

Retrospective observational study on the impact of the Covid-19 pandemic on the prescription of medications for the treatment of Attention Deficit/Hyperactivity Disorder. Comparison of a European and an American cohort

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Summary. Background. Attention Deficit Hyperactivity Disorder (ADHD) is a neuropsychological disorder that affects the development of children and adolescents. The causes are not fully known although the origin of the disorder appears to depend on a combination of environmental, social, biochemical, and genetic factors. There is substantial evidence the Covid-19 pandemic caused an increase in mental disorders and therefore in spending related to the treatment of diseases. **Method.** We conducted a retrospective cohort study in two international centers of very different origins and cultures, one in Europe (Italy) and one in Central America (Costa Rica), to assess the impact of the Covid-19 pandemic on ADHD medication prescriptions and its costs. The analysis resulting from mining the databases in each individual nation allowed for the actual amounts of defined daily dose (DDD) prescribed and dispensed between the years 2019 and 2022 of methylphenidate and atomoxetine. **Results.** The data show that the Italian ADHD medications DDDs and expenditure are aligned with the results in Costa Rica. It was found that from the year 2019 to the year 2022, both methylphenidate and atomoxetine prescriptions grew steadily, confirming a much higher incidence of the condition than in pre-pandemic periods. **Conclusions.** Our study shows that the global pandemic had an influence on the increase in the number of ADHD medication prescriptions. Individuals with ADHD are a population of individuals who may be particularly vulnerable to the distress caused by the pandemic, restrictions, and severe physical removal measures that have occurred in recent years.

Key words. ADHD, Covid-19, drugs, neurology, pandemic, psychiatric disorders.

Studio osservazionale retrospettivo sull'impatto che la pandemia di Covid-19 ha avuto sulla prescrizione di farmaci per il trattamento del disturbo da deficit di attenzione/iperattività (ADHD). Confronto tra una coorte europea e una americana.

Riassunto. Premessa. Il disturbo da deficit di attenzione e iperattività (ADHD) è un disturbo neuropsicologico che colpisce lo sviluppo e la crescita di bambini e adolescenti. Le cause non sono del tutto note, anche se l'origine del disturbo sembra dipendere da una combinazione di fattori ambientali, sociali, biochimici e genetici. Esistono prove sostanziali che la pandemia di Covid-19 abbia causato un aumento dei disturbi mentali e quindi della spesa relativa al trattamento delle malattie. **Metodo.** Abbiamo condotto uno studio retrospettivo di coorte in due centri internazionali di origine e cultura molto diverse, uno in Europa (Italia) e uno in America Centrale (Costa Rica), per valutare l'impatto della pandemia Covid-19 sulle prescrizioni di farmaci per l'ADHD e sui relativi costi. L'analisi risultante dall'estrazione dei dati dai database di ogni singola nazione ha permesso di conoscere le quantità effettive di dose definita giornaliera (DDD) prescritte e dispensate tra gli anni 2019 e 2022 rispettivamente di metilfenidato e atomoxetina. **Risultati.** I dati mostrano che le DDD e la spesa italiana per i farmaci ADHD sono allineate con i risultati ottenuti in Costa Rica. È emerso che dal 2019 al 2022 le prescrizioni di metilfenidato e atomoxetina sono cresciute costantemente, confermando un'incidenza della patologia molto più elevata rispetto al periodo pre-pandemia. **Conclusioni.** Il nostro studio dimostra che la pandemia globale ha influito sull'aumento del numero di prescrizioni di farmaci per l'ADHD. I soggetti con ADHD sono una popolazione di individui che può essere particolarmente vulnerabile al disagio che è stato causato dalla pandemia, dalle restrizioni e dalle severe misure di allontanamento fisico che si sono dovute mettere in pratica negli ultimi anni.

Parole chiave. ADHD, Covid-19, disturbi psichiatrici, farmaci, neurologia, pandemia.

