Utilisation of drugs for the treatment of psychiatric diseases in the paediatric population: focus on off-label use

Stella Pesiou

Departament de Farmacologia de Terapèutica
i de Toxicologia
Universitat Autònoma de Barcelona
Programa de Doctorat en Farmacologia

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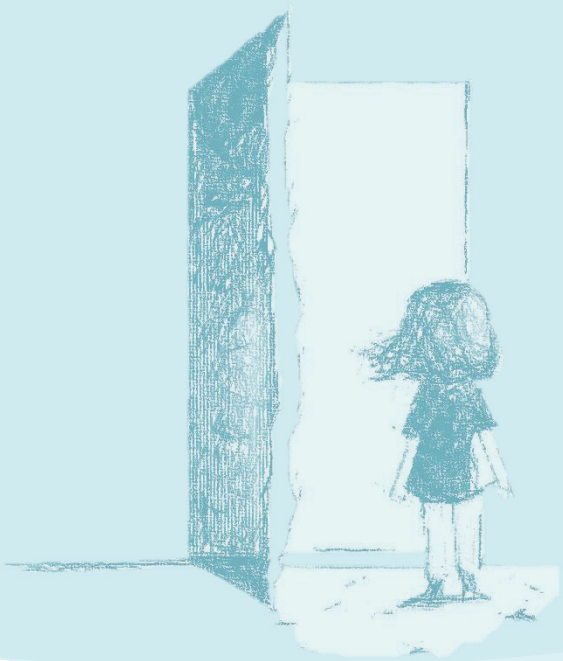

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UAB Universitat Autònoma de Barcelona

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Human behaviour flows from three main sources: desire, emotion and knowledge.

Plato (427-347 BC), The Republic

Η ανθρώπινη συμπεριφορά πηγάζει από τρεις κύριες πηγές: επιθυμία, συναίσθημα και γνώση.
Πλάτωνας (427-347 π.Χ.), Πολιτεία

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To conclude, I would like to mention that this journey was an excellent way to test myself and as my favourite quote says:

All we have to decide is what to do with the time that is given us.

(J.R.R. Tolkien)

SUMMARIES

Abstract

There is an increasing use of psychotropics in children and adolescents. Since many drugs are used that do not have authorised indications, off-label risk is frequent and the guarantees of quality, safety and efficacy are nor granted to the same level than for adult authorised indications. A retrospective observational study was done to estimate the prevalence of psychotropic use in the paediatric population of Catalonia (Spain) and Greece, with a focus on off-label use. A protocol was authorised by ethics committee in compliance with legal requirements. Anonymised data on dispensation of psychotropic drugs to paediatric patients, and basic information on demography and other related data were requested to the healthcare management of Catalonia and Greece.

Catalan dispensation data for the period from 2008 to 2017 and Greek dispensation data from 2016 to 2019 were obtained. The prevalence of use of psychotropics was between 40.8 and 64.2 per 1,000 paediatric inhabitants in Catalonia, and between 5.1 and 14.6 per 1,000 paediatric inhabitants in Greece. Hydroxyzine-only represented two thirds of dispensations. After removing these data, the prevalence of use of psychotropic drugs in the paediatric population was between 26.4 and 32.2 per 1,000 paediatric inhabitants and between 3.1 to 6.5 per 1,000 paediatric inhabitants in Catalonia and Greece, respectively. Adolescents and boys were more likely to receive a psychotropic in both regions. Psychostimulants were the most prevalent exposure in Catalonia, mainly due to methylphenidate, while in Greece antiepileptics were the most frequent ones, although diazepam was the single drug with highest exposure in almost all age groups.

Prescription-indication analysis was feasible only for Greek data, and showed that epilepsy was the most frequent diagnosis in children exposed to psychotropic drugs; mental, behavioural and neurodevelopmental disorders were also frequent. In Greece, primary health care physicians prescribed the majority of the dispensed psychotropics, while child psychiatrists had a higher share of antipsychotics, hypnotics/sedatives and antidepressants prescriptions. Children and adolescents residing in urban areas were more likely to receive a psychotropic.

Off-label use was frequent in both settings, with 12% (Catalonia) and 14% (Greece) of paediatric subjects having received at least one medicine with no paediatric information in the product labelling, corresponding to 5.5% (Greece) and 4.6% (Catalonia) dispensed psychotropics. Considering only age range, 7.6% (Greece) and 7.5% (Catalonia) of all dispensed psychotropics were used in a non-authorised age. Off-label was more frequent in adolescents, but the proportion of off-label use vs labelled use was higher in younger populations, boys in Catalonia and girls in Greece. Aripiprazole (Catalonia) and quetiapine (Greece) were the substances with

most frequent off-label use. In Greece, antipsychotics (mainly risperidone) followed by antidepressants (mainly fluoxetine) were the most frequently used off-label drugs considering the clinical indication.

The prescription and reimbursement systems in the studied regions differ, and this may have impacted the observed differences in the psychotropic use rates, as well as the estimations of rates of off-label use. Although we may consider that our methods led to underestimation of off-label uses, our data confirms that off-label use is a frequent reality in paediatric patients. There is some available evidence supporting the observed off-label uses, but long-term studies are lacking. There is an urgent need to systematically ascertain effectiveness and any potential adverse events in children and adolescents in the off-label setting, to generate valuable information for risk-benefit assessment in these populations where extrapolation from adults is not reliable, as well as to produce harmonised guidelines on how to better use psychotropics in children. A future study focusing on the off-label use considering diseases and separate psychotropic groups, and focusing on effectiveness and safety, could be of great importance.

Resum

La utilització de psicotròpics en nens i adolescents és creixent, i sovint empra fàrmacs que no tenen indicacions autoritzades. La utilització de medicaments fora de fitxa técnica és freqüent, i no compta amb les mateixes garanties de qualitat, seguretat i eficàcia que les indicacions autoritzades per a adults.

S'ha fet un estudi observacional retrospectiu per estimar la prevalença de l'ús de psicotròpics a la població pediàtrica de Catalunya i Grècia, amb especial atenció a l'ús fora de fitxa técnica. El protocol de l'estudi el va autoritzar el comitè d'ètica, d'acord a la normativa. Es van sol·licitar a les autoritats sanitàries de Catalunya i Grècia dades anonimizades de dispensació de psicofàrmacs a pacients pediàtrics, i altres dades relacionades.

S'han obtingut dades de dispensació a Catalunya pel període 2008-2017 i a Grècia del 2016 al 2019. La prevalença d'ús de psicotròpics a Catalunya va ser entre 40,8 i 64,2 per 1.000 habitants pediàtrics, i a Grècia entre 5,1 i14,6 per 1.000 habitants pediàtrics. L'ús aïllat d'hidroxizina va ser dos terços de les dispensacions; en eliminar aquestes exposicions, la prevalença de consum va ser d'un 26,4 a un 32,2 per 1.000 habitants pediàtrics i d'un 3,1 a un 6,5 per 1.000 habitants pediàtrics a Catalunya i Grècia, respectivament. La prevalença va ser més alta als adolescents i els nois a ambdues regions. Els psicoestimulants van ser l'exposició més freqüent a Catalunya, principalment el metilfenidat, mentre que a Grècia van ser els antiepilèptics, i el diazepam va ser el principi actiu amb més exposició a gairebé totes les edats.

Les anàlisis de prescripció-indicació es van limitar a les dades gregues; l'epilèpsia va ser el diagnòstic més freqüent en nens exposats a psicotròpics, seguits dels trastorns mentals, del comportament i del neurodesenvolupament. A Grècia, la majoria de prescripcions les feien metges d'atenció primària, però els psiquiatres infantils feien més receptes d'antipsicòtics, hipnòtics/sedants i antidepressius. Els nens i adolescents de zones urbanes van tenir més exposició a psicotròpics.

L'ús d'almenys un medicament fora de fitxa tècnica va ser d' un 12% (Catalunya) i un 14% (Grècia) dels subjectes pediàtrics, i un 5,5% (Grècia) i al 4,6% (Catalunya) dels psicotròpics dispensats, considerant l'absència d'informació pediàtrica a la fitxa técnica del medicament. Considerant només criteris d'edat, el 7,6% (Grècia) i el 7,5% (Catalunya) de tots els psicotròpics van utilitzar en una edat no autoritzada. L'ús fora de fitxa tècnica va ser més freqüent en els adolescents, però la proporció va ser més gran en les poblacions més joves, en els nois a Catalunya i en les noies a Grècia. L'aripiprazol (a Catalunya) i la quetiapina (a Grècia) van ser les substàncies més freqüents. A Grècia, els antipsicòtics (principalment risperidona) seguits dels

antidepressius (principalment fluoxetina) van ser els fàrmacs fora de fitxa tècnica més utilitzats considerant la indicació clínica.

Les diferències en els sistemes de prescripció i reemborsament pot haver afectat les diferències observades en les taxes d'ús de psicotròpics; els nostres mètodes segurament han subestimat els usos fora de fitxa técnica. Tot i així, les nostres dades confirmen que es tracta d'una pràctica freqüent en pacients pediàtrics. Malgrat hi ha alguna evidencia recolzant els usos observats, és necessari poder establir-ne l'eficàcia i la seguretat d'aquests usos en nens i adolescents, per generar evidència destinada a avaluar el risc-benefici en aquestes poblacions, on l'extrapolació d'adults no és fiable, produir directrius harmonitzades sobre com utilitzar millor els psicofàrmacs en nens, i fer estudis futurs que avaluin l'eficàcia i la seguretat de l'ús fora de fitxa tècnica considerant malalties i grups de fàrmacs psicotròpics específics.

Resumen

La utilización de psicotrópicos en niños y adolescentes es creciente, y a menudo utiliza fármacos que no tienen indicaciones autorizadas. La utilización de medicamentos fuera de ficha técnica es frecuente y no cuenta con las mismas garantías de calidad, seguridad y eficacia que las indicaciones autorizadas para adultos.

Se ha realizado un estudio observacional retrospectivo para estimar la prevalencia del uso de psicotrópicos en la población pediátrica de Cataluña y Grecia, con especial atención al uso fuera de ficha técnica. El protocolo del estudio fue autorizado por el comité de ética, de acuerdo a la normativa. Se solicitaron a las autoridades sanitarias de Cataluña y Grecia datos anonimizados de dispensación de psicofármacos a pacientes pediátricos, y otros datos relacionados.

Se han obtenido datos de dispensación en Cataluña para el período 2008-2017 y en Grecia de 2016 a 2019. La prevalencia de uso de psicotrópicos en Cataluña fue entre 40,8 y 64,2 por 1.000 habitantes pediátricos, y en Grecia entre 5,1 y 14,6 por 1.000 habitantes pediátricos. El uso aislado de hidroxizina representó dos tercios de las dispensaciones; al eliminar estas exposiciones, la prevalencia de consumo fue de un 26,4 a un 32,2 por 1.000 habitantes pediátricos y de un 3,1 a un 6,5 por 1.000 habitantes pediátricos en Cataluña y Grecia, respectivamente. La prevalencia fue mayor en los adolescentes y en los varones en ambas regiones. Los psicoestimulantes fueron la exposición más frecuente en Cataluña, principalmente el metilfenidato, mientras que en Grecia fueron los antiepilépticos, y el diazepam fue el principio activo con mayor exposición a casi todas las edades.

Los análisis de prescripción-indicación se limitaron a los datos griegos; la epilepsia fue el diagnóstico más frecuente en niños expuestos a psicotrópicos, seguidos de los trastornos mentales, del comportamiento y del neurodesarrollo. En Grecia, la mayoría de prescripciones las hicieron médicos de atención primaria, pero los psiquiatras infantiles prescribieron más frecuentemente antipsicóticos, hipnóticos/sedantes y antidepresivos. Los niños y adolescentes de zonas urbanas tuvieron mayor exposición a psicotrópicos.

