at T0 to 17.26±5.44 at T1) than for the sertraline (from 13.46±4.29 at T0 to 22.44±6.59 at T1) and trazodone (from 13.57±5.85 at T0 to 21.68±8.03 at T1) groups (p<0.001) (Fig. **1**).

Comparing the Covid-19-related trauma timepoint with 1, 2, 3 and 6 months after Covid-19, MADRS scores indicate a main effect of Time ($F_{(1.000,130.000)}$=25.624, p<0.001, η^2=0.165; from 20.38±7.06 to 16.67±7.20) and an interaction effect, *i.e.*, Time×Gender ($F_{(1.000,130.000)}$=25.624, p=0.008, η^2=0.053) with females showing a greater improvement (from 21.22±7.25 to 15.72±6.96) than males (from 19.51±6.80 to 17.64±7.36) at 6 months (p<0.05). Evaluating the depressive symptom course, data showed a statistically significant improvement ($F_{(1.000,130.000)}$=19.278, p<0.001, η^2=0.129; from 20.38±7.06 at T1 to 18.24±6.49 at T2) from Covid-19-related trauma timepoint to 1 month after. From 1 month to 2 months, a main effect of Time ($F_{(1.000,130.000)}$=4.233, p=0.042, η^2=0.032; from 18.24±6.49 at T2 to 17.70±6.53 at T3) and an interaction, *i.e.*, Time×Treatment effect ($F_{(1.000,130.000)}$=3.667, p=0.028, η^2=0.053) emerged, with a better response for the vortioxetine group (from 14.96±5.59 at T2 to 13.48±5.49 at T3) than for sertraline (from 21.04±5.83 at T2 to 21.23±5.39 at T3) and trazodone (from 18.91±6.59 at T2 to 18.66±6.17 at T3). From 2 to 3 months, data showed a main effect of Time ($F_{(1.000,130.000)}$=10.265, p=0.002 η^2=0.073; from 17.70±6.53 at T3 to 16.89±6.87 at T4). No other significant effects were found.

All patients, regardless of treatment and gender, showed a significant increase in depression at the time of Covid and a progressive decrease in subsequent follow-ups. Specifically, there was a significant increase between the pre-Covid-19 and the Covid-19 period and a significant decrease between the Covid-19-related trauma time point and 6 months post-Covid-19 trauma, with a significant progressive decrease after 1, 2, and 3 months.

Compared to patients treated with trazodone and sertraline, those treated with vortioxetine showed a less prominent increase in depression at the time of Covid-19-related trauma (p<0.001) and a greater decrease in depressive symptoms between 1 and 2 months after the Covid-19-related trauma (p<0.05). Furthermore, only patients treated with vortioxetine showed a significant decrease in depression between the pre-Covid-19 trauma and 6 months post-Covid-19-related trauma (p<0.001). There were no significant differences in the pattern of the course of depression between patients treated with sertraline and trazodone (Table **2**).

Regardless of treatment, females reported lower levels of depression than males at T5 (6 months) compared to T0 and to T1.

3.1.2. HAM-A Scores

Comparing the pre-Covid-19 and Covid-19-related trauma timepoints, results indicate a main effect of time ($F_{(1.000,130.000)}$=100.260, p<0.001, $\eta 2$=0.435; from 13.42±7.14 at T0 to 20.61±7.99 at T1) and a Time×Treatment interaction ($F_{(2.000,130.000)}$=6.836, p=0.002, η^2=0.095), with less impairment for the vortioxetine group (from 13.96±6.26 at T0 to 17.78±7.09 at T1), compared to sertraline (from 13.79±8.36 at T0 to 22.77±7.62 at T1) and trazodone (from 12.39±6.69 at T0 to 21.48±8.55 at T1).

Comparing the Covid-19-related trauma timepoint with 1, 2, 3 and 6 months after Covid-19-related trauma, HAM-A scores indicate a main effect of Time ($F_{(1.000,130.000)}$=36.381, p<0.001, η^2=0.219; from 20.61±7.99 at T1 to 16.22±7.72 at T5) and a Time×Gender interaction ($F_{(1.000,130.000)}$=8.605, p=0.004, η^2=0.062), with females showing a greater improvement (from 21.76±8.32 to 15.51±7.69) than males (from 19.43±7.51 to 16.94±7.74) at 6 months (p<0.05). Evaluating the course of anxiety symptoms, data showed a significant improvement ($F_{(1.000,130.000)}$=10.324, p=0.002, η^2=0.074; from 20.61±7.99 at T1 to 18.40±7.97 at T2) from the Covid-19-related trauma to 1 month post-trauma. From 1

Table 1. Participants' characteristics. Data are expressed as percentage, range or means ± SD, as appropriately.

-	**Study Sample** (n=142)	**Men** (n=70; 49.3%)	**Women** (n=72; 50.7%)	***P***
Age in years ($\bar{x}$±SD) [Student's *t*-test]	39.63 ± 16.84	35.98 ± 15.30	43.18 ± 17.61	*p=0.010*
Age range (years) min-max	(13-79)	(16-79)	(13-77)	
Status (%) [χ^2 test]				
Outpatients throughout	67.6	65.7	69.4	n.s.
Inpatients for one month	32.4	34.3	30.6	n.s.
Marital Status (%) [χ^2 test]				
Single	44.4	52.9	36.1	n.s.
Married	43.0	40.0	45.8	n.s.
Separated/Divorced	12.0	7.1	16.7	n.s.
Widowed	0.7	0.0	1.4	n.s.
Educational level (%) [χ^2 test]				
Primary School	7.0	7.1	6.9	n.s.
Middle School	38.0	34.3	41.7	n.s.
High School	45.1	50.0	40.3	n.s.
College/University, Master classes, Specialty, Ph.D.	9.9	8.6	11.1	n.s.
Diagnosis (%) [χ^2 test]				
MDD	40.8	31.4	50.0	n.s.
BD	23.2	15.7	30.6	n.s.
SSOPDs	35.9	55.2	19.4	*p=0.004*
Drug-treatment (%) [χ^2 test]				
Vortioxetine	35.2	32.9	37.5	n.s.
Sertraline	33.8	32.9	34.7	n.s.
Trazodone	31.0	34.3	27.8	n.s.
Presence of Alcohol or Substance Use Disorder (%) [χ^2 test]				
No AUD or SUD	35.2	40.0	30.6	n.s.
AUD and/or SUD	64.8	60.0	69.4	n.s.

Abbreviations: AUD, alcohol use disorder; BD, bipolar disorder; MDD, major depressive disorder; n.s., not significant; SD, standard deviation; SSOPDs, schizophrenia spectrum and other psychotic disorders; SUD, substance use disorder; $\bar{x}$, mean; χ^2, chi-squared test.

to 2 months, results indicate a Time×Gender interaction ($F_{(1.000,130.000)}$=4.759, p=0.031, η^2=0.035), with females showing a stronger improvement (from 18.52±7.80 to 17.74±7.73) than males (from 18.27±8.19 to 18.34±8.05) (p<0.05). From 2 to 3 months post-trauma, data showed the main effect of Time ($F_{(1.000,130.000)}$=7.738, p=0.006 η^2=0.056; from 18.03±7.87 to 17.13±7.42). No other significant effects were found.

All patients, regardless of treatment and gender, showed a significant increase in anxiety at the time of Covid-19 and a progressive decrease in subsequent follow-ups. Specifically, there was a significant increase in anxiety from baseline (before trauma, T0) to the very moment of the trauma (T1) and a significant decrease of anxiety between baseline (T0) and 6 months after trauma (T5), with a significant progressive decrease at 1 month after trauma (T2) and between T3 and T4 (2 and 3 months after the trauma).

