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**Impact of the COVID-19 outbreak on the reporting of adverse drug reactions
associated with self-medication**

**Impact de l'épidémie de COVID-19 sur les notifications d'effet indésirables
médicamenteux associés à l'automédication.**

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Running head adverse drug reactions and self-medication in COVID 19

Principal Investigator : Sophie Liabeuf

HIGHLIGHTS

- Self-medication is not risk-free, it can induce adverse drug reactions, microbial resistance, drug interactions, addiction, and substance abuse.
- Preliminary evidence suggests that symptoms of anxiety and depression and self-reported stress are common psychological reactions to the COVID-19 pandemic; in turn, these reactions might lead to unjustified self-medication.
- The present study is the first to give an overview of officially notified ADRs linked to self-medication during the COVID-19 outbreak in 2020 first wave.
- Our results highlighted a higher proportion of ADRs linked with self-medication during the COVID-19 period, relative to the same calendar period 12 months previously.
- Half of the notified ADRs were considered to be “serious”, and 62.5% were linked to overdoses and medication errors. Accidental ingestion of drugs by children was a particular concern.

ABSTRACT

Objectives: The primary objective of the present study was to describe the characteristics of adverse drug reactions (ADRs) linked to self-medication that were notified to the French Pharmacovigilance Database (FPVD) during the COVID-19 outbreak in 2020 first wave. The secondary objective was to compare the characteristics of these ADRs in 2020 with those notified during the same calendar period a year previously

Material and methods: We analyzed ADRs recorded in the FPVD between March 15th and May 31st, 2020 vs. the same dates in 2019. Only ADRs linked to self-medication were analyzed. Descriptive statistics were used to obtain an overview of the types and characteristics of these ADRs.

Results Of 3114 ADRs notified to the FPVD during the COVID-19 period in 2020, 114 (3.7%) were linked to self-medication. The equivalent proportion in 2019 was 1.6% (113 out of 7097). Half of the ADRs notified in 2020 were “serious”. The median age of affected patients was 30.5, and 22% of the ADRs concerned children. Of the 114 ADRs linked to self-medication, 107 (66%) were for prescription-only drugs. The three mostly frequently suspected ATC classes were analgesics, psycholeptics, and antibacterials for systemic use. The most frequent ADRs were general disorders, gastrointestinal disorders, and nervous system disorders. The main difference between the non-COVID-19 period and the COVID-19 period was the higher proportion of medication errors during the latter.

Conclusion The present study is the first to have reported on ADRs linked to self-medication and notified during a COVID-19 outbreak. Further studies of self-medication patterns and their consequences in a pandemic context are mandatory and effective information on medication use (including self-medication and its dangers) during a pandemic is essential.

RESUME

Objectifs: L'objectif principal de la présente étude était de décrire les caractéristiques des effets indésirables médicamenteux (EIM) liés à l'automédication qui ont été notifiés dans la base nationale française de pharmacovigilance (BNPV) lors de l'épidémie de COVID-19 pendant la première vague de 2020. L'objectif secondaire était de comparer les caractéristiques de ces EI en 2020 avec celles notifiées au cours de la même période calendaire un an auparavant

Matériel et méthodes: Nous avons analysé les effets indésirables enregistrés dans la BNPV entre le 15 mars et le 31 mai 2020 par rapport aux mêmes dates en 2019. Seuls les EIM liés à l'automédication ont été analysés. Des statistiques descriptives ont été utilisées pour obtenir un aperçu des types et des caractéristiques de ces effets indésirables.

Résultats : Sur 3114 effets indésirables notifiés au FPVD au cours de la période étudiée en 2020, 114 (3,7%) étaient liés à l'automédication. La proportion équivalente en 2019 était de 1,6% (113 sur 7097). La moitié des EIM notifiés en 2020 étaient «graves». L'âge médian des patients était de 30,5 ans et 22% des EIM concernaient des enfants. Sur les 114 EIM liés à l'automédication, 107 (66%) concernaient des médicaments sur prescription uniquement. Les trois classes les plus fréquemment suspectées étaient les analgésiques, les psycholeptiques et les antibactériens à usage systémique. Les effets indésirables les plus fréquents étaient les troubles généraux, les troubles gastro-intestinaux et les troubles du système nerveux. La principale différence entre la période COVID-19 et la période non COVID-19 était la proportion plus élevée d'erreurs de prise médicamenteuse pendant la période COVID-19.

