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Patterns of pharmaceuticals use during the first wave of COVID-19 pandemic in Athens, Greece as revealed by wastewater-based epidemiology



Aikaterini Galani^a, Nikiforos Alygizakis^a, Reza Aalizadeh^a, Efstathios Kastritis^b, Meletios-Athanasios Dimopoulos^b, Nikolaos S. Thomaidis^{a,*}

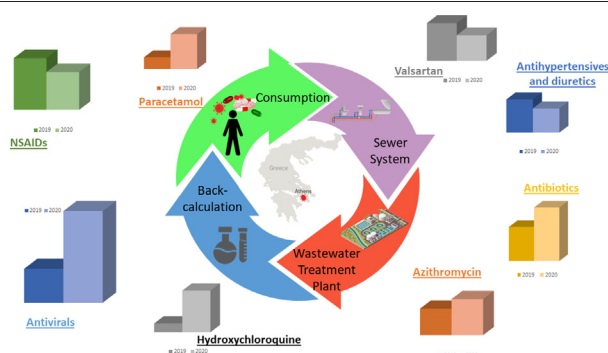
^a Laboratory of Analytical Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis Zografou, 15771 Athens, Greece

^b Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, 15528 Athens, Greece

HIGHLIGHTS

- Significant increase was observed for antiviral drugs (170%) and paracetamol (198%).
- Hydroxychloroquine consumption showed a 387% increase during lockdown.
- The consumption levels for hypertensive agents were reduced in 2020.
- Antibiotics demonstrated a noteworthy increase (57%).
- NSAIDs consumption showed a 27% decrease during lockdown.

GRAPHICAL ABSTRACT



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ABSTRACT

Since 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), impaired public health with considerable morbidity and mortality due to the lack of vaccines and effective treatment. The severe disease mainly harmed adults with predisposing medical comorbidities (such as heart disease, hypertension, chronic lung disease), while it can occur in healthy individuals that may be asymptomatic. Wastewater-based Epidemiology (WBE), a non-invasive, objective, chemical tool was used to monitor and estimate the changes in drug's consumption and prescription patterns under normal conditions (2019) and under COVID-19 pandemic conditions (2020). NSAIDs, antihypertensives, diuretics, antiepileptics, antilipidemics, antibiotics, analgesics, antivirals, anticancer drugs, contrast iodinated drugs, antidiabetics, antiallergic drugs, antiulcers and other pharmaceuticals were studied in wastewater and revealed the application of various treatments during the first wave of the pandemic in Athens, Greece. Data were correlated with COVID-19 infection therapeutical plans. The result of the analysis revealed a remarkable increase for antiviral drugs (170%), hydroxychloroquine (387%), and antibiotics (57%), which were the most applied treatments against COVID-19 during the first wave in Greece. In agreement with related authorities urge, NSAIDs presented decrease (27%) during the first lockdown, while paracetamol demonstrated a remarkable increase (198%). The use levels for Angiotensin II receptor blockers such as valsartan, and co-administrated diuretics, such as hydrochlorothiazide, were reduced during 2020, by 32% and 26% respectively.

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* Corresponding author.

E-mail address: ntho@chem.uoa.gr (N.S. Thomaidis).

1. Introduction

On March 2020, WHO declared a global pandemic for COVID-19. In Greece, restrictive measures started on February 27th 2020, and by March 23rd 2020 a general strict lockdown was implemented, affecting every aspect of economic and social life, including access to hospitals, primary care facilities and pharmacies and potentially the delivery of treatments to non-COVID-19 patients (Oikonomou et al., 2020). A concern regarding treatment adherence and access to special care, especially for those with chronic conditions (cardiovascular, metabolic, rheumatic or malignant diseases) was also raised during this period. Furthermore, hypotheses about risks of infection or severity of COVID-19 associated with the use of certain drugs such as angiotensin converting enzyme inhibitors (ACEi) / Angiotensin II receptor blockers (ARBs) (Kussmaul, 2020; Patel and Verma, 2020) or potential antiviral effects of others, like hydroxychloroquine, may have also affected their use. However, there is only limited data about changes in prescription patterns (Vaduganathan et al., 2020) of the various drugs and about their actual consumption during the lockdown period.

