Outpatients prescribed with fluvoxamine around the time of COVID-19 diagnosis are not at a reduced risk of unfavorable COVID-19 course compared to their non-prescribed peers: a nationwide matched cohort study

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July 13, 2022

Abstract

Aim. To assess the relationship between a fact of being prescribed fluvoxamine around the time of COVID-19 diagnosis and subsequent hospitalizations and mortality in COVID-19 outpatients. Methods. Using administrative data, we identified adult COVID-19 outpatients diagnosed up to August 15, 2021 in Croatia. Subjects prescribed fluvoxamine around the time of COVID-19 diagnosis (Group A), their peers suffering similar psychiatric difficulties but not prescribed with fluvoxamine (Group B) and those free of psychiatric difficulties/treatments (Group C) were mutually exactly matched on a range of pre-COVID covariates. We determined relative risks of COVID-19-related hospitalization, 30-day all-cause hospitaliziation and of COVID-19-related mortality. Results. Out of 416030 outpatients, 1016 were Group A subjects, 749 of whom were matched to 31336/95984 Group B subjects, while 866 were matched to 22792/275804 Group C subjects. Group B and C patients were matched 82323 to 268778. Matched A vs. B relative risks (95%CI/CrI), frequentist and Bayes with skeptical, otpimistic and pesimistic priors, were: COVID-related hospitalization 1.73 (0.56-3.33), 1.15 (0.55-2.11), 1.03 (0.56.1.96) and 1.43 (0.63-2.94), respectively; 30-day all-cause hospitalization 1.88 (0.76-4.67), 1.76 (1.39-2.25), 1.76 (1.39-2.24) and 1.86 (1.43-2.38), respectively; COVID-19 related mortality 0.73 (0.35-1.55), 0.93 (0.53-1.76), 0.79 (0.40-1.54) and 0.88 (0.37-2.11), respectively. Conslusion. COVID-19 outpatients prescribed fluvoxamine around the time of COVID-19 diagnosis were not at a reduced risk of subsequent hospitalizations and mortality compared to COVID-19 outpatients suffering similar psychiatric difficulties but not prescribed with fluvoxamine, or compared to COVID-19 outpatients free of psychiatric difficulties and related treatments

Introduction

The TOGETHER randomized trial (RCT) suggested an early commenced 10-day fluvoxamine treatment (2x100 mg/day) in adult, non-vaccinated symptomatic mild COVID-19 outpatients as an option to relevantly reduce the risk of disease progression [1]. However, totality of the still modest amount of RCT data might not be as convincing[2] resulting in some uncertainty about the extent of benefit one could expect of fluvoxamine in this setting – a point hopefully to be resolved by on-going trials (listed in ref. 3).

In evaluation of efficacy of therapeutic/prophylactic interventions, agreement between experiments and observations strengthens specific claims. [4] In the specific setting of fluvoxamine for COVID-19 outpatients, methods based on admininistrative databases/electronic health records face obstacles beyond their standard limitations. [5] Fluvoxamine exerts some antiviral and anti-inflammatory effects [6] but has no clinical use in such conditions; people treated with fluvoxamine at a critical period of early COVID-19 are primarily treated for some underlying psychiatric disorder. As recently reviewed, [7,8] mental disorders, including mood and anxiety disorder for which fluvoxamine is typically used, may favor poorer COVID-19 outcomes. Hence, in respect to fluvoxamine, one needs to separate associations (with the outcome) of two simulta-