El uso de al menos un medicamento fuera de ficha técnica fue de un 12% (Cataluña) y un 14% (Grecia) de los sujetos pediátricos, y un 5,5% (Grecia) y el 4,6% (Catalunya) de los psicotrópicos dispensados, considerando la ausencia de información pediátrica en la ficha técnica del medicamento. Considerando sólo criterios de edad, el 7,6% (Grecia) y el 7,5% (Cataluña) de todos los psicotrópicos se utilizaron a una edad no autorizada. El uso fuera de ficha técnica fue más frecuente en los adolescentes, pero la proporción fue mayor en las poblaciones más jóvenes, en los chicos en Cataluña y en las chicas en Grecia. Aripiprazol (en Cataluña) y quetiapina (en Grecia) fueron las sustancias más frecuentes. En Grecia, los antipsicóticos (principalmente

risperidona) seguidos de los antidepresivos (principalmente fluoxetina) fueron los fármacos fuera de ficha técnica más utilizados considerando la indicación clínica.

Las diferencias en los sistemas de prescripción y reembolso pueden haber afectado a las diferencias observadas en las tasas de uso de psicotrópicos; nuestros métodos seguramente han subestimado sus usos fuera de ficha técnica. Sin embargo, nuestros datos confirman que se trata de una práctica frecuente en pacientes pediátricos. A pesar de que existe alguna evidencia apoyando los usos observados, es necesario poder establecer su eficacia y seguridad de estos usos en niños y adolescentes, para generar evidencia destinada a evaluar el riesgo-beneficio en estas poblaciones, donde la extrapolación desde adultos no es fiable, producir directrices armonizadas sobre cómo utilizar mejor los psicofármacos en niños, y realizar estudios futuros que evalúen la eficacia y la seguridad del uso fuera de ficha técnica considerando enfermedades y grupos de fármacos psicotrópicos específicos.

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Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ADR	Adverse Drug Reaction
ASD	Autism Spectrum Disorder
AEMPS	*Agencia Española de Medicamentos y Productos Sanitarios* (Spanish Agency of Medicines and Medical Products)
ATC	Anatomic Therapeutic Code
CBT	Cognitive Behavioural Treatment
DSM-5	5th edition of the Diagnostic and Statistical Manual of Mental Disorders
HCP	Health Care Professional
HTA	Heath Technology Assessment
EMA	European Medicines Agency
EOF	Εθνικός Οργανισμός Φαρμάκων (Greek Medicines Agency)
EOPPY	*Εθνικός Οργανισμός Παροχής Υπηρεσιών Υγείας* (National Organisation for Health Care Services Provision)
EU	European Union
FDA	Food and Drug Administration
ICD	International Classification of Diseases
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDD	Major Depressive Disorder
NCA	National Competent Authority
NICE	National Institute for Health and Clinical Excellence
OCD	Obsessive-Compulsive Disorder
OECD	Organisation for Economic Co-operation and Development
PDD	Pervasive Developmental Disorder
PTSD	Post-Traumatic Stress Disorder
RCT	Randomised Controlled Trial
RWE	Real World Evidence
SmPC	Summary of Product Characteristics
SSRIs	Selective Serotonin Reuptake Inhibitors
UK	United Kingdom
US/USA	United States of America
WHO	World Health Organisation

1 INTRODUCTION

1.1 Mental health

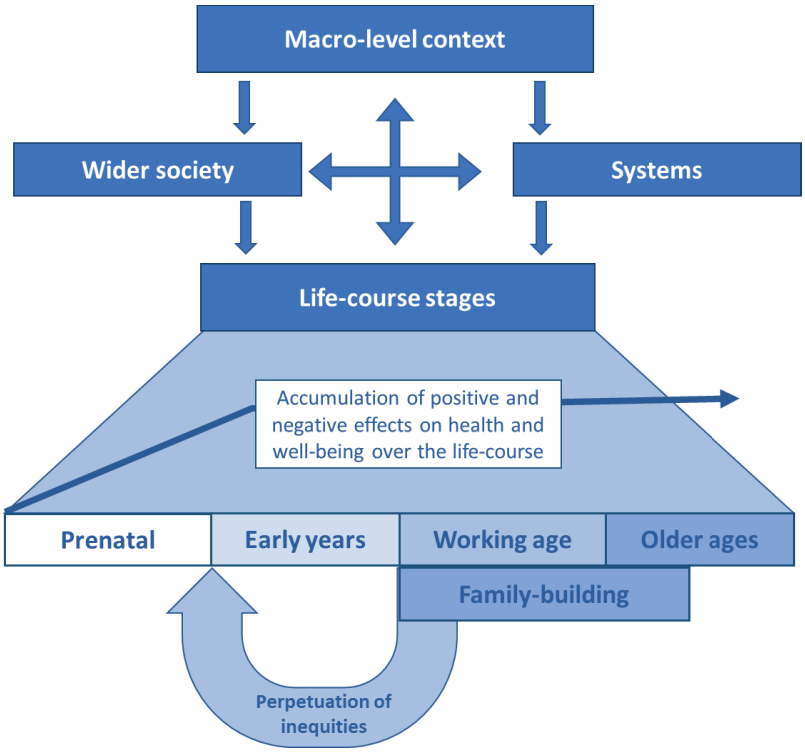
1.1.1 General context

According to the World Health Organization (WHO), mental health is '*a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community'.* The WHO also states that '*Mental health is fundamental to our collective and individual ability as humans to think, emote, interact with each other, earn a living and enjoy life'.* Thus, there is a great relevance in ensuring that appropriate efforts are directed to preserve, promote, restore and protect mental health, as a key axis of the overall subject and community wellbeing and functionality.(1)

While mental health is a wide concept that overcomes the simple absence of mental disease to approach the concept of wellbeing, mental disorders can be defined as a series of conditions that impair mental health in a number of ways, distorting different aspects of the individual function, and potentially compromising quality and years of life of the involved individual and his or her close relationships. The report on the social determinants of mental health published by the WHO in 2014 concludes that good mental health is integral to health and human well-being.(2) The mental health of the person and many of the mental disorders have to do most commonly with the economic, social and physical environment of people. The impact of social determinants throughout life varies and their influence is different depending on the person's age, gender, and vital stages. While actions on mental health will be needed along all the individuals' life, there is a considerable evidence base and scientific consensus that it is key to ensure that children live in the best and healthy environment possible since this will be paralleled by societal and mental health benefits. To that purpose, actions need to be universal and proportionate to disadvantages, to attenuate social gradients and reduce inequalities (Figure 1).(2)

The burden of mental health disorders is huge. Epidemiological projections suggest that one in four people will suffer from diverse types of mental disorder throughout life, and a sustained growth of mental disorders prevalence is observed, with a 13.00% increase in mental health conditions and substance use disorders between 2007 and 2017. Estimations suggest that 1 in 5 years lived with disability are currently related to poor mental health and the yearly global economic burden derived from depression and anxiety has been estimated about 1 trillion of US$. Regarding children and adolescents, global estimates suggest that roughly 1 in 5 have a mental health condition, and suicide has been reported to be the second leading cause of death in the age range of 15-29 years.(3)

Figure 1. A life course approach to tackle inequalities in health



***Source**: World Health Organization and Calouste Gulbenkian Foundation* (2)

1.1.2 Mental health disorders

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), mental disorder is defined as *'a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behaviour that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning'*.(4) Mental disorders generally combine abnormal thoughts, perceptions, emotions, behaviour and relationships with others.(3) Depending on the underlying process and the symptomatic expression, mental disorders are grouped into diagnostics and disorders.

The DSM-5 is a taxonomic and diagnostic tool that includes in its second section 23 chapters with diagnostic criteria and codes by mental disorder groups that was published in 2013 (Table 2). Previous versions of the manual had a separate chapter for disorders usually first diagnosed in infancy, childhood, or adolescence, but these are now listed in other chapters as appropriate in the DSM-5 version. The main changes since the inception of the DSM are summarised in Table 3 below.(5–7) Age-related aspects of disorders are arranged chronologically in each diagnostic chapter, so that diagnostics most applicable to infancy and childhood, adolescence, adulthood and later years are sequentially listed.(8)

Even though some of the main disorders have a high prevalence per se, the global impact of mental conditions is considered substantial if taken together. The Global Burden of Diseases,

Injuries, and Risk Factors Study in 2017 described that the disease burden due to mental disorders in both sexes and across all age groups has been huge in the last 3 decades. More than 14% of age-standardised years lived with disability are attributable to mental disorders, which have greater than 10% prevalence in all twenty-one regions studied.(9) Epidemiological estimates show that mental disorders emerge in childhood with idiopathic intellectual disability and autism spectrum disorders (ASDs), and continues into older ages with depressive disorders, anxiety disorders, and schizophrenia. By 2017 up to 264 million persons were affected by depression, 45 million persons by bipolar disorder, 50 million persons by dementia and 20 million persons by schizophrenia and other psychoses, amongst other diseases.(3)

Table 2. Diagnostic and Statistical Manual of Mental Disorders (DSM) (5th edition) chapters.

Section II
Neurodevelopmental Disorders
Schizophrenia Spectrum and Other Psychotic Disorders
Bipolar and Related Disorders
Depressive Disorders
Anxiety Disorders
Obsessive-Compulsive and Related Disorders
Trauma- and Stressor-Related Disorders
Dissociative Disorders
Somatic Symptom and Related Disorders
Feeding and Eating Disorders
Elimination Disorders
Sleep-Wake Disorders
Sexual Dysfunctions
Gender Dysphoria
Disruptive, Impulse-Control, and Conduct Disorders
Substance-Related and Addictive Disorders
Neurocognitive Disorders
Personality Disorders
Paraphilic Disorders
Other Mental Disorders
Medication-Induced Movement Disorders and Other Adverse Effects of Medication
Other Conditions That May Be a Focus of Clinical Attention

***Source**: adapted from American Psychiatric Association* (4)

Table 3. Diagnostic and Statistical Manual of Mental Disorders (DSM) - history and main milestones.

DSM	Publication date	Nº of diagnosis categories	Milestones and main changes	Milestones and main changes in paediatrics
DSM-I	1952	102	1st edition	
DSM-II	1968	182	- Further expansion of the definitions of mental illness to include milder conditions seen in the general population. - Increased systematic categorisation and specificity by multiple subdivisions of former disorder categories. - Removal of the psychodynamic term "reaction", referring to the maladaptive response of an individual to socio-environmental sources of distress. - More alignment with ICD-8.	First introduction of hyperkinetic syndromes.
DSM-III *(DSM-III-R)*	1980 (*1987*)	265 (*292*)	- Introduction of a multiaxial or multidimensional approach for diagnosing mental disorders. - Increase on the specificity leading to increase in the number of stand-alone disorder categories. - Removal of the category "Homosexuality". - Inclusion of standards for differential diagnosis of several categories of disorder that share similar characteristics, and the minimum duration of signs and symptoms required for a clinical diagnosis to be made. - ICD-9-CM used.	Increase on and introduction of childhood and adolescence disorders (such as three categories of Attention-Deficit Disorder).
DSM-IV *(DSM-IV-TR)*	1994 *(2000)*	297	- Refinement on the classification system and the diagnostic criteria. - Organisation into a five-part axial system. - Increased congruence between the two systems and fewer meaningless differences in wording. - ICD-9-CM used. *Revision: pervasive developmental disorder not otherwise specified, and Asperger's syndrome significantly changed; more alignment with ICD-9-CM.*	Update on the criteria of mental retardation.

DSM	Publication date	Nº of diagnosis categories	Milestones and main changes	Milestones and main changes in paediatrics
DSM-5 *(DSM-5-TR)*	2013 *(2022)*	298	- Diagnosis transformation by incorporating genetics, imaging, cognitive science, and other levels of information to lay the foundation for a new classification system to be more biologically based. - Removal of the five-axis system. - Reconceptualisation of Asperger syndrome from a distinct disorder to an autism spectrum disorder (ASD). - Elimination of subtypes of schizophrenia and deletion of the "bereavement exclusion" for depressive disorders. - Renaming of gender identity disorder to gender dysphoria. - Inclusion of binge eating disorder as a discrete eating disorder, hoarding disorder, and premenstrual dysphoric disorder (PMDD). - Splitting of disorders 'not otherwise specified' into other specified disorders and unspecified disorders. - Arabic numeral rather than Roman. - ICD-10-CM used. *Revision:* - *Revision of criteria for 70 disorders as well as added a new diagnosis, prolonged grief disorder.* - *New symptom codes allowing clinicians to indicate the presence or history of suicidal behaviour and non-suicidal self-injury.* - *Necessary clarifications to certain diagnostic criteria and alignment with ICD-10-CM.* - *Revised language surrounding gender dysphoria and race.*	Inclusion of disruptive mood dysregulation disorder, in part to decrease the over-diagnosis of childhood bipolar disorders. Addition of social communication disorder and of disruptive mood dysregulation disorder (DMDD). More precise criteria for disorders affecting: - only children: Attention Deficit/Hyperactivity Disorder (ADHD) and post-traumatic stress disorder (PTSD) - age criteria updated; - adults and children: specific learning disorder, autism spectrum disorder, gender dysphoria, depressive disorders, trauma- and stressor-related disorders, feeding and eating disorders, intermittent explosive disorder and sleep-wake disorders.

