The effectiveness and tolerability of agomelatine in the treatment of depression after COVID-19 infection in Russian daily clinical practice (TELESPHOR study)

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Abstract

Aim: Affective disorders such as depression and anxiety are one of the most prevalent symptoms observed in patients following coronavirus disease 2019 (COVID-19). The aim of the TELESPHOR study was to evaluate the antidepressant effectiveness and tolerability of agomelatine therapy in daily clinical practice in patients with major depressive episodes (MDE) post-COVID-19. **Methods**: This multicenter, observational study enrolled outpatients aged 18-65 years who experienced an MDE (17 item Hamilton Rating Scale for Depression [HAMD-17] total score of 8-24) within 3 months of laboratory confirmed SARS-CoV-2 infection and who had initiated treatment with agomelatine. Study visits occurred at weeks 2, 4 and 8. The primary outcome was the antidepressant effectiveness of agomelatine assessed by change in HAMD-17 total score at week 8. Secondary outcomes included changes in HAMD-17 item 10 (anxiety psychic) and item 11 (anxiety somatic), the proportion of responders ([?]50% decrease in baseline HAMD-17) and remitters (HAMD-17 score [?]7 at week 8), and impact on quality of life (QoL) (Short Form Survey [SF-36] questionnaire). Tolerability was assessed at each study visit. **Results**: The full analysis set comprised 103 patients of whom 73 (70.9%) were women. Median age was 45 years, and in the past 3 months 81 (78.6%) had experienced mild and 22 (21.4%) moderate COVID-19. The mean time from onset of infection to study inclusion was 2.1±0.7 months. At study entry, 55 (53.4%) had mild and 48 (46.6%) had moderate MDE. Agomelatine was associated with a significant improvement in depression severity with decreases in mean total HAMD-17 score compared with baseline of 2.6±3.3, 6.7±5.3, and 10.9±4.9 at weeks 2, 4, and 8, respectively ($P<0.0001$ for all). Significant reductions in anxiety psychic and anxiety somatic were also observed. Mental and physical components of SF-36 were significantly improved compared with baseline ($P<0.0001$). The proportion of responders was 81.4% and the proportion of remitters was 71.6%. Agomelatine was well tolerated over the 8-week follow-up. **Conclusion**: Treatment with agomelatine was associated with rapid and significant antidepressive and anxiolytic effectiveness, improved QoL, and good tolerability in the treatment of patients with an MDE after COVID-19.

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Conclusion : Treatment with agomelatine was associated with rapid and significant antidepressive and anxiolytic effectiveness, improved QoL, and good tolerability in the treatment of patients with an MDE after COVID-19.

KEYWORDS: agomelatine, COVID-19, major depressive disorder, routine clinical practice

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the causative agent of coronavirus disease 2019 (COVID-19), a disease with a wide range of manifestations, from asymptomatic to severe or fatal (Wiersinga et al., 2020). In addition to the acute symptoms, a growing body of scientific and clinical evidence highlights long-term consequences that can affect multiple organ systems (Gupta et al., 2020). Depression, anxiety, fatigue, sleep difficulties, and cognitive impairment have been found to be the most common long-term neuropsychiatric consequences following COVID-19, highlighting the importance for consensus on specific neuropsychiatric needs in the multidisciplinary management of patients after the acute disease (Khraisat et al., 2022; Medvedev, 2021). In a systematic review of psychiatric sequelae in COVID-19

patients the most frequently reported symptoms were depression and/or anxiety, examined in 47 of the 66 included studies (Schou et al., 2021). Clinically significant depression has been noted in approximately 30-40% of patients at 1, 3, and 6 months after COVID-19, suggesting that long-term depressive effects occur in many patients after the acute infection (Rogers et al., 2020; Renaud-Charest et al., 2021). A Chinese study which examined the long-term health consequences of COVID-19 following discharge from hospital reported anxiety, depression, and sleep difficulties were present in approximately one-quarter of patients in the 6 months post-discharge (Huang et al., 2021).