Patients treated with vortioxetine showed a smaller increase in anxiety at the time of Covid-19 trauma (T1) (p<0.01). Furthermore, they showed a stronger improvement

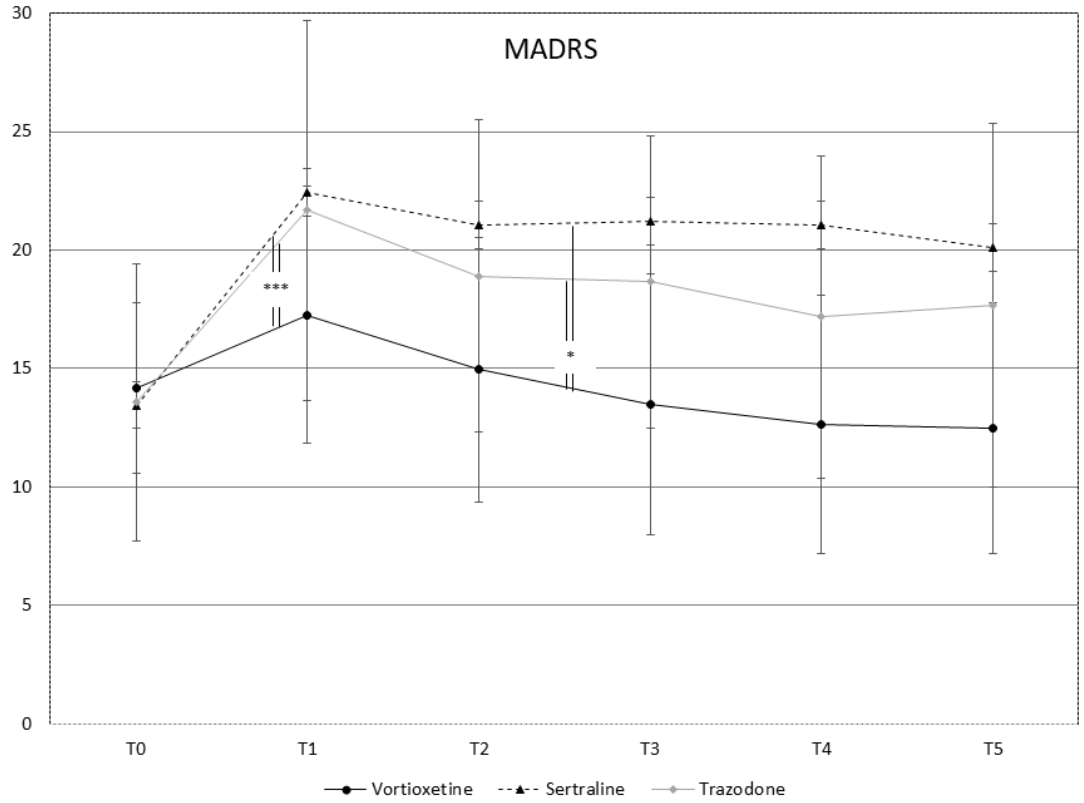

Fig. (1). MADRS scores across the study for each drug administered. Depressive symptoms worsen for all drugs, but while with sertraline and trazodone depressive symptoms persist, with vortioxetine there is a tendency towards the re-establishment of initial values. Statistically significant results were shown between vortioxetine and the two other drugs at the T0-T1 and T2-T3 intervals. Bars, standard deviation (SD); *p<0.05; ***p<0.001. Note that the range of the MADRS is 0-60, but in no timepoint did the mean ± SD was above the score of 30.

in anxiety symptoms from the pre-Covid-19 timepoint (T0) to 6 months after Covid-19-related trauma (T5) (p<0.01), when compared to patients treated with sertraline and trazodone.

Considering the period between the time of trauma (T1) and 6 months after trauma (T5), there are no inter-treatment differences in anxiety levels.

Regardless of the treatment, female patients reported a greater decrease in anxiety levels over time than male patients. Specifically, the former showed a more prominent decrease in anxiety levels between 1 month (T2) and 2 months (T3) after trauma (p<0.05) and between the time of trauma (T1) and 6 months after trauma (T5) (p<0.05). There were no other significant gender differences at the other follow-ups.

3.1.3. BPRS Scores

Comparing the pre-Covid-19 and Covid-19-related trauma timepoints, results indicate a main effect of time ($F_{(1.000,130.000)}$=71.749, p<0.001, η^2=0.356; from 38.01±9.11 at T0 to 47.80±14.18 at T1) and an interaction effect, *i.e.*, a Time×Treatment effect ($F_{(2.000,130.000)}$=8.851, p<0.001, η^2=0.120), with less impairment for the vortioxetine group (from 37.56±7.11 at T0 to 44.06±11.45 at T1) than with sertraline (from 39.48±9.57 at T0 to 47.56±10.95 at T1) or trazodone (from 36.91±10.52 at T0 to 52.30±18.48 at T1), and less impairment for the sertraline group compared to trazodone (p<0.05).

Comparing the Covid-19-related trauma point with 1, 2, 3 and 6 months after Covid-19, the BPRS scores indicate a main effect of Time ($F_{(1.000,130.000)}$=32.302, p<0.001, η^2=0.199; from 47.80±14.18 at T1 to 40.16±13.32 at T5). Assessing the course of general psychopathological symptoms from the Covid-19-related trauma timepoint to 1 month post-Covid-19-related trauma, data showed a significant improvement ($F_{(1.000,130.000)}$=12.418, p=0.001, η^2=0.087; from 47.80±14.18 at T1 to 44.24±13.91 at T2) and a Time×Treatment interaction ($F_{(2.000,130.000)}$=3.969, p=0.021, η^2=0.058), with a greater improvement for the trazodone group (from 52.30±18.48 at T1 to 44.89±15.51 at T2), compared to vortioxetine (from 44.06±11.45 at T1 to 39.98±10.54 at T2) and sertraline (from 47.56±10.95 at T1 to 48.08±14.47 at T2). From 1 to 2 months after Covid-19-related trauma, results indicate an interaction effect, *i.e.*, Time×Gender ($F_{(1.000,130.000)}$=6.569, p=0.012, η^2=0.048) with only females showing improvement (from 42.93±12.77 to 41.66±13.96), in contrast to males (from 45.59±14.96 to 46.43±15.06). From 2 to 3 months, data showed a main effect of Time ($F_{(1.000,130.000)}$=15.201, p<0.001, η^2=0.105; from 44.01±14.65 to 41.00±12.94). No other significant effects were observed.

All patients, regardless of treatment and gender, showed a significant increase in general psychiatric symptoms at the time of Covid-19 trauma (T1) as compared to baseline (T0) (p<0.001) and a progressive decrease in subsequent follow-

ups. Specifically, there was a significant improvement of symptoms between the time of trauma (T1) and 6 months after trauma (T5) (p<0.001), and a significant progressive decrease of scores at 1 month after trauma (T2) and between 2 months after trauma (T3) and 3 months after trauma (T4) from the Covid-19-related trauma (T1) (p<0.01). There were no other significant differences based on gender in the other follow-ups.

At the time of Covid-19-related trauma (T1), patients treated with vortioxetine showed a smaller increase in general psychiatric symptoms than those associated with the other two antidepressants, while patients treated with sertraline showed a smaller increase in general psychiatric symptoms than patients treated with trazodone (p<0.001).

In the period between trauma (T1) and 1 month after trauma (T2), patients treated with vortioxetine showed greater decreases in general psychiatric symptoms than patients treated with other antidepressants (p<0.05). During the same period, patients treated with trazodone showed a greater decrease in general psychiatric symptoms than those treated with sertraline (p<0.05).

Considering the periods between baseline (T0) and 6 months after trauma (T5) and between the time of trauma (T1) and 6 months after trauma (T5), there was no significant variation in general psychiatric symptoms for any of the three antidepressants.

3.2. VAS-crav Scores

Craving scores significantly varied among treatments ($F_{(1.000,130.000)}$=12.930, p<0.001, η^2=0.130), with lower values showed by patients treated with sertraline (from 0.77±1.84 at T0 to 0.94±2.16 at T1) when compared to trazodone (from 1.34±2.15 at T0 to 2.11±3.32 at T1) (p<0.01). Vortioxetine scores at T0 were 1.40±2.19 and increased to 1.64±2.65 at T1. Craving scores did not differ between vortioxetine and sertraline nor between vortioxetine and trazodone.

When comparing Covid-19-related trauma with 1, 2, 3 and 6 months later, craving scores indicated a main effect of Time ($F_{(1.000,130.000)}$=9.555, p<0.01, η^2=0.714; from 1.17±2.07 to 0.80±2.02), with significant improvements between the Covid-19-related trauma timepoint (T1, 1.55±2.75) and 2 (T3) (0.81±1.74; p<0.05), 3 (0.77±1.80; p<0.001) and 6 (T5) (0.80±2.02; p<0.001) months after, respectively. The drop in VAS-crav scores was much significant for vortioxetine (p<0.00001), less significant for trazodone (p=0.0037), and not significant for sertraline (p=0.846) (Table **2**).

No significant effect of gender, or any interaction between time and treatment, was found.

Patients with SUD showed significant increase in craving at the time of Covid-19 trauma (T1) as compared to baseline (T0), and a significant decrease during the period between trauma (T1) and 6 months after trauma (T5). Specifically, there was a significant decrease in craving 1 month after trauma (T2) and in the period between 1 month after trauma (T2) and 2 months after trauma (T3).

3.2.1. WHOQOL Scores

Comparing the pre-Covid-19 and Covid-19-related trauma timepoints, results indicated a main effect of time ($F_{(1.000,130.000)}$=67.085, p<0.001, η^2=0.340; from T0 to T1). Comparing the Covid-19-related trauma timepoint with 1, 2, 3 and 6 months after Covid-19, WHOQOL scores indicated a main effect of Time ($F_{(3.016,392.070)}$=2.620, p=0.05, η^2=0.020; from T1 to T2, T3, T4, and T5).

