Psychotropic drug prescribing before and during the COVID-19 pandemic among people with depressive and anxiety disorders: a multinational network study

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Summary

Background People with mental health conditions were potentially more vulnerable than others to the neuropsychiatric effects of the COVID-19 pandemic and the global efforts taken to contain it. The aim of this multinational study was to examine the changes in psychotropic drug prescribing during the pandemic among people with depressive and anxiety disorders.

Methods This study included electronic medical records and claims data from nine databases in six countries (France, Germany, Italy, the UK, South Korea, and the USA) of patients with a diagnosis of depressive or anxiety disorders between 2016 and 2021. The outcomes were monthly prevalence rates of antidepressant, antipsychotic, and anxiolytic drug prescribing. The associations between the pandemic and psychotropic drug prescribing were examined with interrupted time series analyses for the total sample and stratified by sex and age group. People with lived experience were not involved in the research and writing process.

Findings Between Jan 1, 2016 and Dec 31, 2020, an average of 16 567 914 patients with depressive disorders (10 820 956 females [65·31%] and 5 746 958 males [34·69%]) and 15 988 451 patients with anxiety disorders (10 688 788 females [66·85%] and 5 299 663 males [33·15%]) were identified annually. Most patients with depressive disorders and anxiety disorders were aged 45–64 years. Ethnicity data were not available. Two distinct trends in prescribing rates were identified. The first pattern shows an initial surge at the start of the pandemic (eg, antipsychotics among patients with depressive disorders in MDCD_US (rate ratio [RR] 1·077, 95% CI 1·055–1·100), followed by a gradual decline towards the counterfactual level (RR 0·990, 95% CI 0·988–0·992). The second pattern, observed in four databases for anxiolytics among patients with depressive disorders and two for antipsychotics among patients with anxiety disorders, shows an immediate increase (eg, antipsychotics among patients with anxiety disorders in IQVIA_UK: RR 1·467, 95% CI 1·282–1·675) without a subsequent change in slope (RR 0·985, 95% CI 0·969–1·003). In MDCD_US and IQVIA_US, the anxiolytic prescribing rate continued to increase among patients younger than 25 years for both disorders.

Interpretation The study reveals persistently elevated rates of psychotropic drug prescriptions beyond the initial phase of the pandemic. These findings underscore the importance of enhanced mental health support and emphasise the need for regular review of psychotropic drug use among this patient group in the post-pandemic era.

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Introduction

The COVID-19 pandemic led to increased morbidity and mortality globally. In addition to the direct adverse health outcomes associated with COVID-19 infection, the implementation of unprecedented public health measures and financial difficulties contributed to emotional distress and elevated risk of adverse mental health outcomes for the general population.[1,2] People with common mental illnesses, including depressive and anxiety disorders, were potentially more vulnerable than others to the adverse psychological, social, and neuropsychiatric effects of the pandemic.[3] Beyond the disruptions of daily routines and support structures due to lockdowns, the reduction in access to health-care services might have created additional barriers for people with mental disorders to access health care. These challenges might have exacerbated symptoms and triggered relapse, resulting in increased prescriptions of psychotropic drugs. Although psychotropic medications can be effective in treating mental health conditions, their increased use during the pandemic has raised concerns about potential over-prescribing and increased adverse effect burden.[4,5] It is therefore important to understand whether, and to what extent, the pandemic has affected

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Research in context

Evidence before this study

Concerns have been raised about the potential negative impact of the COVID-19 pandemic on individuals with mental disorders, as indicated by an observed increase in the prescription of psychotropic drugs. We systematically searched PubMed for research articles published in English, with titles or abstracts including the search terms ((“psychotropic” OR “antipsychotic*” OR “antidepressant” OR “anxiolytic”) AND (“mental health” OR “mental disorder” OR “depress*” OR “anxiety”) AND (“pandemic” OR “COVID”)). So far, studies on psychotropic drug prescribing have been limited to the general population of a single country, or specific population subgroups such as nursing home residents and people living with dementia. Based on data from a commercial health insurance database, a US study found an increase in prescription of various psychotropic drugs in the general population. A Canadian study of nursing home residents reported similar findings. However, single-database studies conducted in general populations reported mixed results. Existing evidence on the mental health consequences of the pandemic is limited to the changes in the prevalence and incidence of mental health conditions. No investigation has been conducted to examine the potential changes in psychotropic drug prescribing among people with common mental disorders, including depressive and anxiety disorders.

Added value of this study

To our knowledge, this is the first multinational population-based cohort study to use a common analytical code to analyse data from nine databases across six countries, providing empirical evidence on the changes of monthly rates of psychotropic drug prescribing for people with depressive and anxiety disorders before and during the COVID-19 pandemic. The study found an overall increase in psychotropic prescribing during the acute phase of the pandemic, with some databases showing a subsequent decrease while others did not. Notably, anxiolytic prescribing for people with depressive disorders remained continuously elevated across four databases in France, the UK, South Korea, and the USA. Additionally, we discovered preliminary evidence indicating that in two USA databases, the rate of anxiolytic prescribing continued to rise among individuals younger than 25 years, both for those with depressive disorders and those with anxiety disorders.

Implications of all the available evidence

The persistently elevated prescribing rates of anxiolytics during the COVID-19 pandemic underscore the importance of enhanced mental health support and emphasise the need for regular review of psychotropic drug use among patients with depressive and anxiety disorders in the post-pandemic era.

the prescribing rate of psychotropic drugs among people with mental disorders.

The association between the COVID-19 pandemic and psychotropic drug prescribing has been examined in different populations. For example, a US study using data from a commercial health insurance database reported an increase in Z-hypnotic, SSRI, and SNRI prescription in both men and women and an increase in benzodiazepine prescription in women.[6] A Canadian study of nursing home residents in Ontario found an increase in the use of antipsychotics, benzodiazepines, antidepressants, trazodone hydrochloride, and anticonvulsants following the start of the pandemic.[7] A French study found that prescribing of psychotropic medications substantially and persistently increased after the onset of the pandemic among children and adolescents.[8] Population-based studies have been conducted in many other countries, such as Australia, Denmark, Israel, and Portugal, reporting mixed findings.[9–12]

Robust evidence about trends in psychotropic prescribing during the pandemic should be generated using data from multiple populations, and different health systems, with sufficiently long follow-up periods to ensure any changes observed are not due to systematic bias or only applicable to a specific region. This study provides a comprehensive examination of the association between the COVID-19 pandemic and changes in psychotropic drug prescribing rates among people with depressive and anxiety disorders in nine databases from six countries.