Depression after COVID-19 can affect survivors' cognitive performance, symptoms of fatigue, and daily functioning, increasing the burden of noncommunicable illness associated with psychiatric disability (Rogers et al., 2020; Renaud-Charest et al., 2021). Some authors have noted the presence of continued sleep-wake cycle disturbances after recovery from COVID-19 (Salehinejad et al., 2022; Xu et al., 2022; Abuhammad et al., 2023). However, no assessment of the affective state of these patients has been made, suggesting that in some patients sleep disturbances may be part of the affective disorders

Despite the large number of affected patients, there are a paucity of data on the effectiveness of pharmacological treatments for depression disorders in post-acute COVID-19 patients. Some studies have focused on the potential antiviral properties of antidepressants such as fluoxetine (Pashaei, 2021; Hoertel et al., 2021; Dąbrowska et al., 2021) and fluvoxamine (Lenze et al., 2020; Boretti, 2023; Dobrodeeva et al., 2022), mostly during the active COVID-19 infection period. In contrast, research on the efficacy of antidepressants for post-COVID depressive disorders is limited to a few studies with selective serotonin reuptake inhibitors (SSRI) (Dobrodeeva et al., 2022; Mazza et al., 2022; Di Nicola et al., 2023).

Agomelatine is an antidepressant acting as a melatonergic MT1/MT2 receptor agonist with 5-HT2C serotonergic receptor antagonist properties. It is effective against a range of depressive symptoms in patients with moderate to severe major depressive episode (MDE) with an effect size comparable to that of other currently available antidepressive drugs (de Bodinat et al., 2010; Taylor et al., 2014; Cipriani et al., 2018). Efficacy has been demonstrated in short-term and long-term controlled studies, as well as in clinical practice and in patients with somatic diseases (Medvedev et al., 2016; Medvedev, 2018; Medvedev, 2017; Medvedev et al., 2019; Demyttenaere et al., 2013; Kennedy & Rizvi, 2010; Kennedy et al, 2016). Other aspects of clinical efficacy such as well-being, improvement of sleep disorders, daily functioning, and sexual function have also been demonstrated (Kennedy & Rizvi, 2010). The safety profile of agomelatine has been established in a number of randomized controlled trials. These have demonstrated an incidence of adverse events with agomelatine similar to that observed for placebo (agomelatine 42.4% versus placebo 42.5%) (Olié & Kasper, 2007) and sertraline (agomelatine 48.0% versus sertraline 49.1%) (Kasper et al., 2010), and lower than that observed with venlafaxine (agomelatine 51.2% versus venlafaxine 57.1%) (Lemoine et al., 2007) and escitalopram (agomelatine 66.2% versus escitalopram 81.8%) (Quera-Salva et al., 2011). Good tolerability is important for adherence and persistence with treatment and ultimately for a drug's effectiveness. A recent network meta-analysis has confirmed the favorable safety profile of agomelatine (Cipriani et al., 2018).

Agomelatine may be a favorable therapeutic choice for use in patients with depression onset after COVID-19, but data are currently lacking on its clinical effectiveness in this population in routine clinical practice. The primary objective of the current study was therefore to describe the antidepressive effectiveness and tolerability of agomelatine in patients with a post-COVID-19 MDE in an outpatient setting.

METHODS

Study design

TELESPHOR was a multicenter, observational study conducted in outpatient ambulatory state and private clinics in four cities in Russia between March 2022 and February 2023. The study included adults aged 18-65 who experienced an MDE within 3 months of polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection in whom treatment with agomelatine was initiated. The depressive episode was measured with the 17 item Hamilton Rating Scale for Depression (HAMD-17) where scores of 0–7 are considered normal, 8–16 suggest mild depression, 17–23 moderate depression, and scores over 24 are indicative of severe

depression (Zimmerman et al., 2013). In the current study, patients with a total HAMD-17 score of 8-24 were considered to be suffering an MDE. Patients ineligible to participate in the study were those diagnosed with suicidal risk (score [?]2 in item 3 of the HAMD-17 scale and/or according to clinical evaluation by the investigator), psychotic symptoms (according to clinical evaluation by the investigator), or other mental disorder or disease; noncompensated serious somatic or neurological disease; and COVID-19 that could not be confirmed. Agomelatine was administered in accordance with the approved Summary of Product Characteristics (SmPC) in Russia, local standards and guidelines.