neous exposures, i.e., fluvoxamine and underlying psychiatric condition – the fluvoxamine non-prescribed (non-exposed) controls should come from the same population as the exposed subjects. This limits the exposed vs. non-exposed comparisons to a specific subset of people and observational data would supplement trial data (where participants are typically free of psychiatric disorders, see e.g., ref. 1) only if the"exposed vs. non-exposed" difference is the same irrespectively of the presence of a psychiatric disorder (i.e., there is no treatment-confounder interaction) – an assumption which may or may not hold. In this context, "not prescribed" fluvoxamine implies being prescribed with some other treatment for the underlying psychiatric condition, and the contrast between "prescribed" and "non-prescribed" patients regarding COVID-19 outcomes would be informative about fluvoxamine only if "not prescribed fluvoxamine" means also "not being treated for COVID-19" in the sense implied for fluvoxamine. Fluoxetine is another serotonine selective reuptake inhibitor (SSRI) that shows some antiviral and anti-inflammatory activity in non-clinical models [9]. One observational study [10] included laboratory confirmed COVID-19 adult outpatients in the pre-vaccination era: a cohort of patients prescribed fluoxetine (n=470) at a critical peridiagnostic period were matched (propensity-score based, 1:15) to patients not prescribed any SSRI or a related treatment (i.e., vilazodone, vortioxetine) – and yielded a relatively 25% lower mortality. No such association was observed for patients prescribed other SSRI or vilazodone or vortioxetine, while there were only 11 fluvoxamine prescribed patients, hence it was not individually evaluated [10]. However, unlike in the case of fluvoxamine, no human RCT has so far indicated any clinical benefit ascribable to fluoxetine (reviewed in ref. 11; also, two major clinical trial registries [ICTRP Search Portal (who.int), Home - ClinicalTrials.gov, both accessed June 1, 2022] harbor no RCT results pertitent to fluoxetine in COVID-19. Moreover, pharmacokinetic modelling indicates that standard fluoxetine doses (unlike fluvoxamine) by far fail to achieve concentrations correspoding to those effective *in vitro* [12]. It therefore appears reasonable to consider exposure to any "other treatment" as an appropriate contrast to exposure to fluvoxamine in people suffering psychiatric disorders that require treatment with antidepressants/anxyolytics.

In an attempt to supplement present efforts to characterize therapeutic potential of early fluvoxamin treatment to prevent COVID-19 progression, we aimed to compare adult COVID-19 outpatients who received prescriptions for fluvoxamine around the time of COVID-19 diagnosis and their fluvoxamine non-prescribed peers regarding the risk of subsequent hospitalizations and mortality.

Patients and Methods

Study outline

We aimed to assess whether the fact of being prescribed with fluvoxamine around the time of COVID-19 diagnosis was related to probability of subsequent *COVID-19-related hospitalization* , *all-cause 30-day hospitalization* and *COVID-19-related mortality* in adult COVID-19 outpatients. Anonymized routinely collected data were linked into a database including all subjects in the country diagnosed with COVID-19 between start of the pandemic (February 25 2020) and October 15 2021 (Figure 1A). Linked were data on: date and mode of COVID-19 diagnosis; demographics and COVID-19 vaccination status at diagnosis; medical histories from January 1 2019 to October 31 2021, including comorbidities (International Classification of Diseases [ICD-10] codes), all issued prescriptions (Anatomical Therapeutic Chemical codes, ATC) and other medical care, hospital admissions and diagnoses and dates and causes of death (Figure 1A). Raw data were further tided-up (Figure 1B) to keep only adults that qualified as COVID-19 outpatients, since diagnosed at points of mass laboratory testing (ICD-10 U07.1) or based on clinical/epidemilogical criteria (ICD-10 U07.2) by their family physicians. In Croatia, prescriptions for fluvoxamine are repeatable[13]: one issued prescription can cover a maximum of 12 months of treatment. We reasoned that prescriptions that would pertain to a period of time shorter than 3 months were not likely (i.e., no need for a repeatable prescription), and also that prescriptions for a period much longer than 3 months were not very likely – the treated conditions require medical follow-up and reconsideration of treatment. Next, all children and adults (including unemployed as long as registered at the National Bureau for Employment) are insured by the Croatian Health Insurance Fund. Most of the antidpressant/anxyolytic treatments are fully reimubrsed, but fluvoxamine is partly reimbursed (out-of-the-pocket expense is around 6 number of people prescribed