***Source**: adapted from Kawa and Giordano* (5,7)*, Suris et al.* (7) *and Substance Abuse and Mental Health Services Administration* (10)

1.1.3 Main paediatric mental disorders

Human overpopulation is acknowledged as being one of the major concerns of environmental scientists, world economy experts and governmental institutions highlighting that our planet may not be sustainable in the near future. Despite seen that the overall population was increased from approximately 1 billion around 1830 to approximately 2.5 billion by the year 1950 reaching now almost 8 billion people, the paediatric population seems not to follow the same steep increase pattern. The increase rate of the paediatric population between 1950 and 2019 was almost doubled, with children under 15 years of age representing approximately one fourth of the total human population nowadays.(11)

Several advances in medicine and society resulted to a shrinkage of paediatric deaths after birth. While there is no steep increase in the numbers, to date children still represent quite a big part of humanity by being almost one fourth of the total human population.(11) However, the healthcare system is not equally developed in order to address adequately all paediatric medical needs. Identified unmet medical needs observed in paediatric subspecialty care, such as paediatric psychiatry, can affect adulthood since health care influences the physical and emotional development of children and subsequently their capacity to reach a full potential as adults.(12,13)

Childhood and adolescence are periods of rapid development of the brain and personality. Social, cognitive and emotional competences develop during this period, and the quality of the environment where a child grows as well as the way the growth is achieved will shape his or her future role as a person in the society. Hence, the impact of mental disorders in children is magnified by the consequences of mental disease in future adults. Considering that the majority of children and adolescents with mental conditions do not receive care, it is expected that this will have consequences that will extend to their adulthood, limiting their opportunities of having fulfilling lives.(14,15)

Evidence exists on the increasing numbers of children diagnosed with a disorder under the umbrella of mental health conditions.(16) Paediatric mental diseases are considered very prevalent, involving globally up to 10% of the population below the age of 18 years old, and represent major causes of disability and a substantial burden to this patient population. According to the WHO, half of the mental conditions start by the age of 14 years old, while suicide is considered the third leading cause of death in adolescents aged 15 to 19 years old.(15)

Three main diagnostic types of paediatric psychiatric diagnosis have been proposed: internalising disorders (depression, anxiety, and somatisation), externalising disorders [(oppositional defiant disorder, conduct disorder, and Attention-Deficit/Hyperactivity Disorder

(ADHD)], and developmental disorders (autism, speech and learning disabilities).(17) In general, the most frequent mental morbidities in children include disorders like epilepsy, depression, anxiety, behavioural disorders and developmental disabilities. ADHD, anxiety and depressive disorders are common in children and adolescents being associated with significant morbidity, comorbidity and secondary psychopathology, whereas children and adolescents with intellectual disabilities are more vulnerable to mental health problems significantly at a younger age.(18) Depressive and anxiety disorders are also responsible for an increase in the risk of suicidality in adolescents.(19) In general, paediatric mental disorders are not easy to get diagnosed correctly because they cannot be detected by genetic, neuronal or physiological correlates as is the case of somatic disorders, and several factors can influence this decision-making process.(20)

1.1.4 Mental disorders burden in Catalonia (Spain) and Greece

A survey conducted in twenty-eight countries in Europe demonstrated that there are significant differences concerning the child and adolescent mental health services, concluding that clearer national policies are needed including the assessment of treatment effectiveness. Spain and Greece were among the countries participating in the study, but no data were included for Catalonia only.(13)

Catalonia (Spain)

In the region of Catalonia, according to data derived from the survey of health of Catalonia (*Enquesta de Salut de CAtalunya* or *ESCA*) in 2019, more than 1 in 4 inhabitants aged 15 years and older report some degree of emotional distress, with one in five men (22.20%) and one in three women (30.10%) been affected. The proportion increases with the age, reaching to 38.30% of people aged 75 years and older; in less favoured social classes and lower educational level groups the proportion is also higher being 30.50% and 32.50% in the lowest categories as opposed to 17.70% and 17.00% in the highest ones, respectively. Both in general and in each of the subgroups, women have a higher percentage of emotional distress that reaches difference as high as 15.00% in the lowest social and educational levels compared to men.(21)

An increase of the primary care mental health consultations has paralleled this self-reported trend in recent years, so that by 2019 up to 1,261,493 visits in adults and 546,143 visits in boys and girls aged less than 18 years of age occurred. The five main diagnosis in adults were related to humour disorders, schizophrenia and other psychosis, anxiety, adaptive disorders and personality disorders. On the other hand, the five main disorders observed in the group of children and adolescents included ADHD and conduct disorders which are usually first diagnosed during infancy, childhood, or adolescence, as well as adaptive disorders, anxiety

disorders and developmental disorders. Of note, the DSM-5 codes have not been implemented yet in the Catalan health system with regard to the medical records, so that data are coded mostly using the International Classification of Diseases (ICD) in its tenth version, ICD-10 or ICD-10-CM (22), or even on version 9 (ICD-9) depending on the setting.(23)

Social inequalities seem to also affect the mental health of the children and youth population. According to data from the ESCA survey in 2019, 7.50% of the population aged 4 to 14 years old have probabilities to experience a mental health problem, with no differences observed based on sex. In less favoured social classes, children have a higher chance of mental health problems than the one observed in higher social classes (9.20% vs 4.60%); similarly, children with parents who had only secondary education, have higher probability to suffer from a mental problem than those with parents with university studies (9.40% vs 3.60%).(21)

According to a health survey conducted by the Spanish National Statistics Institute in 2011, more than 3,000 children under the age of 14 years are hospitalised every year in Spain due to mental health problems.(24) In the region of Catalonia, the total number of people attended in the Child and Adolescent Mental Health Centres (*CSMIJ* for their Catalan spelling) has increased by 25.00% since 2008. In 2014, a total of 62,634 persons attended in the *CSMIJ*, of which 7,328 were due to serious mental illness.(25) In addition, 288,512 visits corresponding to 46,741 children under the age of 15 years were attributed to the *CSMIJ* during 2017, with an average of 6.2 visits per patient. Even though girls seem to use this centre resource less than the boys, they still generate a similar number of visits (6.4 visits per patient for boys and 5.7 for girls).(26)

The group of diagnoses accumulating the most cases is the group of ADHD, which affects 30.80% of boys and 21.30% of girls treated at the *CSMIJ*. Adaptive disorders, with 11.70% and 19.20%, and anxiety disorders, with 10.00% and 16.00%, in boys and girls respectively, rank second and third as per the most frequent diagnosis group (Table 4). More than half of the children receiving care in the *CSMIJ* had a primary diagnosis of any of these groups, almost one of third of whom consulted also a primary health care for a diagnosis pertained in these groups.(26)

Table 4. Most frequent diagnostics at Child and Adolescent Mental Health Centres in Catalonia (Spain), 2017.

Diagnostic group	Boys	Girls
ADHD	9,816	3,177
Adaptation disorders	3,713	2,865
Anxiety disorders	3,174	2,380
All diagnoses	**31,849**	**14,892**

***Source**: adapted from Servei Català de la Salut Divisió d'Anàlisi de la Demanda i l'Activitat* (26)

Greece

According to the European Health for all database of the WHO Regional Office for Europe, there are no recent general data on the incidence and prevalence mental disorders from Greece for the total of the population.(27) In a national representative survey published in 2013, 14.06% of participants identified with a general psychiatric morbidity of at least mild severity, while generalised anxiety disorder and depressive episode being the most commonly presented and women being more likely to report a common mental problem.(28) During the economic crisis a worsening health status across the total population was observed. Data revealed a raise in the prevalence of severe depression in the whole population (from 3.30% in 2008 to 12.30% in 2013) as well as an increase in the suicide attempts and hospitalisation (29), with the proportion of women suffering from chronic depression being higher than in men. In 2017, Greek patients with chronic depression represented 4.70%; the standarised death rate for intentional self-harm was 4.5 per 100,000 inhabitants with a very high male predominance (7.7 men vs 1.7 in women), which was further increased in the population older than 65 years of age.(30) One year later, a high percentage of adults reported symptoms of psychological distress reaching 15.00%, a rate that was higher than the EU average (11.00%).(31)

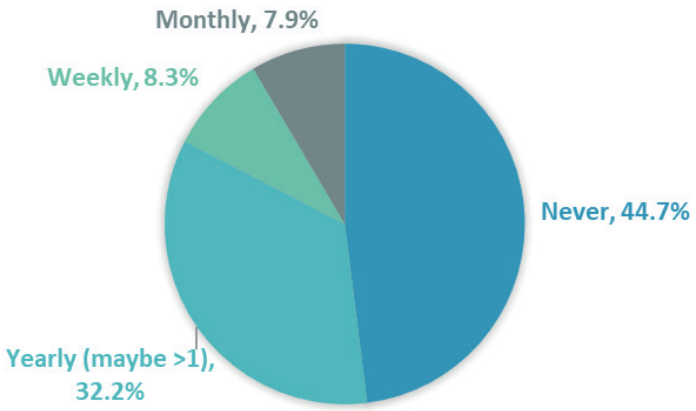
In a more recent study conducted in two cities in Greece with the objective to identify high-risk adult subpopulations suffering from stress, anxiety, depression and somatisation using self-reported instruments with high psychometric properties, 1,803 and 1,713 of the 2,425 participants had normal or mild levels of depression and somatisation respectively, while lower levels of anxiety (65.30%) and distress (57.10%) were observed. In the sample, 10.8% of the participants were identified with severe depressive symptoms, while anxiety, distress and somatisation were reported by 12.00%, 13.00% and 5.30% of the participants, respectively. Women again were identified as having higher scores than males concerning anxiety, distress, and somatisation, while younger participants showed higher levels of anxiety, distress and depression than the older ones. Professional and educational statuses were correlated with a higher prevalence where the unemployed and adults of a lower education profile were more affected.(32)

By remaining one of the three EU Member States with the highest risk for children to live in poverty or social exclusion, the state of a financial along with a refugee crisis increased psychological stress in children living in Greece compared to the rest of Europe.(33) A survey in a representative sample of both public and private child psychiatric institutions between 2007 and 2011, identified a significant increase in the new cases in public outpatient services for children (39.80%) and for adolescents (25.50%), while a decrease was observed in the private sector (35.40%). An increase in the psycho-social problems (40.00%), cases of conduct

disorders (28.00%) and of suicide attempts (20.00%) was also revealed. The hospital admission of adolescents was raised by up to 84.00% in the studies period with the diagnosis of borderline conditions, severe behavioural disorders, acute psychotic crises, self-harm behaviours, and other similar conditions being 30.00% more in 2011.(29)

In 2017, 1.50% of the Greek population suffering from chronic depressive disorder was between 15 and 24 years of age, remaining in a low ranking among other EU Member States.(30) Moreover, in a random and representative sample of adolescents from schools in the greater area of Athens, 10.90% had scored for emotional symptoms, 11.90% for conduct problems and 10.60% for hyperactivity.(34) A health survey conducted in 2019 by questioning the parents, defined that the prevalence of depression in children aged 2 to 14 years is of 0.20% with the same prevalence to be reported also for epilepsy. Finally, 15.20% of children aged 5 to 14 years had an episode of anxiety, nervousness, or restlessness at least once per week in 2019. Figure 5 below presents the frequency of episodes for this age subgroup.(35)

Figure 5. Frequency of episodes of anxiety, nervousness or restlessness in Greek children 5-14 years old, 2019.