At baseline, severity of depression, level of anxiety, and quality of life (QoL) status in addition to clinical and sociodemographic data were collected from all included patients. Data on the history of COVID-19 infection and its severity were collected retrospectively and extracted from medical records. Patients were seen at baseline, with further clinic visits at 2, 4, and 8 weeks of prospective observation. Due to the observational nature of the study, the protocol did not mandate any assignment of the included patients to one or another treatment strategy. Agomelatine prescription was not decided in advance by a trial protocol, but was determined by the current prescribing practice of the investigating physician and was separate from the decision to include a patient in the study. All included patients were recommended to start treatment with agomelatine 25 mg/day taken at bedtime for at least 8 weeks. In case of insufficient effectiveness of agomelatine after 2 weeks of treatment, and based on the investigating physician's opinion, the daily dose could be increased to 50 mg/day at bedtime.

The primary outcome was the mean change in HAMD-17 total score from baseline to week 8 under agomelatine treatment. Key secondary effectiveness outcomes were changes in the HAMD-17 item 10 "anxiety psychic" and item 11 "anxiety somatic" scores, and investigator-determined global severity of the patient's illness assessed by the Clinical Global Impressions-Improvement of Illness Scale (CGI-I). Patient QoL was assessed with the 36 item Short Form survey (SF-36). Additional secondary effectiveness outcomes included the proportion of patients with a response to agomelatine treatment (defined as a decrease of [?]50% in the baseline HAMD-17 score), as well as the proportion of those with remission (defined as a HAMD-17 total score [?]7 at week 8 of the observational period). The number and proportion of patients with reported adverse events and adverse drug reactions were analyzed, including those that could lead to discontinuation of the drug during the study.

The study protocol was approved by the Moscow Inter-Academic Ethics Committee on March 17, 2022 (approval protocol # 3) and was conducted in compliance with the Declaration of Helsinki, and local regulatory requirements. All participants provided their informed consent before inclusion in the study (NCT05323994).

2.2 Statistical considerations

Descriptive and comparative statistics were used to present the results of this non-interventional observational study. Continuous variables are reported as mean +- standard deviation or median and interquartile range (if not normally distributed). Categorical data are expressed as numbers (percentages). Only patients for whom data on the primary outcome (HAMD-17 score evaluation) were available at baseline and at the end of the follow up period were included in the statistical analysis. Adjusted means and standard errors were calculated with generalized linear modelling to explore associations between the observed antidepressive effectiveness of agomelatine and clinically important parameters. For this, univariate regression modeling was performed using the following covariates for adjustment analysis: age, sex, baseline total HAMD-17 score, severity of COVID-19 infection, time since COVID-19 infection onset, and status of taking any antidepressants prior to the enrollment visit. The level of statistical significance for the univariate analysis was set at $P<0.05$. For each significant predictor identified in the univariate analysis we also conducted multivariate linear regression modelling.

To estimate required study sample size the following assumptions were made. We calculated that approximately 28 study subjects would be sufficient to detect at least a 3.0-point difference between the sample and population means with 90% power at a 0.005 one-sided significance level. Considering the observational nature of the study a dropout rate of approximately 30% was assumed. A minimum number of 40 outpatients

was therefore required to be enrolled in the study.

RESULTS

A total of 104 patients were enrolled. One patient did not meet the inclusion criterium for depression severity at baseline and was excluded. Data for 103 (99.03%) patients therefore comprised the full analysis set (FAS). One patient in the FAS terminated participation in the study prematurely due to a lack of treatment effect with agomelatine, requiring the administration of another antidepressant.