Conclusion Cette étude est la première à rapporter les EIM associés à l'automédication et notifiés pendant une période de confinement. D'autres études portant sur les conséquences de l'automédication en période de pandémie semblent importantes à mener afin de cibler des messages de prévention.

Key words self-medication, pharmacovigilance, adverse drug reaction, COVID-19

Mots clés automédication, pharmacovigilance, effet indésirable médicamenteux, COVID-19

INTRODUCTION

In December 2019, a previously unknown form of pneumonia was identified in Wuhan, China. Coronavirus RNA was detected in some of the affected individuals, leading to the recognition of coronavirus disease 2019 (COVID-19). Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2, the pathogen causing COVID-19) currently poses a major threat to the wellbeing of people and nations worldwide. On March 11th, the World Health Organisation (WHO) declared that COVID-19 constituted a global pandemic [1]. European countries have been affected by the pandemic to varying extents; France was one of the countries with the most cases and most deaths [2].

In an attempt to manage the COVID-19 pandemic and stop healthcare systems being overwhelmed, most European countries have sought to curb the spread of the virus [3]. These measures included containment of the population and a ban on non-essential travel [3]. The first measures were adopted in Italy, Spain, France and Germany, with other countries soon following [4–6]. Each country set its own lockdown restrictions and time frames as a function of the national infection rates. Although government responses to the COVID-19 pandemic varied [7], many member countries of the European Union implemented mechanisms for controlling the pandemic. In France, first lockdown measures were applied from March 17th, 2020, to May 11th, 2020. The measures notably affected the citizens' freedom of movement as a result of school closures, workplace closures, unemployment, and social isolation.

Data on the outbreak's impact on psychological distress and the symptoms of mental illness are now emerging. The preliminary evidence suggests that symptoms of anxiety and depression (16–28%) and self-reported stress (8%) were common psychological reactions to the COVID-19 pandemic, and may have been associated with poor sleep quality [8]. One can reasonably hypothesize that psychological distress and the fear of a new disease may lead to dramatic changes in behaviour, including addiction and unjustified self-medication. We recently reported that in a large cohort of students, stress is a key independent factor associated with inappropriate self-medication [9]. As an element of self-care, responsible self-medication has been defined by the WHO as “the practice whereby individuals treat ailments and conditions with medicines which are approved and available without prescription, and which are safe and effective when used as directed” [10].

The WHO does not recommend self-medication with any medicines (including **anti-infective agents**) as a prevention or cure for COVID-19 [11]. However, detailed reports on self-medication and its consequences during the COVID-19 pandemic are lacking.

The primary objective of the present study was to describe the characteristics of ADRs linked to self-medication as notified to the French Pharmacovigilance Database (FPVD) during the **first French COVID-19 outbreak (from March to May 2020)**. The secondary objective was to compare the incidence and characteristics of ADRs linked to self-medication notified during the COVID-19 outbreak with those notified during the same calendar period a year previously (i.e. before the outbreak).

MATERIALS/PATIENTS

France's national pharmacovigilance system was established in 1973. It consists of a network of 31 regional centres to which physicians, pharmacists, midwives, and dentists must, by law, notify ADRs. Other healthcare professionals and patients can also report ADRs. Each notification of an ADR in the FPVD should include information about the patient (age, gender, medical history, etc.), the reaction itself (e.g. the date of occurrence, chronology, and outcome), drug exposure (suspected drugs and other associated but non-suspected drugs) and the type of incident (overdose, medication error, addiction, drug interaction, breastfeeding, or other non-specific ADR), along with a summary of the clinical report. For each report, causality is assessed according to the French national pharmacovigilance system's standard procedure [12]. If a drug is considered to be definitely or probably responsible for the adverse event, it is defined as being "suspect". If the suspect drug was taken in the context of self-medication, this variable is noted. An ADR is categorized as being "serious" if it results in any untoward medical occurrence that (at any dose) results in death, is life-threatening, results in persistent or significant disability/incapacity, requires initial or prolonged hospitalization, induces a congenital anomaly or birth defect or is judged medically serious. The ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 22.1) [13].