Considering differences between T0 and T1, on the physical WHOQOL domain, patients on vortioxetine did not vary significantly (from 69.30±16.291 at T0 to 62.82±16.650 at T1; t= 1.967; p=0.052, n.s.), while those on trazodone (from 74,886±14,564 at T0 to 59.636±20.756 at T1; t=3.99; p=0.0001) and those on sertraline (from 75.271±12.836 at T0 to 66.542±15.760 at T1; t=2.97541; p=0.004) deteriorated. On the psychological WHOQOL domain, patients on vortioxetine (from 66.22±17.969 at T0 to 61.50±17.455 at T1; t=1.332; p=0.186) and those on trazodone (from 74.25±18.079 at T0 to 66.795±21.065 at T1; t=1.781; p=0.078) did not deteriorate significantly, while those on sertraline (from 71.521±13.616 at T0 to 62.812±16.851 at T1; t=2.7849; p=0.006) did. On the social relations WHOQOL domain, patients on vortioxetine (from 62.24±16.828 at T0 to 57.68±18.377 at T1; t=1.294; p=0.199) did not deteriorate significantly, while those on trazodone (from 69.159±16.644 at T0 to 57.159±19.425 at T1; t=3.112; p=0.0025) and those on sertraline (from 70.208±12.367 at T0 to 59.708±15.953 at T1; t=3.604; p=0.0005) did. On the environmental WHOQOL domain, patients on vortioxetine (from 68.60±14.680 at T0 to 63.68±17.995 at T1; t=1.498; p=0.137) again did not deteriorate significantly, while those on trazodone (from 72.341±12.658 at T0 to 64.636±15.155 at T1; t=2.588; p=0.011) and those on sertraline (from 73.042±11.966 at T0 to 65.708±15.036 at T1; t=2.644; p=0.01) did.

Regarding differences from T1 to T5, on the physical WHOQOL domain, patients on vortioxetine (from 62.82±16.650 at T1 to 67.04±15.301 at T5; t=-1.32; p=0.190), on sertraline (from 66.542±15.760 at T1 to 60.021±17.984 at T5; t=1.889; p=0.062) or on trazodone (from 59.636±20.756 at T1 to 67.045±17.986 at T5; t=-1.789; p=0.077) did not vary significantly. On the psychological WHOQOL domain, patients on vortioxetine (from 61.50±17.455 at T1 to 63.24±17.375 at T5; t=-0.500 p=0.618), trazodone (from 66.795±21.065 at T1 to 70.477±21.028 at T5; t=-0.821; p=0.414), or sertraline (from 62.812±16.851 at T1 to 60.458±16.266 at T5; t=0.696; p=0.488) did not show significant improvement. On the social relations WHOQOL domain, patients on vortioxetine (57.68±18.377 at T1 to 59.60±17.027 at T5; t=-0.542; p=0.589), trazodone (from 57.159±19.425 at T1 to 64.818±18.842 at T5; t=-1.877; p=0.064) or sertraline (from 59.708±15.953 at T1 to 59.021±14.742 at T5; t=0.219; p=0.827) did not vary significantly. Also on the environmental WHOQOL domain, patients on vortioxetine (from 63.68±17.995 at T1 to 62.28±14.831 at T5; t=0.425; p=0.672), on trazodone (from 64.636±15.155 at T1 to 66.386±17.509 at T5; t=-0.501; p=0.617) or on sertraline (from 65.708±15.036 at T1 to 61.042±15.893 at T5; t=1.478; p=0.143) did not show significant T1-T5 differences.

As for differences from T1 to T2, on all WHOQOL domains there were no significant changes for all three drugs (physical WHOQOL domain, vortioxetine, from 62.82 ± 16.650 at T1 to 64.32±16.270 at T2; t=-0.456; p=0.650; sertraline, from 66.542±15.760 at T1 to 63.958±17.429 at T2;

Table 2. Time course of scores on assessment scales according to antidepressant treatment received (repeated-measures ANOVA).

-	T0	T1	T2	T3	T4	T5	*F*	*p*
Whole group (N=142) Mean±SD								
MADRS	13.75±4.60	20.38±7.06	18.24±6.49	17.70±6.53	16.89±6.87	16.67±7.20	42.256	<0.00001
Ham-A	13.42±7.14	20.61±7.99	18.40±7.97	18.04±7.87	17.33±7.42	16.22±7.72	37.723	<0.00001
BPRS	38.01±9.11	47.80±14.18	44.24±13.91	44.01±14.66	41.01±12.94	40.16±13.32	29.256	<0.00001
VAS-crav	1.17±2.07	1.55±2.75	1.06±2.09	0.81±1.74	0.77±1.80	0.80±2.02	9.481	<0.00001
WHOQOL phys	73.05±14.82	63.09±17.84	64.63±18.54	65.90±17.91	67.03±18.51	64.67±17.29	16.490	<0.00001
WHOQOL psy	70.50±16.88	63.58±18.46	65.67±19.35	66.16±19.05	64.04±18.42	64.54±18.58	9.072	<0.00001
WHOQOL soc	67.08±15.71	58.20±17.85	61.48±18.66	61.46±18.55	62.81±19.07	61.02±16.97	11.895	<0.00001
WHOQOL env	71.26±13.25	64.67±16.09	65.27±16.80	65.85±16.18	52.68±29.73	63.13±16.10	26.020	<0.00001
Vortioxetine (N=50)								
MADRS	14.20±3.60	17.26±5.44	14.96±5.59	13.48±5.49	12.64±5.46	12.48±5.27	17.558	<0.00001
Ham-A	13.96±6.26	17.78±7.09	14.96±6.29	14.06±5.88	13.42±5.73	12.14±5.34	13.708	<0.00001
BPRS	37.56±7.11	44.06±11.45	39.98±10.54	38.86±12.26	36.9±11.62	36.08±11.01	9.883	<0.00001
VAS-crav	1.40±2.19	1.64±2.65	1.04±1.77	0.60±1.23	0.50±1.18	0.34±0.89	8.931	<0.00001
WHOQOL phys	69.30±16.29	62.82±16.65	64.32±16.27	66.28±15.22	65.44±15.62	67.04±15.30	3.591	=0..0075
WHOQOL psy	66.22±17.97	61.50±17.45	63.38±19.01	64.24±17.98	64.22±17.90	63.24±17.38	2.009	=0.0947 n.s.
WHOQOL soc	62.24±16.83	57.68±18.38	61.5±17.77	61.2±16.76	61.44±17.21	59.60±17.03	1.968	=0.1009 n.s.
WHOQOL env	68.60±14.68	63.68±17.99	64.48±16.29	64.38±15.50	58.72±23.80	62.28±14.83	3.968	=0.0040
Sertraline (N=48)								
MADRS	13.46±4.29	22.44±6.59	21.04±5.83	21.23±5.39	21.04±5.60	20.10±6.42	26.222	<0.00001
Ham-A	13.79±8.35	22.77±7.62	22.19±8.45	21.98±7.76	21.60±6.42	19.85±7.19	21.991	<0.00001
BPRS	39.48±9.57	47.56±10.95	48.08±14.48	47.13±14.78	44.60±11.87	43.46±13.51	8.652	<0.00001
VAS-crav	0.77±1.84	0.94±2.16	0.92±2.08	0.88±1.95	0.81±2.06	0.90±2.26	0.346	=0.846 n.s.
WHOQOL phys	75.27±12.84	66.54±15.76	63.96±17.43	64.73±17.04	63.56±17.25	60.02±17.98	14.186	<0.00001
WHOQOL psy	71.52±13.62	62.81±16.85	62.06±17.81	62.85±17.82	60.19±18.03	60.46±16.27	8.925	<0.00001
WHOQOL soc	70.21±12.37	59.71±15.95	57.92±16.43	58.10±16.80	59.25±17.39	59.02±14.74	12.742	<0.00001
WHOQOL env	73.04±11.97	65.71±15.03	63.67±17.02	64.00±16.88	52.00±28.10	61.04±15.89	11.711	<0.00001
Trazodone (N=44)								
MADRS	13.57±5.85	21.68±8.03	18.91±6.59	18.66±6.17	17.18±6.80	17.68±7.67	19.849	<0.00001
Ham-A	12.39±6.69	21.48±8.55	18.19±7.42	18.25±7.89	16.48±7.69	16.89±8.47	16.228	<0.00001
BPRS	36.91±10.52	52.30±18.48	44.89±15.51	46.48±15.70	41.75±14.40	41.20±14.56	16.147	<0.00001
VAS-crav	1.34±2.15	2.11±3.32	1.22±2.44	0.98±1.99	1.02±2.07	1.23±2.54	4.041	=0.0037
WHOQOL phys	74.89±14.56	59.64±20.76	65.70±22.18	66.75±21.62	72.73±21.71	67.05±17.99	8.731	<0.00001
WHOQOL psy	74.25±18.08	66.80±21.07	72.20±20.12	71.95±20.58	68.02±18.88	70.48±21.03	2.203	=0.0707 n.s.
WHOQOL soc	69.16±16.64	57.16±19.43	65.34±21.39	65.43±21.69	68.25±21.87	64.82±18.84	5.305	=0.0005
WHOQOL env	72.34±12.66	64.64±15.16	67.93±17.19	69.52±15.92	46.57±36.18	66.39±17.51	12.863	<0.00001