Patient baseline demographic and clinical characteristics are presented in *Table 1.* Participants were mostly female (73 [70.9%]) with a mean age of 44.0+-13.3 years. The majority was employed (79.6%) and none of the patients had received any prior treatment with antidepressants. At baseline, 21.4% of patients reported they had suffered moderate COVID-19 infection in the past 3 months, and 78.6% had a history of mild COVID-19. The mean time from infection onset until the enrollment visit was 2.1+-0.7 months. Initial assessment of the severity of the depressive episode showed that patients were almost equally distributed between mild (n=55, 53.4%) and moderate (n=48, 46.6%) depression. The mean total HAMD-17 score at baseline was 16.3+-4.7 and mean scores for the two anxiety components of the HAMD-17 scale (questions 10 and 11) were 1.4+-0.9 and 1.3+-0.8, respectively. Mean baseline SF-36 QoL scores were 39.7+-8.4 for the physical component and 37.2+-8.7 for the mental component of the questionnaire.

3.1 Effectiveness

A significant improvement in depression severity assessed by the HAMD-17 scale was observed after initiation of agomelatine treatment. The mean total HAMD-17 score decreased compared with baseline by 2.6 +- 3.3 (P<0.0001) at week 2, and by 6.7 +- 5.3 and 10.9 +- 4.9 at the week 4 and 8 visits (P<0.0001 for both), respectively (Figure 1). Agomelatine was also associated with a significant improvement in symptoms of anxiety. Item 10 (anxiety psychic) of the HAMD-17 score was reduced from 1.4+-0.9 at baseline to 0.5+-0.6 at week 8 (Figure 2); the mean change from baseline was 0.9 (95% CI -1.1 -0.7, P<0.0001). Item 11 (anxiety somatic) of the HAMD-17 score was reduced from 1.3+-0.8 at baseline to 0.6+-0.6, with a mean change of 0.7 (95% CI -0.8 -0.5; P<0.0001) at week 8 (Figure 3).

There was a significant improvement in depression severity at each study visit based on investigators' clinical judgement. Mean CGI-I score decreased from 3.4+-0.8 at week 2 to 2.3+-1.0 at week 4 (mean change -1.0; P<0.0001) and to 1.3+-0.6 at week 8 (mean change -2.0 vs week 2 visit; P<0.0001) (Figure 4). At the week 8 visit, 81.4% of patients responded to treatment with agomelatine having at least a 50% decrease from baseline in total HAMD-17 score. In addition, 71.6% of patients had a remission of depression (total HAMD-17 score [?]7).

There was a significant improvement in patients' QoL reflected by an increase in the mean scores of both the SF-36 physical (Figure 5) and mental components (Figure 6). The physical component increased from 39.70+-8.41 at baseline to 45.80+-7.69 at week 4 (mean change -6.20+-8.64 vs baseline, P<0.0001), and to 50.50+-5.70 at week 8 (mean change -11.10+-7.30 vs baseline, P<0.0001). The SF-36 mental component score increased from 37.30+-8.67 at baseline to 39.80+-8.28 (week 2), 47.60+-8.55 (week 4), and 58.70+-6.91 (week 8) resulting in mean changes of 2.70+-4.84, 10.50+-6.89, and 21.40+-8.92 at the week 2, 4 and 8 visits, respectively (P<0.0001 for all timepoints vs baseline).

3.2 Additional effectiveness analyses

To explore the relations between demographic and clinical characteristics and the observed clinical effectiveness of agomelatine on depression we performed several linear regression analyses. The following characteristics were selected as covariates of interest: age, sex, severity of depressive disorder at baseline according to HAMD-17 total score, COVID-19 severity, and time passed since COVID 19 infection onset. Univariate regression analysis showed that depression severity at baseline (regression coefficient: -0.741; P<0.0001), moderate severity COVID-19 (regression coefficient: -3.395; P=0.0035), and time since onset of infection (regression coefficient: -2.395; P=0.0006) were the parameters with a statistically significant relationship with the observed decrease in HAMD-17 total score at the end of follow up (week 8 visit). All coefficients were

negative indicating that the relations between these parameters and the observed improvement in depression severity were reciprocal. However, after multivariate regression analysis the only parameter remaining significantly related to improvement in depression severity at week 8 was baseline depression severity expressed as total HAMD-17 score (regression coefficient: -0.70; P<0.0001). When univariate regression analyses were conducted to explore relations between the covariates of interest and the effectiveness of agomelatine at reducing anxiety severity and improving patients' QoL, mean total HAMD-17 score at baseline was again the only parameter with a significant relation with the observed improvement in both anxiety and patients' QoL (*Table 2*).