In the present study, the study period (from March 15th to May 31st, 2020) corresponded to the COVID-19 outbreak in France. Although lockdown measures were applied from March 17th to May 11th, 2020, we considered that a large proportion of the French population was socially isolated until the end of May 2020. For comparative purposes, we selected a period 12 months previously, i.e. from March 15th to May 31st, 2019. We examined all ADRs recorded in the FPVD during each of the two periods and selected those linked to self-medication (i.e. overdoses, medication errors, addiction, drug interaction, breastfeeding, or other non-specific ADR) with the "suspect" drug.

The present dataset analysis was approved by the 31 regional pharmacovigilance centres and the French National Healthcare Product and Drug Safety Agency [*Agence nationale de sécurité du médicament et des produits de santé* (ANSM), Paris, France], which manages

the database and helped us with data extraction. It should be noted that the authors of the present article were solely responsible for interpretation of the data, and that the ANSM was not involved in this process.

Statistical analysis

Descriptive statistics were reported for the main study variables. Results were expressed as median [interquartile range] or the number (percentage). The frequency of ADRs linked to self-medication was calculated as the proportion of all ADRs notified over the same period. Data were compared by year using Fisher's test. **A p value ≤ 0.05 was considered to be statistically significant.** All statistical analyses were performed using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Corp, Redmond, WA, USA).

RESULTS

Data collected during the COVID-19 outbreak

Of the 3114 notifications recorded in the FPVD from March 15th to May 31st, 2020, 114 (3.7%) were linked to self-medication. Most of these 114 cases were reported by specialist physicians, only 14% of the ADRs were reported by the patient. Fifty-eight of the 114 notifications (51%) were serious: 33 cases of hospitalization, 9 life-threatening ADRs, 1 death, and 15 other cases with serious medical conditions. The median [interquartile range] age of the affected patients was 30.5 [15.0;57.5], 25 of the 114 ADRs concerned children, and 65 (57%) concerned females; With regard to comorbidities, 13 people (11%) presented anxiety and depressive symptoms, 9 (8%) had a history of suicide attempts, and 6 (5%) were drug addicts.

Medication errors and overdoses accounted for 31.5% and 31% of the ADRs linked to self-medication, **respectively (Figure 1A)**. Of the 36 medication errors, 15 were linked to a drug administration problem (such as non-compliance with the dose), 14 were linked to accidental exposure (including 12 cases of accidental ingestion by children), and 7 were linked to confusion between drugs. Some cases of accidental exposure of children can reasonably be considered as self-medication: the child was "playing doctor" and ate the drug to treat themselves. Although no details were provided in the other cases, we can safely presume that the ingestion was involuntary for infants and toddlers. With regard to overdoses, the most frequent reason was a suicide attempt; the most frequently involved drugs were anxiolytics, analgesics, antihistamines, and hypnotics.

The ADRs linked to self-medication most frequently resulted in general disorders (n=37 (32.5%)), gastrointestinal disorders (n=32 (28.1%); mainly abdominal pain and vomiting), and nervous system disorders (n=30 (26.3%); mainly somnolence) (**Figure 2**).

For the 114 notifications, a total of 162 self-medicated drugs were classified as being “suspect”. Of these, 107 (66%) were prescription-only drugs. The three mostly frequently suspected ATC classes were analgesics (n=38 (23.5%)), psycholeptics (n=31 (19.1%)), and antibacterials for systemic use (n=13 (8%)) (**Table 1**).

Comparison of period with and without COVID-19

Overall, there were twice as many ADR notifications from March 15th to May 31st, 2019 (n=7097) than for the corresponding period in 2020. However, the number of notifications linked to self-medication was similar (n=113). Hence, the proportion of notifications linked to self-medication was significantly lower in 2019 (1.6%) than in 2020 (3.7%; $p<0.001$). With regard to the type of ADRs, medication errors were significantly more frequent for the period in 2020 (n=36 (31.5%)) than in 2019 (n=14 (12.5%); $p<0.001$); this was especially true for accidental ingestion by children (12 in 2020 and none in 2019) (**Figure 1B**).

The distribution of the disorders resulting from the ADRs linked to self-medication types during the 2019 and 2020 periods is shown in **Figure 2**. The three most frequent types of self-medication ADRs were the same in the two periods.