Wastewater-based epidemiology (WBE) is a non-invasive, objective, chemical tool which provides unbiased epidemiological information about a population in real time (Gracia-Lor et al., 2017). Due to this fact, WBE demonstrates a wide range of applications such as the estimation of chemical exposure (Gago-Ferrero et al., 2020; Gracia-Lor et al., 2017), as well as changes in drug and other substance consumption (Thomaidis et al., 2016; van Nuijs et al., 2011). Human activity leaves chemical traces in sewage, including licit and illicit drugs (Kim and Oh, 2020; Lai et al., 2016; Reinstadler et al., 2021; Thomaidis et al., 2016; Wang et al., 2020; Zhang et al., 2019). Parent drugs and their metabolites end up in Wastewater Treatment Plants (WWTPs) and their determination in influents provides data about their consumption, supporting public health authorities with valuable data (Gago-Ferrero et al., 2020).

In the present study, WBE was used to determine changes in consumption levels of different pharmaceutical compounds during 2019 and 2020. All the samples were collected from the WWTP of Athens which is serving a population that represents the 33% of the total Greek population and it is one of the largest WWTP in Europe. This fact implies that the results are representative for the Greek population. Biomarkers of public health (parent compounds and their metabolites) were identified and quantified in both years. LC-MS/MS methodologies were used to identify and quantify target analytes. In addition, High Resolution Mass Spectrometry (HRMS) accompanied by novel data treatment tools, that gain popularity in the WBE field, were used in order to identify known and unknown compounds that are present in complex matrices. Suspect screening gives the opportunity for retrospective analysis and identification of new analytes (Alygizakis et al., 2018). In this study, HRMS and suspect screening were used to enrich the data obtained from LC-MS/MS analysis with more biomarkers of public health (Aalizadeh et al., 2019; Muter and Bartkevics, 2020). Thus, the objective of the study was to investigate the drug use patterns and reveal the application of various treatments during the first lockdown in Greece by estimating the consumption of 14 drug classes of interest and comparing the use patterns between the same calendar period of 2019 and 2020.

2. Material and methods

2.1. Chemicals and reagents

Pharmaceuticals (divided in the following sub-categories: NSAIDs, antihypertensives, diuretics, antiepileptics, antilipidemics, antibiotics, analgesics, antivirals, anticancer drugs, contrast drugs, antidiabetics, antiallergic drugs, antiulcers and pharmaceutical with different use) were purchased by Merck (Chalkidona, Greece) and Alfa-Aesar (Voula, Athens, Greece). More details about the used chemicals and reagents can be found in the supplementary information (SI) at Section S1.

2.2. Sampling campaign

24-h flow proportional influent wastewater samples were collected from the WWTP of Athens. This facility serves 4,562,500 people. It also receives hospital effluents of Attica peninsula. The WWTP of Athens is designed with primary sedimentation, activated sludge process with biological nitrogen and phosphorus removal and secondary sedimentation. The real number of inhabitants served by the WWTP of Athens as well as the pharmacokinetic data (excretion rate and bioavailability) for the detected compounds and the daily flow rates were used to back-calculate the consumption of the pharmaceutical compounds. In this study, the amount of the inhabitants was real-time calculated for each sample in 2019 and 2020 based on concentrations of P, N, BOD, COD and NH₄-N. One inhabitant is equivalent with 1.7 g/day P, 12.5 g/day N, 59 g/day BOD, 128 g/day COD and 8.1 g/day NH₄-N as described by van Nuijs et al. (2011) and Been et al. (2014). The concentration of each of the five parameters was transformed into an amount of inhabitants (SI Table S2A, S2B and S2C). The sampling campaign in 2020 started on 25th of March, two days after the lockdown announcement, while in 2019, on 13th of March. The same period (spring months) was chosen, in order to have comparable results and also to avoid underestimations and variances in consumption levels resulting from the sampling period. More specifically, 7 24-h flow proportional influent wastewater samples were collected and analyzed in 2019 under non-pandemic conditions (13–19 of March), whereas 15 were collected and analyzed in 2020 under lockdown conditions (25 of March to 8 of April). Each year, on 25th of March Greek people celebrate Greek Independence Day. One of the greatest events in Athens is the military parade that takes place in the largest square of Athens. In 2020, the military parade as well as the celebrations were canceled due to lockdown and restrictions. In Greece, as mentioned previously, the first lockdown was announced on 23rd of March and lasted 6 weeks. During March and April, the number of infections was low, compared to other European countries, according to the World Health Organization, WHO (<https://covid19.who.int/>) and National Public Health Organization, NPHO (<https://eody.gov.gr/en/>).