with fluvoxamine would be limited. Considering these and other specifics of the research question and the setting, we defined three subsets of COVID-19 outpatients (detailed in Table 1): (i) **Group A** – people suffering difficulties requiring antidepressant/anxyolytic treatment, who were presecribed (and presumably exposed to) fluvoxamine around the time of COVID-19 diagnosis (Table 1); (ii) **Group B** – people needing antidepressant/anxyolytic treatment, but not prescribed fluvoxamine around the time of COVID-19 diagnosis (Table 1) and (iii) **Group C** – people free of psychiatric difficulties and related treatments at the time around the COVID-19 diagnosis (Table 1). We planned three direct comparisons (contrasts) (Table 1) based on exactly matched subsets: Group A vs. B, a comparison of primary interest, informative regarding fluvoxamine; and comparisons of Group A and B subjects each with Group C subjects. We considered that the latter two comparisons would be informative about the relationship between psychiatric difficuluties and related treatments and the COVID-19 course, and would thus provide indirect (supportive) insight about fluvoxamine.

Data source and curation

Raw data was prepared by the Croatian Institute for Public Health (CIPH) from nationwide databases on: (i) COVID-19 laboratory test results (polymerase chain reaction [PCR]-based or rapid antigen tests [RAT]) and COVID-19 patients diagnosed on clinical/epidemiological criteria (without laboratory tests); (ii) COVID-19 vaccinations; (iii) all hospitalizations; (iv) deceased individuals; (v) Central Health Information System (CEZIH) - primary healthcare database maintained by the Ministry of Health. All subjects diagnosed with COVID-19 between February 25 2020 and October 15 2021 were identified, and data were linked to the hospitalizations database, database of deceased persons and to their primary healthcare data (January 1 2019 - October 31 2021 for all) (Figure 1A). We received anonymized merged database (Figure 1B) and we: a) excluded patients who were diagnosed by a PCR test first performed when seeking hospital services, so that only patients who could be reasonably considered as "outpatients" (diagnosed at public mass testing points, or clinical/epidemiological diagnosis by family physicians) were retained; b) excluded subjects <16 years of age; and c) excluded subjects for whom data on sex, date of birth, COVID-19 testing date/result/date of diagnosis, or vaccination status/dates were missing or were erroneously entered. We identified subjects with more than one COVID-19 episode: we considered that positive PCR/RAT tests or ICD-10 code U07.1/U07.2 entries or hospitalizations related to COVID-19 that were [?]30 days apart indicated two separate COVID-19 episodes. Only the first documented COVID-19 episode for each subject was included (Figure 1B). We set the cut-off date for COVID-19 diagnosis at August 15 2021, to allow for a follow-up period long-enough for outcomes to occur (until October 31). Finally, we identified patient subsets of interest (see Table 1 for details), their outcomes and their matching covariates (detailed in Table 2) (Figure 1B).

Outcomes

We defined three outcomes for which we deemed that jointly would adequately inform about unfavorable develompents in COVID-19 outpatients. *COVID-19-related hospitalization* – hospitalization that followed within 45 days since the index COVID-19 diagnosis, with U07.1/U07.2 as the leading discharge diagnosis; or hospitalization that followed within 30 days since the index COVID-19 diagnosis and U07.1/U07.2 is listed among discharge diagnoses. *30-day all-cause hospitalization* – hospitalization that follows within 30 days since the index COVID-19 diagnosis. *COVID-19-related death* – we considered that death was "related to" COVID-19 if meeting any of the following (i) COVID-19 (U07.1/U07.2) is listed as a cause of death; (ii) death occurred within 14 days since the index COVID-19 diagnosis, regardless of the declared cause; (iii) death occurred in hospital, where hospitalization was COVID-19 related hospitalization (as defined above).

Identification of exposure, other treatments and covariates and the matching procedure

Exposure/non-exposure to fluvoxamine was identified based on timing of prescriptions with the respective ATC code (N06AB08) relative to the index COVID-19 diagnosis. All other psychiatric and other treatments required for identification of patient subsets and covariate matching are listed in Appendix, Table A1. We implemented exact matching using package *MatchIt* [14] in R[15]. For all contrasts (Group A vs. B, A vs. C and B vs. C), patients were matched in respect to age, sex, vaccination status (type of vaccine

and timing relative to the index COVID-19 episode), calendar period of COVID-19 diagnosis, and a range of comorbidities and pharmacological treatments (detailed in Table 2). For the Group A vs. Group B comparisons, additional matching included also psychiatric diagnoses (Table 2). Comparisons vs. Group C patients did not include these covariates, since Group C patients were free of psychiatric conditions (by definition). Identification of all comorbidities used for matching is detailed in Appendix, Table A2-Table A4, and section on immunocompromised and diabetic patients.