***Source**: adapted from Hellenic Statistical Authority* (35)

Even though, the suicide rate in the population between 15 to 19year-olds in Greece remains the lowest in Europe (1.49/100.000), mental health still renders a major issue for the youngest population.(36) In a retrospective patient record study (2005-2014) in Northern Greece, 36.30% of the involuntary hospitalisations of children and adolescents in psychiatric wards had a diagnosis of neurodevelopmental disorders [schizophrenia, pervasive developmental disorder (PDD), intellectual disability]. The average length of stay in hospital was of 14 days average, but it was shorter during the last 5 years of the study, while these involuntary admissions could have been avoided in a more patient-oriented healthcare system.(37)

In Greece, the health care system was already pressured before the financial crisis and additional burdens were introduced since 2009 with the austerity measures and the restrictions imposed on the health budget. Mental health services were used by only one third of the patients with a reported mental disorder, and mostly used by patients with panic disorder and comorbid disorders.(28) In addition, mental health services are limited, especially in rural areas and islands: for the whole country only three hospitals have limited capacity for urgent and short-term hospitalisation of paediatric patients with serious mental health disorders. There is not community-based care for children and adolescents with mental health issues, or for parents with mental health problems.(33) The vast majority of the psychiatrists and psychiatry residents participating in a study conducted in 2015 reported that the public primary care and mental health services in the community were inadequate, and that patients could not have access to adequate treatment and interventions due to financial problems.(36)

According to Eurostat data, the available options for the paediatric population with serious mental health problems are limited, where patients can be hospitalised urgently or for a short-term in only three hospitals with a limited capacity. Moreover, significant shortages of staff and services are reported partially due to the financial crisis and the need to limit the healthcare costs.(30) Specialist health care professionals (HCPs), such as child neurologists, child psychiatrists and specialised nurses, are scarce affecting particularly the health of children with disabilities.(38) Thus, even though in Greece the number of psychiatrists per inhabitant may seem high compared to the majority of the other EU Member States, access to a specialised care is considered problematic (30); despite the need, 4.20% of patients older than 15 years of age did not have any mental health care attendance (by a psychologist or psychiatrist) due to financial constraints (39), which is considered worrisome.

1.2 Scientific evidence and regulation of drugs in children

1.2.1 Difficulties of clinical research in paediatrics

Despite the relevance of early diagnosis and the effective treatment of mental health conditions in the paediatric age range group, children and adolescents have been traditionally considered a neglected population. The level of their care is often below optimal standards, where neither early medical diagnosis nor well-researched and documented treatments are enough, available and/or accessible to the paediatric patients. Unfortunately, this fact is consequently linked to the unfair relationship between impaired mental health and poorer cognitive and social outcomes, with the causal relationship between both being more than plausible.(40) Explanations for such an unfortunate and serious issue include the intrinsic clinical difficulty to identify mental signs

and symptoms along with the developmental changes, the lack of awareness on the frequency and importance of mental conditions in children, as well as social stigma on mental disorders.(41) Hence, despite the large magnitude of the healthcare problem, children are still neglected concerning access to effective and safe mental health care including any treatment options.

For long periods, non-pharmacological and pharmacological treatments aimed to treat mental conditions in the paediatric population did not receive a great attention. With almost no dedicated pharmacological research, the tools available for properly helping children diagnosed with a mental condition have been very limited. While this has been mainly led by the reluctance to conduct research in children, regulatory initiatives have helped to advance, and progressively the medical and scientific communities have realised that it is not ethically acceptable to have lower safety standards in drug therapy for children and adolescents than for adults. Meanwhile, a large list of reasons has been acting as a large barrier regarding pharmacological treatments to obtain evidence-based treatment options for children.(42)

Traditionally, countries and governments have left pharmacological research to self-regulate, as the decision of the investments and choices of research projects mostly resided at the initiative and sponsorship of the pharmaceutical industry. Companies act with a global view and market driven strategy, which may not match with what would be required by a public health perspective. Since the business logics of pharmaceutical industry includes a risk-avoiding behaviour, the choice of their research activity targets patient populations and drugs for development with the best possible favourable business-oriented success/failure ratio.

As a result to the business policies, small populations, diseases limited to low-income countries and areas of research that may pose risk to a company's reputation due to stigma or (unfunded) ethical concerns, are left aside. Since children are considered a vulnerable population due to the intrinsic difficulties to implement the autonomy principle, ethical concerns on clinical research with paediatric participants have resulted in minimal activity in the field for most of the 20th century.(43)

On top of fears on ethical acceptability of paediatric clinical research, additional issues may compromise the feasibility of paediatric trials, and may act as barriers challenging enough for pharmaceutical companies being reluctant to take risks. Paediatricians often state that '*children are not young adults'* to explain that the physiology and organ/systems of children can be totally different than the ones of adults and among different moments of the individual development. Thus, a disease course can be different from the one presented in adults, but also pharmacokinetics and pharmacodynamics may be changing across age groups. These differences require that clinical trial designs need to adapt to the different stages of development, and often

result in the need of several separate studies in different age groups. Trials may require new or different endpoints suitable for specific age and developmental subgroups, which in turn may require independent validation and interpretation. The need of multiple trials increases further the costs of the research, magnified by the fact that recruiting is often challenging in lower age ranges. The identification of eligible paediatric patients is often difficult, especially because of the limited number of available paediatric specialised research centres and care facilities or networks.(44) On top of that, families and paediatricians face practical and economic challenges when it comes to clinical trials, especially if several visits are needed, that may interfere to the family daily routine and might require job leaves for the parents.(45)

In addition, there are many ethical concerns regarding paediatric studies, not only regarding the acceptable level of risk for which trial participation of children is deemed justified, but also because of parent/legal guardian hesitance to give consent due to emotional and/or physical burden. The convenience of participation, reluctance to accept randomisation or placebo use, or the perception of lack of direct clinical benefit from the specific experimental intervention when there might be existing authorised alternatives, are additional impeding factors.(46,47) Of note, perceived ethical concerns may limit not only parents' consent, but also physicians' attitude and prejudices, who may not be proactively comfortable offering experimental participation to their patients. While patient protection is the basic argument supporting the need of methodologically robust trials in children, and since lack of evidence in therapeutics represents a huge risk and lack of guarantees to patients, it may be difficult to the HCPs participating in the research to realise such general benefits for the community when taking decisions at an individual level. Complex study designs may be required to handle ethical issues and ensure that the trial recruits only the minimum number of participants needed to resolve the research question; unconventional designs may pose additional difficulties and increase regulatory risk perception by industry.(46,48)

Furthermore, documentation of long-term safety in paediatrics can be even more challenging when compared to the adult drug development programs. Specific adverse events and/or medicine-related impact on development, growth, organ/system maturation and function which are all strongly connected with the age, cannot be always identified in a short-term clinical study set. Therefore, paediatric development usually will require longer duration of monitoring or follow-up studies to ensure detection of undesirable effects on development, growth and maturation of the individual.(49,50)

Formulations and presentations designed for adult use may render difficult the administration of drugs to younger populations. A wrong dose or an inadequate formulation or administration can lead to an increase in medication errors, leading to increased risks in adverse events due to

overdosing or inefficacy due to underdosing. Hence, alternative or specific paediatric formulations, new routes of administration, new dosage and/or packaging of a medicinal product will be required to address specific needs of children, with the accompanying pharmaceutical, production, analytical and quality developments. From an industry production point of view, these investments may further hamper the economic interest of paediatric research, and the time required to develop an age-appropriate formulation could lead into a delay of paediatric patients' access to innovative medicines. However, some initiatives have been started aimed to mitigate these risks.(51)

Considering the above-mentioned challenges, it seems not strange that the pharmaceutical industry is not proactively seeking to invest in research to address paediatric patients and drug needs. From a market perspective, investments on paediatric drug development plans and studies render higher failure rates and lower value returns than adult developments, with a lower potential market gain in smaller target patient groups as well as reputational risks in case of safety or ethical issues coming to the public domain through media. Although this has been changing lately (52), the result of many decades of lack of research has led to a situation where many drugs currently used in children are lacking clinical evidence in paediatric conditions, and physicians need to extrapolate their practice from the adult studies or the knowledge acquired by clinical experience along the years.(46)

1.2.2 Off-label use in paediatrics

According to article 6(1) of Directive 2001/83/EC, it is prohibited to market medicinal products without a marketing authorisation (MA) in the European Union (EU) states, meaning that all medicinal products that can be legally found on the market need to first obtain MA by either an EU Member State or by the Commission in the respective territory. There are several routes to authorise a medicinal product in the EU: the centralised, the de-centralised, the mutual recognition and the national routes. Depending on the route selected, a marketing authorisation application (MAA) should be submitted to the corresponding regulatory authority. The European Medicines Agency (EMA), through its Scientific Committees (especially the Committee for Medicinal Products for Human Use (CHMP)), is responsible to assess the MAA containing all the supporting data for all those medicinal products following the centralised procedure, while National Competent Authorities (NCAs) are responsible for all other procedures following a different authorisation route.(53)

It is the role of the regulatory authorities to ensure that the marketed products are safe and efficacious by performing a scrutinised regulatory review on the submitted MAA. The submitted MAA and corresponding dossier include a range of information related to the development of

the medicinal product. The information includes data on drug manufacturing, laboratory and non-clinical studies, benefits and side effects observed in patients included in clinical studies and other sources, as well as a risk management plan, and information proposed to be provided to patients and HCPs.(54)

Among the submitted clinical data, a wide variety of information is enclosed, including data related to the target group of patients to whom the medicinal product is proposed to be administered. These data are mostly based on the subjects of the clinical trials supporting the MAA. The decision if an MA will be granted or refused is based on an assessment of the quality, efficacy, and safety of the medicinal product, as well as on a benefit/risk assessment focusing on a specific condition in a specific subpopulation investigated in clinical trials included in the dossier. After the assessment of the dossier and the decision to grant an MA, the product is to be placed on the market, with the labelling - Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) - including the conditions of use. The SmPC will include in its section 4 details concerning the correct way to administer the medicinal product according to the authorised indication, the authorised age group, posology and route of administration.(54,55)

The EU legislation regulates the requirements for commercialisation of a medicinal product, and the use of authorised medicinal products by prescribers in their routine clinical practice must be guided by the recommendations of SmPC. However, all patients´ needs and characteristics may not always be reflected in the SmPC. The regulation recognises that it is an inherent part of the medical practice to decide the best treatment for a given patient based on the best available knowledge and clinical judgement when clinically required, so that a medicinal product may be exceptionally - but intentionally - administered outside of the conditions covered by the terms of its MA (as reflected in the SmPC and the PIL), under an 'off-label use' status. There are several types of off-label use based on use in different than the approved indications, by different populations, at different dosage frequencies or durations, or by different routes of administration (55); according to EMA, the off-label use is defined as the '*use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration'*.(56)

Since the Member States of the EU are the ones holding the responsibility of health policy and delivery of health services in the union's territory, it is on their remit how to organise their healthcare system and subsequently how healthcare professionals prescribe/administer the authorised medications. According to the European Court of Justice *'off-label prescribing is not prohibited, or even regulated, by EU law'*. Further, the Court indicated that '*there is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted'*.(55)

In view of the above, the off-label use is often referred to the national drug regulations. Off-label use is generally and legally accepted as a part of clinical practice, and generally the national regulations establish limitations to this type of use. The off-label use is generally deemed justified when there is a clinical need lacking authorised medications, and either evidence or clinical practice suggest that an alternative drug or regime lacking specific authorisation to the particular clinical situation may benefit the patient.(55,57)

By nature, off-label use is thus intended to be an exceptional circumstance. In this exceptional case, paediatric patients may have the option of receiving a medicinal product aimed and authorised in a different use than the labelled indication, and/or with a dose scheme and/or via a route of administration that was never checked as appropriate for the patient's age. However, the off-label use exposes children to the uncertainties and risks of receiving a treatment that was not previously validated as efficacious or safe for them. Considering that the pharmacological response to a given drug may differ substantially in children and adults, and data supporting efficacy and safety are not granted by a previous review and authorisation, the off-label use poses the treated paediatric patient population in a higher potential risk.(55,58) Hence, assuming that the lack of evidence should be regarded basically as an uncertainty that poses patients to high risk, the off-label use should not become a routine practice; yet it is currently a frequent phenomenon in many therapeutic fields in paediatrics.(59)