2.3. Sample preparation and instrumental analysis

All samples were stored at -20°C until the end of the campaign and were analyzed in one-batch each year using solid phase extraction (SPE). More specifically, the samples were pre-treated and analyzed immediately after the end of the sampling campaigns in 2019 and in 2020, to avoid chemical degradation. Information about the SPE and quality assurance can be found in SI at Sections 2 and 3 respectively. The extracts were analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS) and ultra-performance liquid chromatography quadrupole-time-of-flight mass spectrometry (UPLC-Q-ToF-MS). The validated methods are described in detail elsewhere (Gago-Ferrero et al., 2020; Thomaidis et al., 2016) and in SI at Section S4.

2.4. Software

All the raw files obtained by LC-HRMS analysis were processed using Bruker Data Analysis 4.4 and TASQ 1.4 software (Bruker Daltonics, Bremen, Germany) for target and suspect screening. CompassXport 3.0.9.2. (Bruker Daltonics, Bremen, Germany) was used to convert the Bruker binary files to mzML. Data files together with meta-data (contributor details, instrumental information, sample and sample-preparation information) were uploaded to DSFP (Alygizakis et al., 2019) to screen for the presence of pharmaceutical compounds with known fragmentation not included in the target list. Wilcoxon signed-rank test was used to compare the change of the consumption levels between pandemic and non-pandemic conditions using stats R-package.

2.5. Estimation of drug use

It is known that back-calculate drug use remains a challenge, due to the existence of many parameters that must be considered (population, flow rates, pharmacokinetic data, in sewer stability) (Gracia-Lor et al., 2017) and affect the results. The real-time calculation of the number of inhabitants (based on COD, BOD, P, NH₄-N, N) that a WWTP serves, the daily flow rates as provided by the examined WWTP, as well as pharmacokinetic data and metabolites of the examined compounds, reduce the uncertainty of the results. There are numerous studies, providing the correction factors and the equations used for back-calculation purposes, especially for illicit and psychoactive drugs (Lai et al., 2016; Reinstadler et al., 2021) but there are limited data about many compounds from different pharmaceutical classes. Although WBE is widely used to reveal the use patterns for many pharmaceutical compounds (e.g. paracetamol, metoprolol, tramadol etc.), in most of the cases no correction factor or metabolite of the parent compound were used for back-calculations (Reinstadler et al., 2021; Wang et al., 2020; Zhang et al., 2019). On the contrary, each analyte is used as biomarker of its own consumption. In this study, all the aforementioned parameters together with bioavailability and % excretion for target analytes were used to estimate drug consumption. In cases in which pharmacokinetic data were not available, the loads of pharmaceutical compounds were reported. Loads and consumed quantities were estimated using two equations:

$$\text{Load (g day}^{-1}\text{)} = C \times Q \times 10^{-6} \quad (1)$$

$$\text{Consumption (g day}^{-1}\text{)} = \frac{\text{Load (g day}^{-1}\text{)}}{R_{\text{abs}} \times R_{\text{excreted}} + 1 - R_{\text{abs}}} \times \frac{P_T}{P_S} \quad (2)$$

where C (ng/L) represents the measured concentration in untreated wastewater, Q (m³ day⁻¹) the flow rate of wastewater measured each day, R_{abs} is the absorption rate of the drug (bioavailability), R_{excreted} the percentage of the parent compound that excreted unchanged, P_T the population of Athens (4,000,000) and P_S the served population by the WWTP of Athens, based on physicochemical parameters (Thomaidis et al., 2016).