See Online for appendix

Methods

Study design and data sources

This multinational network cohort study used electronic health records and claims data between Jan 1, 2016, and Dec 31, 2021, from nine databases in France, Germany, Italy, the UK, South Korea, and the USA. The electronic health record databases were: IQVIA Longitudinal Patient Database France (IQVIA_France), IQVIA Disease Analyzer Germany (IQVIA_Germany), IQVIA Longitudinal Patient Database Italy (IQVIA_Italy), IQVIA Medical Research Data UK (IQVIA_UK), Ajou University School of Medicine database from South Korea (AUSOM_KR), and Kangwon National University database from South Korea (KNU_KR). The claims-based databases were all from the USA, comprising IBM MarketScan Multi-State Medicaid adjudicated US health insurance claims for Medicaid Database (MDCD_US), IBM MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR_US), and IQVIA Open Claims US (IQVIA_US). These databases have been extensively utilized in previous studies.[13,14] Details of each database are presented in the appendix pp 2–4. The study periods started on Jan 1, 2016, for all databases but differed in end dates due to variations in data availability (tables 1, 2).

All databases were converted to the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM), version 5, with standardised structure, content, and semantics maintained by the Observational Health Data Sciences and Informatics (OHDSI) network.[15] The CDM enables data partners to execute a common analytical code locally in a federated fashion without sharing individual-level data.[16] The study protocol was collaboratively drafted, reviewed, and updated by an international team of researchers, data partners, and industry stakeholders through the OHDSI community. The study protocol and analytical package are available online. The data partners have obtained institutional review board exemption for their participation in this study. Informed consent was waived because the study used deidentified data and no patients were contacted.

Study participants

We included patients of all ages with a diagnosis of depressive or anxiety disorders during the study period. People younger than 65 years were excluded from MDCR_US because Medicare covers people aged 65 years or older, certain younger people with disabilities, and those with end-stage renal disease. All patients were

For the **study protocol and analytical package** see https://github.com/ohdsi-studies/Cervello

	IQVIA_France, July 31, 2021	IQVIA_Germany, Aug 31, 2021	IQVIA_Italy, June 30, 2021	IQVIA_UK, March 31, 2021	AUSOM_KR, June 30, 2021	KNU_KR, June 30, 2021	MDCD_US, March 31, 2021	MDCR_US, June 30, 2021	IQVIA_US, Nov 30, 2021
Annual number of patients	120 071	220 465	71 362	40 657	2552	3664	106 4708	159 102	148 85333
Sex									
Female	83 668 (69·68%)	144 282 (65·44%)	50 792 (71·18%)	25 155 (61·87%)	1789 (70·10%)	2168 (59·17%)	733 448 (68·89%)	100 888 (63·41%)	967 8766 (65·02%)
Male	36 403 (30·32%)	76183 (34·56%)	20 570 (28·82%)	15 502 (38·13%)	763 (29·90%)	1496 (40·83%)	331 260 (31·11%)	58 214 (36·59%)	520 6567 (34·98%)
Age group, years									
<18	663 (0·55%)	3427 (1·55%)	123 (0·17%)	831 (2·04%)	67 (2·63%)	152 (4·15%)	148 997 (13·99%)	..	100 1762 (6·73%)
18–24	2809 (2·34%)	8459 (3·84%)	770 (1·08%)	5383 (13·24%)	168 (6·58%)	197 (5·38%)	101 962 (9·58%)	..	128 1476 (8·61%)
25–44	24 752 (20·61%)	44 883 (20·36%)	8132 (11·40%)	16 725 (41·14%)	413 (16·18%)	415 (11·33%)	322 929 (30·33%)	..	403 5402 (27·11%)
45–64	53 335 (44·42%)	95 171 (43·17%)	25 290 (35·44%)	12 560 (30·89%)	1006 (39·42%)	1061 (28·96%)	341 120 (32·04%)	..	518 7709 (34·85%)
65–74	20 287 (16·90%)	28 183 (12·78%)	15 098 (21·16%)	2741 (6·74%)	443 (17·36%)	669 (18·26%)	82 724 (7·77%)	72 430 (45·52%)	235 5275 (15·82%)
75–84	12 664 (10·55%)	28 840 (13·08%)	14 842 (20·80%)	1738 (4·27%)	386 (15·13%)	891 (24·32%)	41 417 (3·89%)	56 027 (35·21%)	102 3709 (6·88%)
≥85	5561 (4·63%)	11 502 (5·22%)	7107 (9·96%)	679 (1·67%)	69 (2·70%)	279 (7·61%)	25 559 (2·40%)	30 645 (19·26%)	..

IQVIA_France=IQVIA Longitudinal Patient Database France. IQVIA_Germany=IQVIA Disease Analyzer Germany. IQVIA_Italy=IQVIA Longitudinal Patient Database Italy. IQVIA_UK=IQVIA Medical Research Data UK. AUSOM_KR=Ajou University School of Medicine database from South Korea. KNU_KR=Kangwon National University database from South Korea. MDCD_US=IBM MarketScan Multi-State Medicaid adjudicated US health insurance claims for Medicaid Database. MDCR_US=IBM MarketScan Medicare Supplemental and Coordination of Benefits Database. IQVIA_US=IQVIA Open Claims US. *Since the full-year data for 2021 were not available, the annual number of patients was averaged based on data from 2016–20.