Data analysis

Outcomes were analyzed in matched sets by fitting log-binomial models, frequentist (with cluster robust sandwich estimator of the standard error) and Bayesian with three different priors for the effects of interest: (i) *skeptical prior* – moderatly informative neutral prior consistent with an *a priori* hypothesis of no effect, centered at 0 for the Ln(RR) with standard deviation 0.355. It assigns equal probability (50%) for an RR >1.0 and an RR <1.0, with 95% probability between RR=0.50 and RR=2.0; (ii)*optimistic prior* – moderately informative prior centered at -0.199 for the Ln(RR), with standard deviation 0.4, i.e., 18% relative risk reduction as seen in an up-dated Bayesian meta-analysis of randomized trials of fluvoxamine in this setting[2], but with 30% probability of an RR >1.0; (iii) *pesimistic prior* – weakly informative prior centered at 0.199 for Ln(RR) (reciprocal to the optimistic prior) with a standard deviation of 0.77. Although it suggests harm, it leaves 40% probability of an RR <1.0. We used SAS 9.4 for Windows (SAS Inc, Cary, NC) (*proc glimmix*) to fit frequentist and package*rstanarm* [16] in R[15] to fit Bayesian models. Since the number of people prescribed with fluvoxamine was low and the outcomes of interest were rather infrequent in matched sets, to increase the precision of the A vs. B comparisons, we conducted network meta-analysis of results in matched sets A vs. B, A vs. C and B vs. C. Although derived from the same pools of original patients, matched contrasts were based on different pseudopopulations (by selection and weighting). We performed frequentist (package*netmeta* [17] in R[15]) and Bayesian (package *BUGSnet* [18] and package*gemtc* [19] in R[15], with default priors) network meta-analysis using weighted counts from matched sets, and also using the effect measures (RR) generated in Bayesian analyses with the skeptical prior. We made no multiplicity adjustments of the alpha level: present analysis did not aim at "discoveries"; we intended to simply estimate quantities of interest and see how they related to the RCT data.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[20]

Results

Patients

Present analysis refers to first COVID-19 episodes in 416030 adults who qualified as COVID-19 outpatients (Figure 1). Presence/severity of their symptoms at the time of COVID-19 diagnosis remained unknown, but all were diagnosed before eventual hospital/emergency room admittance (for any reason). Of them, 1016 were identified as Group A patients (definition in Table 1) (mean±SD age 54.6±18.2, range 16-99 years; 43.4% men), 95984 were identified as Group B patients (Table 1) (age 57.5±16.8, range 16-105 years; 35.0% men), 275804 were identified as Group C patients (Table 1) (age 42.6±16.2, range 16-96 years; 50.2% men) and 43226 subjects remained unclassified (age 52.2±16.7, range 16-101 years; 39.7% men) (Figure 1B). In Group A and B patients, raw incidence of COVID-19-related hospitalization (3.3%), of all-cause 30-day hospitalization (12.0%) and of COVID-19 related deaths (4.0%) was 2-4 times higher then in Group C patients (Figure 2).

Analysis in matched sets

Before matching, 1016 Group A patients moderately differed from 95984 Group B patients in a range of covariates (listed in Table 2) (Appendix, Table A5), and 749 of the former could be exactly matched to 31336 of the latter (Appendix,Table A5). All but one Group A patients and 86.2% Group B patients were

prescribed with at least one drug from the ATC groups N05 (psycholeptics), N06 (psychoanaleptics) and N07 (other nervous system drugs) at any time between January 1 2019 and the date of the index COVID-19 diagnosis. Next, 866/1016 Group A patients could be exactly matched to 222792/275804 Group C patients (Appendix , Table A6), and 82323/95984 Group B patients could be exactly matched to 268778/275805 Group C patients (Appendix, Table A7).