3. Results and discussion

In this study, we examined changes in consumption levels of pharmaceutical compounds and how the ongoing pandemic affected physical health of the examined population. However, there is an extended study about changes in chemical compounds use that are not included in this study, but will be published separately. A substantial increase in hydroxychloroquine consumption (387%) and a lower but significant increase in azithromycin consumption (36.3%) was observed during the lockdown period (Table 1). During the same period, there was also a major increase in the consumption of various antiviral drugs (by

170%), most of which are registered for use in patients with HIV or HBV infections (Table 1 & Table S5A). There was also an important increase (61%) in the consumption of other antibiotics (even after excluding azithromycin, the consumption of which was also increased). There was also a remarkable increase in paracetamol consumption (198%), while a reduction in the consumption of opioid analgesics by 79.3% was observed. Interestingly, a significant decrease in the consumption of commonly used cardiovascular drugs such as angiotensin converting enzyme inhibitors (ACEi) / Angiotensin II receptor blockers (ARBs) (29.4%) was observed, but also in beta-blockers and other antiarrhythmic drugs. More information about concentrations and consumption levels of the studied compounds, are presented in SI, Section 5.

3.1. Antibiotics and antivirals

There are antiviral drugs which are effective to SARS-CoV-2, such as remdesivir. Some preliminary data indicated possible benefit by the use of some drugs which were not confirmed later. Despite the lack of solid data, physicians may have combined different antiviral drugs and antibiotics due to the lack of vaccines and effective treatment, in order to treat COVID-19. This fact was reflected in the identification of many substances from both pharmaceutical classes only in 2020 and not in 2019 such as tinidazole, linezolid, ritonavir, and entacapone. It is also important that access to antibiotics is rather liberal in Greece (Plachouras et al., 2014; Plachouras et al., 2010), allowing for the public to get them even without prescription according to the National Public Health Organization (NPHO). As a result, an overall increase of the consumption levels of both pharmaceutical classes in 2020 (170% for antiviral drugs, *p*-value<0.05 and 57% for antibiotics, *p*-value<0.05) was observed (Fig. 1). A possible explanation may be related to either in-hospital or out of hospital unregistered use of these drugs, since initially there was some confusion about their potential activity. Darunavir and tenofovir, which are widely used to treat HIV, showed an enormous increase during 2020 (664 and 198 g day⁻¹ respectively); their increase however may be associated with other reasons, not related to the pandemic. The macrolide antibiotic azithromycin has been considered as a possible therapeutic agent for patients with COVID-19 in the beginning of the pandemic. As a result, azithromycin was one of the antibiotics with the highest relative increase in consumption in 2020 comparing with the other substances of the class (from 2222 g day⁻¹ in 2019 to 3028 g day⁻¹ in 2020, *p*-value <0.05). Metronidazole, demonstrated a significant increase during lockdown (from 2664 g day⁻¹ in 2019 to 4349 g day⁻¹ in 2020, *p*-value<0.05), another pharmaceutical compound that has been postulated to decrease the levels of several cytokines, which are increased during COVID-19 (Gharebaghi et al., 2020). All the examined compounds with antiviral activity showed increase during 2020, as antivirals are the drugs with the strongest correlation to a viral disease such as the one caused by the novel coronavirus (Costanzo et al., 2020). Hydroxychloroquine is an anti-malarial and an essential treatment for many patients with rheumatologic conditions, however, this drug gathered widespread attention as a potential

Table 1

Selected drugs of interest during the COVID-19 outbreak and relative changes in their consumption. Consumption (g day⁻¹) and standard deviation of specific drugs and of 7 drug classes and their % change during the same calendar period (March / April 2019–2020) are shown.