When comparing the ATC classes of “suspect” drugs in the 2019 vs 2020 periods, there were few differences. However, there were trend towards a lower frequency of reports on non-steroidal anti-inflammatories and a higher frequency of reports on antimalarials, antibiotics (macrolides), and antipsychotics during 2020, relative to 2019 (**Table 1**). In the 2020 period, five ADRs were related to self-medication with hydroxychloroquine; three concerned people hoping to avoid infection by SARS-COV-2 (including an 11-year-old child medicated by his mother) and two concerned self-medication by people with a diagnosis of COVID-19. The associated ADRs were diarrhoea & vomiting (n=1), rash (n=1), syncope (n=1), ECG modification (prolonged QTc, n=1) and cardiopulmonary arrest (n=1). For the case of syncope and the case of ECG modification, the suspects drugs were an azithromycin-hydroxychloroquine combination.

DISCUSSION

This is the first report on self-medication and on ADRs linked to self-medication in the context of the COVID-19 outbreak. The study's objective was to describe the main characteristics of ADRs linked to self-medication, as recorded in a national pharmacovigilance database during

a COVID-19 period. Firstly, we found that ADRs linked to self-medication (most of which were notified by physicians) accounted for 3.7% of all ADRs registered in the database during the COVID-19 period; this proportion was twice that recorded for a similar but COVID-19-free period one year previously (1.6%). Second, we found that half of the notifications concerned “serious” ADRs, and almost two thirds concerned overdoses and medication error (including a significant number of accidental ingestions by children). Three drug classes accounted for a little more than half of the notifications: analgesics, psycholeptics, and antibacterials for systemic use.

Firstly, it appears that the proportion of reported ADRs linked to self-medication was higher during the COVID-19 outbreak - even though this variable was probably underestimated due to poor notification. The ADRs linked to self-medication proportion was 1.6% in COVID-19-free period one year previously; the value is in line with a previous analysis (1.3%) of the same database in another period [14]. The number of ADR (n=114) related to selfmedication could appear low in comparison to the French population. A well-known problem in the spontaneous reporting system is the underreporting of ADRs [15], however spontaneous notifications (as in the present report) represent an important tool to identify safety signal. In a disease context that many people had never lived through before, fear of viral contamination led to a decrease in physician consultations; hence, more frequent self-medication would not be unexpected. In the present study, two thirds of the drugs used for self-medication were prescription-only. In a survey of 1257 students, we previously reported that 52% of self-medicating individuals used medications left over from an old prescription. Although “responsible” self-medication (i.e. the use of appropriate over-the-counter drugs) could be encouraged in some cases, this practice is not risk-free and can led to ADRs, microbial resistance, drug interactions, addiction, and abuse.

Indeed, we found that medication errors and overdoses accounted for respectively 31.5% and 31% of the ADRs linked to self-medication. A short report from a poison control centre stated that during the COVID-19 outbreak, excessive house cleaning and the misuse of cleaning products for personal hygiene or for food cleaning led to an increase in exposure to chlorine and enhanced the potential risk of in-home poisoning of young children [16,17]. In the present analysis, 12 of the 36 medication errors were related to accidental ingestion by children. With school closures, young children spent more time at home and thus were more likely exposed to dangerous substances - including their parents’ medications. Most of the overdoses (86%) were related to suicide attempts. Indeed, there is evidence to suggest that the COVID-19 outbreak was associated with an increased prevalence of symptoms of

anxiety and depression [8]. However, the proportions of reported overdoses with self-medication were similar in 2020 and 2019.

Today, social media (such as Twitter, Facebook, and Instagram) have become one of the source of information (including medical information) for the general population. **Even if social media could be an interesting screening tools to identify adverse drug reactions** [18], a number of statements from “influencers” may trigger unjustified self-medication. The use of hydroxychloroquine of unproven efficacy has been a major issue during the COVID-19 pandemic. In the present report, five notified ADRs were linked to self-medication with hydroxychloroquine. A recent report suggested that the off-label use of drugs like hydroxychloroquine and azithromycin in COVID-19 increases the risk of cardiac ADRs [19].

Education of the general public is crucial for reducing harmful self-medication. The COVID-19 outbreak is challenging public health systems and compromising their ability to effectively communicate with the population. It is noteworthy that in the present study, ADR reports linked to non-steroidal anti-inflammatory agents were slightly less frequent in 2020 than in 2019. This difference might have been due to chance or to the information given to the public; at the beginning of the French COVID-19 epidemic, the French Minister for Health claimed that people showing symptoms of Covid-19 should use paracetamol (acetaminophen) rather than other non-steroidal anti-inflammatory drugs like ibuprofen, since anti-inflammatory agents might aggravate the infection by “damping down” the immune system.

