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Effets de la pandémie à COVID-19 sur la consommation de psychotropes

Paul Benistand

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

Pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Par

BENISTAND Paul

Présentée et soutenue publiquement le 23 juin 2022

Effets de la pandémie à COVID-19 sur la consommation de psychotropes

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Monsieur le Professeur Philippe VORILHON, Professeur des Universités, Département de Médecine Générale, CHU Clermont-Ferrand

Nous vous remercions de l'immense honneur que vous nous faites en acceptant la présidence de cette thèse. Veuillez trouver ici l'expression de mon profond respect.

A notre jury de thèse :

A mon directeur de thèse,

Monsieur le Professeur Frédéric DUTHEIL, Professeur des Universités, Praticien Hospitalier Médecine et Santé au Travail, CHU de Clermont-Ferrand

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A Monsieur Antoine CHARAZAC, Docteur en Médecine générale, Sousceyrac-en-Quercy

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A Madame Senem ALTUN, Attaché de Recherche Clinique, CHU Clermont-Ferrand

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Table des matières

Remerciements	9
Liste des figures.....	29
Liste des Abréviations	12
1. Introduction	13
2. Article.....	13
2.1 Title page	13
2.2 Abstract.....	14
2.3 Introduction.....	15
2.4 Methods	16
Database for medication	16
The ATC classification for medications	16
Selected psychotropic medication.....	17
Statistical analysis.....	17
2.5 Results.....	18
Participants.....	18
The influence of the pandemic on overall psychotropic medication	18
The influence on each class of psychotropic medication.....	19
2.6 Discussion.....	19
Psychotropic consumption.....	20
Disparities between classes of psychotropic drugs.....	21
Limitations	22
2.7 Conclusion	23
2.8 References.....	24
Figures	29
3. Conclusion.....	34

Liste des Abréviations

COVID-19 : Coronavirus Disease 2019

SNDS : Système Nationale des Données de Santé

ITSA: Interrupted Time Serie Analysis

95CI: 95% Confidence Interval

ATC: Anatomical Therapeutic Chemical

PTSD: Post Traumatic Stress Disorder

1. Introduction

2. Article

2.1 Title page

Effect of the COVID-19 pandemic on the Psychotropic Drug Consumption

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2.2 Abstract

Importance: Although the COVID-19 pandemic has had a negative impact on mental health, there is no comprehensive longitudinal study of the entire population of a country without selection bias.

Objective: The objective of this study was to evaluate the prescription of psychotropic drugs during the COVID-19 pandemic, using data from the French national health data system (SNDS).

Design, settings, and participants: Prescriptions for psychotropic drugs (antidepressants, anxiolytics, hypnotics and antipsychotics) from January 1, 2015 to September 30, 2021 were collected from administrative data provided by the SNDS. This database includes more than 99% of the French population, i.e. 67 million people. The data were analyzed using an interrupted time series analysis (ITSA) model.

Main outcomes and measures: Consumption of psychotropic drugs was aggregated in months and expressed in number of boxes per thousand inhabitants.

Results: During the study period, more than 1.3 billion boxes of psychotropic medications were dispensed. Comparison of psychotropic drug dispensing before and after the pandemic showed a relative increase of 0.76 (95CI 0.57 to 0.95, $p < 0.001$) boxes per month per thousand inhabitants, all classes of psychotropic drugs combined. Three classes saw their consumption increase in an almost similar proportion, respectively by 0.23 (0.15 to 0.32, $p < 0.001$) boxes for antidepressants, 0.27 (0.20 to 0.34, $p < 0.001$) boxes for anxiolytics and 0.23 (0.17 to 0.30, $p < 0.001$) boxes for hypnotics. The change in antipsychotic consumption was very small, with an increase of 0.04 boxes (0.02 to 0.06, $p = 0.001$) per month per thousand population.

Conclusion and relevance: The COVID-19 pandemic had led to an increase in the consumption of psychotropic drugs, confirming the significant impact of the pandemic on the mental health of the general population.

2.3 Introduction

Mental health is a global public health issue.¹ The onset of the COVID-19 pandemic in March 2020 has led to major changes in the daily lives of populations with the implementation of government measures to contain the spread of the disease.² This resulted in the lockdown of billions of people around the world for the first time in human history. Proofs from previous epidemics showed that these isolation measures in an outbreak context were a source of severe mental problems and psychological distress.^{3,4} The COVID-19 pandemic, by its magnitude, is no exception, with an increase in depressive symptoms, anxiety, and sleep disorders from the first phase of the pandemic.⁵⁻¹⁰ However, most studies were cross-sectional, on selected population, and explored mainly the short-term effects of the pandemic. Consumption of anxiolytics, antidepressants, hypnotics and antipsychotics using administrative data provided by the French National Health System is an alternative method for assessing the mental health of the population.¹¹⁻¹³ This method also has the benefits of studying the whole population of an entire country, without any selection bias, using repeated long-term longitudinal data. Considering that several epidemiological studies showed an increase in the consumption of psychotropic drugs following wide-ranging psychological distress such as during natural,¹⁴ industrial,¹⁵ or economic disasters,¹⁶ we hypothesized that the pandemic has led to an increase in the use of medication linked to stress-related disorders.