Abbreviations: BPRS, Brief Psychiatric Rating Scale; Ham-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; n.s., not significant; SD, standard deviation; T0, pre-Covid-19 pandemic; T1, Covid-19-related trauma; T2, 1 month after trauma; T3, 2 months after trauma; T4, 3 months after trauma; T5, 6 months after trauma; VAS-crav, Visual Analogue Scale for Craving, WHOQOL phys, World Health Organisation Quality of Life scale 2.0 BREF, physical domain; WHOQOL psy, World Health Organisation Quality of Life scale 2.0 BREF, psychological domain; WHOQOL soc, World Health Organisation Quality of Life scale 2.0 BREF, social domain; WHOQOL env, World Health Organisation Quality of Life scale 2.0 BREF, environmental domain. Repeated-measures ANOVA analyses refer to the entire T0 to T5 period.

t=0.762; p=0.448; trazodone, from 59.636±20.756 at T1 to 65.705±22.179 at T2; t=-1.325; p=0.189; psychological WHOQOL domain, vortioxetine, from 61.50±17.455 at T1 to 63.38±19.010 at T2; t=-0.515; p=0.608; sertraline, from 62.812±16.851 at T1 to 62.062±17.806 at T2; t=0.212; p=0.833; trazodone, from 66.795±21.065 at T1 to 72.205±20.119 at T2; t=-1.232; p=0.221; social relations WHOQOL domain, vortioxetine, 57.68±18.377 at T1 to 61.50±17.769 at T2; t=-1.057; p=0.293; sertraline, from 59.708±15.953 at T1 to 57.917±16.428 at T2; t=0.542; p=0.589; trazodone, from 57.159±19.425 at T1 to 65.341±21.386 at T2; t=-1.879; p=0.064; environmental WHOQOL domain, vortioxetine, from 63.68±17.995 at T1 to 64.48±16.291 at T2; t=-0.233; p=0.816; sertraline, from 65.708±15.036 at T1 to 63.667±17.021 at T2; t=0.623; p=0.535; trazodone, from 64.636±15.155 at T1 to 67.932±17.192 at T2; t=-0.954; p=0.343).

Evaluating the progression of scores on the quality-of-life scale, a significant worsening was found from the pre-pandemic baseline to the Covid-19-related trauma timepoint ($F_{(1.000,130.000)}$=5.338, p=0.022, η^2=0.039; from 73.05±14.82 at T0 to 63.09±17.84 at T1 for the WHOQOL-BREF physical subscale, from 70.50±16.88 at T0 to 63.58±18.46 at T1 for the WHOQOL-BREF psychological subscale, from 67.08±15.71 at T0 to 58.20±17.85 at T1 for the WHOQOL-BREF social relations subscale, and from 71.26±13.25 at T0 to 64.67±16.09 at T1 for the WHOQOL-BREF environmental subscale) and a Time×Treatment interaction ($F_{(2.000,130.000)}$=4.821, p=0.010, η^2=0.069). Considering the entire course of the curves, there was an improvement from T1 to T5 only in the trazodone group on the WHOQOL-BREF scales, but this was not significant. Lack of significance regarded all WHOQOL domains (from 59.64±20.76 at T1 to 67.05±17.99 at T5 for the WHOQOL-BREF physical subscale (Student's t=-0.76; p=0.45), from 66.80±11.07 at T1 to 70.48±21.03 at T5 for the WHOQOL-BREF psychological subscale (t=-0.44; p=0.66), from 57.16±19.43 at T1 to 64.82±18.84 at T5 for the WHOQOL-BREF social relations subscale (t=-1.36; p=0.17), and from 64.64±15.16 at T1 to 66.39±17.51 at T5 for the WHOQOL-BREF environmental subscale (t=0.80; p=0.42)), and the same occurred in the vortioxetine group, with three WHOQOL scales improving minimally and one worsening not significantly (from 62.82±16.65 at T1 to 67.04±15.30 at T5 for the WHOQOL-BREF physical subscale (t=-1.32; p=0.19), from 61.50±17.45 at T1 to 63.24±17.38 at T5 for the WHOQOL-BREF psychological subscale (t=-0.50; p=0.62), from 57.68±18.38 at T1 to 59.60±17.03 at T5 for the WHOQOL-BREF social relations subscale (t=-0.54; p=0.59), and from 63.68±17.99 at T1 to 62.28±14.83 at T5 for the WHOQOL-BREF environmental subscale (t=0.42; p=0.67)). Sertraline was associated with a worsening on all WHOQOL-BREF subscales, although none was significant (from 66.54±15.76 at T1 to 60.02±17.98 at T5 for the WHOQOL-BREF physical subscale (t=1.89; p=0.06), from 62.81±16.85 at T1 to 60.46±16.27 at T5 for the WHOQOL-BREF psychological subscale (t=0.70; p=0.49), from 59.71±15.95 at T1 to 59.02±14.74 at T5 for the WHOQOL-BREF social relations subscale (t=0.22; p=0.83), and from 65.71±13.25 at T1 to 64.67±16.09 at T5 for the WHOQOL-BREF environmental subscale (t=1.48; p=0.14)). From 2 to 3 months, results indicate a main effect of Time ($F_{(1.000,130.000)}$=14.188, p<0.001, η^2=0.098; from 64.98±15.02 to 61.79±15.75). No other significant effects were observed.

All patients, regardless of treatment and gender, showed impairment in quality of life (QoL) between baseline (T0) and 6 months after trauma (T5) and between the moment of trauma (T1) and 6 months after trauma (T5). Specifically, regardless of treatment and gender, QoL levels were significantly decreased at the time of Covid-19-related trauma (T1) as compared to baseline (T0).

A significant increase in QoL was registered in the period between the trauma (T1) and 1 month after the trauma (T2), whereas in the period between 2 (T3) and 3 months after trauma (T4) there was a general impairment in quality of life, regardless of the treatment administered.

3.3. Effects of Antidepressant Treatment on Hospitalisations

After a major Covid-19-related trauma, 46 (32.4%) patients needed to be hospitalised for a month and 96 (67.6%) were supported as outpatients. Of the patients needing hospitalisation, 12 were treated with vortioxetine (24% of patients treated with vortioxetine and 26.09% of patients needing hospitalisation), 17 with trazodone (38.63% of patients taking trazodone and 36.96% of patients needing hospitalisation), and 17 with sertraline (35.42% of patients on sertraline and 36.96% of patients needing hospitalisation). Considering patients not needing hospitalisation, 38 were assuming vortioxetine (76% of patients on vortioxetine and 39.58% of patients needing hospitalisation), 27 trazodone (61.36% of patients on trazodone and 28.125% of patients needing hospitalisation), and 31 sertraline (64.58% of patients on sertraline and 32.29% of patients needing hospitalisation) (Fig. **2**).

The *Chi*-Square test (χ^2) was performed to evaluate differences between treatment groups in hospitalisation rates. Although a lower hospitalisation rate was observed for the vortioxetine group (24%) compared to sertraline (35.42%) and trazodone (38.58%), the difference was not significant ($\chi^2_{(2)}$, p=0.27).

Despite patients treated with vortioxetine were less susceptible to a worsening of the clinical picture at the moment of the trauma, and therefore to hospitalisation, no drug treatment was found to protect significantly more than the others from psychiatric symptom impairment.

Hospitalised patients receiving trazodone, who received the intravenous or intramuscular formulation, needed no benzodiazepine adjunction during their hospital stay.