According to a national survey in children for the years 2012-2013 in Spain, which was part of the OL-PED study, almost two thirds of the participating paediatricians stated that they do prescribe medicines for off-label indications.(60) On a European level and based on self-reporting questionnaires, it seems that paediatricians, child psychiatrists and neonatologists are the leading specialities as regards the off-label prescribing.(55,61) However, even though HCPs with their choices may contribute to address unmet needs by having the opportunity to prescribe an innovative medicinal product as off-label, liability issues are not well-addressed in case of any negative consequence caused by this use.(55) Along with these concerns, we can also highlight that often the frequency of off-label administration in children is so high that physicians ignore that the medicinal products they prescribe are not licensed for that particular use. Within the results of a study published in 2017 by the EC, a systematic literature review revealed that the off-label use in the paediatric population was widespread, covering a range of different therapeutic areas and being a common practice for many prescribers in both inpatient and outpatient settings in most of EU Member States. The observed percentage of off-label inpatient prescriptions varied between 13.00% and 69.00% according to an analysis based on data from sixteen EU Member States, while for the outpatient ones the range was of 2.00-100.00% according to data derived from twelve EU Member States. Even when these numbers

could be considered quite comparable with the numbers for the adult population (7.00-95.00% and 6.00-72.00% respectively), there is no doubt that the high off-label use in the paediatric setting is considered riskier due to the vulnerability of those patients.(55)

As a part of the documentation for the present study, a literature review up to October 2nd of 2021 was done to define further the off-label use, as well as to update and fill the gap of information to present. A free-text search using the term 'off-label' in PubMed (62) brought 10,882 references. The topic has been of ever-increasing interest, with 5,112 publications pertaining to the last 5 years, and 1,810 publications retrieved only in the last year reflecting likely not only the interest of the subject, but its special implications during the outbreak of the coronavirus pandemics in 2020 and 2021. Only few of these publications (193 observational studies) are studies reporting the prevalence and incidence of off-label use in paediatrics. Of those, only 9 describe off-label use in paediatrics in Spain (63–71) while only one describes the off-label use of paediatric drugs (antibiotics only) in Greece.(72) Details of the studies, including reporting of the different rates of off-label use depending on the setting, are summarised in Table 6. The higher rates of off-label use, close to 50.00%, are described in intensive care settings, both in neonatal units and in general paediatric care. The main reasons for the off-label prescriptions in the neonatal care were dosing and age ranges, while in paediatric intensive care units the main reasons for the off-label prescription were indications and dosing. A study on palliative care reported about 40.00% of off-label use, while the outpatient off-label use was estimated to be only 8.00% when using a large database; however, results should be interpreted in the context that neither dose nor indication details were analysed. Studies collecting individual and detailed data from outpatients show estimates around 30.00% to 50.00% of off-label use, in this case mainly due to lack of authorised indication in general or for the specific age range, or due to differences in dosage.

Respiratory drugs were the ones most frequently prescribed to outpatients, followed by anti-inflammatories and antipyretics, and antibiotics; those were also the groups responsible for most cases of the off-label prescription.(65,66) Hospital and intensive care units had similar profiles although some included also neurological drugs in their top ranking of the off-label prescriptions (67); this is consistent with studies done in other settings such as in Brazil, where it is also reported that respiratory and antimicrobials were the leading groups for the off-label prescription.(73) However, one Spanish study reported that the group with the higher proportion of off-label use was the Anatomic Therapeutic Chemical (ATC) 'A' group (digestive and metabolism), likely because it is the group with less products labelled for children.(66)

The off-label use may be considered as a part of routine practice and not always incorrect, but several problems have been identified in the post-marketing pharmacovigilance setting

associated with this exceptional drug use. The new EU pharmacovigilance legislation (Directive 2010/84/EU) not only acknowledges the existence of off-label use, but it also states that marketing authorisation holders (MAHs) are responsible to provide all available information on their authorised products including any use of the product outside the MA terms (Art 23(2) of Directive 2001/83/EC). Available evidence in Europe demonstrates that there is a relationship between off-label use in children and an increased percentage and severity of adverse drug reactions (ADRs); in particular, neuro-psychiatric ADRs are detected more frequently in children compared to adults.(74) According to other studies, between 23% to 60% of all ADRs in children may be related to drugs used out of their authorised conditions.(75–77)

Some initiatives were developed in the past to provide recommendations for clinicians on how to evaluate the appropriateness of medicines intended to be used as off-label, offering some useful results.(78) In Europe, different policies exist among Member States with regard to the off-label use since this part is not harmonised in the European territory. During an expert meeting, different stakeholders explored a set of policy options on how to better handle the complex issue of the off-label use, where the generally accepted approach was of providing guidelines and collecting evidence during practice.(55)

1.2.3 Drug regulatory background in paediatrics

The off-label use is related with several problems: the patient is on its own trial; the risk of medication errors is high due to not suitable formulations; safety and efficacy data are not collected in a systematic way, and cumulated experience is lost and not shareable; the prescriber is taking the burden of any associated risks or undesirable effects; and the MAH is not accountable for any drug-related problem if drugs are used outside of the authorised conditions.

The need to regulate the off-label use and the high ADR incidence observed in the paediatric population were among the reasons behind the adoption of regulations to foster investment in drug development that will cover unmet needs of these vulnerable patient populations around the globe. By the end of the ‘90s and early 2000s, several countries and international public organisations enhanced a number of incentives, and also obligations, aimed to improve evidence for paediatric drugs, such as those included in the United States of America (USA) paediatric research equity act (79) and the European paediatric regulation.(80,81)

The main goal of regulations was to minimise the uncertainties in the use of current or future treatment options in the paediatric population, by increasing the clinical development and improving the MA information of medicinal products for the paediatric population. The objective was to ensure that these medicines are subject to high quality research, without exposing children into unnecessary studies. However, while the regulations improved partially the lack of

Table 6. Summary of previous studies reporting paediatric off-label use in Spain and Greece

Author	Year	Country	Setting	Sample size	Definition of off-label use	Reported proportion of off-label use
Ruíz-Antorán et al	2013	ES	Outpatients	695 patients visited for first time at GI clinic, of which 207 reported 331 prescriptions	Age, dose, indication or route not in SmPC	33.20% off-label overall (47.30% of those with prescriptions)
Blanco-Reina et al	2015	ES	Outpatients	388 children with 462 prescriptions	Age, dose, indication or route not in SmPC	27.40% off-label overall, due to: - 60.00% age range - 21.50% dose - 12.00% indication - 7.00% route
Morales-Carpi et al	2010	ES	Outpatients	462 children attending emergency ward, of which 336 had 667 prescriptions	Age, dose, indication or route not in SmPC	50.70% off-label overall (67.90% of those with prescriptions) 38.10% dose 32.70% indication 24.30% no SmPC information 4.70% age range
Lizano-Diez et al	2021	ES	Outpatients	IQVIA database of dispensed drugs with >150 million prescriptions	Not for children use according to BotPlus 2.0.	Between 6.00% and 8.00% of all outpatient prescriptions.
Blanco-Reina et al	2017	ES	Hospital	190 prescriptions	Requested by physician to a committee	100% (description of requests with no denominator)
Porta et al	2010	GR IT UK	Hospital	157 Greek patients (10 with 27 antibiotic prescriptions in intensive care, 147 with 249 antibiotic prescriptions in wards)	Limited to antibiotics: Age, dose, indication or route not in SmPC	22.00% of antibiotics in intensive care 19.70% of antibiotics in ward
García López et al	2020	ES	Palliative care unit	85 patients with 1198 prescriptions		39.60% off-label overall due to: - 36.10% indication - 33.80% dosage - 26.60% age (100% patients at least one OL) 12.90% unlicensed prescriptions (81.20% patients at least one)
Arocas Casañ et al	2017	ES	Neonatal intensive care	41 patients with 273 prescriptions	Age, dose, indication or route not in SmPC Unlicensed: contraindicated or no	41.40% off-label overall 42.00% age range 31.00% dose

Author	Year	Country	Setting	Sample size	Definition of off-label use	Reported proportion of off-label use
					mention to children or not in market	16.80% frequency 8.80% frequency and dose 5.50% unlicensed drugs 90.00% at least 1 out of SmPC
Sucasas et al	2019	ES	Neonatal intensive care	84 patients with 564 prescriptions	Age, dose, indication or route not in SmPC Unlicensed: contraindicated or no mention to children or not in market	22.50% off-label overall 8.00% unlicensed drugs 59.50% patients at least 1 drug out of SmPC
Blanco-Reina et al	2016	ES	Intensive care	81 children with 601 prescriptions	Age, dose, indication or route not in SmPC Unlicensed: contraindicated or no mention to children or not in market	52.00% off-label overall, due to: - 79.00% dose - 13.50% indication - 5.00% age range - 2.50% route 5.00% unlicensed drugs
García-López et al	2017	ES	Intensive care	42 patients with 696 prescriptions	Age, dose, indication or route not in SmPC	53.90% off-label overall due to: 55.70% indication 31.20% age range 12.00% dose 1.10% route 8.60% unlicensed drugs 100% patients at least 1 drug out of SmPC

paediatric clinical evidence for innovative medicines since their implementation, the fact is that for decades there have been very few developments of treatments to support areas of low commercial interest, such as paediatrics in general, and mental health care strategies particularly in children.

A report published by the European Commission was reflecting on the ten-year period since the implementation of the Paediatric Regulation in Europe. The report noted that the increased off-label use of adult medicines by the paediatric population could not be completely addressed and concluded that the positive results of the Regulation have not been evenly distributed among all therapeutic areas.(82) Similarly, a recent analysis compared authorised medicines with a paediatric indication with those authorised in adults; the study showed that the former continues being less, that authorisation of new medicinal products is driven mainly by the adult patient needs and that it would be opportune to review the Regulation.(83)

On the positive site of the implementation of the Regulation, it seems that clinical trials in Europe concerning paediatric developments have been increased since its implementation, especially in neonates, as well as the amount of the amended drug labelling with information concerning paediatrics. However, data show that paediatric drug developments do not necessarily correspond with the highest paediatric disease burden, such the one observed in mental and behavioural disorders.(84) Moreover, there are warnings on the fact that a paediatric clinical trial has a high risk to be discontinued or to not have its results published. This leaves thousands of children exposed to a treatment that had no benefit, and thus it is of utmost importance to ensure that the collection or dissemination of useful and relevant information for this vulnerable group of patients is not missed, as it will lead to persistence of paediatric unmet needs.(85)

1.3 Paediatric psychopharmacology and unmet needs

Among the clinical areas of interest in paediatric drug research, the area of psychiatry is found among those having still a high unmet medical need, and the central nervous system therapeutic area was among the ones where substantial off-label use in children is detected.(55) Many of the authorised drugs used in psychiatry have been developed before any of the paediatric regulation initiatives, and therefore most of the currently available therapeutic arsenal in psychopharmacology may have never been tested in children. Drug treatments for ADHD, enuresis, depression, anxiety disorders, obsessive-compulsive disorder (OCD) and psychoses are intended for being used in children, but the number of psychotropic drugs that hold a MA for the paediatric population is really low compared to those intended for adults. Actually, most of these medicines have only been tested in the adult population, and often, no efficacy and safety data in

the context of a paediatric clinical trial are available, or the only limited data have been produced by relying on extrapolation to paediatric use from evidence generated in adults.(17)

Hence, there is a limited number of medicinal products labelled as to be used in paediatric psychiatric disorders, and these do not cover all relevant paediatric age subsets. Nonetheless, it seems that evidence supporting the use of psychotropic medication for children and adolescents with psychiatric disorders has increased the past years, and initiatives exist on how to guide HCPs to treat better children and adolescent patients.(86)

Of note, broad pharmacovigilance databases have shown evidence on a high proportion of adverse events of psychiatric medications in paediatric patients, rising reasons for concern to prescribing physicians.(87,88) Thus, uncertainties exist not only related to the efficacy, but also the safety profile of drugs. As an example, antidepressants were associated to a different safety profile in children and adolescents, and in particular with a higher risk of suicidal ideation. In fact, such concerns eventually led to the introduction of the warning black box for selective serotonin reuptake inhibitors (SSRIs) by United States Food and Drug Administration (US FDA) in 2004.(89) Further analysis identified gaps in evidence, suggesting that the data actually did not support a contraindication in absolute terms against the use of antidepressants in this population.(90) Accordingly, the off-label use of antidepressants (or antipsychotics) did not increase risk for serious ADRs in youth when done in a closely monitored clinical setting.(91) Yet, several additional uncertainties remain requiring further study to bridge gaps between knowledge from trials and real-world clinical settings.