3.3 Safety

One adverse event in one patient (0.97%) was reported during the study. This event was classified as a lack of agomelatine treatment effect and led to the withdrawal of the patient from agomelatine treatment followed by initiation of treatment with another antidepressant. No serious adverse events or drug reactions related to treatment with agomelatine were observed.

DISCUSSIONThe antidepressant effectiveness of agomelatine in patients with a post-COVID 19 depressive episode was demonstrated in this study with statistically significant improvements at each visit. At baseline, all patients had mild or moderate depression. After initiation of agomelatine, a significant improvement in the total HAMD-17 score was already observed after only 2 weeks of therapy. Improvements continued throughout the study and at 8 weeks the HAMD-17 score had decreased by 10.9 points to a mean of 5.4 (a score of 0-7 is considered normal (Zimmerman et al., 2013)). The improvement in depressive symptoms with agomelatine treatment was confirmed by the CGI-I data at week 8, which showed statistically significant improvements compared with baseline. Anxiety is common in patients with depression and is associated with a worse prognosis, increased disability and more frequent medication use. It is also a frequent neuropsychiatric symptom post-COVID 19, particularly among patients that are hospitalized during the acute infection (Premraj et al., 2022). In the current study, both HAMD-17 anxiety scores (item 10 anxiety psychic and item 11 anxiety somatic) were continuously improved following initiation of agomelatine with statistically significant decreases in score compared with baseline already apparent after 2 weeks and persisting at each study visit. The observed positive effect of treatment on all types of anxiety symptoms is consistent with the antianxiety effects of agomelatine previously reported in other observational studies in patients with more severe depression (Avedisova et al., 2013; Volel, 2015). In the EMOTION study, the mean difference in HAMD-17 item 10 (anxiety psychic) from baseline to week 6 was 0.9 (P<0.00001) (Medvedev et al., 2016). Similar dynamics were observed for the HAMD-17 item 11 score (anxiety somatic) with a mean difference from baseline to week 6 of 1.21 points (P<0.00001) (Medvedev et al., 2016). Comparable results were demonstrated in the CHRONOS study with mean differences in the anxiety psychic and anxiety somatic scores of 0.6 and 0.5, respectively, after 6 weeks of treatment with agomelatine (Ivanov & Samushiya, 2014). In both the EMOTION and CHRONOS studies, the decrease in both anxiety items was already statistically significant after 2 weeks of treatment (Medvedev et al., 2016; Ivanov & Samushiya, 2014).

In this study, sensitivity analyses with regression remodeling were performed to explore if the clinical effectiveness of agomelatine was dependent on certain parameters known to be able to influence the size of the clinical effect. The only parameter that was significantly and negatively associated with the clinical effectiveness of agomelatine was the initial severity of depression (regression coefficient -0.70, P<0.0001). The negative value of the coefficient indicates that with each 1.0 point increase in mean total HAMD-17 score at baseline, a mean reduction of 0.7 points was observed at the end of the follow-up. In other words, the more severe the depression at baseline, the more pronounced the antidepressive effectiveness of agomelatine at the end of the follow-up. Regression modelling also revealed that age, gender, baseline COVID-19 severity and time after onset of COVID-19 infection had no effect on the antianxiety effectiveness of agomelatine. The only clinical characteristic that influenced agomelatine anxiety effectiveness was again baseline HAMD-17 score with a regression coefficient of -0.053 (P=0.003) for item 10 (anxiety psychic) and -0.035 (P=0.029) for item 11 (anxiety somatic), implying that for each increase of 1 point in the total HAMD-17 score at baseline, the mean scores of items 10 and 11 decreased by 0.035 and 0.053 points, respectively. In other

words, agomelatine demonstrated greater improvements in anxiety status in those patients who had more severe depression at the baseline.