3.4. The Role of Antidepressants on Specific Psychopathological Dimensions. The Case of Insomnia

To evaluate insomnia in every patient we used a composite index. For each patient, we divided by 6 the score on each specific insomnia item of the MADRS and by 4 each insomnia item of the Ham-A, and summed the two ratios. At T2 (1 month after suffering Covid-19-related trauma), T3 (2 months after suffering Covid-19-related trauma), and T4 (3 months after suffering Covid-19-related trauma), trazodone had the lowest insomnia rates. Repeated-measures ANOVA showed significant differences from both the pre-trauma period to the end of the study and at the time of trauma through the end of the study. However, the three drugs

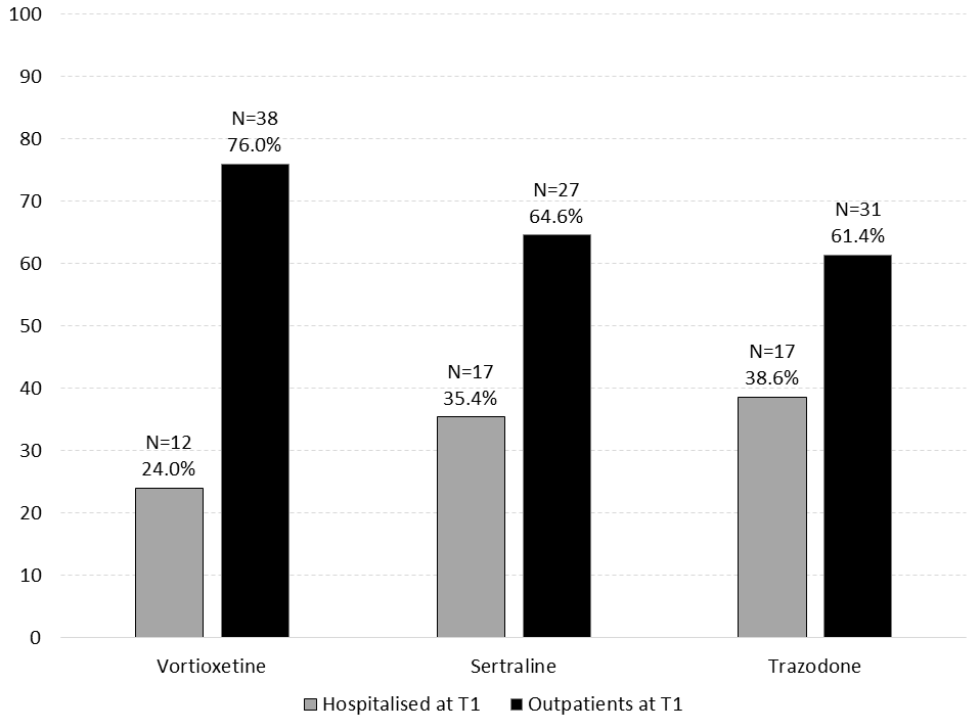

Fig. (2). Percentages of patients needing hospitalisation according to the antidepressant they were receiving. Although differences were not significant, patients on vortioxetine needed hospitalisation at least 10% less than patients on sertraline or trazodone. T1, time of Covid-19-related trauma.

behaved differently; insomnia increased significantly with all drugs from pre-trauma to trauma, but decreased significantly between trauma and six months later only for vortioxetine on Student's *t* test. While for vortioxetine and trazodone there was a significant decrease between the trauma and six months later on the repeated measures ANOVA, with sertraline the levels of insomnia from the time of Covid-19-related trauma to the sixth month post-trauma remained relatively stable. Changes in the levels of insomnia across the study are shown in Table **3**. The composite score of insomnia did not correlate with scores on the WHOQOL domains at any timepoint for any drug, with Pearson's r correlations ranging from -0.187 to as low as -0.0003 and statistical significance ranging from p=0.064 to 0.999.

4. DISCUSSION

In this study we evaluated the effects of a major Covid-19-related trauma (intended as being infected with SARS-CoV-2 and developing Covid-19 infection or witnessing it in a close relative, death of a loved one due to Covid-19, domestic violence or job loss related to Covid-19 restrictions) on a population of outpatients treated for depressive symptoms in MDD, BD and SSOPDs with three different antidepressants: vortioxetine, sertraline and trazodone. We found people who were previously stabilised on an antidepressant to worsen on all psychopathological assessments (MADRS, BPRS, Ham-A, VAS-crav and WHOQOL-BREF), particularly on anhedonia, avolition and apathy associated with depression, here considered as a cross-psychopathological dimension. Thus, they needed augmentation or dosage increase, with some of them requiring hospitalisation for one month. However, at the subsequent assessments, depression-related scores (MADRS) improved gradually (2, 3, and 6 months post-trauma). We might not speculate as to whether the improvement was actually related to continued drug intake or adjustments or to the natural self-righting properties of the organisms or both and to what extent each. The worsening and the subsequent improvement involved all the antidepressants tested here, so to discuss about the pharmacological mechanisms involved in the effects of these drugs we needed that these drugs had possibly differential effects on the clinical course of the patients. This was not the case, possibly due to the reduced sample sizes of each treatment group.

A proportion of the outpatients had such a remarkable worsening of symptoms that they had to be hospitalised for one month, where they could benefit from close monitoring and treatment adjustment, and even alternative routes of drug administration. For instance, during hospitalisation, patients treated with trazodone could receive intravenously or intramuscularly twice a day for 6 days. However, this is only an observational finding, as the small sample sizes did not allow for inter-drug differences to emerge.

QoL of patients suffered a stroke at the moment of the Covid-19-related stressful life event; six months after having suffered the event, patients had barely approached their initial QoL levels. While sertraline was related to inability to reach prior wellbeing, vortioxetine and trazodone were associated with a tendency towards improvement, or at least with a tendency to resist to the event-related deterioration.

In this study we observed a post-trauma worsening of the core psychopathological symptoms, which required continuous or adjusted pharmacotherapy, or even hospitalization,

Table 3. ANOVA-1way differences between the three drugs across the various timepoints on the composite insomnia index (MADRS insomnia item/6 *plus* Ham-A insomnia item/4).

Time	Vortioxetine ($\bar{x}$ ±SD)	Trazodone ($\bar{x}$ ±SD)	Sertraline ($\bar{x}$±SD)	df	*F*	*p*
T0 (pre-Covid-19)	0.237±0.292	0.150±0.273	0.205±0.277	2	1.90	0.307, n.s.
T1 (Covid-19 trauma)	0.403±0.354	0.407±0.449	0.505±0.498	2	0.91	0.404, n.s.
T2 (1 month post-trauma)	0.375±0.362	0.250±0.329*	0.446±0.404	2	3.54	0.032*
T3 (2 months post-trauma)	0.377±0.369	0.258±0.342**	0.505±0.442	2	4.98	0.008**
T4 (3 months post-trauma)	0.333±0.352	0.235±0.309**	0.495±0.440	2	6.13	0.003**
T5 (6 months post-trauma)	0.222±0.343	0.252±0.364	0.337±0.361	2	1.43	0.243, n.s.
Repeated measures ANOVA *F* for T0 through T5	6.941	7.218	17.214	-	-	-
p	0.00003***	0.00002***	<0.00001***	-	-	-
Repeated measures ANOVA *F* for T1 through T5	6.147	5.199	4.071	-	-	-
p	0.00011***	0.0005***	0.00342**	-	-	-
Student's *t* for T0 to T1	-2.631	-3.374	-3.782	-	-	-
p	0.0098**	0.0011**	0.000268***	-	-	-
Student's *t* for T1 to T2	0.394	1.948	0.673	-	-	-
p	0.694, n.s.	0.055, n.s.	0.503, n.s.	-	-	-
Student's *t* for T1 to T5	2.652	1.845	1.969	-	-	-
p	0.00928**	0.068, n.s.	0.052, n.s.	-	-	-

*p<0.05; **p<0.01; ***p<0.001. df, degrees of freedom; Ham-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; n.s., not significant; *p*, significance; SD, standard deviation; $\bar{x}$, mean.

that promptly responded after one month and continued over the entire observation period. It is not possible to ascribe this effect to pharmacological treatment alone, as it is possible patients were spontaneously recovering from the trauma due to their innate self-righting properties [55]. However, the few differences among antidepressants that did not reach statistical significance stimulated us to further investigate their effects in larger samples. The timeline of response to an acute traumatic experience involves three stages according to Herman [56], *i.e.*, establishment of safety, remembrance and mourning, and reconnection with ordinary life. However, no timeline has been provided in this paper. Another study investigated in acute stress disorder ROIs such as amygdala and hippocampus, which are definitely altered in post-traumatic stress disorder (PTSD) [57], and found no alterations after four weeks while the patients had recovered [58]. It is possible that different patients have different timelines to recovery from trauma and some of them might develop PTSD and others do not; cumulating their response curves may confound the overall curves, but we did not subdivide our sample into PTSD-positive and PTSD-negative subsamples, as the sizes within each drug treatment would have been very small.

One core problem with stressful traumatic events is insomnia [59] and insomnia in turn may affect patients' quality of life [60]. We could have expected that some of the effects of antidepressants on QoL would have been mediated through insomnia, but the two measures correlated poorly.

However, patients treated with vortioxetine are worth considering. More than the other treatments, this patient group showed a smoother symptom surge with the trauma, particularly depressive and anxious symptoms, a better improvement the following months, and decreased odds for being hospitalised. This finding could be attributed to vortioxetine's multimodal pharmacodynamics, which, on one hand, enhances serotonergic activity, and on the other, modulates other mechanisms involved in mood balance and in other aspects of depression, such as cognitive impairment [61, 62]. Vortioxetine's tolerability could have ensued in increased quality of life and in a better global clinical picture [63]. Sexual dysfunction is similar to placebo in the vortioxetine group; the drug is not associated to weight gain [64], and does not affect driving performance [65].