Incidence of COVID-19-related hospitalizations and of COVID-19-related mortality was <1.5% in all matched sets, while all-cause hospitalizations were considerably more common (Figure 3). There was no indication that outpatients prescribed fluvoxmine around the time of COVID-19 diagnosis (Group A) were at a reduced risk of any of the outcomes as compared to their peers burdened with similar psychiatric difficulties but not prescribed fluvoxamine over the critical period of time (Group B), or as compared to COVID-19 outpatients free of psychiatric difficulties and related treatments (Group C) (Figure 3): all relative risk estimates, frequentist and Bayesian with different priors, were around 1.0 or somewhat higher than 1.0. Comparisons between matched Group B and Group C patients were based on considerably larger number of subjects than other comparisons (Figure 3), hence estimates were much more precise (narrower confidence intervals), but in terms of the point-estimates, A vs. C and B vs. C differences were closely similar.

Network analysis of matched sets

For all three outcomes, direct and indirect comparisons between Group A and Group B subjects were consistent, so it was justified to combine then (Figure 4): there was no indication that outpatients prescribed fluvoxmine around the time of COVID-19 diagnosis (Group A) were at a reduced risk of any of the outcomes as compared to their peers burdened with similar psychiatric difficulties but not prescribed fluvoxamine over the critical period of time (Group B) (Figure 4). Closely similar patterns were seen for the Group A vs. Group C comparisons (not shown).

Discussion

At present, randomized controlled trial (RCT) data on efficacy of fluvoxamine in prevention of severe forms of COVID-19 in infected individuals are modest and burdened with uncertainty[2]. In particular, two largest RCTs[1,21] yielded ambiguous results. In Stop COVID 2[21] (terminated early for technical reasons), mildly symptomatic, adult, non-vaccinated COVID-19 outpatients were commenced on an early (within 7 days since the COVID-19 diagnosis) 15-day fluvoxamine regimen (2x100 mg to 3x100 mg/day) (n=272) or placebo (n=275): 15-day risks of the primary outcome (hospitalization or a new onset hypoxemia) or of hospitalization appeared similar in the two arms (4.8% fluvoxamine vs. 5.4% placebo and 4.0% fluvoxamine vs. 4.4% placebo, respectively).[3,21] In a subsequent larger TOGETHER trial[1] with closely similar patient characteristics, early commenced fluvoxamine (2x100 mg over 10 days) (n=741) appeared superior to placebo (n=756) in respect to the 28-day risk of the primary outcome (hospitalization or emergency room stay longer than 6 hours) or (somewhat less so) regarding hospitalizations (11.0% fluvoxamine vs. 16.0% placebo and 10.0% fluvoxamine vs. 13.0% placebo, respectively)[1]. Under specific circumstances, non-randomized studies of interventions might be comparable to RCTs in terms of validity and accurracy in detecting a causal treatment effect.[22] Treatment of early COVID-19 with fluvoxamine is a specific setting in which this kind of inference based on observational data is highly questionable. Given that in real life fluvoxamine is prescribed exclusively to alleviate specific psychiatric symptoms, the source population for the "treatment-control" comparison of interest (in the present study - Group A vs. Group B) is unavoidably limited to people who, at the time of COVID-19 diagnosis, suffer conditions requiring antidepressant/anxyolytic treatment. This also means that in contrast to a "standard" situation in which treatment is commenced only after the condition to be treated has occurred, "exposure/treatment" of interest (fluvoxamine) is likely in place at the time of occurrence of COVID-19. Theoretically, this may generate bias: if pre-existing mood disorders/exposure to fluvoxamine affect the risk of COVID-19 infection, then by inclusion of only COVID-19 diseased people one conditions on a post-baseline factor. There is rather sound evidence that mood disorders as such do not affect susceptibility to COVID-19 infection.[23] However, it is unknown whether this holds also for exposure to fluvoxamine at the time of the contact with the virus. Next, prescription issuance is a proxy for "exposure" and actual treatment cannot be directly measured. The present definitions of "exposed" (Group A, implying a drug supply around