One strength of the present study was its report on the harmful use of self-medication in the context of COVID-19. Indeed, disproportionate fear of COVID-19 is likely to prompt dramatic changes in behaviour that reduce contact with physicians and lead to excessive, inappropriate self-medication and thus to related ADRs.

The present study also had limitations – notably the inherent limitations associated with pharmacovigilance database analyses, including underreporting. The degree of underreporting is probably especially high for self-medication; in the present study, only 14% of the ADRs were reported by the patient.

CONCLUSION

The present study is the first to have reported on ADRs linked to self-medication and notified during a COVID-19 outbreak. Half of the ADRs were classified as “serious”, and the majority concerned overdoses and medication errors. Worldwide, further studies of self-medication patterns and their consequences in a pandemic context are mandatory. Giving too much

information about a problem makes it difficult to identify a solution; this is referred to as an “infodemic”; hence, providing effective information on medication use (including self-medication and its dangers) during a pandemic is essential [20].

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Author contribution : M.G., V.G-C., K.M. and S.L. designed the present project. M.G., V.G-C., S.L. and J.M. analyzed the data. V.G-C., K.M and S.L. helped to interpret the results. M.G., V.G-C. and S.L. wrote the first draft of the article; J.M., P.D., D.L., K.M. and S.L. provided critical feedback, helped shape the research, the analysis and the final draft of the manuscript, and approved the version to be published.

Data availability statement : Research data are not shared

List of Figure Legends

Figure 1 : Types of ADRs linked to self-medication in the 2020 (A) and 2019 (B) study periods

Figure 2: Disorders associated with ADRs linked to self-medication in the study periods in 2019 and 2020

Table 1: Suspected drugs by ATC class

ATC class	Suspected drugs 2019, n (%) N=157	Suspected drugs 2020, n (%) N=162	P value
Analgesics	37 (23.6)	38 (23.5)	1.00
<i>Non-opioids</i>	20	27	0.34
<i>opioids</i>	17	11	0.20
Psycholeptics	23 (14.6)	31 (19.1)	0.30
<i>anxiolytics</i>	15	14	0.80
<i>antipsychotics</i>	4	12	0.07
<i>hypnotics</i>	4	5	1.00
Antiinflammatory agents, non-steroids	22 (14.0)	12 (7.4)	0.07
Antihistamines for systemic use	4 (2.5)	9 (5.6)	0.25
Antibacterials for systemic use	8 (5.1)	13 (8.0)	0.37
<i>beta-lactam, penicillins</i>	5	6	1.00
<i>other beta-lactam</i>	1	1	1.00
<i>sulfonamides</i>	0	1	1.00
<i>macrolides</i>	1	5	0.20
<i>quinolones</i>	1	0	0.50
Antidepressants	7 (4.5)	5 (3.1)	0.57
Antiseptics and disinfectants	3 (1.9)	6 (3.7)	0.50
Antiepileptics	6 (3.8)	3 (1.9)	0.33
Antithrombotic agents	3 (1.9)	3 (1.9)	1.00
Stomatological preparations	2 (1.3)	3 (1.9)	1.00
Drugs used in addictive disorders	4 (2.5)	1 (0.6)	0.21
Antimalarials	0	5 (3.1)	0.06
Ophthalmologicals	2 (1.3)	3 (1.9)	1.00
<i>antiinfectives</i>	2	2	1.00
<i>antiglaucoma preparations</i>	0	1	1.00
Agents acting on the renin- angiotensin system	2 (1.3)	2 (1.2)	1.00
<i>ACE inhibitors</i>	1	1	1.00
<i>ACE inhibitors combinations</i>	1	0	0.50
<i>Angiotensin II receptor blockers</i>	0	1	1.00
Beta blocking agents	2 (1.3)	2 (1.2)	1.00
Topical products for muscular pain	4 (2.5)	0	0.06
Throat preparations	2 (1.3)	2 (1.2)	1.00
Nasal preparations	2 (1.3)	2 (1.2)	1.00