Table 1: **Sample characteristics of patients with depressive disorders between 2016 and 2020* in each database**

	IQVIA_France, July 31, 2021	IQVIA_Germany, Aug 31, 2021	IQVIA_Italy, June 30, 2021	IQVIA_UK, March 31, 2021	AUSOM_KR, June 30, 2021	KNU_KR, June 30, 2021	MDCD_US, March 31, 2021	MDCR_US, June 30, 2021	IQVIA_US, Nov 30, 2021
Annual number of patients	147 686	138 353	9804	42 145	2017	2360	104 5223	117 077	144 83786
Sex									
Female	97 047 (65·71%)	92 636 (66·96%)	6317 (64·43%)	26 711 (63·38%)	1166 (57·81%)	1376 (58·31%)	714 370 (68·35%)	81 873 (69·93%)	966 7292 (66·75%)
Male	50 639 (34·29%)	45 717 (33·04%)	3487 (35·57%)	15 434 (36·62%)	851 (42·19%)	984 (41·69%)	330 853 (31·65%)	35 204 (30·07%)	481 6494 (33·25%)
Age group, years									
<18	4915 (3·33%)	8043 (5·81%)	168 (1·71%)	5414 (12·85%)	70 (3·47%)	131 (5·55%)	234 642 (22·45%)	..	141 2289 (9·75%)
18–24	7025 (4·76%)	7738 (5·59%)	642 (6·55%)	5204 (12·35%)	119 (5·90%)	104 (4·41%)	94 414 (9·03%)	..	138 1220 (9·54%)
25–44	38 768 (26·25%)	37 163 (26·86%)	3020 (30·80%)	16 305 (38·69%)	399 (19·78%)	261 (11·06%)	320 383 (30·65%)	..	470 3577 (32·47%)
45–64	56 564 (38·30%)	54 831 (39·63%)	3979 (40·59%)	11 135 (26·42%)	891 (44·17%)	755 (31·99%)	287 321 (27·49%)	..	464 7304 (32·09%)
65–74	21 348 (14·45%)	14 020 (10·13%)	1113 (11·35%)	2397 (5·69%)	285 (14·13%)	509 (21·57%)	60 507 (5·79%)	57 329 (48·97%)	167 1871 (11·54%)
75–84	13 413 (9·08%)	12 648 (9·14%)	666 (6·79%)	1295 (3·07%)	216 (10·71%)	491 (20·81%)	29 181 (2·79%)	39 590 (33·82%)	667 525 (4·61%)
≥85	5653 (3·83%)	3910 (2·83%)	216 (2·20%)	395 (0·94%)	37 (1·83%)	109 (4·62%)	18 775 (1·80%)	20 158 (17·22%)	..

IQVIA_France=IQVIA Longitudinal Patient Database France. IQVIA_Germany=IQVIA Disease Analyzer Germany. IQVIA_Italy=IQVIA Longitudinal Patient Database Italy. IQVIA_UK=IQVIA Medical Research Data UK. AUSOM_KR=Ajou University School of Medicine database from South Korea. KNU_KR=Kangwon National University database from South Korea. MDCD_US=IBM MarketScan Multi-State Medicaid adjudicated US health insurance claims for Medicaid Database. MDCR_US=IBM MarketScan Medicare Supplemental and Coordination of Benefits Database. IQVIA_US=IQVIA Open Claims US. *Since the full-year data for 2021 were not available, the annual number of patients was averaged based on data from 2016–20.

Table 2: **Sample characteristics of patients with anxiety disorders between 2016 and 2020* in each database**

followed up from the diagnosis of depressive or anxiety disorders until the end of continuous enrolment (for IQVIA_UK, MDCD_US, and MDCR_US) or the last health-care encounter (for IQVIA_France, IQVIA_Germany, IQVIA_Italy, AUSOM_KR, KNU_KR, and IQVIA_US). All patients with depressive or anxiety disorders between Jan 1, 2016, and Dec 31, 2021, were included. The observation period was divided into 72 calendar months. For each month, a cohort of patients who received a diagnosis of depressive or anxiety disorders before or during that month was created. Diagnoses of depressive and anxiety disorders were identified using SNOMED CT codes, aligning with past research (appendix pp 5–6).[14] A patient could be included in both diagnostic groups.

Involvement of people with lived experience

People with lived experience were not involved in shaping the research question and study design, choosing outcome measures, planning recruitment, writing up the study, or delivering the dissemination of its findings.

Measures and exposure

Three classes of psychotropic drugs were examined following the Anatomical Therapeutic Chemical classification: antidepressants (N06A; appendix pp 7–8), antipsychotics (N05A; appendix pp 9–10), and anxiolytics (N05B; appendix p 11).

The prevalence rate of people prescribed each class of psychotropic drugs among patients with depressive disorders and among those with anxiety disorders were calculated for each month. The exposure in this study was defined as the COVID-19 pandemic, which was declared by WHO on March 11, 2020.[17] As the observation unit was set by month, the start of the exposure period was defined as April 1, 2020. This choice of start date was supported by the COVID-19 Stringency Index obtained from the Oxford COVID-19 Government Response Tracker.[18] The index shows that all countries included in the study implemented lockdown policies in the middle of March, 2020. March, 2020, was defined as a transition month and excluded from the analysis.

Statistical analysis

Demographic characteristics of each database were tabulated. The average monthly rates of psychotropic drug prescriptions among people with depressive and anxiety disorders were computed during the period from April 1–Dec 31, 2020, and compared with the mean proportions during corresponding months in 2019. The associations between the COVID-19 pandemic and psychotropic drug prescribing were examined with interrupted time series analyses using segmented regressions. Quasi-Poisson regression models using a log link function were employed to account for overdispersion.[19] The model included a time variable measuring the time (in months) elapsed since the start of the study (Jan 1, 2016), a dummy variable which took the value 0 before the pandemic and 1 during the pandemic exposure, and the interaction between the dummy variable and the time elapsed since the beginning of the pandemic (April 1, 2020). For the monthly prescription rate calculation, the denominator was the cumulative number of people with depressive or anxiety disorder diagnoses before or during that month, and the numerator was the number of people prescribed psychotropic drugs in the corresponding month. Fourier terms with two sine–cosine pairs (one for modelling the regular wave and one for harmonics) were added to the model to account for a potential seasonality effect.[20] All parameters were expressed as rate ratios (RRs) with a 95% CI. Autocorrelation function and partial autocorrelation function plots,[21] along with Durbin–Watson tests,[22] were generated to assess autocorrelation. Stationarity was tested using augmented Dickey–Fuller tests.[23] The linearity assumption was assessed using residual plots (residuals against fitted values).[24] Another set of autoregressive integrated moving average models with a step function and a ramp function were fitted to test the robustness of results generated from segmented regressions in case of autocorrelation detection.[25]

The analyses were conducted for each class of psychotropic drug separately for patients with depressive disorders and those with anxiety disorders. Subgroup analyses were performed by sex and age group (<25, 25–64, and ≥65 years). The objective of our study is to examine within-database trend in psychotropic drug prescribing before and during the COVID-19 pandemic. Therefore, no correction was conducted for multiple comparisons as our conclusions did not solely rely on statistical significance. All analyses were conducted using R (version 4.3.0).