Therefore, our main objective was to demonstrate the increase in the use of psychotropic drugs following the pandemic, using nation-wide data. More specifically, we intended to describe the delivery of psychotropic drugs in city pharmacies during the 18 months following the onset of the pandemic, in comparison with the previous 5 years.

2.4 Methods

Database for medication

Data were extracted from National Health Insurance (Sécurité sociale). More precisely, we used the Medic'AM open database, which is part of the SNDS (Système National de Données de Santé).¹⁷ This database is exhaustive, anonymized, and gathers the drugs delivery in city pharmacies – hospital deliveries are not considered. The Medic'AM database, due to his “open status”, only provide aggregated data, with no socio-demographic details. The Medic'AM database collect only the number of boxes delivered per month, per drugs classified according to their Anatomical Therapeutic Chemical (ATC) class.

The ATC classification for medications

The ATC system is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOC) and was first published in 1976. This pharmaceutical coding system classifies drugs into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. The ATC classification is based on five levels of classification that correspond to the target organ(s) and the therapeutic, pharmacological and chemical properties of the different products.¹⁸ The general form of the code for a molecule is LCCLCC, where L is a letter and C is a number (example: A01AA01). Each letter and each digit doublet represent a successive level. The first level (first letter) defines one of 14 anatomical groups. The second level (first two digits) gives the main pharmacological or therapeutic subgroup. The third and fourth levels (second and third letters) correspond to chemical, pharmacological or therapeutic subgroups. The fifth and last level (last two digits) indicates the chemical substance.

Selected psychotropic medication

In our study, we selected the psychotropic medications based on the fourth level of the ATC. We focused on psychotropic medications including antidepressants (ATC code N06A), anxiolytics (ATC code N05B), hypnotics (ATC code N05C), and antipsychotics (ATC code N05A). We included monthly medication from January 1st, 2015, till September 30th, 2021. We decided to divide the study period into two time periods. The first, from January 2015 to March 2020, was our control, pre-pandemic period. The second phase, from March 2020 through the end of September 2021, was our COVID-19 pandemic part of the study period. All persons who had a reimbursed delivery of a psychotropic molecule (ATC code N05A, N05B, N05C and N06A) in the period from January 2015 to September 2021 were included in this study.

Statistical analysis

We chose to analyse the data using a long-term Interrupted Series Analysis (ITSA) model with medication aggregated in months and expressed in number of boxes per thousand inhabitants. The purpose was to test the hypothesis that the occurrence of the COVID-19 pandemic was associated with a significant change relative to the forecasted evolution in the volume of medication delivery. Statistics were computed using Stata 15 (StataCorp, College Station, TX). For each psychotropic molecule, crude numbers of boxes reimbursed per month were divided per the total French population according to the National Institute of Statistics and Economic Studies (INSEE references), to adjust medication delivery per month and per habitant. Data was then deseasonalized according to monthly seasonal coefficients calculated from 2010 to 2018. Then analyses were performed – for each molecule of interest- using a long-term Interrupted Series Analysis (ITSA) model.¹⁹⁻²¹ The data before the 1st lockdown (from 2015 till March

2020) were used to modelized the counterfactual evolution after the 1st lockdown, to test changes in trends of medication delivery. Trends coefficients before and after the 1st lockdown, and coefficients of change after relative to before the pandemic were expressed with their 95% confidence intervals (95CI) and plotted accordingly. All tests were two-sided and a P value < 5% was considered significant.

2.5 Results

Participants

The database includes more than 99% of the French population i.e. 67 million people. All persons covered by the health insurance system were included. Since all patients are extracted from a national database, there is no study selection bias or attrition bias. Over the study period, more than 1.3 billion boxes of psychotropic drug were delivered.

The influence of the pandemic on overall psychotropic medication

The delivery of all psychotropic drugs was decreasing by -0.29 (95CI -0.40 to -0.18, $p < 0.001$) boxes per month per thousand inhabitants between January 2015 and March 2020, whereas there was an increase of 0.47 (0.32 to 0.62, $p < 0.001$) boxes per month per thousand inhabitants following the first lockdown in March 2020. The differences between slopes before and after the first lockdown was a relative increase of 0.76 (0.57 to 0.95, $p < 0.001$) boxes per month and per thousand inhabitants.