Although numerically and not significantly, QoL improvement on most scales from T1 to T2 was higher for trazodone with respect to vortioxetine and sertraline. However this is not readily explainable or correlated to other measures. In the trazodone group, one major difference between being followed as outpatients and being hospitalised for one month was that during hospitalisation, injectable (intravenous and intramuscular) trazodone administration was made available, which is little prescribed for home use.

Our clinical impression is that patients who received trazodone intravenously for one week, as is current practice in some Italian contexts [66,67], responded rapidly to the treatment as regards anxiety, psychomotor agitation, and agitated depression. However, this cannot be shown in our sample, perhaps due to reduced sample size of people who received i.v. trazodone. The route of administration apparently does not affect plasma levels or pharmacokinetics of trazodone in the animal [68] and man [69], but to justify the occurrence of more rapid onset of antidepressant action and a fast action to soothe psychomotor agitation with the intravenous formulation there is need for more adequately sampled systematic clinical studies. At any rate, the result of trazodone was only numerical and did not attain statistical significance. Consistently, while adjusting therapy at the time of trauma to treat psychomotor agitation, using parenteral trazodone allowed us to avoid adding benzodiazepines, the use of which should be reduced to avoid common adverse events like respiratory depression, disorders of consciousness, risk of fall, and cognitive impairment [70].

Limitations. Limitations include small sample sizes and lack of assessment of post-traumatic stress disorder symptoms. Pooling the results of MDD, BD, and SSOPDs patients may have obscured differences among these patient populations. These limitations do not allow generalisability of the results. The main strength is that the study was an observational, naturalistic, real word study. Future studies should focus on the relationship between i.v./i.m. trazodone or oral trazodone and QoL or response latency.

CONCLUSION

We found all antidepressant drugs used in our population, *i.e.*, vortioxetine, sertraline, and trazodone, to improve depression and anxiety scores in patients with a major depressive episode independently of whether the patient had MDD, BD, or a SSOPD. Vortioxetine showed a small advantage over the others in patients with an MDE during the course of MDD, BD or SSOPDs. While patients on vortioxetine had decreased nominal need for hospitalisation compared to other drugs, the difference was not significant, presumably due to the small sample size. Trazodone improved more markedly QoL than the other two drugs, in the very first month of treatment after trauma, although not significantly. All three antidepressant drugs used were similarly effective and with small, but distinctive differences.

AUTHORS' CONTRIBUTIONS

GDK, GL, and SDF conceived the study; GL, MM, GL, GT and SDF saw the patients and carried out treatment; EA, FP, MM, ADG and GL assessed and followed up the patients; EA, FP, MM, VG, GDK, and GL implemented the database; VG, ADG, EA, GL, MM, and GDK performed literature searches; FP, GL and GDK performed statistical analyses; GL, FP, SDF, and GDK wrote the first draft; GL, MM, FP, GT and GDK wrote Introduction, Methods, and Results; GL, MM, VG, ADG, GDK, EA, GT and SDF wrote the Discussion and Conclusions; GL, GDK and SDF supervised the final form. All authors wrote substantial portions of the paper and viewed and approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the local ethical committee (ASL RM2). All patients were provided free informed consent to participate in the study and for treatments received.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. This study used human data; it was conducted in accordance with the Principles of Human Rights, as adopted by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964, subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

CONSENT FOR PUBLICATION

All patients were explained study aims and methods and asked and freely informed provided consent for publication of their data. All patients provided consent for treatment received.

STANDARD OF REPORTING

STROBE guidelines and methodologies were followed.

AVAILABILITY OF DATA AND MATERIALS

Available in electronic form upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

STROBE-checklist is available on the publisher's website along with the published article.

REFERENCES

[1] Adhikari, S.P.; Meng, S.; Wu, Y.J.; Mao, Y.P.; Ye, R.X.; Wang, Q.Z.; Sun, C.; Sylvia, S.; Rozelle, S.; Raat, H.; Zhou, H. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect. Dis. Poverty*, **2020**, *9*(1), 29. http://dx.doi.org/10.1186/s40249-020-00646-x PMID: 32183901

[2] Pierce, M.; Hope, H.; Ford, T.; Hatch, S.; Hotopf, M.; John, A.; Kontopantelis, E.; Webb, R.; Wessely, S.; McManus, S.; Abel, K.M. Mental health before and during the COVID-19 pandemic: a

longitudinal probability sample survey of the UK population. *Lancet Psychiatry,* **2020**, *7*(10), 883-892. http://dx.doi.org/10.1016/S2215-0366(20)30308-4 PMID: 32707037

[3] Rogers, J.P.; Chesney, E.; Oliver, D.; Pollak, T.A.; McGuire, P.; Fusar-Poli, P.; Zandi, M.S.; Lewis, G.; David, A.S. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry,* **2020**, *7*(7), 611-627. http://dx.doi.org/10.1016/S2215-0366(20)30203-0 PMID: 32437679

[4] Janiri, D.; Carfì, A.; Kotzalidis, G.D.; Bernabei, R.; Landi, F.; Sani, G. Posttraumatic stress disorder in patients after severe COVID-19 infection. *JAMA Psychiatry,* **2021**, *78*(5), 567-569. http://dx.doi.org/10.1001/jamapsychiatry.2021.0109 PMID: 33599709

[5] International Federation of Red Cross and Red Crescent Societies, UNICEF, WHO.. *Social stigma associated with COVID-19. A guide to preventing and addressing social stigma*; International Federation of Red Cross and Red Crescent Societies: Geneva, CH, **2020**.

[6] Kofman, Y.B.; Garfin, D.R. Home is not always a haven: The domestic violence crisis amid the COVID-19 pandemic. *Psychol. Trauma,* **2020**, *12*(S1), S199-S201. http://dx.doi.org/10.1037/tra0000866 PMID: 32478558

[7] World Health Organization. *Mental health and psychosocial considerations during the COVID-19 outbreak*; World Health Organization: Geneva, CH, **2020**.

[8] Rajkumar, R.P. COVID-19 and mental health: A review of the existing literature. *Asian J. Psychiatr.,* **2020**, *52*, 102066. http://dx.doi.org/10.1016/j.ajp.2020.102066 PMID: 32302935

[9] Zhang, L.; Pan, R.; Cai, Y.; Pan, J. The prevalence of post-traumatic stress disorder in the general population during the COVID-19 pandemic: A systematic review and single-arm meta-analysis. *Psychiatry Investig.,* **2021**, *18*(5), 426-433. http://dx.doi.org/10.30773/pi.2020.0458 PMID: 33910325

[10] Shinn, A.K.; Viron, M. Perspectives on the COVID-19 pandemic and individuals with serious mental illness. *J Clin Psychiatry,* **2020**, *81*(3), 20com13412. http://dx.doi.org/10.4088/JCP.20com13412 PMID: 32369691

[11] Yao, H.; Chen, J.H.; Xu, Y.F. Patients with mental health disorders in the COVID-19 epidemic. *Lancet Psychiatry,* **2020**, *7*(4), e21. http://dx.doi.org/10.1016/S2215-0366(20)30090-0 PMID: 32199510

[12] Wang, Q.; Xu, R.; Volkow, N.D. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. *World Psychiatry,* **2021**, *20*(1), 124-130. http://dx.doi.org/10.1002/wps.20806 PMID: 33026219

[13] Nemani, K.; Li, C.; Olfson, M.; Blessing, E.M.; Razavian, N.; Chen, J.; Petkova, E.; Goff, D.C. Association of psychiatric disorders with mortality among patients with COVID-19. *JAMA Psychiatry,* **2021**, *78*(4), 380-386. http://dx.doi.org/10.1001/jamapsychiatry.2020.4442 PMID: 33502436

[14] Adhanom Ghebreyesus, T. Addressing mental health needs: an integral part of COVID-19 response. *World Psychiatry,* **2020**, *19*(2), 129-130. http://dx.doi.org/10.1002/wps.20768 PMID: 32394569

[15] Steel, Z.; Marnane, C.; Iranpour, C.; Chey, T.; Jackson, J.W.; Patel, V.; Silove, D. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int. J. Epidemiol.,* **2014**, *43*(2), 476-493. http://dx.doi.org/10.1093/ije/dyu038 PMID: 24648481

[16] Li, J.; Yang, Z.; Qiu, H.; Wang, Y.; Jian, L.; Ji, J.; Li, K. Anxiety and depression among general population in China at the peak of the COVID-19 epidemic. *World Psychiatry,* **2020**, *19*(2), 249-250. http://dx.doi.org/10.1002/wps.20758 PMID: 32394560

[17] Maes, M.; Christophe, A.; Delanghe, J.; Altamura, C.; Neels, H.; Meltzer, H.Y. Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res.,* **1999**, *85*(3), 275-291. http://dx.doi.org/10.1016/S0165-1781(99)00014-1 PMID: 10333380

[18] Fourrier, C.; Sampson, E.; Mills, N.T.; Baune, B.T. Anti-inflammatory treatment of depression: study protocol for a randomised controlled trial of vortioxetine augmented with celecoxib or placebo. *Trials,* **2018**, *19*(1), 447. http://dx.doi.org/10.1186/s13063-018-2829-7 PMID: 30126458