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, and interpretation or writing of the report.

Results

Between Jan 1, 2016, and Dec 31, 2020, an average of 16 567 914 patients with depressive disorders (10 820 956 females [65·31%] and 5 746 958 males [34·69%]) and 15 988 451 patients with anxiety disorders (10 688 788 females [66·85%] and 5 299 663 males [33·15%]) were identified annually. The monthly numbers of patients are plotted in the appendix (p 24). Excluding the IQVIA_UK and MDCR_US databases, which primarily include individuals aged 25–44 and 65–74 years, respectively, most patients with depressive disorders were aged 45–64 years in all databases (table 1). Most patients with anxiety disorders were aged 45–64 years in all databases except for IQVIA_UK and three databases in the USA (table 2). Due to privacy concerns, only the age group information was available

and the mean ages could not be calculated. Ethnicity data were not available.

The average monthly rates of patients prescribed psychotropic drugs differed substantially between databases (table 3). Despite the differences, an increase in the average proportion was observed in several databases across drug classes. For example, a sizeable increase was observed in antidepressant prescriptions among patients with anxiety disorders in the UK (4·08% [95% CI 1·08–7·08] increase). Five databases (IQVIA_France, AUSOM_KR, KNU_KR, MDCD_US, and IQVIA_US) provided evidence of more than a 1% increase in anxiolytic prescribing for patients with anxiety disorders. Considerable decreases in antidepressant and anxiolytic prescriptions were observed for both patient groups in Germany.

Figure 1 presents results of the interrupted time series analyses among patients with depressive disorders (see appendix [p 25] for the comparison of the observed and fitted values). Immediate increases in rates of psychotropic drug prescribing during the pandemic were observed among patients with depressive disorders across all databases for at least one drug class except IQVIA_Germany. Immediate increases in the prescribing rates of antidepressants were observed in four databases (IQVIA_Italy, AUSOM_KR, MDCD_US, and IQVIA_US), antipsychotics in five databases (IQVIA_Italy, KNU_KR, MDCD_US, MDCR_US, and IQVIA_US), and anxiolytics in five databases (IQVIA_France, IQVIA_UK, AUSOM_KR, MDCD_US, and IQVIA_US). In some databases, the immediate increase was followed by a

	Depressive disorders, observed monthly rate per 100 population (mean [SD])				Anxiety disorders, observed monthly rate per 100 population (mean [SD])			
	Pre-pandemic period*	Pandemic period†	Absolute mean difference (95% CI)	p value‡	Pre-pandemic period*	Pandemic period†	Absolute mean difference (95% CI)	p value‡
Antidepressants								
IQVIA_France	73·03 (0·46)	73·24 (0·58)	0·21 (–1·24 to 1·66)	0·72	36·59 (0·64)	36·08 (1·10)	–0·51 (–3·00 to 1·98)	0·24
IQVIA_Germany	48·85 (0·68)	46·12 (0·97)	–2·73 (–5·05 to –0·41)	<0·0001	29·12 (1·31)	27·93 (1·19)	–1·20 (–4·67 to 2·27)	0·095
IQVIA_Italy	77·21 (0·48)	78·09 (0·45)	0·88 (–0·41 to 2·17)	0·0020	64·91 (1·40)	67·04 (0·65)	2·13 (–0·90 to 5·16)	0·0023
IQVIA_UK	80·16 (0·69)	77·88 (1·81)	–2·28 (–6·08 to 1·52)	0·015	60·57 (0·76)	64·64 (1·33)	4·08 (1·08 to 7·08)	<0·0001
AUSOM_KR	77·09 (0·74)	76·97 (1·92)	–0·12 (–4·15 to 3·91)	0·89	60·13 (2·68)	57·03 (1·82)	–3·10 (–9·45 to 3·25)	0·013
KNU_KR	88·15 (0·66)	88·01 (0·73)	–0·15 (–2·08 to 1·78)	0·48	49·44 (1·08)	52·98 (2·23)	3·55 (–1·31 to 8·41)	0·0013
MDCD_US	38·35 (0·68)	39·13 (0·81)	0·79 (–1·28 to 2·86)	0·064	36·59 (0·62)	37·37 (0·71)	0·77 (–1·08 to 2·62)	0·040
MDCR_US	43·50 (0·75)	42·93 (1·08)	–0·58 (–3·16 to 2·00)	0·22	39·66 (0·66)	39·20 (0·71)	–0·45 (–2·35 to 1·45)	0·34
IQVIA_US	44·88 (0·54)	45·92 (1·23)	1·04 (–1·59 to 3·67)	0·076	42·79 (0·48)	43·01 (0·64)	0·21 (–1·36 to 1·78)	0·49
Antipsychotics								
IQVIA_France	9·36 (0·21)	9·61 (0·27)	0·25 (–0·42 to 0·92)	0·074	5·61 (0·15)	5·52 (0·20)	–0·09 (–0·58 to 0·40)	0·23
IQVIA_Germany	9·93 (0·22)	9·75 (0·33)	–0·18 (–0·96 to 0·60)	0·33	6·48 (0·28)	6·37 (0·23)	–0·10 (–0·81 to 0·61)	0·50
IQVIA_Italy	10·79 (0·22)	11·26 (0·15)	0·47 (–0·05 to 0·99)	0·0012	7·87 (0·41)	8·54 (0·34)	0·67 (–0·37 to 1·71)	0·0010
IQVIA_UK	4·64 (0·36)	5·99 (0·30)	1·34 (0·42 to 2·26)	<0·0001	4·60 (0·24)	6·38 (0·38)	1·78 (0·90 to 2·66)	<0·0001
AUSOM_KR	33·62 (1·10)	33·17 (1·38)	–0·45 (–3·91 to 3·01)	0·53	18·36 (0·80)	19·68 (0·78)	1·32 (–0·87 to 3·51)	0·0027
KNU_KR	12·76 (0·66)	14·49 (0·63)	1·73 (–0·06 to 3·52)	<0·0001	7·63 (0·66)	8·65 (0·61)	1·02 (–0·74 to 2·78)	0·0070
MDCD_US	16·69 (0·23)	17·40 (0·50)	0·71 (–0·37 to 1·79)	0·0079	16·44 (0·22)	17·26 (0·46)	0·93 (–0·07 to 1·93)	0·0018
MDCR_US	7·91 (0·20)	8·09 (0·48)	0·18 (–0·84 to 1·20)	0·42	7·14 (0·23)	7·28 (0·29)	0·14 (–0·59 to 0·87)	0·32
IQVIA_US	9·91 (0·12)	10·42 (0·30)	0·51 (–0·12 to 1·14)	0·0023	8·22 (0·10)	8·29 (0·14)	0·16 (–0·18 to 0·50)	0·032
Anxiolytics								
IQVIA_France	46·14 (0·66)	47·01 (0·59)	0·87 (–0·87 to 2·61)	0·018	55·30 (1·07)	56·91 (1·30)	1·61 (–1·69 to 4·91)	0·025
IQVIA_Germany	5·95 (0·14)	5·48 (0·24)	–0·48 (–1·02 to 0·06)	0·0076	10·17 (0·49)	9·41 (0·53)	–0·76 (–2·17 to 0·65)	0·012
IQVIA_Italy	22·04 (0·52)	20·76 (0·43)	–1·28 (–2·60 to 0·04)	<0·0001	31·54 (1·02)	29·80 (1·43)	–1·73 (–5·17 to 1·71)	0·0010
IQVIA_UK	6·14 (0·48)	7·35 (0·44)	1·21 (–0·07 to 2·49)	0·0010	14·40 (0·85)	13·92 (1·64)	–0·48 (–4·10 to 3·14)	0·33
AUSOM_KR	46·38 (0·90)	50·08 (0·96)	3·70 (1·12 to 6·28)	0·0019	55·62 (2·05)	58·04 (1·21)	2·40 (–2·27 to 7·07)	0·015
KNU_KR	47·34 (1·34)	45·22 (0·94)	–2·12 (–5·33 to 1·09)	0·0019	67·07 (2·19)	68·68 (1·58)	1·62 (–3·67 to 6·91)	0·11
MDCD_US	15·34 (0·34)	16·63 (0·37)	1·30 (0·32 to 2·28)	<0·0001	19·89 (0·50)	21·01 (0·59)	1·12 (–0·40 to 2·64)	0·0015
MDCR_US	11·95 (0·25)	11·72 (0·53)	–0·23 (–1·38 to 0·92)	0·30	24·06 (0·61)	23·63 (1·08)	–0·42 (–2·85 to 2·01)	0·30
IQVIA_US	13·09 (0·26)	13·83 (0·33)	0·74 (–0·08 to 1·56)	0·0004	23·15 (0·38)	24·34 (0·75)	1·19 (–0·46 to 2·84)	0·0041