timing of COVID-19 diagnosis sufficient for at least 3 months of treatment) and of "unexposed" subjects (Group B, no prescriptions issued between 6 months prior to and 21 days after the COVID-19 diagnosis) appear reasonable, but fluvoxamine doses in the approved indications might sometimes be lower than those suggested for early COVID-19 treatment.[13] Therefore, in general, observational data could inform about the effect of fluvoxamine in early COVID-19 if one would consider as reasonable several assumptions: that what is observed in people with psychiatric difficulties is applicable in general; that exposure to fluvoxamine does not affect susceptibility to COVID-19 infection; and that being prescribed with fluvoxamine around the time of COVID-19 diagnosis indicates use of 100-300 mg/day fluvoxamine in the early phases of COVID-19 infection. Under such circumstances, the present data, for what it is worth, is more compatible with the Stop COVID 2[3,21] results than with TOGETHER[1] trial results.

We used routinely collected adminsitrative data and not a dedicated pre-planned research database. As a consequence, some information was inherently missing (e.g., actually delivered treatment and presence/severity of symptoms at COVID-19 diagnosis), and some inaccurracies in identification of exposures, comorbidities and outcomes cannot be excluded. We believe, however, that if present, such inaccurracies were not sources of a relevant bias: i) it does not seem reasonable to assume that their occurrence was "prejudiced" in respect to (non)-issuance of fluvoxamine (or any other) prescriptions; ii) data on key variables such as age, sex, vaccination status, date of COVID-19 test/test result or diagnosis were missing or erroneously entered in only 0.38% of the identified COVID-19 diagnoses (Figure 1) indicating that if present, inaccurracies/chance errors were minor; iii) in Croatia, prescriptions are issued exclusively within the primary healthcare network, and each prescription bears an ATC code and an ICD-10 code. Moreover, for specialists consultations and work-up, patients need to be referred by the primary healthcare physicians who need to record the feedback information. All such acitivities are automatically entered into the Central Health Information System (CEZIH) (Figure 1). We also left a period of a minimum one year + 2 months (from January 1 2019 to the first COVID-19 case in February 2020) to precede the index COVID-19 diagnosis not to miss entries related to comorbidities that did not require recent presecriptions or other medical procedures. Hence, likely, no relevant comorbidity or treatment was missed; iv) incidence of all outcomes was within the expectations having in mind published data[24, 25], which in a way provides external validation of the present observations. Considering raw data, 30-day all-cause hospitalization was closely similar in Group A and Group B patients (around 12.0%) (Figure 2), and the two subsets were also closely similar regarding age and comorbidities (Appendix, Table A5). Incidence was twice lower in Group C patients (5.2%) – in comparison to Group A (Appendix, Table A6) or Group B (Appednix, Table A7) patients, they were younger and considerably less burdened with comorbidities (e.g., Charlson Comorbidity Index was lower, all individual comorbidities were considerably fewer and there was no psychiatric comorbidity in Group C patients). The overall incidence of 6.9% (across all three subsets) at the average age of 46.5 years is in agreement with expected 4.3% to 8.5% hospitalizations among people aged 40-49 years who test positive for COVID-19.[24]Although one could consider all hospitalizations that occur within a month since the COVID-19 diagnosis as "COVID-19-related", we defined a separate outcome where COVID-19 was the lead or at least one of the discharge diagnoses (implying that COVID-19 could have triggerred/worsened some underlying condition). It seems reasonable to assume that these were the "severe" or "critical" patients – Group A and Group B (around 3.3%) were again similar and incidence was (expectedly) much lower (0.94%) (Figure 2) in the younger and considerably less comorbid Group C patients. The overall incidence of 1.5% is within the range of the recently reported expected incidence of severe or critical disease in 30-50-year olds who tested positive for COVID.19 (1.2-2.5%).[25] In line with the other two outcomes, a similar Group A/B vs. C relationship was observed regarding mortality (3.7-4.4% vs. 1.05%) (Figure 2). The overall incidence of 2.5% is in line with the ratio of cumulative COVID-19-confirmed deaths and COVID-19 confirmed cases in Croatia up to October 31, 2021.[26] Of notion, (weighted) incidence of all outcomes, particularly of COVID-19-related hospitalizations and mortality, was lower in all matched sets than in the raw data (Figure 3 in comparison to Figure 2). This is due to the fact that we employed exact matching on a number of covariates and matches were found mainly among less comorbid subjects. Overall, it appears safe to conclude that we were able to resonably accurrately capture exposures, comorbidities, cotreatments and outcomes, and to adequatly control confounding by accounting for a number of known relevant epidemiological, comorbidity and co-treatment covariates.