The influence on each class of psychotropic medication

The prescription of antidepressants was growing by 0.08 (0.05 to 0.11, $p < 0.001$) boxes per month per thousand inhabitants from January 2015 to March 2020, whereas there was an increase of 0.31 (0.23 to 0.39, $p < 0.001$) boxes per month per thousand inhabitants from March 2020. The difference between slopes before and after the first lockdown was a relative increase of 0.23 (0.15 to 0.32, $p < 0.001$) boxes per month per thousand inhabitants.

There was a reversal of the trend for anxiolytics: a decrease of -0.12 (-0.16 to -0.08, $p < 0.001$) boxes per month per thousand inhabitants before the pandemic, followed by an increase of 0.15 (0.09 to 0.21, $p < 0.001$) boxes after the first lockdown, and therefore a relative increase of 0.27 (0.20 to 0.34, $p < 0.001$) boxes per month per thousand inhabitants.

For hypnotics, consumption was decreasing by -0.27 (-0.31 to -0.22, $p < 0.001$) boxes per month per thousand inhabitants before the pandemic, following by a flattening of delivery at -0.03 (-0.070 to 0.005, $p = 0.086$) boxes from the first lockdown. The difference between slopes before and after the first lockdown was a relative increase of 0.23 (0.17 to 0.30, $p < 0.001$) boxes per month per thousand inhabitants.

For antipsychotics, there was a slight increase of 0.01 (0.002 to 0.020, $p = 0.023$) boxes before the pandemic, followed by an increase of 0.05 (0.03 to 0.07, $p < 0.001$) boxes per month per thousand inhabitants after March 2020. The difference between slopes before and after the first lockdown was a relative increase of 0.04 (0.02 to 0.06, $p = 0.001$) boxes per month per thousand inhabitants.

2.6 Discussion

The main findings were characterized by a clear break in the long-term consumption of psychotropic drugs. Antidepressants, anxiolytics, and hypnotics had the strongest change in

trend marked by an increase in delivery after the pandemic, relative to the long-term trend before. In the other hand, antipsychotics underwent a very slight and perceptible increase.

Psychotropic consumption

Many studies have been conducted since the beginning of the pandemic on mental health. These studies showed an upsurge in anxiety, stress, and depressive symptoms, directly linked with the health situation.⁴⁻⁸ Our results corroborate these data at a national level. Moreover, the use of psychotropic drugs was objectively measurable and independent of any observer. Despite two studies showing an increase in the delivery of psychotropic drugs during the COVID-19 pandemic, our study had an exhaustive sample size²² and a long-term follow-up.²³ On the opposite, some studies did not find significant variation in the prescription of psychotropic drugs following the pandemic²⁴⁻²⁸ that may be explained by specificities of the lockdown in each country. For example, Sweden,²⁸ Poland²⁴ or Northern California²⁷ showed only an isolated peak in March 2020. The discordance of results between countries may be explained by difference in the severity of lockdown restrictions, with a variable impact on daily life.²⁹ The French government imposed several measures to limit the spread of the disease such as strict containment, with schools closed and non-essential activities halted.³⁰ Certainly, the first lockdown has left its mark by the violence of the changes it has caused in the daily life of the general population.² Several studies on containment measures implemented during past epidemics showed that these social isolation measures increased anxiety, stress, and depressive symptoms.³ A frequent increase in the use of stress-related medication has also been shown in the aftermath of a traumatic or stressful event affecting the general population.¹⁴⁻¹⁶ The global lockdown of more than 4 billion people simultaneously, with alarming media coverage centered on the pandemic (daily number of contaminations and daily deaths), can surely be considered as a traumatic event.³¹⁻³³ The extensive use of social media further accentuated this

psychological distress.³⁴ The novelty of our results also lies in the long-term increase of psychotropic drugs delivery. The months that followed the first lockdown maintained a climate of anxiety with successive waves of contamination and restrictions. During the time of our study, France experienced three strict lockdowns, interspersed with curfew periods, that were somewhat anxiogenic. These long-time measures have undermined the resilience of the population, with a feeling of endless situation and contributed to the development of COVID-19 psychological fatigue.³⁵ The fear of an economic crisis due to the pandemic also contributed to this anxiety.^{36,37} This prolonged exposure to a state of high stress led to the development of post-traumatic stress disorder (PTSD) in some patients, health care workers, and even in the general population.³⁸⁻⁴⁰