Introduction

HYPERACTIVITY DEFICIT DISORDER AND DRUG TREATMENT

Attention-Deficit Hyperactivity Disorder (ADHD) is a disorder found in 3%-5% of school-age children and characterized by intense motor activity, impulsivity, and inattention, often compounded by neuropsychiatric disorders such as anxiety and depression. Easy distractibility is mainly manifested in a lack of attention to detail and an inability to complete actions^{1,2}. Impulsivity, on the other hand, is manifested by difficulty in organizing complex actions, rapid switching from one activity to another, and difficulty and lack of patience in keeping one's turn in waiting situations. These disorders affect the overall functioning of the child's social life. Several neurotransmitter systems are involved at the basis of these disorders, such as alteration of the noradrenergic, serotonergic, and dopaminergic systems, especially in the prefrontal cortex^{3,4}. The prevalence of ADHD among children aged 4-17 years increased by 42% between 2003 and 2011 (from 7.8% to 11%). Boys have a higher prevalence of ADHD than girls, with prevalence rates of 15.1% and 6.7% in 2011, respectively. The prevalence of ADHD among adults aged 18-44 years is 4.4%, with a lifetime prevalence of 8.1%. Nearly 10 million adults in the United States have a diagnosis of ADHD^{5,6}. The causes of attention deficit hyperactivity disorder are not fully known, but the origin of the disorder appears to depend on a combination of environmental, social, biochemical, and genetic factors. The 2019 coronavirus pandemic (Covid-19) has caused unprecedented challenges at every level of society. Individuals with attention deficit hyperactivity disorder (ADHD) are a population of individuals who may be particularly vulnerable to the distress caused by the pandemic, restrictions, and severe physical removal measures that have occurred in recent years, causing an increase in behavioral problems⁷. The goal of ADHD therapy is to intervene with a multimodal approach, through psychosocial interventions combined with pharmacological treatments. Clinical evidence shows that the use of psychostimulant medications can yield clinical improvements in 80% of treated cases⁸. The most used medications are methylphenidate and D-amphetamine, which act by blocking norepinephrine and dopamine transporters and stimulating dopamine release from postsynaptic dopaminergic terminals^{1,9}. Pemoline is little used because of the high risk of hepatotoxicity. In clinical practice, methylphenidate is the most widely used drug and is considered the drug of first choice. Another pharmacological agent used is atomoxetine, a selective norepinephrine reuptake inhibitor, with

minimal affinity for dopamine and serotonin transporters, but which by blocking the norepinephrine transporter increases the concentration of this neurotransmitter in the synaptic cleft, especially in the prefrontal cortex^{10,11}. In Italy and Costa Rica, prescriptions for methylphenidate and atomoxetine are strictly regulated by special national registries whose function is to ensure strict monitoring of therapy and appropriate prescribing^{12,13}.

RELATIONSHIP BETWEEN ADHD AND COVID-19: OBJECTIVES OF THE STUDY

The pandemic caused by SARS-CoV-2, termed Covid-19 (Coronavirus Disease 2019), had a social and health impact with few precedents in human history^{14,15}. The pandemic has also had an important and significant impact on children with ADHD^{7,16}. In particular, the increasingly restrictive measures taken by various countries to cope with the pandemic in recent years, such as the closure of schools and public places and social distancing, have affected the entire social and educational environment of children with ADHD¹⁷⁻¹⁹. However, even during the periods of restriction and closure of public places, telemedicine and measures taken by various countries still ensured that ADHD patients could continue to receive their medication prescriptions²⁰. Moreover, in addition to social and environmental aspects, Covid-19 infection itself can cause mild or severe symptoms such as metabolic, cardiovascular, and neuropsychiatric disorders, greatly affecting the clinical course of ADHD patients. Although children and adolescents are less likely than adults to have severe symptoms caused by Covid-19, the symptoms can still affect the ability to attend school and complete activities of daily living, affecting the lives of patients with ADHD. ADHD is a neurological disorder that has been increasing in the world population in recent years and affects not only children but also adults²¹⁻²³. In fact, in recent years, the main drugs used, such as methylphenidate and atomoxetine, have seen their use expand more and more^{24,25}. This study aims to test whether the pandemic negatively affected this disorder by analyzing prescription data before (2019), during (2020-2021), and after (2022) the worst period of the pandemic. In addition, ADHD is a pathological form often caused by computerization and an increasingly social network-dependent society, and for these reasons, the pandemic, by forcing people into ironclad isolation, may have fostered computer addiction resulting in increased ADHD²⁶⁻³⁰. Indeed, through a pharmacological study, this analysis aims to determine whether, comparing four years straddling the pandemic, a link might have existed between the pandemic and the potential increase in the consumption of these two drugs. Specifically, an extraction of consumption and

spending in Italy and Costa Rica was conducted with the aim of testing whether there was indeed massive overuse resulting from increased expression of ADHD in the population.