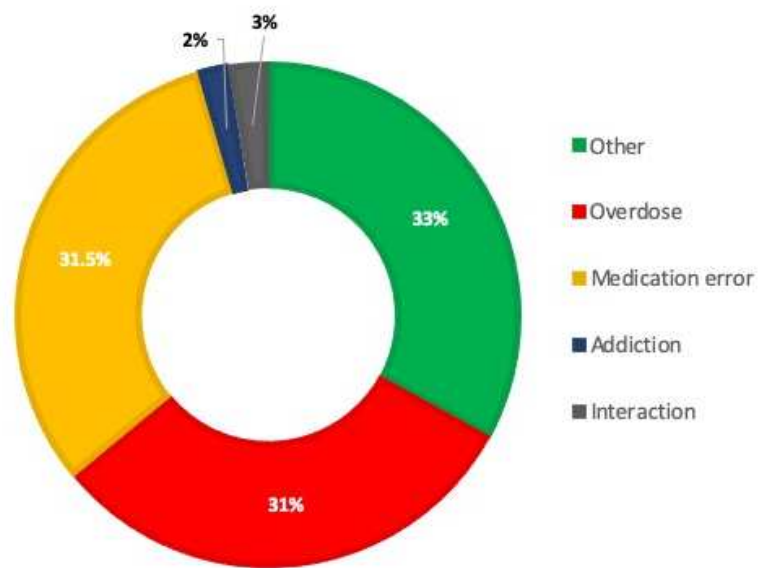
Corticosteroids for systemic use	1 (0.6)	2 (1.2)	1.00
Drugs for peptic ulcer	1 (0.6)	2 (1.2)	1.00
Drugs for constipation	2 (1.3)	1 (0.6)	0.62
Muscle relaxants	3 (1.9)	0	0.12
Cough and cold preparations	2 (1.3)	1 (0.6)	0.60
Drugs for obstructive airway diseases	0	2 (1.2)	0.50
Drugs for functional gastrointestinal disorders	0	2 (1.2)	0.50
Calcium channel blockers	1 (0.6)	1 (0.6)	1.00
Antiemetics	2 (1.3)	0	0.25
Antidiarrhoeals	0	2 (1.2)	0.50
Sex hormones	1 (0.6)	2 (1.2)	1.00
Vitamins	0	2 (1.2)	0.50
Mineral supplements	1 (0.6)	0	0.50
Tonics	0	1 (0.6)	1.00
Anabolic steroids	1 (0.6)	0	0.50
Antiarrhythmics	0	1 (0.6)	1.00
High-ceiling diuretics	1 (0.6)	0	0.50
Emollients and protectives	1 (0.6)	0	0.50
Dermatological preparations	1 (0.6)	0	0.50
Thyroid preparations	0	1 (0.6)	1.00
Antimycotics for systemic use	1 (0.6)	0	0.50
Antivirals for systemic use	1 (0.6)	0	0.50
Hormone antagonists	1 (0.6)	0	0.50
Local anaesthetics	1 (0.6)	0	0.50
Antigout preparations	1 (0.6)	0	0.50
Antiparkinson drugs	0	1 (0.6)	1.00
Antinematodal agents	1 (0.6)	0	0.50
Otologics - corticosteroids	0	1 (0.6)	1.00

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A



B

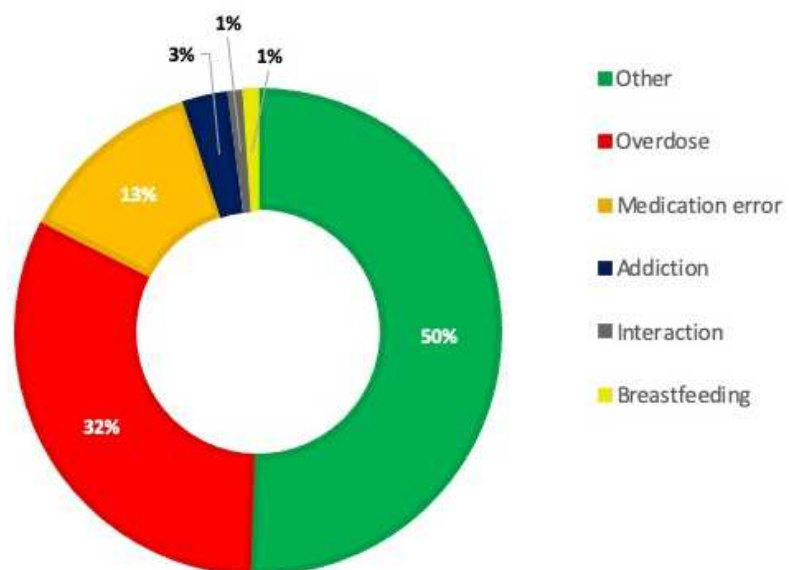


Figure 1. Types of ADRs linked to self-medication in the 2020 (A) and 2019 (B) study periods