Disparities between classes of psychotropic drugs

Our results showed an increase in the delivery of psychotropic drugs since the beginning of the pandemic. Nevertheless, there were some disparities according to the therapeutic class studied. Indeed, the increase in antidepressants, anxiolytics and hypnotics consumption were similar in proportion. Some studies already demonstrated the negative impact of the COVID-19 pandemic on mental health, using self-administrated questionnaires or medical interview-based epidemiological surveys.^{29,39,41-43} These studies showed the increase in depressive symptoms, anxiety and sleep disorders.^{10,41,44} Our study confirmed the severity of those symptoms, that were translated into a global increase in the delivery of antidepressants, anxiolytics, and hypnotics. Most effective public health measures to prevent depressive symptoms, anxiety and sleep disorders are behavioral such as practicing a regular physical activity,^{45,46} and having social interaction. Both were particularly limited during the first lockdown.⁴⁷⁻⁴⁹ Therefore, despite the fear of the COVID-19 itself, the lockdown and its associated behavioral restriction might have increase prevent depressive symptoms, anxiety, and sleep disorders. For the most

severe patients, some non-medication approach exists to treat depressive symptoms, anxiety and sleep disorders, such as intervention of a mobile psychiatric team, a close follow-up by a psychiatric nurse, or psychotherapy.^{50,51} However, the first lockdown was marked by a massive limitation in the access to psychiatric structures.^{52,53} The only resource available was the prescription of antidepressants, anxiolytics and hypnotics. Alarmingly, despite the reopening of those structure in the following months, the symptoms were judged sufficiently severe by medical doctors to require a drug treatment. The analysis of administrative databases is a complementary and necessary approach to follow mental health of population.¹¹ Our study does not show a significant change in the dispensing of antipsychotics. These drugs are prescribed to patients with severe psychiatric pathologies, requiring in addition a close follow-up. The beginning of the pandemic was marked by a disorganization of care structures, particularly psychiatric care,^{52,53} to limit the spread of the virus. The difficulties of follow-up associated with the health situation make these patients more sensitive than the general population to the deterioration of mental health secondary to the pandemic.⁵⁴ In case of psychiatric decompensation, treatment is with an antidepressant, an anxiolytic, or a hypnotic, without changing the antipsychotic treatment.

Limitations

Our study may suffer from some limitations. We do not have basic information such as sociodemographic (age, sex), delivery localization, or prescribers. However, we used a massive database derived from the SNDS, that include more than 99% of the French population. Since all patients are extracted from a national database, there is no selection bias, nor attrition or generalizability bias. Our database gives us information on the delivery and not on the consumption of psychotropic drugs. The French population being a large consumer of psychotropic drugs,⁵⁵ several individuals may have taken medications already at home. Despite

an increase in the use of these stocks would go unnoticed in our study, our results provide a high level of evidence for an increase of consumption of psychotropic drugs because of the pandemic. We chose to use an international classification to gather drugs, which may have hidden variations specific to certain drugs. Further studies should compare national databases from different countries, in the light of specific restrictions measures.

2.7 Conclusion

The COVID-19 pandemic resulted in a significant increase in the dispensing of psychotropic drugs to the general population in France. The increase was most noticeable for antidepressants, anxiolytics, and hypnotics. Further studies are needed to explain the increase in psychotropic drug dispensing during the pandemic, as well as the population most at risk, to build effective preventive strategies.

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List of the figures

Figure 1: Flow chart

Figure 2: Influence of the COVID-19 pandemic on the psychotropic drug delivery

Figure 3: Influence of the Covid-19 pandemic on the psychotropic drugs delivery, by class of psychotropic drugs

Figure 4: Slopes and the COVID-19 effect on the psychotropic drugs delivery

Figures

Figure 1. Flow chart.