Methods

A draw was made in the years 2019 to 2022 of the main drugs used for the treatment of ADHD (atomoxetine and methylphenidate) with the aim of verifying pre- and post-pandemic prescription, consumption, and expenditure data. A comparison study has been conducted in Italy and Costa Rica, although the prevalence of ADHD may be higher in developed countries, a study by Fayyad et al.³¹ showed that the prevalence of this pathology could be higher in some Latin American countries compared to European countries. Also, the access and availability of atomoxetine and methylphenidate in both countries are equal, being the only difference in the cost of each medication which is slightly higher in Costa Rica compared to Italy. In Italy, the study took as reference the Asl Napoli 3 Sud, a local health authority with a very large territory of more than 1 million inhabitants that includes 5 hospitals and 10 health districts, while in Costa

Rica the same analysis was held at Hospital Clínica Bíblica (HCB), a private hospital which is one of the most important medical centers in the country, that includes one main hospital, one branch clinic, with full pharmacy services that serve a population of 2,6 million inhabitants within the Costa Rican metropolitan area. In Italy, the Tessera Sanitaria (TS) database was queried, and all ADHD-related prescriptions and dispensations made at pharmacies affiliated with the National Health System (NHS) were analyzed. At the same time in Costa Rica, the HCB electronic records database was referenced. This extraction allowed for the timeliness of data for a total population of more than three million people identified in Italy and Costa Rica. Methylphenidate and atomoxetine are the only two drugs approved for ADHD in Italy and Costa Rica, and for this reason only these two medications are analyzed in this study. They were searched in the computer system according to their anatomical, therapeutic, and chemical classification (ATC) system so that all medicinal specialties could be viewed, and their prescribing trends verified. To easily verify and compare the consumption and expenditure data of these drugs over the 4 reference years, a comparison table was created for each country under study (table 1). Consumption was analyzed by calculating

Table 1. Consumption and gross amount of methylphenidate and atomoxetine in the years 2019-2022 in Italy at Asl Napoli 3 SUD, and in Costa Rica at Hospital Clínica Bíblica.

		ADHD 2019 Italy		ADHD 2019 Costa Rica	
Code ATC	Description Drug ATC	DDD Consumed	Gross amount	DDD Consumed	Gross amount
N06BA09	Atomoxetine	29.75	291.92 €	49.88	632.90 €
N06BA04	Methylphenidate	5,435.00	8,754.56 €	13,524.00	29,269.02 €
Total		5,464.75	9,046.48 €	13,573.87	29,901.92 €
		ADHD 2020 Italy		ADHD 2020 Costa Rica	
Code ATC	Description Drug ATC	DDD Consumed	Gross amount	DDD Consumed	Gross amount
N06BA09	Atomoxetine	119.00	1,156.03 €	185.50	1,698.46 €
N06BA04	Methylphenidate	6,440.00	10,595.16 €	9,329.00	20,437.41 €
Total		6,559.00	11,751.19 €	9,514.50	22,135.87 €
		ADHD 2021 Italy		ADHD 2021 Costa Rica	
Code ATC	Description Drug ATC	DDD Consumed	Gross amount	DDD Consumed	Gross amount
N06BA09	Atomoxetine	31.50	350.30 €	57.75	588.45 €
N06BA04	Methylphenidate	8,770.00	15,203.68 €	13,598.00	32,487.11 €
Total		8,801.50	15,553.98 €	13,655.75	33,075.56 €
		ADHD 2022 Italy		ADHD 2022 Costa Rica	
Code ATC	Description Drug ATC	DDD Consumed	Gross amount	DDD Consumed	Gross amount
N06BA09	Atomoxetine	63.00	700.62 €	77.88	916.75 €
N06BA04	Methylphenidate	11,065.00	19,987.18 €	23,305.00	55,533.62 €
Total		11,128.00	20,687.80 €	23,382.87	56,450.37 €

the Defined Daily Dose (DDD), which corresponds to the average daily dose of the drug in relation to its main clinical indication. This is an international parameter that allows the comparison of drugs on the market in different packages and dosages. Costs, on the other hand, should be understood as gross and in euros. Costa Rican prices have been converted to euros according to the current exchange rate (March 2023). Expenditures and consumption generated are to be considered exclusively made by contracted or private pharmacies, since drugs dispensed through public hospital corporate facilities have negligible costs and dispensing data.