Thus, increasing availability and improving evidentiary support for a safe and efficacious use of drug treatments in paediatrics is an important goal. However, this should not be the only focus, and a growing trend, both in adult and paediatric mental health, is to avoid overreliance on patient medication at the expense of underutilisation of non-pharmacological interventions, such as psychotherapeutic and family-based interventions. While lack of evidence is an area for improvement, overuse of drugs and excessive medicalisation of life is also a reason for concern.(92) To that respect, families and patients' organisations are very interested to take an active role and being involved in improving children's treatment interventions in many areas including psychiatry.(84)

1.3.1 Use of psychotropics in the paediatric population

The use of psychotropic drugs in children is a recurrent subject of research, although generally is approached by only describing a single pharmacological group or drugs used for a given medical condition. A broad approach to the use of this type of drugs, together with a detailed knowledge

on all actual uses of psychotropic drugs and the evidence supporting each use, are key to improve the quality and rationality of drug use in such a vulnerable population.

In order to define the background of the study, in particular on the extent of use of psychotropics in the paediatric population, we conducted a systematic review of the medical literature, which is part of the objectives and results of the project and described in upcoming sections. However, some findings are mentioned here in order to ease the context of the project. In summary, between 2000 and 2021, 76 studies have reported retrospective observational data on the use of psychotropics in children, mostly in the USA and Europe. Most studies were focused on describing only one type of psychotropic drugs, mostly antidepressants, but also psychostimulants, antipsychotics, hypnotics/sedatives, anxiolytics and antiepileptics in descended order; only 10 out of 76 studies reported the prevalence on psychotropics in general. Two studies reported seven different categories of medicines, but the majority reported only one category. The reported prevalence rates of use varied widely across studies and periods, depending on data sources, studies drugs and applied definitions, but generally were providing figures between 0,30% and 3.00% for overall exposure, led by antidepressants, anxiolytics and stimulants, with variation in leading groups across territories and periods. Focus on off-label data were scarce.

We also conducted a systematic search to summarise the available information on the off-label use of psychotropic drugs in paediatrics. The objectives, methods and results are detailed in upcoming sections, but some key findings are included here to ease setting the context of the project. In summary, 22 publications reported relevant data on off-label use, of which only one was done with Spanish data and none with Greek data. Antidepressants, anxiolytics, antipsychotics, stimulants and antiepileptic drugs were studied, but again, the studies differed substantially in definitions and approaches (by drug, by therapeutic groups or by medical condition), and in general provided high proportions of off-label use, often in the range of 50.00%.

The results of both systematic reviews are detailed in upcoming sections, but the main findings made evident that the quality and depth of the information available on psychotropic use in children was fragmented and incomplete, as was the information on off-label use for children using psychotropic drugs. Subsequently, we decided that accurately and exhaustively describing the prevalence of exposure to psychotropic drugs, focusing on off-label use in areas lacking supportive data, could contribute to improve therapeutics of paediatric mental health conditions.

1.3.2 Use of medicines in the paediatric population in Catalonia (Spain) and Greece

In addition to the sparsity of published international data on the use of psychotropic drugs, it is important to consider the background information on the use of psychotropic drugs in the areas where we aimed to execute the study. To that purpose, we summarised the available information on the use of these medications in Catalonia and Greece, in the context of overall drug use.

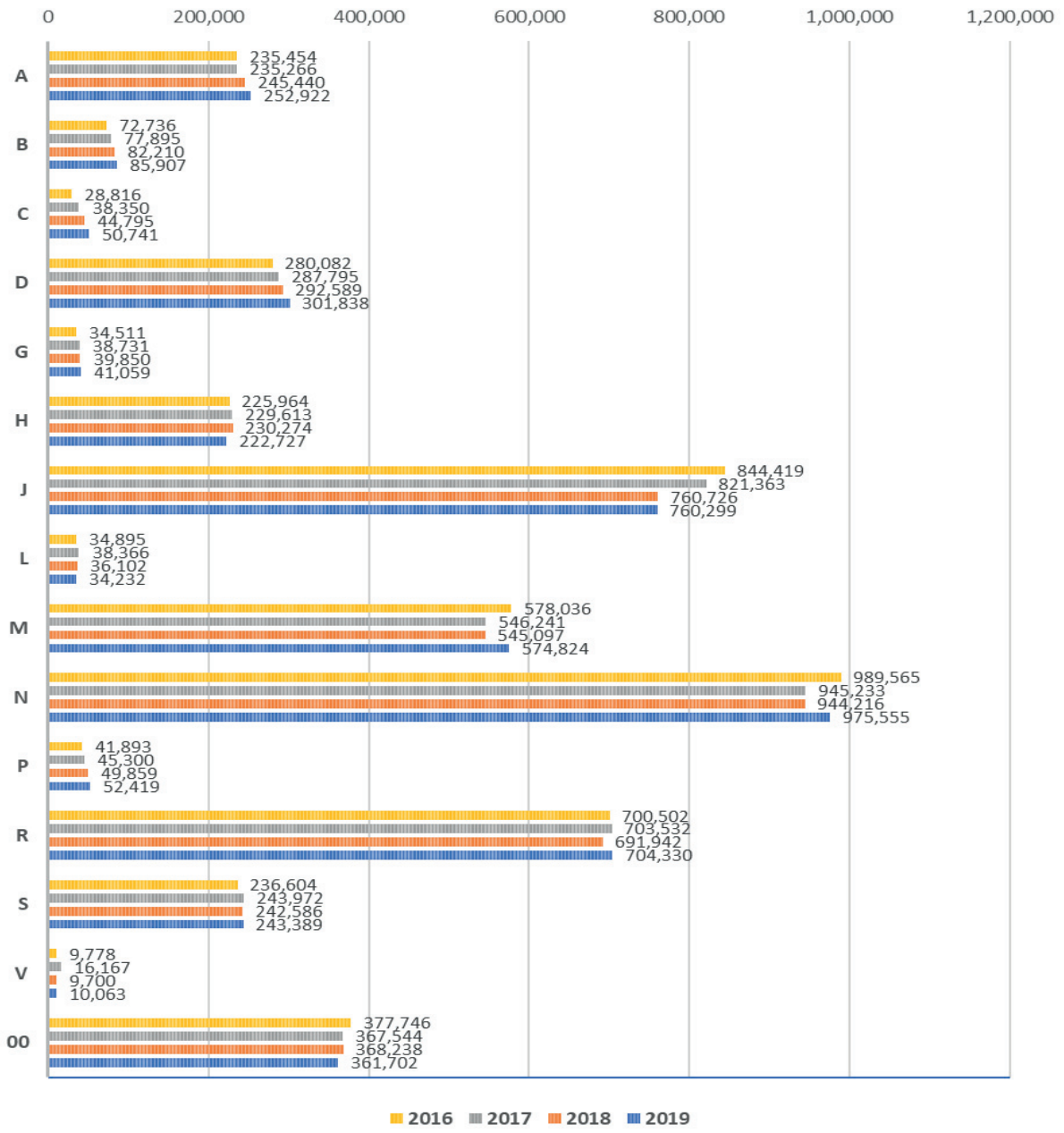
Catalonia (Spain)

As in the rest of Spain, Catalonia has a health system that provides universal coverage of all citizens. In Catalonia, both public and private owned entities offer reimbursed healthcare to the population according to a defined portfolio of services that is decided at a national level, and with no financial charge to users. Drugs, however, have a co-payment system; so, there are variable percentages of user's contribution depending on annual income and based on tax payments.(93)

The use of any type of medicines in Catalonia, in the setting of universal healthcare coverage used by the vast majority of inhabitants, has high prevalence across all ages. A growing trend of overall use of drugs is observed across the years, according to data derived from the public funded invoicing of dispensed medications.(94) The open data from the Catalan Health System show that drug use in the paediatric range (<18 years) accounted for 4,691,001 prescriptions in 2016, 4,635,368 in 2017, 4,583,624 in 2018 and 4,672,007 in 2019. The use of drugs in paediatrics is mainly due to short courses of treatment aimed to acute conditions. According to the WHO Anatomic Therapeutic Code (ATC) by system-organ grouping, the group N (nervous system) is the one with highest number of prescriptions (mostly led by widespread use of paracetamol), followed by J (antimicrobials) and R (respiratory drugs). Figure 7 below presents in detail the data on overall use of the different ATC groups for the period 2016-2019. This pattern is constant along years, although there is a trend to decrease the use of antimicrobials, likely related to interventions on rational use of antibiotics.(94)Qualitative data on drug use in Catalonia considering source of prescriptions, active principles and age group is available for 2018.(26) During 2018, 3.9 million prescriptions were dispensed to more than 710,000 children under the age of 15, representing 5.4 prescriptions per child and year and an annual expenditure of €51 per person treated. Three out of four children in primary care received a prescription in 2018, and prescriptions issued in primary care accounted for 79.60% of all prescriptions and 3.2 million recipes with an average of 3.7 recipes per child and year and an annual expenditure of €29 per person treated. The remaining prescriptions corresponded to 16.70% of prescriptions issued in the external consultations from hospitals and 3.40% in mental health centres (see Figure 8).(26)Anti-inflammatory and anti-rheumatic products were dispensed to 44.00% of

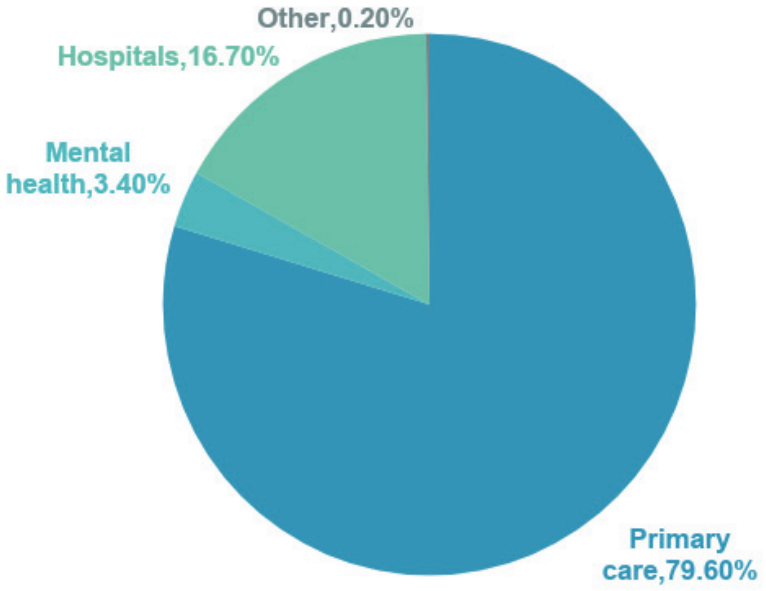
patients who received any medication. Ibuprofen was prescribed to more than 300,000 children. Systemic antibacterials were the group with most prescriptions in patients 15 years or younger (16.50%); of every 10 antibiotic prescriptions, 7.5 were amoxicillin. The groups with the highest expenditure were bronchodilators (11.80%) and psychoanaleptics (10.00%). Compared to previous years, invoicing data reflect reduction of users and prescriptions but increase in costs along the years (see Table 9).(26)

Figure 7. Number of prescriptions invoiced to users aged <18 years in Catalonia (Spain), 2016 to 2019.



***Source**: Portal de transparència de Catalunya* (94)

Figure 8. Source of prescriptions to Catalan (Spanish) users aged <15 in 2018.