Under these circumstances, direct comparisons of Group A to Group B patients and to Group C patients, and combined direct and indirect comparisons of A and B patients consistently yieled relative risks for all three outcomes closely around unity or slightly above unity, i.e., we observed no estimate that would go "in favor" of the fact of being prescribed fluvoxamine around the time of COVID-19 diagnosis.

In conclusion, the present nationwide matched cohort study strongly suggests that outpatients prescribed with fluvoxamine around the time of COVID-19 diagnosis are not at a reduced risk of subsequent hospitalizations or death compared to their peers suffering similar psychiatric difficulties but not prescribed with fluvoxamine, or as compared to their peers free of psychiatric difficulties and respective treatments. Considering the specifics of the setting, present data could be viewed informative about efficacy of early fluvoxamine treatment in COVID-19 outpatients to prevent disease progression only under several strong assumptions. In this context, present observations are more compatible with trial data that failed to demonstrate a practically relevant benefit of fluvoxamine treatment than with the data that supprot efficacy of fluvoxamine in this setting.

Disclosures and Declarations

Ethics

This is an observational study that used anonymized administrative data standardly collected on routine procedures, hence ethical approval was waived by the Ethics Committee of the Zagreb University School of Medicine and Croatian Institute for Public Healthy.

Funding

The study was funded by School of Medicine, Zagreb University.

Conflicts of interest

Authors declare that they have no financial or non-financial conflict of interest.

Author contributions

Vladimir Trkulja and Ivan Kodvanj designed the study, prepared and analyzed the data, drafted the manuscript and completed the final version.

Acknowledgments

Computing was done on high-throughput computing resources (HTC Cloud) provided by the University of Zagreb Computing Centre (SRCE). We are thankful to all the personnel at the Croatian Institute for Public Health (CIPH) for preparing the raw data, and especially for the kind support of Tamara Poljičanin MD, PhD, who supervised data preparation process at CIPH.

Data availability

Data can be obtained upon a reasonable request directly from the CIPH.

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Table 1 . Subsets of people diagnosed with COVID-19 (up to August 15, 2021) in respect to exposure to fluvoxamine around the time of COVID-19 diagnosis and contrasts between exactly matched subsets.

Group A. People suffering difficulties requiring antidepressant/anxyolytic treatment **and exposed to fluvoxamine** – at l
Group B. People suffering difficulties requiring antidepressant/anxyolytic treatment **not exposed to fluvoxamine** – (i) a
Group C. People free of psychiatric difficulties and **not exposed to fluvoxamine** or to any other pharmacological psychi
Group A vs. Group B: the two subsets differ regarding the (presumed) exposure to fluvoxamine in the early phases of C
Group A vs. Group C: the two subsets differ regarding the burden of psychiatric conditions and the fact of exposure to
Group B vs. Group C: the two subsets differ regarding the burden of psychiatric conditions including their respective tr

Table 2 . Covariates used for exact matching between patient subsets (groups based on burden of psychiatric conditions and exposure to fluvoxamine.