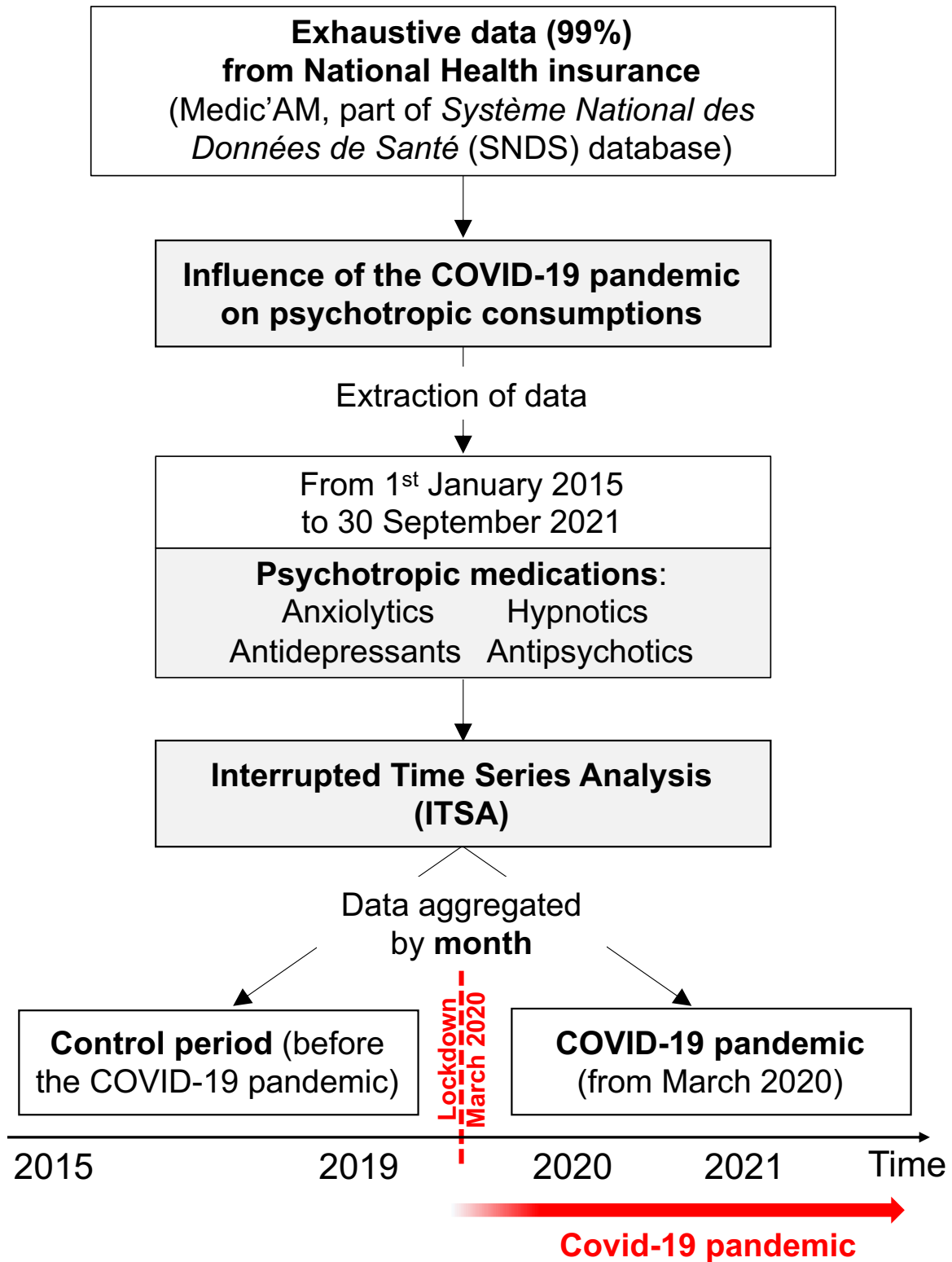
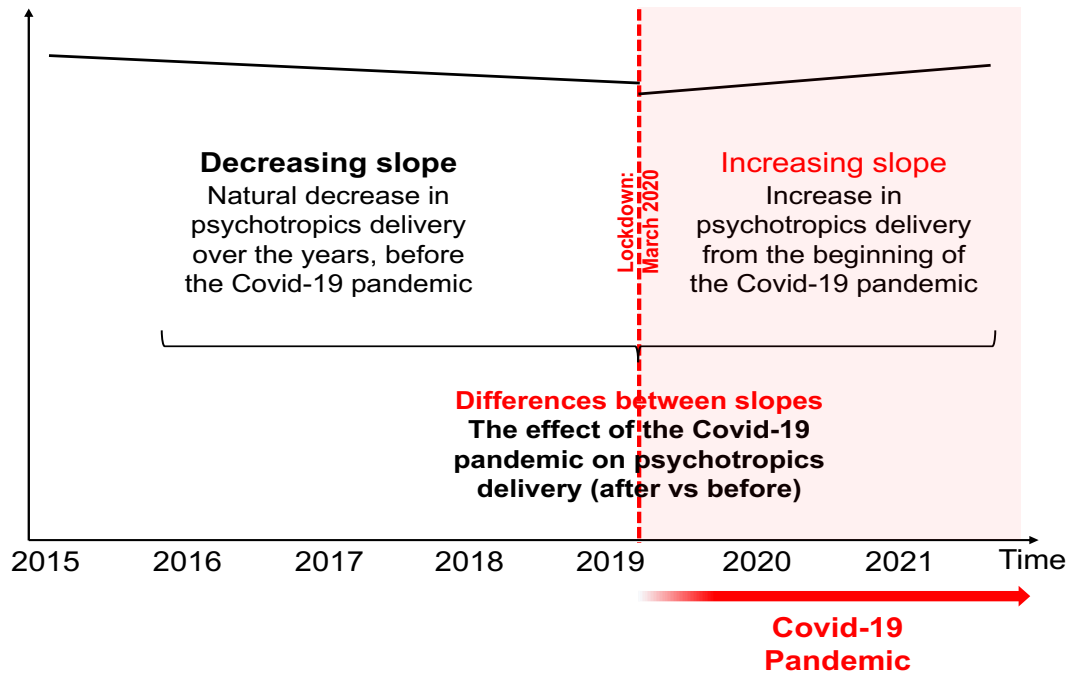