Source: adapted from Servei Català de la Salut Divisió d'Anàlisi de la Demanda i l'Activitat (26)

Table 9. Drug consumption in Catalonia (Spain) for users aged <15 years, 2016 to 2018.

Invoicing data	2016	2017	2018
Number of users	730,313	720,587	712,858
Prescriptions	4,035,353	3,964,027	3,884,122
Prescriptions per user (mean)	5.50	5.50	5.40
Expense (Euros)	35,778,614	36,013,553	36,728,517
Expense per user (Euros)	49.00	50.00	51.50

Source: adapted from Servei Català de la Salut Divisió d'Anàlisi de la Demanda i l'Activitat (26)

Using the Catalan Health System open data on units invoiced by high level ATC groups, and focusing only on the ATC1 group N (Nervous System), the most used group of drugs in Catalonia in children between 2016 and 2018 were N02BE (anilids), containing paracetamol as the leading compound. The second most invoiced group is N06BA (centrally acting sympathomimetics), led by treatments for ADHD. N05AX (other antipsychotics) group follows, which is a group of antipsychotic drugs including amongst others risperidone, paliperidone and aripiprazole, as well as N03AG (fatty acid derivatives) a group of antiepileptic drugs including amongst others valproic acid and vigabatrin; N05BB (diphenylmethane derivatives), a group of anxiolytics -containing mostly hydroxyzine- are completing the data (see Table 10).(94)

Table 10. Dispensations with ATC1 'N' invoiced to the Catalan Health Service 2016-2018, users aged <18 years.

ATC group (level 4)	2016	2017	2018
Anilids	416,116	387,342	394,221
Centrally acting sympathomimetic agents	221,065	211,405	200,709
Other antipsychotics	59,318	59,306	60,195
Fatty Acids Derivatives	57,238	57,301	56,961
Diphenylmethane derivatives	51,988	42,178	37,357
Other antiepileptics	37,442	39,048	40,467
Benzodiazepine derivatives	33,343	34,824	35,331
Selective serotonin reuptake inhibitors	30,037	30,942	33,667
Pyrazolines	16,739	17,857	20,698
Diazepines, oxazepanes, thiazepines and oxepines	12,234	12,149	13,210
Carboxamide derivatives	12,088	11,793	11,199
Opioids combined with other painkillers	7,168	7,263	6,435
Amides	5,791	5,794	5,572
Barbiturates and derivatives	5,049	4,486	3,866
Tertiary amines	2,863	3,115	3,791
Succinimide derivatives	3,164	3,062	2,779
Phenothiazines with aliphatic side-chain	3,083	2,797	2,559
Non-selective monoamine reuptake inhibitors	2,712	2,597	2,548
Other antidepressants	2,286	2,209	2,692
Selective serotonin agonists (5-HT1)	1,888	2,003	2,307
Others	7,953	7,762	7,652

***Source**: adapted from Portal de transparència de Catalunya* (94)

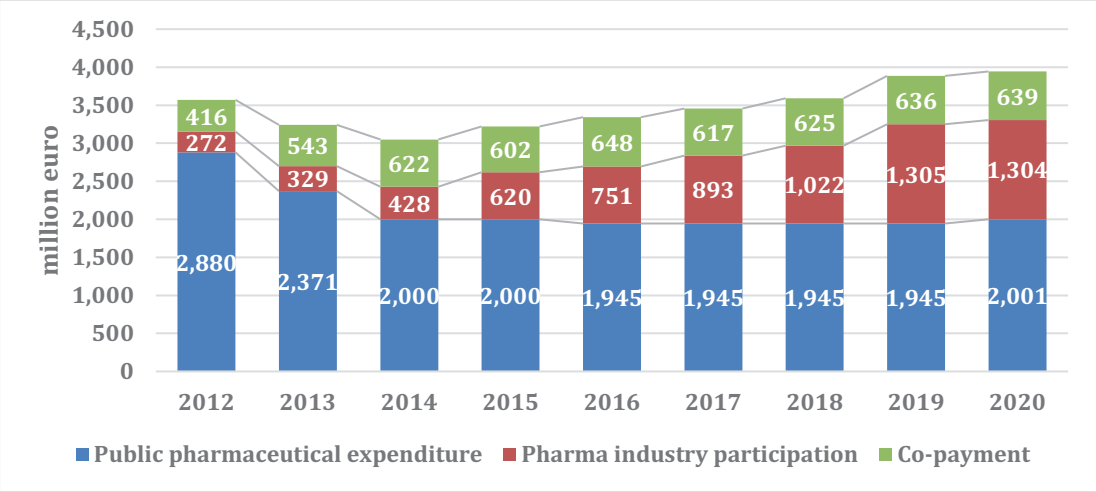
While paracetamol and hydroxyzine are used mostly in acute episodes, many of the drugs in the N group are intended for chronic neurological and psychiatric conditions and are likely responsible of a substantial part of all chronic pharmacological exposure in children. Thus, their rational use is of utmost importance, considering their potential impact on the underlying disease, but also on healthy development and maturation of children and adolescents, as well as their potential chronic effects on ability to thrive. To that purpose, it is critical to guide the prescription of these medications and to ensure that their utilisation is both based on the best and more robust possible scientific evidence obtained from and for the relevant target population.

Greece

Greece has a universal health care system provided through national health insurance, and private health care. Prescription drugs are co-paid by users in a three-tier co-insurance system that considers the severity of the condition treated, so that no payment is made for life-threatening conditions, chronic conditions have a 10% co-payment, and all other diseases are paid a 25% by users – a fixed €1 fee per dispensed prescription is also paid by users.(95)

In Greece, data on prescriptions are not available in the public domain and the relevant studies are scarce and mostly related to the pharmaceutical expenditure. The total outpatient pharmaceutical expenditure is high after more than a ten-year financial crisis, reaching almost €4.0 billion in 2020. Despite the decrease in the public outpatient pharmaceutical expenditure from €5.1 billion to €2.0 billion in 2009 and 2020 respectively, this has been compensated by clawbacks and discounts, and also by a higher contribution of patients to co-payment, as it can be seen for 2012 to 2020 in Figure 11.(96)

Figure 11. Total outpatient pharmaceutical expenditure in Greece, 2012-2020.



Source: adapted from Hellenic Association of Pharmaceutical Companies (SFEE) (96)

Surveys conducted by the Hellenic Statistical Authority in 2009, 2014 and 2019, revealed that almost half of the subjects aged above 15 years have used medicines (including dietary supplements such as herbal medicines or vitamins) that were prescribed or recommended by a doctor or dentist during the past two weeks preceding the survey. Even though a decrease was observed over the years (Table 12), women and elderly groups were found to be consistently more exposed. Concerning the same period and the consumption of over-the-counter medicines or those taken without recommendation by a doctor or dentist, an increase from 2009 to 2014 was reported, with the younger age groups been more prone to use them as compared to medications recommended by HCPs. In 2014, 64.90% of the participants used medicines without recommendation rather than herbal medicines or vitamins, and more specifically two

out of ten used antibiotics. In 2019, a decrease of 26.50% was observed compared to 2014 and only 28.10% of the subjects have used medicines in comparison to herbals or vitamins, with 15.70% of them exposed to sedative or hypnotic medicines and 30.50% to antibiotics.(97–99)

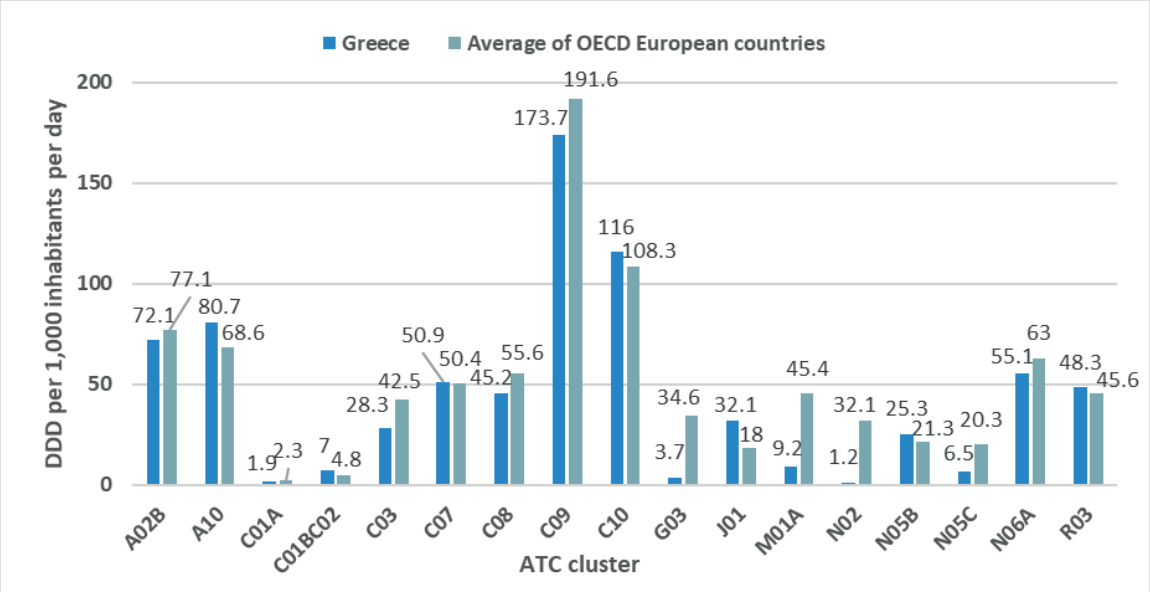
Table 12. Drug consumption in Greece for users aged >15 years, 2009, 2014 and 2019.

Use of medicines	2009	2014	2019
>15 years old			
Prescribed or recommended by a doctor or dentist	48.80%	47.40%	43.50%
Not prescribed or recommended by a doctor or dentist	24.60%	27.50%	20.20%
>15-24 years old			
Prescribed or recommended by a doctor or dentist	-	14.90%	9.20%
Not prescribed or recommended by a doctor or dentist	-	25.00%	14.20%

***Source**: adapted from Hellenic Statistical Authority* (97–99)

No further analysis per ATC group is included into the aforementioned reports. However, the Organisation for Economic Co-operation and Development (OECD) includes the consumption of medicinal products based on the ATC/DDD system in its reports, where twenty-seven different countries, among those twenty-three European ones, are compared. Figure 13 below demonstrates the consumption of medicinal products per ATC cluster, and per 2nd and 3rd ATC level in Greece compared to other European Countries. According to the 2017 data, in Greece the consumption of medicines was 143,5 DDD/1,000 inhabitants/day for the ATC cluster N. Even though the same pattern is followed for the respective indicators for the hypnotics/sedatives (N05C) and antidepressants (N06A), the consumption of medicines for anxiolytics (N05B) is higher than the average in Europe.(100)

Figure 13. Consumption of medicines (2nd and 3rd ATC level) - Greece vs OECD European countries.



***Source:** Institute for Health Economics (i-hecon)* (100)

Unfortunately, no separate data on paediatrics could be found on the prescription of medicines in the Greek paediatric population, indicating the lack of nationwide pharmacoepidemiologic data on outpatients in the country despite the use of the electronic prescription since 2012.

1.4 Justification of the project

Children suffering from a disorder under the umbrella of psychiatry exist, and the past decades can be considered as a significant progress on early identification of signs and symptoms, leading to an early diagnosis of such disorders, mostly due to the campaigns targeting the elimination of the stigma and those of boosting mental health for people of all ages. Yet the epidemiology of mental disorders in the paediatric population still has room for improvement, and few and generally fragmented data are available on the prevalence of the different conditions and their treatment, since many countries do not have the appropriate information systems to obtain it.

Observational studies using already available information in administrative and clinical databases are often referred to as real world evidence (RWE) data. RWE studies may serve to a number of purposes, that are summarised in Table 14.(101)

Data on the use of medicines are useful to understand the epidemiology of a specific health problem, especially in a population for which the participation in clinical studies is often not considered ethical or easily manageable. Therefore, RWE data can be useful for prescribers and patients by complementing information derived from Randomised Controlled Trials (RCTs). Observational studies have the benefit of external validity, that ensures representativeness of the overall target population and provide results from longer follow-up periods than trials use to do. Moreover, effectivity data in clinical practice may complement efficacy and safety data in groups of patients not included in clinical trials, wider samples and diverse cultural and social settings, allowing to clarify uncertainties and to complete missing information.