IQVIA_France=IQVIA Longitudinal Patient Database France. IQVIA_Germany=IQVIA Disease Analyzer Germany. IQVIA_Italy=IQVIA Longitudinal Patient Database Italy. IQVIA_UK=IQVIA Medical Research Data UK. AUSOM_KR=Ajou University School of Medicine database from South Korea. KNU_KR=Kangwon National University database from South Korea. MDCD_US=IBM MarketScan Multi-State Medicaid adjudicated US health insurance claims for Medicaid Database. MDCR_US=IBM MarketScan Medicare Supplemental and Coordination of Benefits Database. IQVIA_US=IQVIA Open Claims US. *Pre-pandemic period is defined as April 1–Dec 31, 2019. †Pandemic period is defined as April 1–Dec 31, 2020. ‡p value was calculated by *t* test for comparison of monthly means before and during the pandemic.

Table 3: **The average monthly rate of patients prescribed psychotropic drugs among patients with depressive and anxiety disorders**

decrease in slope, reflecting a pattern that the prescribing rate increased immediately at the beginning of the pandemic then decreased to the pre-pandemic level or below (ie, the counterfactual level; appendix p 25). For example, in MDCD_US, the rate of antipsychotic prescribing immediately increased with a rate ratio (RR) of 1·077 (95% CI 1·055–1·100), then returned to the counterfactual level (RR 0·990, 95% CI 0·988–0·992; figure 1). In the other databases with immediate increase (appendix p 25), no slope change was observed, suggesting that the prescribing rate remained high until the end of the observation period. This pattern was observed consistently for anxiolytics in four databases (IQVIA_France, IQVIA_UK, AUSOM_KR, and IQVIA_US), with the most substantial level change observed in the UK (RR 1·179, 95% CI 1·031–1·345). Decreased rates