Results

An increase in prescriptions for the drug methylphenidate, which is mainly used in disorders resulting from ADHD, was found in 2022 in Italy and Costa Rica, as for atomoxetine, its use is to be considered as fluctuating in the four years taken as a reference. The trend in increasing prescriptions has been steady for Italy and variable with a growing trend for Costa Rica since the year 2019, in the pre-pandemic era, and, for these reasons, annual data from 2019 to 2022 were extracted to assess the consumption and expenditure incurred for these two medications.

Table 1 refers to the Italian and Costa Rican situa-

tion within the scope of Asl Napoli 3 Sud and Hospital Clínica Bíblica. In Italy DDDs regarding methylphenidate grew steadily and proportionally compared to the previous year going from about 1000 DDDs in 2020 compared to 2019 to almost 2500 DDDs in 2022 compared to 2021, but in Costa Rica, there was a decrease of about 4000 DDDs from 2019 to 2020. The growth of DDDs in 2021 was more than 2000 DDD in Asl Napoli and 4000 DDDs in HCB compared to 2020 at the height of the pandemic. Regarding atomoxetine, the prescribing trend is not constant during the reviewed period, although all years had DDD values higher than in 2019, reaching the highest values during 2020.

From 2019 to 2022, DDDs more than doubled with 103.6 percent more prescriptions of methylphenidate and 111.8 percent more of atomoxetine in Asl Napoli 3 Sud (figure 1). On the other hand, in Clínica Bíblica, DDDs grew significantly at about 56% for atomoxetine and 72% for methylphenidate (figure 2) in 2022 compared to the values of 2019. Comparing both medications DDDs and the financial cost expressed as the gross amount in euros, a similar trend is observed that gradually increases up to the maximum value for each item in 2022 (figure 3). When comparing the situation of Asl Napoli 3 Sud with HCB in terms of percentage difference of DDDs per year, 2020 was the year that had the smallest difference, with 56% for atomoxetine and 45% for methylphenidate, while for the year 2022,