Compound name/classes (number of compounds)	Consumption (g/day) 2019	Standard deviation 2019	Consumption (g/day) 2020	Standard deviation 2020	Change (%) 2019–2020
Hydroxychloroquine	12	1	57	4	+387%
Antivirals-excluding hydroxychloroquine	5576	453	15,010	786	+170%
Azithromycin	2222	168	3028	322	+36.3%
Other antibiotics – excluding azithromycin	11,987	416	19,325	641	+61%
Paracetamol	76,044	4796	226,449	21,859	+198%
11 NSAIDs	99,250	4811	72,524	3770	-26.9%
Antihypertensives ARBs/ACEis	106,706	2872	75,374	3510	-29.4%
B-Blockers	5783	311	5106	331	-11.7%
Antiarrhythmics	217	22	156	12	-28.1%

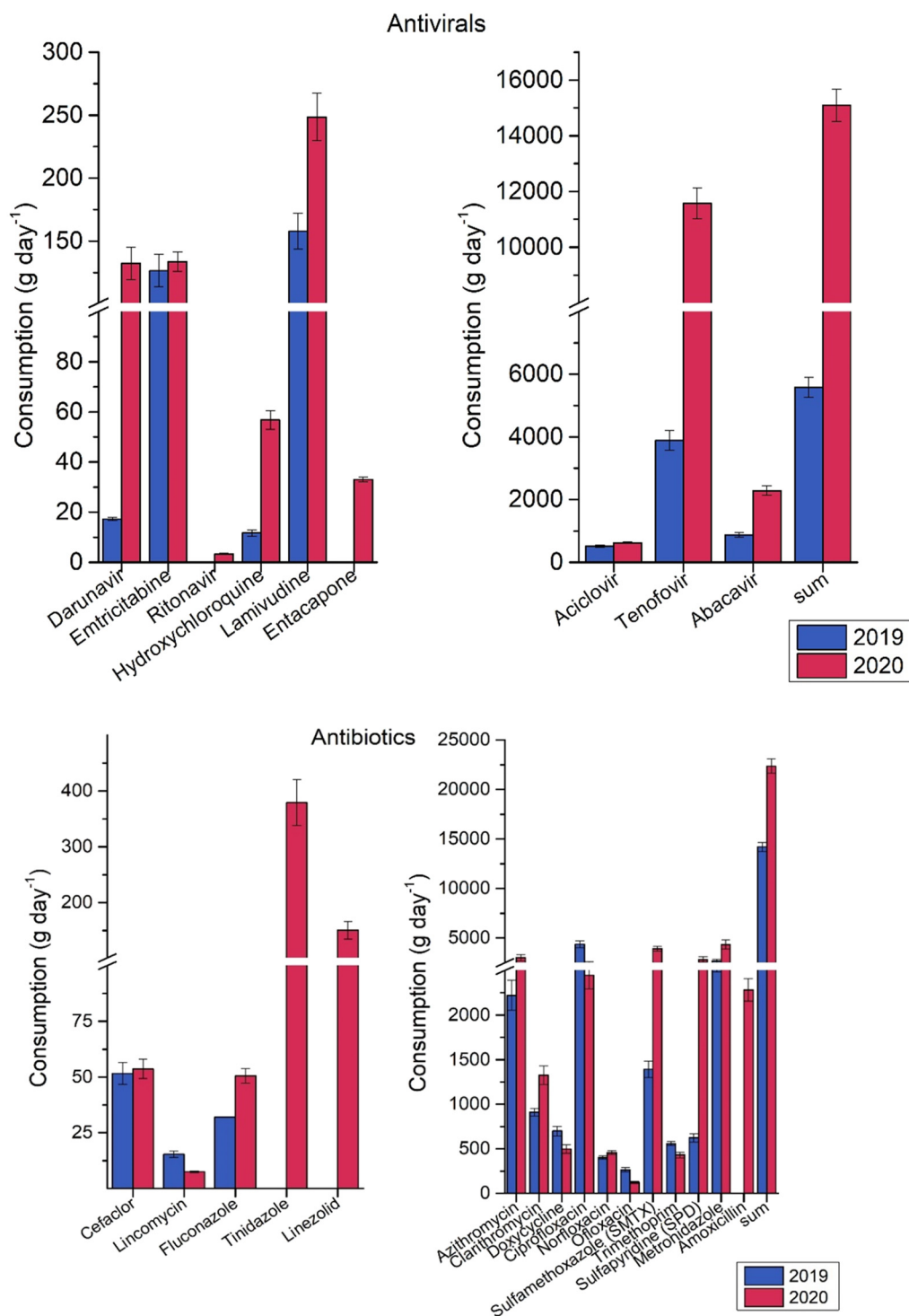


Fig. 1. Bar plots of antibiotics and antivirals during the study period (2019–2020). The results are expressed as consumption (g day⁻¹) and the error bars represent the Standard Deviation (SD).

treatment for COVID-19 infection, based on some early data. During the initial period of the pandemic, hydroxychloroquine, either alone or in combination with azithromycin, was considered as the most promising therapy for COVID-19 and was used for symptomatic patients but also even as prophylaxis after exposure. As a result, there was a remarkable increase in the consumption of hydroxychloroquine by approximately 390%, from 12 g day⁻¹ to 57 g day⁻¹ (*p*-value <0.05). The increased consumption was to some extent expected (Vaduganathan et al., 2020) due to its use for COVID-19, based on preliminary reports that were published or announced at the first months of the pandemic. These findings,

are in agreement with data from numerous research groups worldwide, that have reported increase in consumption levels of antibiotic and antiviral drugs, especially during lockdowns and highlighted the emergence of antimicrobial resistance, one of the most pressing health crisis before the ongoing pandemic (Gonzalez-Zorn, 2021; Reinstadler et al., 2021; Nason et al., 2021; Wang et al., 2020). In Spain, azithromycin, showed 400% increase from February to March 2020 (Gonzalez-Zorn, 2021) while the analysis of sewage sludge in United States demonstrated increase for hydroxychloroquine which had gained popularity during the first wave of COVID-19 pandemic (Nason