	Antidepressants				Antipsychotics				Anxiolytics			
	Level		Slope		Level		Slope		Level		Slope	
	RR	p value	RR	p value	RR	p value	RR	p value	RR	p value	RR	p value
IQVIA_France	0·999	0·829	1·000	0·771	1·026	0·121	0·999	0·327	**1·028**	**0·001**	0·999	0·428
95% CI	0·993–1·006		0·999–1·001		0·994–1·059		0·996–1·001		**1·013–1·044**		0·998–1·001	
IQVIA_Germany	0·952	0·001	1·000	0·724	0·972	0·151	0·997	0·128	0·970	0·152	0·999	0·581
95% CI	0·926–0·979		0·997–1·002		0·936–1·010		0·994–1·001		0·930–1·011		0·995–1·003	
IQVIA_Italy	1·014	0·001	0·999	0·041	1·021	0·046	0·997	0·003	0·985	0·204	0·996	0·002
95% CI	1·006–1·022		0·998–1·000		1·001–1·042		0·995–0·999		0·961–1·008		0·994–0·998	
IQVIA_UK	0·967	0·117	0·999	0·597	1·327	<0·001	0·980	0·040	1·179	0·019	0·996	0·613
95% CI	0·927–1·008		0·993–1·004		1·149–1·528		0·962–0·999		1·031–1·345		0·979–1·013	
AUSOM_KR	1·024	0·046	0·999	0·513	0·951	0·073	1·001	0·670	1·045	0·025	1·001	0·778
95% CI	1·001–1·047		0·997–1·002		0·901–1·004		0·996–1·006		1·006–1·085		0·997–1·004	
KNU_KR	1·011	0·133	1·000	0·593	**1·214**	**<0·001**	1·006	0·271	0·974	0·219	1·000	0·924
95% CI	0·997–1·026		0·999–1·002		**1·098–1·342**		0·996–1·016		0·933–1·016		0·996–1·005	
MDCD_US	**1·046**	**<0·001**	**0·995**	**<0·001**	**1·077**	**<0·001**	**0·990**	**<0·001**	**1·124**	**<0·001**	0·996	0·008
95% CI	**1·024–1·069**		**0·993–0·997**		**1·055–1·100**		**0·988–0·992**		**1·095–1·155**		0·993–0·999	
MDCR_US	1·008	0·498	0·997	0·012	1·064	0·002	0·995	0·004	1·025	0·392	0·999	0·728
95% CI	0·985–1·031		0·995–0·999		1·024–1·105		0·991–0·998		0·969–1·085		0·994–1·004	
IQVIA_US	**1·035**	**<0·001**	**0·998**	**0·001**	**1·049**	**<0·001**	**0·997**	**<0·001**	**1·097**	**<0·001**	1·000	0·792
95% CI	**1·017–1·054**		**0·996–0·999**		**1·029–1·070**		**0·996–0·999**		**1·072–1·122**		0·998–1·001	

Significance level classification
Significant increase with p<0·001 | Significant increase with p<0·01 | Significant increase with p<0·05 | Significant decrease with p<0·001 | Significant decrease with p<0·01 | Significant decrease with p<0·05 | Not significant

Figure 1: **RRs (95% CIs) for the association between the COVID-19 pandemic and psychotropic drug prescribing rate among patients with depressive disorders**
RRs with their 95% CIs were estimated using interrupted time series analyses. Level and slope changes refer to immediate and long-term changes induced by the intervention, respectively. IQVIA_France=IQVIA Longitudinal Patient Database France. IQVIA_Germany=IQVIA Disease Analyzer Germany. IQVIA_Italy=IQVIA Longitudinal Patient Database Italy. IQVIA_UK=IQVIA Medical Research Data UK. AUSOM_KR=Ajou University School of Medicine database from South Korea. KNU_KR=Kangwon National University database from South Korea. MDCD_US=IBM MarketScan Multi-State Medicaid adjudicated US health insurance claims for Medicaid Database. MDCR_US=IBM MarketScan Medicare Supplemental and Coordination of Benefits Database. IQVIA_US=IQVIA Open Claims US. RR=rate ratio.

of antidepressant prescriptions, as shown by either a negative level or slope change, were observed in IQVIA_Germany and MDCR_US. In IQVIA_Italy, the rate of anxiolytic prescription gradually decreased during the pandemic, as suggested by a negative slope change (RR 0·996, 95% CI 0·994–0·998).

Figure 2 presents results of the interrupted time series analyses among patients with anxiety disorders (see also the appendix p 26). Immediate increases in psychotropic drug prescribing rates were observed in all databases for at least one drug class except IQVIA_Germany, AUSOM_KR, and MDCR_US. In most databases with an immediate increase, the rate gradually returned to the counterfactual level or lower (appendix p 26). The largest changes were observed in IQVIA_UK and KNU_KR, in which the antipsychotic prescribing rates increased

	Antidepressants				Antipsychotics				Anxiolytics			
	Level		Slope		Level		Slope		Level		Slope	
	RR	p value	RR	p value	RR	p value	RR	p value	RR	p value	RR	p value
IQVIA_France	**0·965**	**<0·001**	1·002	0·006	0·984	0·401	1·001	0·458	**1·038**	**<0·001**	0·998	0·006
95% CI	**0·947–0·983**		1·001–1·004		0·948–1·021		0·998–1·005		**1·021–1·055**		0·996–0·999	
IQVIA_Germany	0·988	0·528	1·002	0·158	0·990	0·708	1·000	0·916	0·973	0·290	1·000	0·901
95% CI	0·950–1·026		0·999–1·006		0·939–1·043		0·995–1·004		0·924–1·023		0·996–1·005	
IQVIA_Italy	**1·044**	**<0·001**	0·998	0·188	1·048	0·097	1·001	0·638	0·993	0·749	0·993	0·002
95% CI	**1·021–1·067**		0·996–1·001		0·992–1·106		0·996–1·007		0·951–1·037		0·988–0·997	
IQVIA_UK	**1·067**	**0·001**	0·995	0·043	**1·467**	**<0·001**	0·985	0·101	1·058	0·348	0·999	0·898
95% CI	**1·030–1·104**		0·991–1·000		**1·282–1·675**		0·969–1·003		0·941–1·186		0·984–1·014	
AUSOM_KR	0·941	0·011	1·002	0·432	0·987	0·754	1·003	0·457	1·036	0·098	1·003	0·184
95% CI	0·900–0·985		0·997–1·006		0·909–1·071		0·995–1·011		0·994–1·079		0·999–1·007	
KNU_KR	0·991	0·716	1·004	0·121	1·296	0·007	0·990	0·302	1·06	0·003	1·001	0·520
95% CI	0·945–1·040		0·999–1·009		1·078–1·554		0·971–1·009		1·022–1·100		0·997–1·005	
MDCD_US	**1·041**	**0·001**	**0·995**	**<0·001**	**1·073**	**<0·001**	**0·989**	**<0·001**	**1·118**	**<0·001**	0·997	0·015
95% CI	**1·019–1·064**		**0·993–0·998**		**1·047–1·100**		**0·987–0·992**		**1·091–1·145**		0·994–0·999	
MDCR_US	0·986	0·228	0·998	0·126	1·022	0·249	1·002	0·272	1·009	0·762	1·003	0·277
95% CI	0·965–1·008		0·996–1·000		0·985–1·061		0·999–1·005		0·950–1·072		0·998–1·009	
IQVIA_US	1·006	0·464	**0·998**	**<0·001**	1·023	0·008	**0·996**	**<0·001**	**1·09**	**<0·001**	0·997	0·008
95% CI	0·990–1·022		**0·997–0·999**		1·006–1·039		**0·995–0·998**		**1·057–1·124**		0·995–0·999	