Matching variables used for all comparisons

Age
Sex
Vaccination status
Calendar period
Comorbidities
Pharmacological treatments
Matching variables additionally used in the comparison between patients burdened with psychiatric difficulties that may req
Dementia
Mood disorders
Nonpsychotic mood disorders
Substance use
Non-mood psychotic disorders
Cumulatively: F50-F59, F60-F69, F70-F79, F80-F89, F90-F98, F04-F09

Figure 1 . Data sources and curation (see text for details).**A.** Raw data was prepared by the Croatian Institute for Public Health from several databases that it maintains. COVID-19 patients were identified based on positive polymerase chain reaction (PCR) or rapid antigen testing (RAT) performed at dedicated public testing points or hospitals (ICD-10 code U07.1), or based on epidemiological/clinical criteria (ICD-10 code U07.2) and individual data were linked to databases on vaccination, deceased persons, hospitalizations and Central Heath Information System. **B** . Anonymized data were "tidied-up" by exclusion of patients first diagnosed by PCR testing when seeking hospital assistance regardless of the reason, so as to retain only outpatients; subjects younger than 16 years and those with missing/erroneous entries on key variables. Also, repeated COVID-19 episodes were excluded and cut-off date for index COVID-19 diagnosis was set at August 15, 2021. Based on International Classification of Disease version 10 (ICD-10) code entries and Anatomical Therapeutic Chemical (ATC) code entries patients were classified into subsets (Group A, Group B, Group C) in respect to issuance of prescriptions for fluvoxamine and underlying morbidity. Definitions of Group A (patients burdened with conditions requiring antidepressant/anxyolytic treatment and prescribed fluvoxamine around the time of COVID-19 diagnosis), Group B (patients patients burdened with conditions requiring antidepressant/anxyolytic treatment not prescribed with fluvoxamine) and Group C patients (patients free of psychiatric difficulties and of respective treatments) are detailed in Table 1.

Figure 2 . Raw incidence (percentage) of COVID-related hospitalization, all-cause 30-day hospitalization and of COVID-related mortality (composite) (see Patients and Methods for definitions) across the patient subsets: Group A (patients burdened with conditions requiring antidepressant/anxyolytic treatment and prescribed fluvoxamine around the time of COVID-19 diagnosis), Group B (patients burdened with similar psychiatric difficulties, but not prescribed with fluvoxamine) and Group C (patients free of psychiatric difficulties and of respective treatments).

Figure 3. Analysis of outcomes (see Patients and Methods for definitions) in matched sets of patients burdened with conditions requiring antidepressant/anxyolytic treatment and prescribed (Group A) or not prescribed (Group B) fluvoxamine, and those free of such difficulties and related treatments (Group C) around the time of COVID-19 diganosis. Depicted are proportions (percentages) of patients with outcomes in each matched set and respective relative risks (RR). Priors for Bayes estimates: *skeptical* is moderately informative normal prior centered at 0.0 for Ln(RR) with standard deviation 0.355 – gives equal (50%) probability to an RR above and an RR below unity with 95% probability for an RR between 0.5 and 2.0; *optimistic* is a moderately informative normal prior centered at -0.199 for Ln(RR) (i.e., 18% relative risk reduction) with standard deviation 0.40 – suggests a benefit but leaves 30% probability of an RR >1.0;*pesimistic* is a weakly informative normal prior centered at 0.199 for Ln(RR) (i.e., 22% relative risk increase) with standard deviation 0.77 – suggests harm (of the same extent as benefit suggested by the optimistic prior), but leaves 40% probability of an RR <1.0.

Figure 4 . Differences between Group A patients (burdened with conditions requiring antidepressant/anxyolytic treatment and prescribed fluvoxamine around the time of COVID-19 diagnosis) and Group B patients (suffer similar psychiatric difficulties, but are not prescribed with fluvoxamine), i.e., control patients, regarding the outcomes of interest (see Patients and Methods for definitions) generated in network meta-analysis (frequentist and Bayes) that included Group A vs. Group B, Group A vs. Group C and Group B vs. Group C comparisons in matched sets.**A** . Meta-analysis based on weighted proportions. Direct, indirect and total (combined, network) differences. **B.**Meta-analysis based on Ln (RR) generated in primary Bayesian analysis with moderately informative skeptical prior (shown in Figure 3). Only total (combined) effects are shown (as in A, direct and indirect effects were consistent).

List of Appendices

Appendix 1 . Lists of ATC codes and ICD-10 codes used to identify exposure to pharmacological treatments and comorbidities, covariate values in Group A vs. Group B, Group A vs. Group C and Group B vs. Group C comparisons before and after matching