[19] Tomaz, V.S.; Chaves Filho, A.J.M.; Cordeiro, R.C.; Jucá, P.M.; Soares, M.V.R.; Barroso, P.N.; Cristino, L.M.F.; Jiang, W.; Teixeira, A.L.; de Lucena, D.F.; Macedo, D.S. Antidepressants of different classes cause distinct behavioral and brain pro- and anti-inflammatory changes in mice submitted to an inflammatory model of depression. *J. Affect. Disord.,* **2020**, *268*, 188-200. http://dx.doi.org/10.1016/j.jad.2020.03.022 PMID: 32174477

[20] Nobile, B.; Durand, M.; Olié, E.; Guillaume, S.; Molès, J-P.; Haffen, E.; Courtet, P. The anti-inflammatory effect of the tricyclic antidepressant clomipramine and its high penetration in the brain might be useful to prevent the psychiatric consequences of SARS-CoV-2 infection. *Front. Pharmacol.,* **2021**, *12*, 615695. http://dx.doi.org/10.3389/fphar.2021.615695 PMID: 33767623

[21] Keepers, G.A.; Fochtmann, L.J.; Anzia, J.M.; Benjamin, S.; Lyness, J.M.; Mojtabai, R.; Servis, M.; Walaszek, A.; Buckley, P.; Lenzenweger, M.F.; Young, A.S.; Degenhardt, A.; Hong, S.H. (Systematic Review). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Am. J. Psychiatry,* **2020**, *177*(9), 868-872. http://dx.doi.org/10.1176/appi.ajp.2020.177901 PMID: 32867516

[22] Malhi, G.S.; Bell, E.; Bassett, D.; Boyce, P.; Bryant, R.; Hazell, P.; Hopwood, M.; Lyndon, B.; Mulder, R.; Porter, R.; Singh, A.B.; Murray, G. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust. N. Z. J. Psychiatry,* **2021**, *55*(1), 7-117. http://dx.doi.org/10.1177/0004867420979353 PMID: 33353391

[23] Kotzalidis, G.D.; Lombardozzi, G.; Matrone, M.; Amici, E.; Perrini, F.; Cuomo, I.; De Filippis, S. Vortioxetine *vs*. other antidepressants in patients with major depressive episode with or without substance use disorder. *Curr Neuropharmacol,* **2021**, *19*(12), 2296-2307. http://dx.doi.org/10.2174/1570159X19666210113150123 PMID: 33441069

[24] Bang-Andersen, B.; Ruhland, T.; Jørgensen, M.; Smith, G.; Frederiksen, K.; Jensen, K.G.; Zhong, H.; Nielsen, S.M.; Hogg, S.; Mørk, A.; Stensbøl, T.B. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *J. Med. Chem.,* **2011**, *54*(9), 3206-3221. http://dx.doi.org/10.1021/jm101459g PMID: 21486038

[25] Okada, M.; Matsumoto, R.; Yamamoto, Y.; Fukuyama, K. Effects of subchronic administrations of vortioxetine, lurasidone, and escitalopram on thalamocortical glutamatergic transmission associated with serotonin 5-HT7 receptor. *Int. J. Mol. Sci.,* **2021**, *22*(3), 1351. http://dx.doi.org/10.3390/ijms22031351 PMID: 33572981

[26] Koesters, M.; Ostuzzi, G.; Guaiana, G.; Breilmann, J.; Barbui, C. Vortioxetine for depression in adults. *Cochrane Database Syst. Rev.,* **2017**, *7*(7), CD011520. http://dx.doi.org/10.1002/14651858 PMID: 28677828

[27] Talmon, M.; Rossi, S.; Pastore, A.; Cattaneo, C.I.; Brunelleschi, S.; Fresu, L.G. Vortioxetine exerts anti-inflammatory and immunomodulatory effects on human monocytes/macrophages. *Br. J. Pharmacol.,* **2018**, *175*(1), 113-124. http://dx.doi.org/10.1111/bph.14074 PMID: 29057467

[28] Wang, Y.; Gu, J.H.; Liu, L.; Liu, Y.; Tang, W.Q.; Ji, C.H.; Guan, W.; Zhao, X.Y.; Sun, Y.F.; Xu, D.W.; Jiang, B. Hippocampal PPARα plays a role in the pharmacological mechanism of vortioxetine, a multimodal-acting antidepressant. *Front. Pharmacol.,* **2021**, *12*, 673221. http://dx.doi.org/10.3389/fphar.2021.673221 PMID: 34211395

[29] Shin, J.J.; Saadabadi, A. Trazodone. In: *StatPearls*; StatPearls Publishing: Treasure Island (FL), **2021**. https://www.ncbi.nlm.nih.gov/books/NBK470560/ Accessed on June 23, 2021

[30] Daniele, S.; Zappelli, E.; Martini, C. Trazodone regulates neurotrophic/growth factors, mitogen-activated protein kinases and

lactate release in human primary astrocytes. *J. Neuroinflammation,* **2015**, *12*(1), 225. http://dx.doi.org/10.1186/s12974-015-0446-x PMID: 26627476

[31] Hoozemans, J.J.; van Haastert, E.S.; Nijholt, D.A.; Rozemuller, A.J.; Eikelenboom, P.; Scheper, W. The unfolded protein response is activated in pretangle neurons in Alzheimer's disease hippocampus. *Am. J. Pathol.,* **2009**, *174*(4), 1241-1251. http://dx.doi.org/10.2353/ajpath.2009.080814 PMID: 19264902

[32] Wilhelmus, M.M.; Verhaar, R.; Andringa, G.; Bol, J.G.; Cras, P.; Shan, L.; Hoozemans, J.J.; Drukarch, B. Presence of tissue transglutaminase in granular endoplasmic reticulum is characteristic of melanized neurons in Parkinson's disease brain. *Brain Pathol.,* **2011**, *21*(2), 130-139. http://dx.doi.org/10.1111/j.1750-3639.2010.00429.x PMID: 20731657

[33] Stutzbach, L.D.; Xie, S.X.; Naj, A.C.; Albin, R.; Gilman, S.; Lee, V.M.; Trojanowski, J.Q.; Devlin, B.; Schellenberg, G.D. The unfolded protein response is activated in disease-affected brain regions in progressive supranuclear palsy and Alzheimer's disease. *Acta Neuropathol. Commun.,* **2013**, *1*(1), 31. http://dx.doi.org/10.1186/2051-5960-1-31 PMID: 24252572

[34] Hoozemans, J.J.; van Haastert, E.S.; Eikelenboom, P.; de Vos, R.A.; Rozemuller, J.M.; Scheper, W. Activation of the unfolded protein response in Parkinson's disease. *Biochem. Biophys. Res. Commun.,* **2007**, *354*(3), 707-711. http://dx.doi.org/10.1016/j.bbrc.2007.01.043 PMID: 17254549

[35] Halliday, M.; Radford, H.; Zents, K.A.M.; Molloy, C.; Moreno, J.A.; Verity, N.C.; Smith, E.; Ortori, C.A.; Barrett, D.A.; Bushell, M.; Mallucci, G.R. Repurposed drugs targeting eIF2&α;-P-mediated translational repression prevent neurodegeneration in mice. *Brain,* **2017**, *140*(6), 1768-1783. http://dx.doi.org/10.1093/brain/awx074 PMID: 28430857

[36] Emam, A.M.; Saad, M.A.; Ahmed, N.A.; Zaki, H.F. Vortioxetine mitigates neuronal damage by restricting PERK/eIF2α/ATF4/CHOP signaling pathway in rats subjected to focal cerebral ischemia-reperfusion. *Life Sci.,* **2021**, *283*, 119865. http://dx.doi.org/10.1016/j.lfs.2021.119865 PMID: 34358549

[37] Kelmendi, B.; Adams, T.G.; Yarnell, S.; Southwick, S.; Abdallah, C.G.; Krystal, J.H. PTSD: from neurobiology to pharmacological treatments. *Eur. J. Psychotraumatol.,* **2016**, *7*(1), 31858. http://dx.doi.org/10.3402/ejpt.v7.31858 PMID: 27837583

[38] U.S. Department of Veterans Affairs. *VA/DoD clinical practice guidelines: management of posttraumatic stress disorder and acute stress reaction*; US Department of Veterans Affairs: Washington, DC, **2017**.

[39] American Psychological Association (APA). *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults*; American Psychological Association: Washington, DC, **2017**.