Figure 2. Influence of the COVID-19 pandemic on the psychotropic drug delivery

Example of interpretation of an Interrupted Time Series Analysis (ITSA) model



All psychotropics

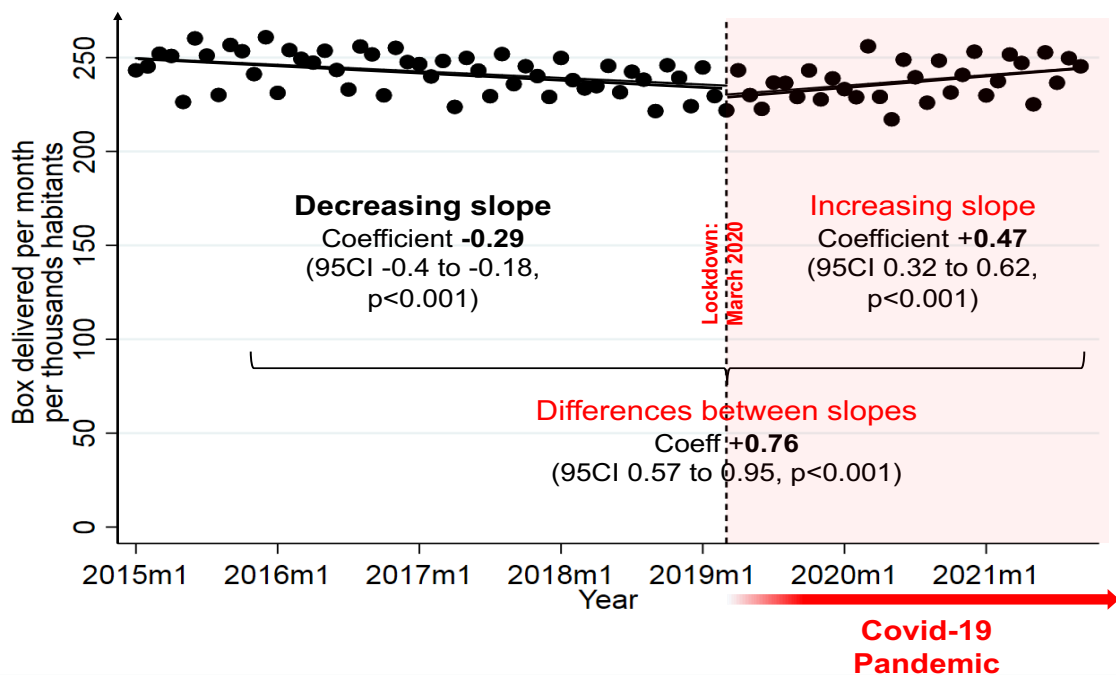


Figure 3. Influence of the Covid-19 pandemic on the psychotropic drugs delivery. by class of psychotropic drugs