et al., 2021). The fact that these studies presented similar consumption trends for antibiotics and antiviral drugs with those reported in the present study, provides confidence in our findings and proved that antibiotic and antiviral consumption increased worldwide. Even though the consumption level of hydroxychloroquine was increased in Athens during 2020, it remained lower than the Predicted Environmental Concentration (PEC) in raw wastewater (833 ng/L), as reported by Kuroda et al. (2021).

3.2. Nonsteroidal anti-inflammatory drugs (NSAID) and analgesics

NSAID and analgesics are used for treatment of acute pain, inflammation and fever. After COVID-19 outbreak, related authorities worldwide advised patients to avoid NSAID. More specifically, they claimed that NSAID such as ibuprofen, diclofenac are associated with higher rates of complications after respiratory tract infections and in order to treat pain, people should prefer analgesics such as paracetamol (Little, 2020). These recommendations could have been reflected in the results for both pharmaceutical classes. Decreasing concentration levels was observed for the class of NSAID, from 99,250 g day⁻¹ to 72,524 g day⁻¹ (p -value = 7.63E-09). Acetylsalicylic acid showed a significant decrease in 2020 (56%). The same trend was observed for salicylic acid (from 9355 g day⁻¹ to 4733 g day⁻¹, p -value<0.05), diclofenac (4021 g day⁻¹ to 2531 g day⁻¹, p -value<0.05) and ibuprofen (7502 g day⁻¹ to 3012 g day⁻¹, p -value<0.05). On the other hand, a noteworthy increase was observed only for two compounds of the NSAID class, ketoprofen (from 425 g day⁻¹ to 1131 g day⁻¹, p -value<0.05) and valdecoxib (from 1999 g day⁻¹ to 2966 g day⁻¹, p -value<0.05). For analgesics, the opposite trend was observed, mainly due to paracetamol. In 2019, the concentration levels for paracetamol were 76,044 g day⁻¹ and in 2020 an approximately 3-fold increase was observed (226,449 g day⁻¹), while decrease was observed in the consumption of opioid analgesics tapentadol and tramadol. Paracetamol demonstrated the same trend in the same calendar period in United States and more specifically weekly and not daily increase (Nason et al., 2021), while in central New York paracetamol was the most consumed substance (sampling period April to July 2020) (Wang et al., 2020). It is noteworthy that 4-aminophenol, a minor nephrotoxic metabolite of phenacetin and paracetamol was found in both years in high levels compared to all the other compounds of the class as revealed by suspect screening results (Fig. S5C, SI). In 2020, the total increase for analgesics was 11%.