Significance level classification
Significant increase with p<0·001 | Significant increase with p<0·01 | Significant increase with p<0·05 | Significant decrease with p<0·001 | Significant decrease with p<0·01 | Significant decrease with p<0·05 | Not significant

***Figure 2*: RRs (95% CI) for the association between the COVID-19 pandemic and psychotropic drug prescribing rate among patients with anxiety disorders**
RRs with their 95% CIs were estimated using interrupted time series analyses. Level and slope changes refer to immediate and long-term changes induced by the intervention, respectively. IQVIA_France=IQVIA Longitudinal Patient Database France. IQVIA_Germany=IQVIA Disease Analyzer Germany. IQVIA_Italy=IQVIA Longitudinal Patient Database Italy. IQVIA_UK=IQVIA Medical Research Data UK. AUSOM_KR=Ajou University School of Medicine database from South Korea. KNU_KR=Kangwon National University database from South Korea. MDCD_US=IBM MarketScan Multi-State Medicaid adjudicated US health insurance claims for Medicaid Database. MDCR_US=IBM MarketScan Medicare Supplemental and Coordination of Benefits Database. IQVIA_US=IQVIA Open Claims US. RR=rate ratio.

immediately with RRs of 1·467 (95% CI 1·282–1·675) for the UK and 1·296 (95% CI 1·078–1·554) for South Korea, and did not decrease afterwards. For anxiolytics, the rates increased immediately in IQVIA_France, KNU_KR, MDCD_US, and IQVIA_US and, apart from in KUN_KR, decreased towards or below the counterfactual level. Decreases in prescribing rates during the pandemic, either immediately after the start of the pandemic (level change) or gradually after the pandemic (slope change), were observed in AUSOM_KR and IQVIA_US for antidepressants and IQVIA_Italy for anxiolytics. No changes were observed in other databases.

Results of subgroup analyses stratified by sex and age group are presented in the appendix (pp 27–36). A considerable difference between males and females was observed in anxiolytic prescribing in MDCD_US for patients with depressive disorders and in MDCD_US and IQVIA_US for patients with anxiety disorders. Although anxiolytic prescribing immediately increased in both sexes, the rate returned to the counterfactual level at the end of the study for females but remained high for males. The rates of antidepressant and anxiolytic prescribing were consistently higher in females than males, but the trends in rates before and during the pandemic were comparable overall. Considerable differences in trends were observed between age groups. Marked differences were observed in anxiolytic prescribing among patients with depressive disorders in the USA (MDCD_US and IQVIA_US), where the rates increased considerably at the start of the pandemic and continued to increase during the pandemic in people younger than 25 years (appendix p 31). Among people with anxiety disorders aged younger than 25 years, anxiolytic prescribing increased substantially at the beginning of the pandemic and continued at a greater rate in the USA (MDCD_US, IQVIA_US; appendix p 34). This pattern was not observed in the other age groups. In the appendix we present results from autocorrelation function and partial autocorrelation function plots (pp 37–60), Durbin–Watson tests (pp 12–17), Dickey–Fuller tests (pp 18–23), and residual plots (pp 61–72). Despite the detection of autocorrelation in multiple databases, the results were not significantly affected, as evidenced by the results from the autoregressive integrated moving average models (appendix pp 73–86).

Discussion

In this multinational network study, we found that the prescribing rate of at least one class of psychotropic drug increased immediately at the beginning of the pandemic in eight databases among patients with depressive disorders and six databases among patients with anxiety disorders. Although the prescribing rates in most databases gradually decreased after the acute phase of the pandemic, the rates remained elevated in some databases, especially for anxiolytics. The rate of anxiolytic prescribing continued to increase in two US databases among patients younger than 25 years for both disorders.

We used data from different health-care settings and countries, including electronic medical records, both primary care and hospital-based, and insurance claims data, observing substantial heterogeneity in the rates of psychotropic drug prescribing across databases. This heterogeneity, which is commonly observed in multinational studies,[14,16,26] could be attributed to differences in database-specific properties, such as clinical practices, patient characteristics, and data capturing or collection methods. These differences pose significant challenges in interpreting our findings. It is, therefore, important to note that the prescribing rates during the pandemic should only be compared with pre-pandemic rates within the same database.

The observed increase in psychotropic medication prescribing can be interpreted in multiple ways. On the one hand, it could indicate improved access to necessary medications, a reduction in the stigma surrounding mental health treatment, or better help-seeking behaviours, which are positive developments. On the other hand, it might reflect increased incidence or severity of psychiatric disorders or over-prescribing, both of which are concerning. It is also possible that a combination of these factors is at play. In our interrupted time series analysis with the exposure period defined as the pandemic, we aimed to isolate the effect of the pandemic on underlying prescribing trends. The observed changes in psychotropic drug prescribing are more likely to be directly related to the pandemic's disruptions to daily routines, care support, and health-care access rather than solely to decreased stigma or increased drug accessibility. However, due to the inherent limitations of the study design and the complexities of real-world data, it is difficult to draw definitive conclusions about the underlying causes of these trends.

Despite these challenges, examining these trends is important for future research. As we enter the post-pandemic era, these insights can underpin further studies aimed at evaluating the long-term effects of the pandemic on mental health care and inform strategies for future health-care emergencies. Our findings provide a foundation for investigations into the reasons behind the observed prescribing patterns and can help inform clinical practice, policy decisions, and research priorities.