Other observational studies with agomelatine conducted in routine clinical practice have shown similar findings (Medvedev et al., 2016; Ivanov & Samushiya, 2014; Smulevich et al., 2011). Patients in the EMOTION, CHRONOS and RHYTHM studies had more severe depression at baseline than those in TELESPHOR, with mean baseline total HAMD-17 of 22.1, 22.4, and 23.6, respectively, compared with 16.3 in TELESPHOR. The observed reductions in total HAMD-17 score were also larger. In the EMOTION study, the mean change in the total HAMD-17 score after 6 weeks of agomelatine therapy was 17.1 points ($P<0.001$) (Medvedev et al., 2016). In the CHRONOS observational study, which included patients with a first episode of depression or preexisting history of an MDE (42.7%), the mean total HAMD-17 score after 8 weeks of agomelatine treatment had decreased by 18 points ($P<0.001$) (Ivanov & Samushiya, 2014). In the RHYTHM prospective observational study, which included patients with preexisting depressive disorders, the overall difference in the total HAMD-17 score after 6 weeks of treatment with agomelatine was even more noticeable and reached 19.9 points ($P<0.001$) (Smulevich et al., 2011). In routine clinical practice, agomelatine effectiveness has therefore been demonstrated across a range of depression severity.

Evidence supports a role for 5-HT2C receptors in the induction of an anxious state, and their antagonism could play an important role in mediating the anxiolytic effects of agomelatine (Stein et al., 2021; Millan, 2022). Onset of symptoms such as depression, anxiety and sleep disturbances within 3 months of SARS-CoV-2 infection is common (Premraj et al., 2022). The precise mechanisms involved in the onset of post-COVID-19 depression are not well established. While depression and anxiety could at least partially have resulted from social isolation during the pandemic, a role for systemic inflammation caused by the acute viral infection is also likely. Indeed, it has been reported that COVID-19 can induce and promote a hyperinflammatory state, which may cause a persistent low-grade inflammation in the long term (Başol et al., 2016; Ozmen & Topsakal, 2022; Savran et al., 2020).

The antidepressive and anxiolytic effectiveness of agomelatine in this study may be additionally explained by its antioxidant, anti-inflammatory, immunomodulatory and anti-cytokine properties (Millan, 2022; Gupta et al., 2017). Agomelatine decreases production of interleukin-1-beta (IL-1-beta), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha), the main mediators of the "cytokine storm" and septic shock). It also depresses the activity of NLRP3 inflammasome, induces autologous processes, prevents macrophage infiltration and microglial cell activation, and decreases cell apoptosis by its effect on the NF-kappa-signaling cascade (Molteni et al., 2013; Hyeon et al., 2017; Kalkman & Feuerbach, 2016). It is hypothesized that the above properties may underlie the antidepressive effectiveness of agomelatine against MDEs occurring after COVID-19. However, further studies examining the relationship between the anti-inflammatory pleiotropic properties of agomelatine and its antidepressive effectiveness are required to provide more assertive and definitive conclusions.

In the TELESPHOR study, agomelatine was also associated with an improvement in patients' QoL with positive and significant changes in SF-36 Physical and Mental component scores. These improvements had already achieved statistical significance after 4 weeks of treatment and remained statistically robust until the end of the follow-up period. The observed findings imply that agomelatine therapy is able to rapidly improve mental and somatic status as well as QoL in patients with initially mild-to-moderate depression in a real-life setting. Other agomelatine studies have demonstrated similar results in a broad range of outpatients. In the PULSE study, treatment with agomelatine was associated with significant changes in both the SF-36 Physical and Mental components from week 3 to week 12 ($P<0.00001$) (Medvedev, 2017). In the EMOTION study, patients' well-being was self-assessed with a visual analog scale (VAS), which revealed a significant increase from 19.7 points at baseline to 73.3 points ($P<0.00001$) after a 6-week period of treatment with agomelatine (Medvedev et al., 2016). Assessment of patients' work capacity also revealed a significant improvement, reflected in an observed increase in VAS score from 14.3 to 70.4 ($P<0.00001$).