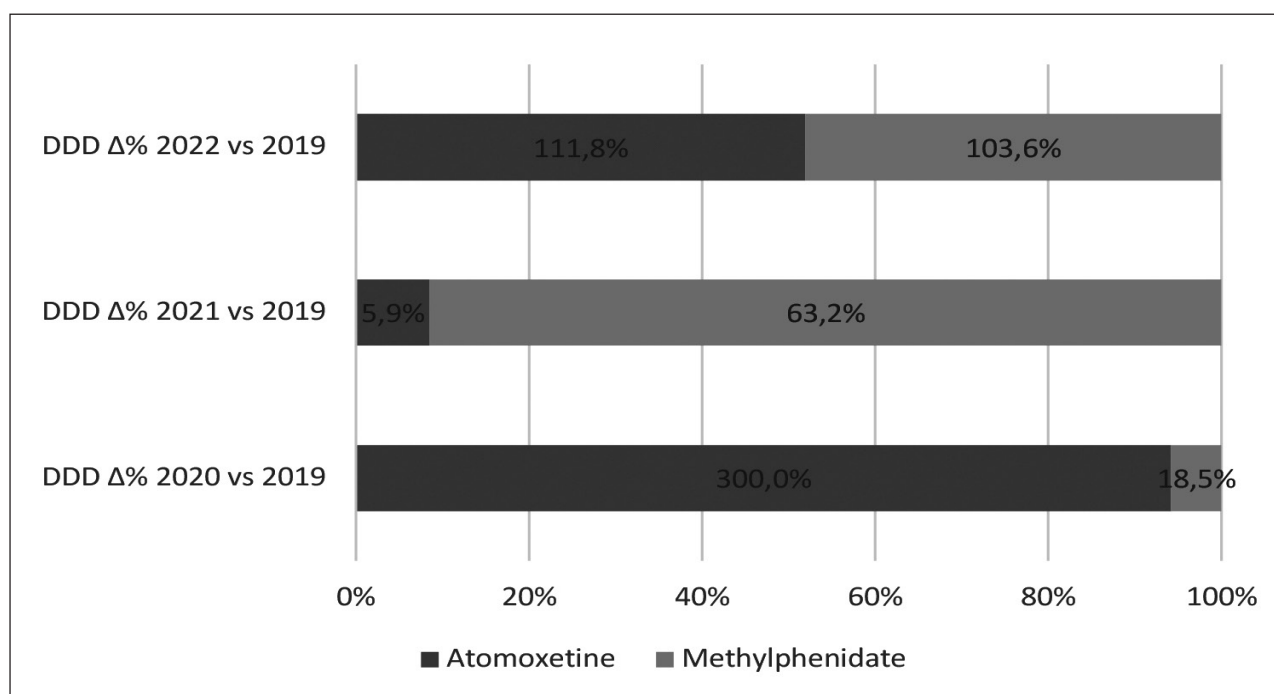


Figure 1. Percentage difference in consumption of methylphenidate and atomoxetine in the years 2019-2022 in Italy at Asl Napoli 3 SUD.

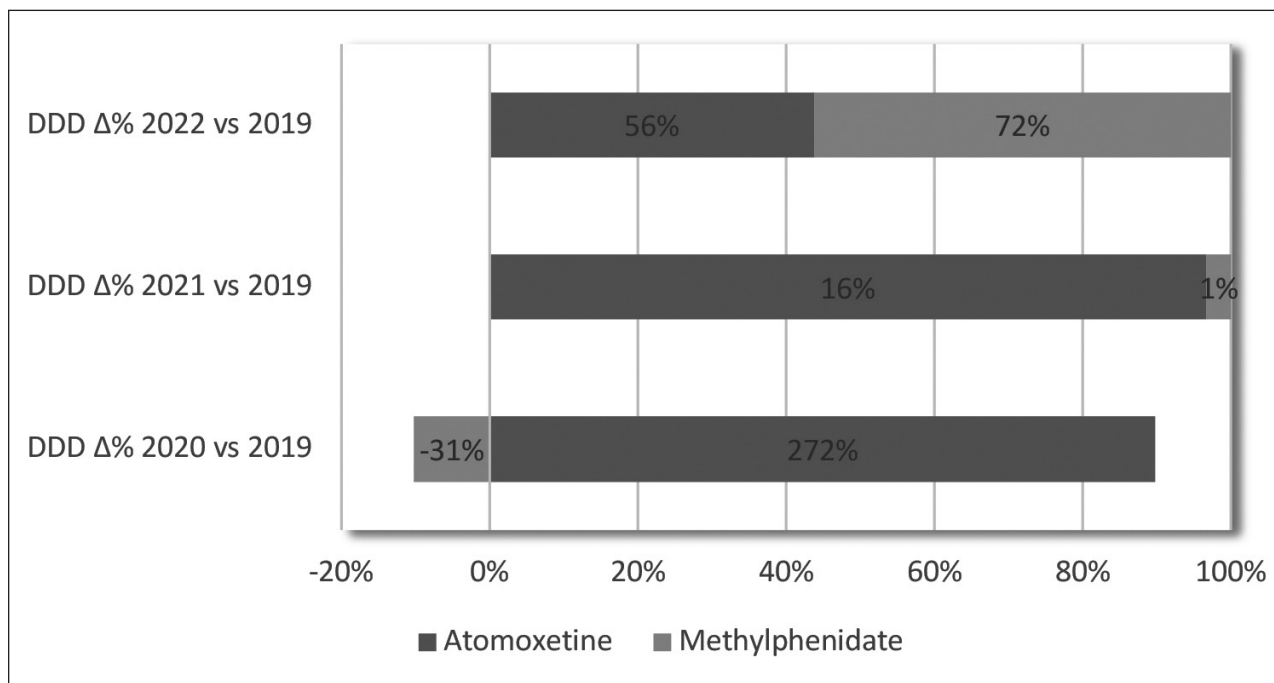


Figure 2. Percentage difference in consumption of methylphenidate and atomoxetine in the years 2019-2022 in Costa Rica at Hospital Clínica Bíblica.