3.3. Antihypertensives, diuretics and antilipidemics

Antihypertensive, diuretic and antilipidemic drugs are pharmaceutical classes that showed decrease during lockdown: from 120,562 g day⁻¹ to 87,888 g day⁻¹ for antihypertensive and diuretics (p -value 2.25E-15) and from 9561 g day⁻¹ to 5083 g day⁻¹ for antilipidemics (p -value = 2.39E-19). The observed decrease for antihypertensive drugs was mainly caused by a noteworthy decrease of valsartan, an angiotensin II antagonist (from 99,814 g day⁻¹ in 2019 to 67,880 g day⁻¹ in 2020, p -value<0.05), and probably the most commonly prescribed in Greece, in various combinations (Thomaidis et al., 2016). Angiotensin-converting enzyme 2 (ACE2) is a functional receptor for coronaviruses and initially it was postulated that its expression could be increased by the use of angiotensin-receptor blockers such as valsartan (Zheng et al., 2020). Although there are no solid data to support this hypothesis and, in contrast, their use may even have positive effects in COVID-19 patients, there had been a debate in the early period of the pandemic, which may have been the main reason that affected their use. Hydrochlorothiazide and furosemide are the two most frequently used diuretics that showed a different trend from 2019 to 2020. For hydrochlorothiazide, a decrease was observed (approximately 26% from 2019 to 2020, p -value <0.05). In general, hydrochlorothiazide is commonly co-administrated with antihypertensive drugs like valsartan and as a result the two substances showed a similar trend. The

measured loads in 2020 for furosemide were higher than in 2019 (from 1214 g day⁻¹ to 2081 g day⁻¹, p -value <0.05). Furosemide is a loop diuretic drug that is used to reduce cardiac load and peripheral edema in patients with heart failure; an improved adherence to heart failure drugs during this period has been postulated. Some studies noticed that statins may have a positive effect during COVID-19 (Rodríguez-Nava et al., 2020). Atorvastatin, a widely prescribed statin, is associated with decreased hazard for death in patients that suffered from COVID-19. However, this observation was announced later than the investigated period of our study but the increase in atorvastatin consumption levels (from 806 g day⁻¹ in 2019 to 2560 g day⁻¹ in 2020, p -value<0.05) may again, at least in part reflect improved adherence. During lockdown, a major decrease in admissions for cardiovascular conditions was observed in hospitals in Athens, as in other countries (De Filippo et al., 2020; Metzler et al., 2020), even among those not severely hit by the pandemic, which may explain the aforementioned observations.

3.4. Antidiabetics, antiallergics and gastric and ulcer drugs

Antidiabetics, antiallergics and gastric anti-secreting (proton pump inhibitors) drugs showed a similar trend during the study period (2019–2020). For antiallergic drugs, the overall decrease (by 27%, p -value = 2.59E-06) was caused by diphenhydramine an antihistamine substance that showed a noteworthy decrease (from 71 g day⁻¹ in 2019 to 36 g day⁻¹ in 2020, p -value <0.05). The total decrease of antiallergic drugs may have been a result of the five-week lockdown and stay-at-home measures during spring months, when the allergic rhinitis and other allergies reach to a peak level (Lorenzo and Picó, 2019). The observed decrease (from 34,150 g day⁻¹ in 2019 to 13,014 g day⁻¹ in 2020, p -value = 5.11E-09) for antidiabetic drugs, was mainly caused by metformin that is used to treat people with type 2 diabetes (63% decrease from 2019 to 2020, p -value<0.05). For gastric anti-secreting (proton pump inhibitors) drugs the consumption levels were higher in 2019 (2885 g day⁻¹) when the conditions were normal and the population's daily routine (e.g work) was specific and sometimes stressful (52% decrease in 2020, p -value = 1.50E-12).