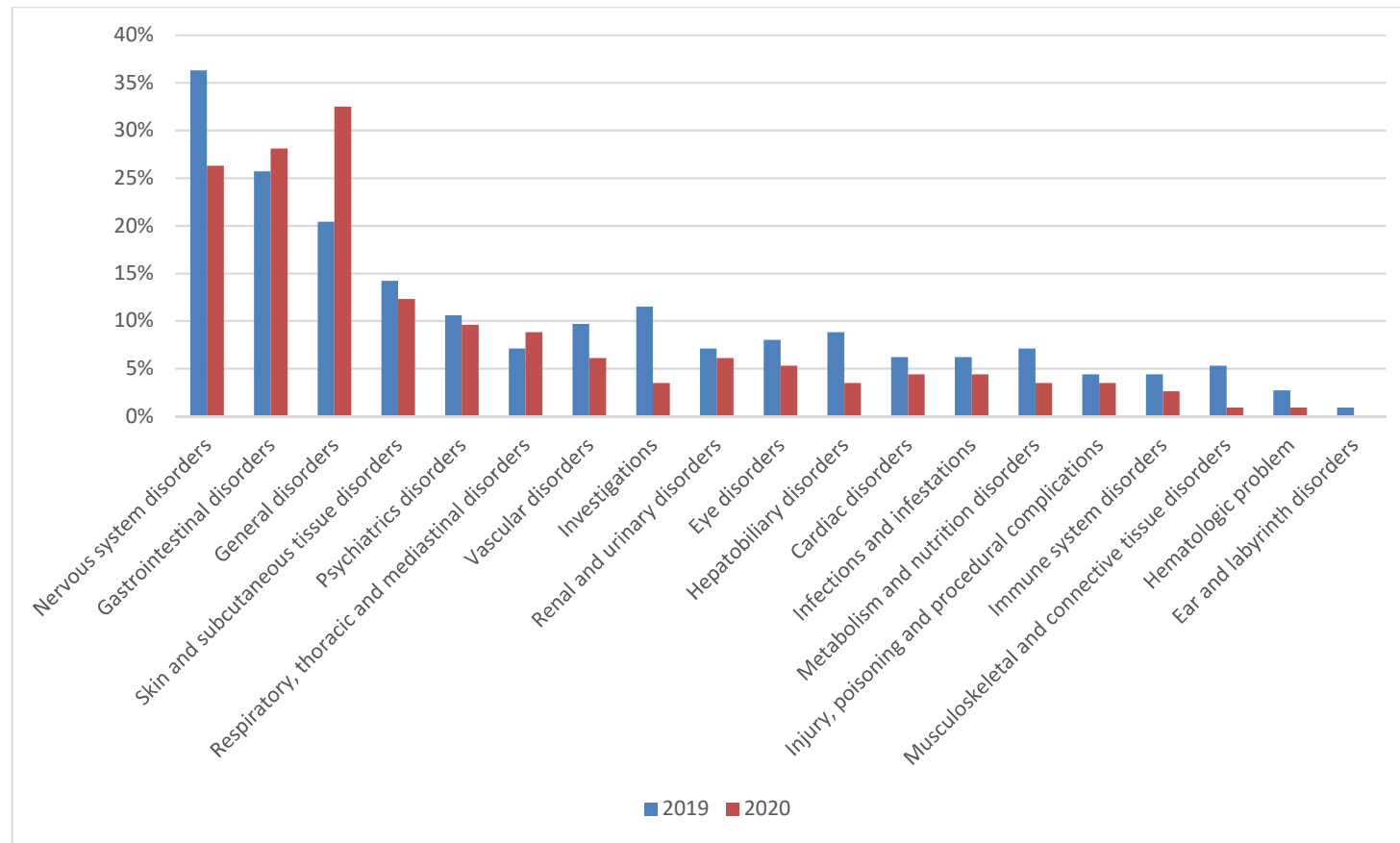


Figure 2: Disorders associated with ADRs linked to self-medication in the study periods in 2019 and 2020 according to MedDRA System Organ Class (SOC)