In a seminal position paper calling for action for mental health science, the ascertainment of the global effects of lockdown and social isolation on people from vulnerable groups was listed as one of the research priorities.[27]

In our study, the trends in individual databases vary. In anxiolytics prescribing among patients with depressive disorders, for example, the rate increased immediately and remained elevated in France, the UK, South Korea (AUSOM), and the USA (IQVIA); increased immediately

but decreased gradually in the USA (MDCD); and decreased in general in Italy. Despite these differences, we identified significant immediate increases in psychotropic drug prescribing during the first month of the pandemic (ie, April, 2020) in half of the databases across drug classes for both depressive and anxiety disorders. This increase can be associated with both deteriorating symptoms and disruptions of psychological and psychosocial interventions for depressive and anxiety disorders, which concurs with earlier concerns that people with existing mental health problems might be particularly affected by the uncertainties about the pandemic, isolation, and disruptions to daily routines and services.[27] However, the observed increase could be attributed to other factors. One potential factor is the over-representation of patients with more severe symptoms, as individuals with milder symptoms might have been less likely to access health-care services when harsh lockdown policies were still in place. This explanation is less likely because we did not observe a considerable reduction in the total number of patients with depressive or anxiety disorders in 2020 in databases with substantial immediate increases, including IQVIA_France, KNU_KR, MDCD_US, and IQVIA_US. Another possible factor is a change in prescribers' practices. Health-care providers might have is sued repeat prescriptions early because of uncertainties about medication access, and hoarding of medications was reported to be prevalent during March, 2020.[28,29] However, the hoarding effect subsided subsequently, with a decrease in psychotropic drug consumption observed in several countries.[30–32] Therefore, this factor alone cannot account for the persistently high rates of prescriptions beyond the initial phase of the pandemic. As information on the indications for psychotropic drug prescribing is not available, reasons for the observed increase cannot be investigated based on the current data.

During the later phase of the pandemic, the rate of antidepressant and antipsychotic prescribing decreased to the counterfactual level in many databases. However, a persistent elevation in the rates of anxiolytic drug prescribing among patients with depressive disorders was observed in France, the UK, South Korea (AUSOM), and the USA (IQVIA). Continuously elevated rates of anxiolytic prescribing were also observed in males and in younger patients in the USA. Adding anxiolytic drugs, predominantly benzodiazepines, to antidepressant treatment is common for treating patients with depressive disorders since anxiety often coexists with depression. However, existing evidence suggests that combining antidepressants and anxiolytics is more effective than antidepressants alone only in the early phase, and is associated with an elevated risk of adverse effects.[33] Therefore, clinical guidelines recommend that anxiolytics such as benzodiazepine should only be a short-term measure for treatment courses of less than 2 weeks.[34] We found a marked increase in anxiolytic prescribing among patients with depressive disorders during the entire pandemic period in four databases, highlighting the need for careful examination of the causes of the increase to ensure the benefits outweigh the risks. Regular review of anxiolytic treatment could be particularly crucial among younger users of anxiolytics, given the high potential for benzodiazepine misuse among this population.[35]

Although continuously elevated prescribing rates were observed only in IQVIA_Italy for antidepressants and IQVIA_UK and KNU_KR for antipsychotics, the increase in antipsychotic rates among patients with anxiety disorders in the UK and South Korea (KNU) was considerable, with the highest RRs observed across all databases and drug classes. No treatment guidelines for general anxiety disorders in primary care settings currently recommend antipsychotic medication. Further research into the reasons for the increase in antipsychotic prescribing and the potential risk and benefit associated with the use of this class of agent in patients with anxiety disorders is warranted.

This study has limitations. First, there are differences in the properties of the databases employed and the inherent measurement issues associated with each database. We included four European databases with electronic medical records collected from primary care, two South Korean databases with patient records from general hospitals, and three US databases containing insurance claims. These databases contained data about patients with different clinical profiles affected by fundamental differences in each data source's contextual factors. For example, the insurance claims database MDCD_US is linked to employment; therefore, individuals without job-based insurance or those who were unemployed were not included, despite potentially being among those most affected by the pandemic. The two South Korean databases, although both contain hospital-based electronic medical records, can show different trends in psychotropic drug prescribing rates due to differences in the proportions of older patients. Additionally, data accumulated in a real-world setting inevitably have measurement issues such as varied levels of diagnostic accuracy and coding bias. However, systematic biases that were unvarying within the same databases should not affect the interpretation of our findings. Second, time-varying confounders such as the indications and severity of depressive and anxiety disorders, vaccination status, socioeconomic status, and health-care access were not available, preventing detailed investigations into factors associated with these changes. Third, findings generated from this study only reflect prescribing patterns rather than the actual intake of these antipsychotic drugs by patients. Additionally, people with lived experience of depressive or anxiety disorders were not involved in the research and writing process. Last, although nine databases were included, adopting the OMOP CDM approach limited the study to a few

high-income countries with infrastructures that could support data conversion. Data from low-income and middle-income countries were not available.

This study provides empirical evidence on psychotropic prescription trends among patients with depressive and anxiety disorders before and during the pandemic. Real-world data covering diverse study populations and health-care settings facilitate the generation of policy-influencing insights for psychotropic prescribing management in the post-COVID-19 era. We found an overall immediate increase in psychotropic drug prescribing across databases. Continuously elevated rates of anxiolytic prescribing were observed among patients with depressive disorders across four databases; and the rates were particularly high among patients younger than 25 years in the USA. Our findings support the reported negative impact of the COVID-19 pandemic on individuals with mental disorders. Further investigations are needed to understand the population-specific causes for the increases in various psychotropic drugs across different databases.

Contributors

HL, YC, KKCM, and ICKW conceptualised the study. HL, YC, SL, XL, CY, SF, DYL, and RWP conducted formal analysis. ICKW acquired funding. HL, YC, WCYL, COT, and KKCM contributed to methodology. YC and SL verified the underlying data. SL did visualisation. HL and YC wrote the original draft. All authors contributed to the writing, review, and editing of the manuscript and revised the manuscript critically for important intellectual content. XL and CY verified and had access to all the IQVIA data, including IQVIA_France, IQVIA_Germany, IQVIA_Italy, IQVIA_UK, and IQVIA_US. DYL and RWP verified and had access to the South Korea data, including AUSOM_KR and KNU_KR. SF and DK verified and had access to the MDCD_US and MDCR_US. HL and YC verified the aggregated results sent by the data partners. All authors had final responsibility for the decision to submit for publication.

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Data sharing

Data used in this study are not publicly available due to restrictions from the data providers.

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