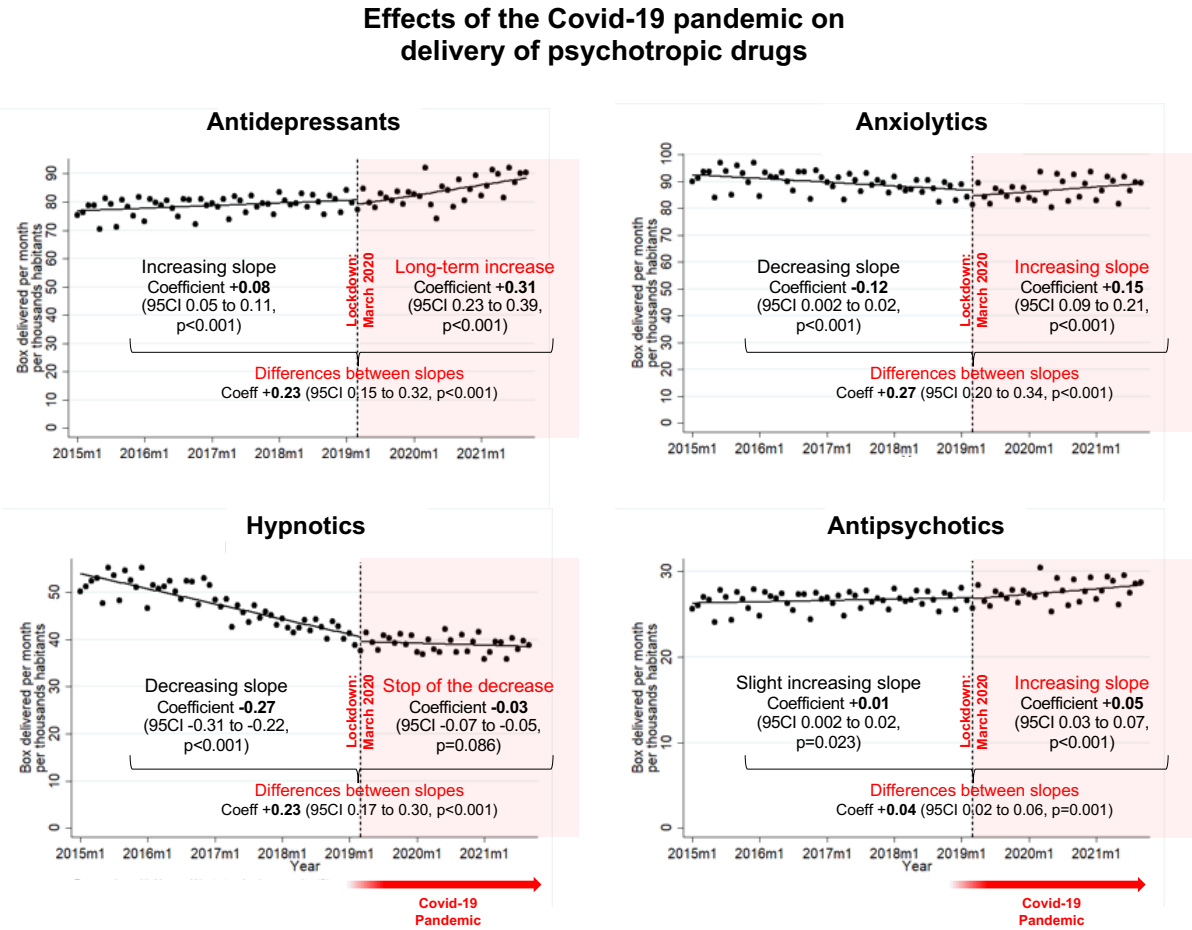
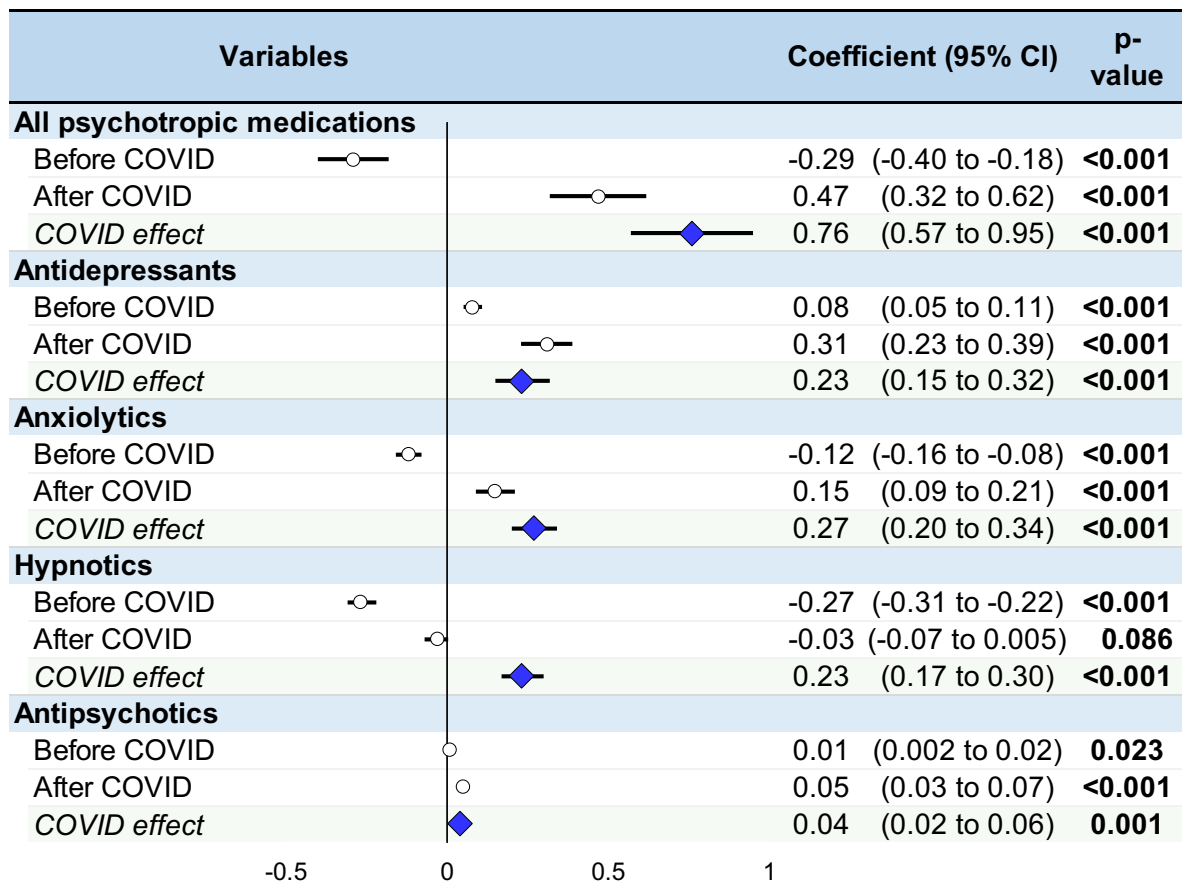