A high percentage of patients (81.4%) in the TELESPHOR study responded to therapy with agomelatine and 71.6% of participants achieved remission of depression at the end of the follow-up period. The observed high

numbers of responders and remitters are consistent with those from other observational studies conducted with agomelatine, in which the proportion of patients responding to treatment ranged from 60% to 97%, while the proportion considered to be remitters ranged from 32% to 81% (Medvedev et al., 2016; Medvedev, 2017; Avedisova et al., 2013; Volel, 2015; Ivanov & Samushiya, 2014; Smulevich et al., 2011; Vorob'eva, 2012; Tsygankov et al., 2011; Yakno & Voznesenskay, 2012). Treatment with agomelatine was safe and well-tolerated as confirmed by the absence of serious adverse events and treatment discontinuations due to adverse drug reactions. Only one adverse event (drug ineffectiveness) occurred in one patient (0.97%). These data are consistent with results from a large systematic review and network meta-analysis of the effectiveness and acceptability of 21 antidepressants which showed that patients receiving agomelatine and fluoxetine had a significantly decreased risk of premature treatment termination compared with either placebo or other antidepressants (Cipriani et al., 2018). Agomelatine is also associated with a low drug-drug interaction profile, which is an important characteristic for patients with COVID-19 who may need to take concomitant antiviral, anti-inflammatory and other medicines (Cipriani et al., 2018).

Emerging data on the effectiveness of agomelatine as well as other antidepressants for post-COVID-19 depression, coupled with their effect on the pathogenesis of viral infection, suggest they may not only be useful to treat long-term post-COVID-19 depression, but also depression in the acute COVID-19 period (University of Liverpool, 2024; Mas et al., 2022; Borovcanin et al., 2022; Firouzabadi et al., 2022).

Observational studies provide important data on the effectiveness and safety of drugs used in everyday clinical practice, which supplement benefit/risk profiles evaluated in randomized clinical studies. However, some limitations related to the observational nature of this study must be acknowledged. First, the study design does not permit any comparative conclusions to be drawn with other antidepressants as it was a single-group study. Second, agomelatine adherence data for outpatients treated in a routine clinical setting were not collected, although it is acknowledged that such data would be of special interest to practicing physicians. Third, despite having performed sensitivity analyses to explore relations between some important demographic and clinical characteristics and the observed agomelatine clinical effectiveness, it remains possible that some unidentified confounding factors could have influenced the antidepressive effectiveness of agomelatine observed in this study.

CONCLUSION

In the TELESPHOR study, treatment with agomelatine was associated with rapid and significant antidepressive and anxiolytic effectiveness in patients with a post-COVID-19 MDE. The demonstrated clinical effectiveness of agomelatine also resulted in statistically significant and clinically meaningful positive changes in patients' QoL. Sensitivity analyses revealed that baseline severity of depression was a significant positive predictor of drug effectiveness in patients with post-COVID-19 depression. The results of this study supplement our knowledge on the antidepressive effectiveness of agomelatine and suggest that it could be a valuable option to treat patients developing MDE post-COVID-19.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from thecorresponding author upon reasonable request

AUTHOR CONTRIBUTIONS

Authors DM, AB and VM designed the study and wrote the protocol. Author DM managed the literature searches and analyses. Authors BK and DM undertook the statistical analysis review, and author BK wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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TABLE 1 Baseline sociodemographic and clinical characteristics.

.	**Characteristic**
	Age (years), mean±SD
	Gender (n, %)
	Male
	Female
	Working status (n, %)
	Student
	Employed
	Unemployed
	Housewife/ Homemaker
	Retired
	Severity of COVID-19 (n, %)
	Mild
	Moderate

.	Characteristic
	Time after COVID-19, months (mean±SD)
	Previous treatment with antidepressants (n, %)
	Yes
	No
	Severity of depression (n, %)
	Mild
	Moderate
	Severe
	HAMD-17 total score, mean±SD
	HAMD-17 total score item 10, mean±SD
	HAMD-17 total score item 11, mean±SD
	SF-36 Physical Component score, mean±SD
	SF-36 Mental Component score, mean±SD

COVID-19, coronavirus disease 2019; HAMD-17, 17 item Hamilton Rating Scale for Depression; SD, standard deviation;

TABLE 2 Univariate linear regression analyses describing relations between covariates of interest and changes in anxiety and QoL observed at the end of treatment with agomelatine.