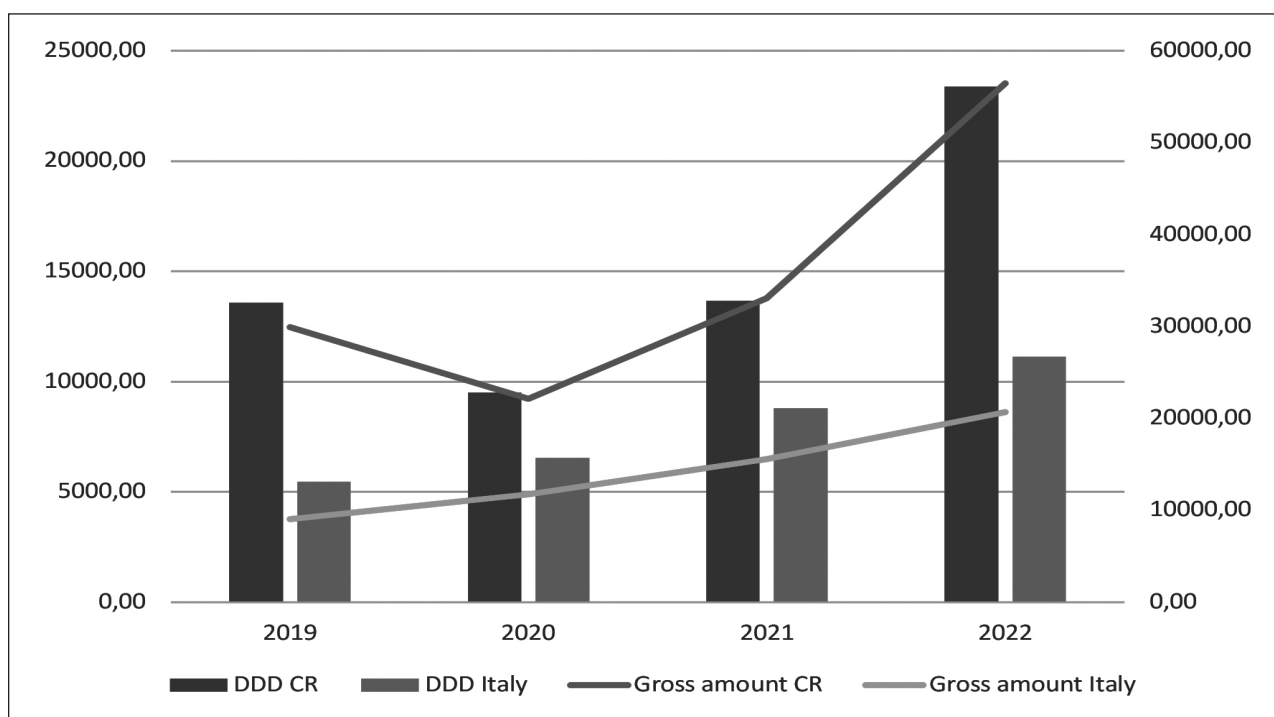


Figure 3. Annual comparison of DDD's and gross amount trends of atomoxetine and methylphenidate for Asl Napoli 3 South and Hospital Clínica Bíblica.

the difference increased significantly in the case of methylphenidate with 111% more DDDs for HCB than Asl Napoli 3 Sud (figure 4).

From a healthcare cost perspective, fortunately,

methylphenidate-related specialties do not have excessive direct costs compared to other medications used in other therapeutic settings. They are somewhat obsolete molecules that are also subject to ge-