Figure 4. Slopes and the COVID-19 effect on the psychotropic drugs delivery



3. Conclusion

La pandémie à COVID-19 a entraîné une augmentation notable de la délivrance de médicaments psychotropes dans la population générale en France. L'augmentation était plus sensible pour les antidépresseurs, les anxiolytiques et les hypnotiques. D'autres études sont nécessaires pour expliquer l'augmentation de la délivrance des psychotropes durant la pandémie, ainsi que la population la plus à risque, afin de construire des stratégies préventives efficaces.

Clermont-Ferrand, le
Doyen de l'UFR de Médecine,
Pierre CLAVELOU



Clermont-Ferrand, le 01/06/22
Président du Jury,
Philippe VORILHON

A handwritten signature in black ink, appearing to be "P. Vorilhon", written over the printed name.

(Conseil national de l'ordre des médecins)

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

Paul BENISTAND

Effets de la pandémie à COVID-19 sur la consommation de psychotropes

Thèse pour le Doctorat de Médecine Générale, Clermont-Ferrand, Année 2022

Résumé

Contexte : Bien que la pandémie de COVID-19 ait eu un impact négatif sur la santé mentale, il n'existe aucune étude longitudinale exhaustive sur l'ensemble de la population d'un pays sans biais de sélection. L'objectif de cette étude était d'évaluer la prescription de médicaments psychotropes durant la pandémie à COVID-19, à partir des données du système national des données de santé français (SNDS).

Méthode : Les prescriptions de psychotropes (antidépresseurs, anxiolytiques, hypnotiques et antipsychotiques) du 1er janvier 2015 au 30 septembre 2021 ont été recueillies à partir des données administratives fournies par le SNDS. Cette base inclut plus de 99% de la population française soit 67 millions de personnes. Les données ont été analysées à l'aide d'un modèle d'analyse des séries temporelles interrompues (ITSA). La consommation de médicaments psychotropes était agrégée en mois et exprimée en nombre de boîtes pour mille habitants.

Résultats : Durant la période étudiée, plus d'1,3 milliard de boîtes de médicaments psychotropes ont été délivrées. La comparaison des délivrances de psychotropes avant et après la pandémie a montré une augmentation absolue de 0,76 (95CI 0,57 à 0,95, $p < 0,001$) boîtes par mois et par millier d'habitants, toutes classes de psychotropes confondues. Trois classes ont vu leur consommation augmenter dans une proportion quasi similaire, respectivement de 0,23 (0,15 à 0,32, $p < 0,001$) boîtes pour les antidépresseurs, 0,27 (0,20 à 0,34, $p < 0,001$) boîtes pour les anxiolytiques et 0,23 (0,17 à 0,30, $p < 0,001$) boîtes pour les hypnotiques. La variation de la consommation d'antipsychotiques était très faible, avec une augmentation de 0,04 boîte (0,02 à 0,06, $p = 0,001$) par mois et par millier d'habitants.

Conclusion : La pandémie de COVID-19 a eu un impact notable sur la santé mentale des Français, avec une nette augmentation de la consommation de médicaments psychotropes.

Mots-clés

COVID-19, Psychotropes, santé mentale

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