Covariate of interest	**Regression coefficient**	**P value**	**P value**
Anxiety: item 10 of HAMD-17 scale	**Anxiety: item 10 of HAMD-17 scale**	**Anxiety: item 10 of HAMD-17 scale**	**Anxiety: item 10 of HAMD-17 scale**
Age, years	-0.008	0.2158	0.2158
Sex (male)	-0.092	0.6222	0.6222
Baseline total HAMD-17 score	-0.053	**0.0027**	**0.0027**
COVID-19 severity (moderate)	-0.009	0.9648	0.9648
Time after COVID-19 onset (months)	-0.228	0.0659	0.0659
Anxiety: item 11 of HAMD-17 scale	**Anxiety: item 11 of HAMD-17 scale**	**Anxiety: item 11 of HAMD-17 scale**	**Anxiety: item 11 of HAMD-17 scale**
Age, years	-0.003	0.6239	0.6239
Sex (male)	0.094	0.5711	0.5711
Baseline total HAMD-17 score	-0.035	**0.0297**	**0.0297**
COVID-19 severity (moderate)	-0.019	0.9168	0.9168
Time after COVID-19 onset (months)	0.013	0.9042	0.9042
SF-36 Physical component	**SF-36 Physical component**	**SF-36 Physical component**	**SF-36 Physical component**
Age, years	Age, years	-0.007	0.8987
Sex (male)	Sex (male)	-1.832	0.2499
Baseline total HAMD-17 score	0.373	**0.0149**	**0.0149**
COVID-19 severity (moderate)	0.692	0.6958	0.6958

Time after COVID-19 onset (months)	-1.708	0.1091	0.1091
SF-36 Mental component			
SF-36 Mental component			
SF-36 Mental component Age, years	-0.079	0.2392	
Sex (male)	-0.693	0.7227	
Baseline total HAMD-17 score	0.557		
0.0027 COVID-19 severity (moderate)	3.428	0.1108	
Time after COVID-19 onset (months)	0.569	0.6644	
COVID-19, coronavirus disease 2019; HAMD-17, 17 item Hamilton Rating Scale for Depression; SF-36, 36 item Short Form survey.			
COVID-19, coronavirus disease 2019; HAMD-17, 17 item Hamilton Rating Scale for Depression; SF-36, 36 item Short Form survey.			

&

SF-36 Mental component
Age, years
Sex (male)
Baseline total HAMD-17 score
COVID-19 severity (moderate)
Time after COVID-19 onset (months)
COVID-19, coronavirus disease 2019; HAMD-17, 17 item Hamilton Rating Scale for Depression; SF-36, 36 item Short Form

&

SF-36 Mental component

Age, years
Sex (male)
Baseline total HAMD-17 score
COVID-19 severity (moderate)
Time after COVID-19 onset (months)
COVID-19, coronavirus disease 2019; HAMD-17, 17 item Hamilton Rating Scale for Depression; SF-36, 36 item Short Form

&

SF-36 Mental component
Age, years
Sex (male)
Baseline total HAMD-17 score
COVID-19 severity (moderate)
Time after COVID-19 onset (months)
COVID-19, coronavirus disease 2019; HAMD-17, 17 item Hamilton Rating Scale for Depression; SF-36, 36 item Short Form

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FIGURE 2 Mean changes in HAMD-17 item 10 scores at each study visit. HAMD-17, 17 item Hamilton Rating Scale for Depression.

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FIGURE 3 Mean changes in HAMD-17 item 11 scores at each study visit. HAMD-17, 17 item Hamilton Rating Scale for Depression.

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FIGURE 4 Mean changes in CGI-I scores. CGI-I, Clinical Global Impressions-Improvement of Illness Scale.

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FIGURE 5 Mean changes in SF-36 Physical Component scores.

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FIGURE 6 Mean changes in SF-36 Mental Component scores. SF-36, 36 item Short Form survey.

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