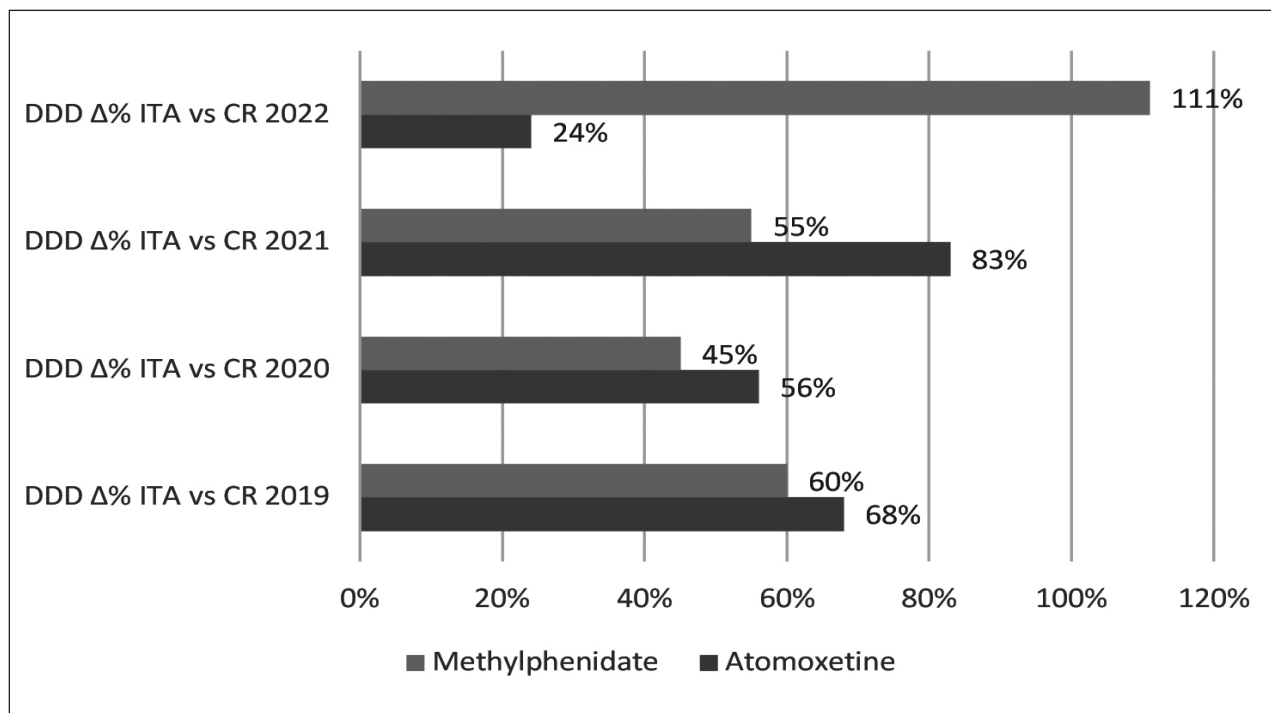


Figure 4. Percentage difference of yearly DDDs of atomoxetine and methylphenidate between Asl Napoli 3 South and Hospital Clínica Bíblica.

nerics, which has led them to reduce costs over time. Despite this, however, it is evident how gross expenditure follows the growth in DDDs consumed. In the Italian healthcare network, gross expenditure for methylphenidate and atomoxetine from 2019 to 2022 more than doubled from € 8,754.56 to € 19,987.18 for methylphenidate and from € 291.92 to € 700.62 for atomoxetine. The expenditure in the Costa Rican Hospital nearly doubled between 2019 and 2022, reaching the highest expense value in 2022 with € 56,450.37 for methylphenidate. By 2022, spending on methylphenidate at Hospital Clínica Bíblica was more than double that at Asl Napoli 3 Sud, and more than € 76,000 was spent on ADHD treatment during 2022 while less than half was spent in the previous four years.

Discussion

Covid-19 has certainly impacted the lives of the world's population in all walks of life and in multiple ways that affect the health status not only directly related to the infection but also indirectly with preventive governmental measures that have led to the development of other pathologies, especially in the neurological field such as precisely that related to ADHD. Cases of so many neurological pathologies developed because of compulsory social restrictions such as antiepileptic seizures, convulsions,

schizophrenia, and depression are not uncommon in the literature³²⁻³⁴. The use of drugs related to the central nervous system has increased in the years since 2019 precisely because of the Covid-19 pandemic. Antipsychotics, antidepressants, and antiepileptics have seen a surge in prescribing³⁵⁻³⁷. In the wake of this information, our clinical investigation focused on another neurological aspect that is often underestimated but is of no less importance, namely ADHD. This disorder is often given little attention because it affects a small field of the population, often young people, and is treated with drugs that do not come at an excessive cost and, for this reason, does not receive much scientific or commercial interest. However, it is a real disease that is spreading more and more and can be a real social problem if it is not treated and curbed in its expansion³⁸. Particularly dangerous is precisely the fact that it affects the youthful population with serious social and productive consequences now but also in the future: a young person with ADHD will be less focused and less imprinted on building his or her future with less attention to the issues of school and education. ADHD was already on the rise long before the pandemic due to the expansion of technology and social networks. The spread of an increasingly social world has brought a host of youth "distractions" that have gone far beyond the relaxation and leisure time resulting from technological advancement. Social networks have created a kind of "drug"