[40] NICE (National Institute for Health and Care Excellence). *Post-traumatic Stress Disorder NICE guideline (NG116)*; London (UK), **2018**. Available from: www.nice.org.uk/guidance/ng116 Accessed on June 23, 2021

[41] Owens, M.J.; Morgan, W.N.; Plott, S.J.; Nemeroff, C.B. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J. Pharmacol. Exp. Ther.,* **1997**, *283*(3), 1305-1322. PMID: 9400006

[42] Tatsumi, M.; Groshan, K.; Blakely, R.D.; Richelson, E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur. J. Pharmacol.,* **1997**, *340*(2-3), 249-258. http://dx.doi.org/10.1016/S0014-2999(97)01393-9 PMID: 9537821

[43] Cusack, B.; Nelson, A.; Richelson, E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. *Psychopharmacology (Berl.),* **1994**, *114*(4), 559-565. http://dx.doi.org/10.1007/BF02244985 PMID: 7855217

[44] Koe, B.K.; Lebel, L.A. Effects of serotoninergic agents on down-regulation of beta-adrenoceptors by the selective serotonin reuptake inhibitor sertraline. *Arch. Int. Pharmacodyn. Ther.,* **1995**, *329*(2), 231-244. PMID: 8540763

[45] Thomas, D.N.; Nutt, D.J.; Holman, R.B. Sertraline, a selective serotonin reuptake inhibitor modulates extracellular noradrenaline in the rat frontal cortex. *J. Psychopharmacol.,* **1998**, *12*(4), 366-370. http://dx.doi.org/10.1177/026988119801200406 PMID: 10065910

[46] Ishima, T.; Fujita, Y.; Hashimoto, K. Interaction of new antidepressants with sigma-1 receptor chaperones and their potentiation of neurite outgrowth in PC12 cells. *Eur. J. Pharmacol.,* **2014**, *727*, 167-173. http://dx.doi.org/10.1016/j.ejphar.2014.01.064 PMID: 24508523

[47] Matsushima, Y.; Terada, K.; Kamei, C.; Sugimoto, Y. Sertraline inhibits nerve growth factor-induced neurite outgrowth in PC12 cells *via* a mechanism involving the sigma-1 receptor. *Eur. J. Pharmacol.,* **2019**, *853*, 129-135. http://dx.doi.org/10.1016/j.ejphar.2019.03.032 PMID: 30902656

[48] Montgomery, S.A.; Asberg, M. A new depression scale designed to be sensitive to change. *Br. J. Psychiatry,* **1979**, *134*(4), 382-389. http://dx.doi.org/10.1192/bjp.134.4.382 PMID: 444788

[49] Overall, J.E. The Brief Psychiatric Rating Scale in psychopharmacology research. In: *Psychological measurements in psychopharmacology: Modern Problems in Pharmacopsychiatry 7*; Pichot, P.; Oliver-Martin, R., Eds.; Karger: Basel, **1974**; pp. 67-78. http://dx.doi.org/10.1159/000395069

[50] Hamilton, M. The assessment of anxiety states by rating. *Br. J. Med. Psychol.,* **1959**, *32*(1), 50-55. http://dx.doi.org/10.1111/j.2044-8341.1959.tb00467.x PMID: 13638508

[51] Nicholson, A.N. Visual analogue scales and drug effects in man. *Br. J. Clin. Pharmacol.,* **1978**, *6*(1), 3-4. http://dx.doi.org/10.1111/j.1365-2125.1978.tb01673.x PMID: 666945

[52] World Health Organization (WHO). *The World Health Organization Quality of Life (WHOQOL)-BREF*; World Health Organization: Geneva, Switzerland, **2004**.

[53] Shapiro, S.S.; Wilk, M.B. An analysis of variance test for normality (complete samples). *Biometrika,* **1965**, *52*(3-4), 591-611. http://dx.doi.org/10.1093/biomet/52.3-4.591

[54] Mauchly, J.W. Significance Test for Sphericity of a Normal *n*-Variate Distribution. *Ann. Math. Stat.,* **1940**, *11*(2), 204-209. http://dx.doi.org/10.1214/aoms/1177731915

[55] Pancheri, L.; Paparo, F. Fattori terapeutici specifici e comuni in psicoanalisi: Il self-righting. *Riv. Psichiatr.,* **2003**, *38*(3), 105-116. [Specific and nonspecific therapeutic factors in psychoanalysis: Self-righting].

[56] Herman, J.L. Recovery from psychological trauma. *Psychiatry Clin. Neurosci.,* **1998**, *52*(S1)(Suppl. 1), S98-S103. http://dx.doi.org/10.1046/j.1440-1819.1998.0520s5S145.x

[57] Bremner, J.D. Effects of traumatic stress on brain structure and function: relevance to early responses to trauma. *J. Trauma Dissociation,* **2005**, *6*(2), 51-68. http://dx.doi.org/10.1300/J229v06n02_06 PMID: 16150669

[58] Szabó, C.; Kelemen, O.; Levy-Gigi, E.; Kéri, S. Acute response to psychological trauma and subsequent recovery: no changes in brain structure. *Psychiatry Res.,* **2015**, *231*(3), 269-272. http://dx.doi.org/10.1016/j.pscychresns.2015.01.005 PMID: 25659474

[59] Werner, G.G.; Riemann, D.; Ehring, T. Fear of sleep and trauma-induced insomnia: A review and conceptual model. *Sleep Med. Rev.,* **2021**, *55*, 101383. http://dx.doi.org/10.1016/j.smrv.2020.101383 PMID: 32992229

[60] Olfson, M.; Wall, M.; Liu, S.M.; Morin, C.M.; Blanco, C. Insomnia and impaired quality of life in the United States. *J Clin Psychiatry,* **2018**, *79*(5), 17m12020. http://dx.doi.org/10.4088/JCP.17m12020 PMID: 30256547

[61] Alvarez, E.; Perez, V.; Artigas, F. Pharmacology and clinical potential of vortioxetine in the treatment of major depressive disorder. *Neuropsychiatr. Dis. Treat.,* **2014**, *10*, 1297-1307. http://dx.doi.org/10.2147/NDT.S41387 PMID: 25075188

[62] de Bartolomeis, A.; Fagiolini, A.; Maina, G. [Vortioxetine in the treatment of major depression]. *Riv Psichiatr,* **2016**, *51*(6), 215-230. http://dx.doi.org/10.1708/2596.26720 PMID: 27996982

[63] Katona, C.L.; Katona, C.P. New generation multi-modal antidepressants: focus on vortioxetine for major depressive disorder. *Neuropsychiatr. Dis. Treat.,* **2014**, *10*, 349-354. http://dx.doi.org/10.2147/NDT.S39544 PMID: 24570588

[64] Baldwin, D.S.; Chrones, L.; Florea, I.; Nielsen, R.; Nomikos, G.G.; Palo, W.; Reines, E. The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies. *J. Psychopharmacol.,* **2016**, *30*(3), 242-252. http://dx.doi.org/10.1177/0269881116628440 PMID: 26864543

[65] Theunissen, E.L.; Street, D.; Højer, A.M.; Vermeeren, A.; van Oers, A.; Ramaekers, J.G. A randomized trial on the acute and steady-state effects of a new antidepressant, vortioxetine (Lu AA21004), on actual driving and cognition. *Clin. Pharmacol. Ther.,* **2013**, *93*(6), 493-501. http://dx.doi.org/10.1038/clpt.2013.39 PMID: 23588319

[66] Fiorentini, A.; Rovera, C.; Caldiroli, A.; Arici, C.; Prunas, C.; Di Pace, C.; Paletta, S.; Pozzoli, S.M.; Buoli, M.; Altamura, A.C. Efficacy of oral trazodone slow release following intravenous administration in depressed patients: a naturalistic study. *Riv. Psichiatr.,* **2018**, *53*(5), 261-266. http://dx.doi.org/10.1708/3000.30005 PMID: 30353201

[67] Buoli, M.; Rovera, C.; Pozzoli, S.M.; Fiorentini, A.; Cremaschi, L.; Caldiroli, A.; Altamura, A.C. Is trazodone more effective than clomipramine in major depressed outpatients? A single-blind study with intravenous and oral administration. *CNS Spectr.,* **2019**, *24*(2), 258-264. http://dx.doi.org/10.1017/S1092852917000773 PMID: 29081313

[68] Rurak, A.; Melzacka, M.; Danek, L. Pharmacokinetics of trazodone after different routes of administration. *Pol. J. Pharmacol. Pharm.,* **1981**, *33*(3), 341-348. PMID: 7322946

[69] Nilsen, O.G.; Dale, O. Single dose pharmacokinetics of trazodone in healthy subjects. *Pharmacol. Toxicol.,* **1992**, *71*(2), 150-153. http://dx.doi.org/10.1111/j.1600-0773.1992.tb00535.x PMID: 1438031

[70] Wang, L.; Pan, Y.; Ye, C.; Guo, L.; Luo, S.; Dai, S.; Chen, N.; Wang, E. A network meta-analysis of the long- and short-term efficacy of sleep medicines in adults and older adults. *Neurosci. Biobehav. Rev.,* **2021**, *131*, 489-496. http://dx.doi.org/10.1016/j.neubiorev.2021.09.035 PMID: 34560134