3.5. Antiepileptics

A slight and statistically non important decrease was observed, from 132,301 g day⁻¹ to 130,882 g day⁻¹ for antiepileptics. Carbamazepine, is one of the most widely prescribed drugs for the treatment of epilepsy and during lockdown the observed increase was from 2210 g day⁻¹ in 2019 to 5605 g day⁻¹ in 2020 (p -value<0.05). Carbamazepine, is also used in schizophrenia and bipolar disorder (Reinstadler et al., 2021). However, COVID-19 pandemic did not affect the consumption levels for the aforementioned pharmaceutical class.

3.6. Iodinated contrast drugs

Iodine-contrast drugs demonstrated a different trend during the study period and an important decrease by 65% was observed (p -value = 8.65E-17). Iodine-contrast agents are used widely in computed tomography (CT), however during the lockdown period many non-essential imaging tests were postponed or canceled, along with a major reduction in hospital visits and non-hospital physician visits. Moreover, public health authorities had advised people to avoid non-essential hospital visits during lockdown.

3.7. Other pharmaceuticals

For the sympathomimetic ephedrine the concentration levels showed a 2-fold increase during lockdown (from 807 g day⁻¹ to 1598 g day⁻¹, p -value<0.05). Moreover, lidocaine showed a similar

trend and an approximately 2-fold increase was observed (from 308 g day⁻¹ in 2019 to 500 g day⁻¹ in 2020, p-value<0.05).

4. Conclusions

To the best of our knowledge, there are limited data about drug consumption monitoring during the lockdown period, especially for certain drugs of interest. Such data can provide information about important aspects of treatment use during this period, which may have affected many patients with chronic conditions, which extend beyond the direct effects of the viral infection. For hydroxychloroquine, the degree of increase that was observed cannot be fully explained by the number of confirmed COVID-19 cases in Athens area during this period, which were only a few hundred. Unregistered use, even in non-confirmed cases, may explain a part of this increase, driven by the public perception that this drug could “protect” or “treat” COVID-19. Antiviral drug and antibiotic consumption was also increased substantially, although there were no data to support their use for COVID-19. Our data also indicate major shifts in drug consumption for other drug classes but the reasons behind these changes are not completely understood. More specifically a significant decrease in the consumption of commonly used cardiovascular drugs such as angiotensin converting enzyme inhibitors (ACEi) / Angiotensin II receptor blockers (ARBs) was observed, but also in beta-blockers and other antiarrhythmic drugs. Some reduction in drug consumption for certain drugs may be due to difficulty to reach health care facilities or visit physicians to refill prescriptions. Although the option to remotely refill prescriptions *via* SMS or e-mail became available during this period, this was not adopted by all patients from the beginning while there may have been some difficulties or even fear to reach pharmacies.

Thus, major shifts in the consumption of several drug classes was observed. The changes may reflect several different aspects of the challenges phased by the health care system. Although more investigation is needed in order to understand these trends, such data can be of value to the authorities in order to prepare healthcare and public services for the future challenges of the ongoing pandemic. In general, the study showed that the COVID-19 pandemic is clearly affecting habits, lifestyle, mental and physical health, and has already created a new socioeconomic and health reality.

CRedit authorship contribution statement

Conceptualization, N.S.T.; formal analysis, investigation and writing—original draft preparation A.G., N.A, E.K. and R.A.; computational analysis, N.A. and R.A.; review, M.-A. D.; review and supervision, N.S.T.;

All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2021.149014>.

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