to which one is addicted by fostering a deficit of attention from what are the normal duties that accompany human growth^{39,40}. A future with less educated people will lead to a widening social gap with serious consequences on what is the normal growth and cultural development of the civilized world, this effect can be observed in several countries regardless of their economic power, since according to the World Bank, in Costa Rica by 2021 there was a greater percentage of the population (83%) using the internet more than Italy (75%)⁴¹. The study carried out in Italy and Costa Rica is intended to precisely highlight this and to sound a social alarm of undoubted global scientific and political interest in ADHD. Regardless of geographic location, this disease in recent years has been spreading more and more, and the pandemic has exacerbated this growth as much as the case of other mental illnesses such as depression and anxiety⁴². In just four years in the Italian and Costa Rican cohorts, there have been more than doubled the number of prescriptions for drugs used in ADHD with data that are entirely comparable. These effects are probably silent because such drugs are not high cost and therefore national governments do not mind such expansion in controlling their budgets, but nonetheless, they are worrisome because of the harmful implications said earlier. Inclusive, although methylphenidate is more expensive in Costa Rica than in Italy, by 2022 DDDs were more than double for Costa Rica, perhaps explained by two factors. One is the amount of population covered by the medical center analyzed in Costa Rica compared to Italy, and the second is the prevalence of ADHD in each country, in Costa Rica was 5% of the sample of one study conducted in 2011, while in Italy it was 0.9% of another study conducted in 2017^{31,43}.

When we compare the expenditure related to methylphenidate and atomoxetine, it is higher in Costa Rica, being the methylphenidate more expensive per unit in this country than in Italy. Probably in Italy, the existence of a national regulatory agency (AIFA) allows and ensures greater price bargaining with pharmaceutical companies by entering into agreements when drugs are placed on the

market. Managed Entry Agreements (MEAs) created by AIFA and a system that relies on competitive tendering are Italian examples of excellence in Europe regarding drug price negotiation^{44,45}. Drug prices in Costa Rica have higher prices compared to other countries in the area. A recent study concluded that the structure of the market in Costa Rica and poor regulatory monitoring by public entities generated little competition in medicines in this country^{46,47}.

After all, even if the direct costs of ADHD drugs are relatively low, the full clinical management of the condition is not low in addition to certainly difficult future social costs to which this condition will lead if appropriate measures are not issued to prevent its continued unrestrained expansion. The Covid-19 pandemic, with its lockdowns and restrictions, if on the one hand has led to obvious neurological repercussions on the world's population that still represent the greatest damage caused by this period of health crisis, on the other hand has also fostered the expansion of technologies with both positive and negative effects on the lives of citizens.

Conclusions

In summary, the pandemic of Covid-19 and related measures of social restriction and physical removal have had a huge impact on the increase in the prescription of drugs for the treatment of ADHD. In our study, we showed that from 2019 to 2022, the number of prescriptions for psychostimulants to treat ADHD more than doubled, which also indirectly suggests an increase in diagnosed cases of ADHD. On this basis, the risks, and benefits of initiating or maintaining psychostimulant treatment for ADHD need to be carefully evaluated. The European Commission and the French government^{48,49} already have proposed the inhibition of the use of social networks to children under 13-16 years of age precisely because of the lethal effects of using technologies that seem harmless today but could be very wasteful in the future in having a population less inclined to economic, professional, and civic productivity and growth are becoming evident.

Take home messages.

The Covid-19 pandemic caused an increase in mental disorders and thus in spending treatment related.

We carried out a retrospective cohort study to evaluate the impact of the Covid-19 pandemic on ADHD medication prescriptions and its cost.

The data show that in two different international countries during the pandemic prescriptions rose steadily.

Our study shows how the global pandemic of Covid-19 affected the number of ADHD medication prescriptions, impacting on the incidence of the increase in the number of diagnoses.

Authors contributions: FF: conceptualization, writing - original draft, methodology, supervision, validation; EZ: writing - original draft, methodology, supervision, validation; AV: writing - original draft, methodology and review; JAV: data processing and review; AZ: writing - original draft, supervision and review; RL: supervision, validation; BS: data processing and review; UT: supervision, validation; SA: validation and review; EN: supervision, validation; PD: validation and review; EB: supervision, validation; GR: supervision, validation.

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Availability of data and materials: full availability of data and materials. All stated data can be provided on request to the reader.

Other: the authors declare that the opinions expressed are of a personal nature and do not in any way commit the responsibility of the Administrations to which they belong.

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