Thus, children being a vulnerable population for which a severe lack of data on the best use of safe and effective medicines is still an outstanding issue, observational studies can be of special benefit in this population. Pharmacodynamic differences and developmental changes preclude the extrapolation of efficacy from adult studies, and adverse events related to medication are higher and most of the times more severe in children, devastating children's life and thereinafter their well-being in their adulthood. Despite the efforts of the past decades to incentivise research in children, mostly driven by the paediatric regulations in Europe and the USA, both clinical trials and drug utilisation studies in paediatric psychiatry are still limited. Besides, most of them are coming from northern Europe and the USA, so that southern countries can count on

very scarce information on drug effectiveness in clinical practice: Spanish data are limited to 3 studies, and no Greek studies were found.

Furthermore, data on the off-label use of adult medicines in paediatrics are limited, as is the research on off-label use and its consequences. The few existing research is mostly hospital-based (e.g. intensive care units), focused on specific medicines (e.g. antibiotics) or specific age groups (e.g. neonates). Available data on the off-label use of psychotropics in outpatients are even more scarce, and again mostly coming from northern European countries too. In our literature review briefly described previously, only one study was found to be related to outpatient off-label use of antidepressants in Spain and none of them referred to data coming from Greece.

It is important to advance the generation of information in neglected areas, in order to facilitate resources that may increase the chances for academia, research organisations and regulatory authorities to invest on this field of research. Paediatric health problems are affecting a big and sensitive part of the population, that will eventually take the driver's seat in the society as adults, and thus merits a special focus and effort. Because of the close implications of mental health and society, culture and education, there are substantial differences internationally on how mental health is addressed and tackled, and therefore it is of utmost importance to count on relevant data – in our case, data from South Europe are of a great interest – to progress further.

The present project, built around the execution of a thorough drug utilisation study, aimed to describe the use of psychotropics in the paediatric population in Catalonia, an autonomous community in the north-east part of Spain, and in Greece. The aim was to emphasise especially on the quantitative assessment of the exposure to the different therapeutic drug groups (antidepressants, antipsychotics, treatments for ADHD, anxiolytics, etc.) and the assessment of the off-label use of these medicinal products in order to identify the main areas of uncertainty in drug use concerning the paediatric population.

Table 14. Potential uses of real world-evidence data.

Incentive the interest of the pharmaceutical industry	Inform on unmet needs and generate hypothesis for trials.
	Inform on current standards of treatment for a disease.
	Support to widen labelling: Demonstration of beneficial effects in unapproved indications, new populations (paediatrics, geriatrics, etc. or changes in dose, dosage or route of administration.
	Testing feasibility of clinical trials of new medicines.
Support to regulatory decisions	Post-authorisation studies, through the programs established by the regulatory agencies such as the EMA or the FDA, both for the determination of safety and effectiveness in cases where a lack of information was observed with the data of the authorisation.
	Pharmacovigilance studies through observational or pragmatic studies.
	Complement data from clinical trials in the entire indicated population and in regular clinical practice.
	Re-evaluation of medicines, through the determination of the value of the medicine, which can lead to an adjustment of the established recommendations or adjustment of the clinical practice guidelines.
Support for planning clinical development	Guidance of design of trials: information on the characteristics of target population for stratification, natural history of the disease, selection of outcomes, timing for assessment of results.
	Inform on the best study design based on natural history of the disease and described prognosis.
	Identification of new drug development tools (i.e.: biomarkers).
	Use data for external control of single arm clinical trials.
	Obtaining results reported by patients (Patient reported outcome measures - PROMs).
	Support to sample size calculation.
	Support methodological choices on minimum changes that are deemed relevant in superiority or non-inferiority settings.
Healthcare planning and management	Starting point to define the landscape of a disease in a region and the healthcare needs of the population.
	Basis to define health policies and to implement them.
	Support for cost-effectiveness analysis through determination of global costs by pathology or treatment.
	Basis to assign healthcare resources and budgeting.
	Implement pay per performance of drugs or other types of managed access.
	Obtaining data for the development of predictive models and other types of studies based on data structures and patterns for the application of artificial intelligence.

***Source**: adapted from Roig-Izquierdo* (101)

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

The prevalence of use of psychotropics in Catalonia's (Spain) and Greece's paediatric population is increasing in time and is substantial, and often the use of these medicinal products in children is done outside of the authorised conditions and in the absence of an authorised paediatric use.

2.2 Objectives

2.2.1 Primary

Description of the use of psychotropic medicines in different paediatric age groups in Catalonia (Spain) and Greece, focusing on the quantitative evaluation of the off-label use.

2.2.2 Secondary

1. To conduct a comprehensive literature search and systematic reviews regarding the previous data on the prevalence of psychotropics and their off-label drug use in the paediatric population worldwide.
2. Description of the psychotropic groups most frequently used in children, by age group, and the evolution of use in time.
3. Qualitative analysis of the proportion of psychotropic drug use outside of the authorised age groups.
4. Description of the clinical diagnosis most frequently present in children exposed to psychotropic drugs, and of the most frequently used drugs by clinical diagnosis groups.
5. Identification of the most frequent off-label clinical indications, and description of the available clinical information supporting their use.
6. Description of differences in drug use data between Spain and Greece, according to the differences in prescribing, dispensing, billing and funding between both countries.

3 METHODS

3.1 Systematic reviews

3.1.1 Systematic review on the prevalence of psychotropic drug use in the paediatric population worldwide

To define the use of psychotropics in the paediatric population, we systematically searched publications reporting the prevalence of psychotropics in this population worldwide. We searched in two databases from their inception to December 31st of 2018 which then extended to May 31st of 2020: Web of Science (including MEDLINE) and Scopus.(102,103) Reports from nationwide prescription datasets or representative databases that covered over at least 5% of the population of the region of reference and those only written in English were included. Two independent researchers extracted relevant prevalence data and any discrepancies were resolved in consensus meetings under the supervision of at least one senior researcher. The studies' quality (risk of bias) was assessed using the risk of bias in prevalence studies tool.(104) The PRISMA guidelines were followed (105) and the protocol was registered at PROSPERO (CRD42019128648) (106); more details on the design of this review are described in the study protocol attached in Annex I (see *Protocol for the systematic review on the prevalence of psychotropic drug use in the paediatric population worldwide*).

3.1.2 Systematic review on the off-label use of psychotropics in the paediatric population

To further investigate the off-label use of psychotropics, and additional systematic review was conducted using the PICO search tool of the EMBASE database on May 21st of 2022. EMBASE was selected as of its broader coverage: contains all of the articles that can be found in MEDLINE/PubMed and also over seven million records that cannot be accessed via the latter. The PICO search tool was selected as it helps to create a sensitive search string by adding synonyms to search blocks and automatically nesting them within parentheses.(107)

Initially several terms were used to identify all the psychotropics and specific ATC groups pertained to psychotropics, as well as all the proposed synonym terms (see search strategy details in Annex I). We followed the recommendations from the PRISMA guidelines for this review too.(105)

3.2 Retrospective observational population-based quantitative and qualitative study

3.2.1 Design

We conducted a retrospective observational population-based quantitative and qualitative study of psychotropic consumption in the paediatric population of two separate European regions: Catalonia (Spain) and Greece. The analysis period was different for the two regions with the common full year period being the 2017.

3.2.2 Data sources

3.2.2.1 Catalonia (Spain)

Pharmacy billing data from the Catalan Health Service (*CatSalut*) for a ten-year period (2008 to 2017) were used. *CatSalut* was one of the first to be implemented in the Spanish territory, and the pharmacy reimbursement data are considered representative of the region's population, since all residents in Catalonia (approximately 7.72 million, 16.40 % of Spain´s total population) (108) are covered by the public system. The data used for this analysis were provided by the *Agència de Qualitat i Avaluació Sanitàries de Catalunya* (*AQuAS*) through the *PADRIS* program (*Programa públic d'analítica de dades per a la recerca i la innovació en salut a Catalunya*) upon records linkage with an administrative database and a procedure aiming to maintain the data confidentiality via double encryption and removal of personal identifiers.

The linked database contains information on demographics and outpatient prescription dispensations from the public health care system of all patients residing in Catalonia. Outpatient database contains information on the dispensation dates, the prescribing physician's specialty, the WHO ATC code. Diagnosis or indication data for prescribing are not collected in these two databases.

3.2.2.2 Greece

Pharmacy billing data of almost a four-year period (from March 2016 to October 2019) from the nationwide electronic prescription database of the National Organisation for Health Care Services Provision (*EOPYY*) were used. *EOPYY* is the largest social security service provider in Greece, reimbursing health expenses for almost the entire Greek population (109) including the uninsured population, viz the unemployed and the family members with a social security number. According to latest estimations, medical expenses of only approximately 1.80–2.70% of the Greek population (mainly permanent military personnel and their family members, and people without social security number) are reimbursed by authorities other than *EOPYY*.(110)

Electronic prescription is mandatory for all medical activities since 2012 and *EOPYY*'s digital medicine prescription database runs under surveillance of the Electronic Governance of Social Insurance (*IDIKA* for the Greek spelling) on behalf of the Greek Ministry of Health.(95,111) The database contains demographics (date of birth and gender), the unique citizens' social security number, information on the prescribed medicines (active substance, ATC code, number of packages and dosage), the relevant ICD-10 codes connected to the concerned medicine, as well as the prescribing physician's specialty. Following the national legislation, the data were anonymised before received.

3.2.3 Study population

The requested data were specified using criteria based on the characteristics of the databases and the targeted population. The general criteria for the selected subjects were all paediatric population under the age of 18 years covered by the corresponding social security of each region with one or more dispensations of a psychotropic medicine as defined in Table 15 below.

The Catalan study population consisted of all paediatric subjects under the age of 18 years covered by the Catalan social security system for each calendar year from 2008 to 2017 with one or more dispensations of psychotropics as per Table 15 below, except for the ATC group N06C as it was not identified by the time of the data request.

The Greek study population consisted of *EOPYY* beneficiaries and the uninsured population (unemployed and family members bearing social security number) that was entitled to pharmaceutical care between end of March 2016 and end of October 2019. All paediatric individuals under the age of 18 years registered to the Greek social security with one or more dispensations of a psychotropic medicine included in Table 15 were selected for the initial database and extracted by the corresponding authorities.

The medicines included in the study were the ATC groups mostly used in psychiatry (Table 15).(112) All these psychotropic medicines are included in the drug list reimbursed by the public systems in both regions. Among the selected ATC groups, we included also antiepileptics (N03A) as they are often used in patients suffering from a psychiatric disorder, for example as mood stabilisers.(113)

Since the largest exposure observed by far was due to the use of hydroxyzine, an antihistamine agent that has several short-term uses for the management of several conditions, including allergy and itching, we decided to remove subjects exposed to hydroxyzine only. Hence, the final target group of subjects exposed and analysed in the study was limited to subjects exposed to at least one psychotropic and with or without hydroxyzine.

Table 15. WHO ATC classification system codes included in this analysis.

ATC code	ATC name
N03A	Antiepileptics
N05A	Antipsychotics
N05B	Anxiolytics
N05C	Hypnotics and Sedatives
N06A	Antidepressants
N06B	Psychostimulants, agents used for ADHD and nootropics
N06C	Psycholeptics and psychoanaleptics combination
N07B	Drugs used in addictive disorders

***Source**: WHO Collaborating Centre for Drug Statistics Methodology* (112)

3.2.3.1 Reference study population

The most recent data of the inhabitant reference population that was used as the denominator in our analysis, derived from the official statistics institutes of both regions: the National Statistics Institute (*INE*) for the Catalan data and the Hellenic Statistical Authority (*ELSTAT*).(114,115) According to the methodology followed by both institutes, the last population census was in 2011 for both regions and therefore the reference populations were calculated based on the population determined in those censuses by adjustments to the concerned study years. These data were also described by age strata and year for each region.

3.2.4 Studied variables

3.2.4.1 Demographics

The demographic characteristics of the studied population was described, including analysis per age strata and sex. In the analysis of demographics per age strata, each subject was considered only once and entered in the age strata corresponding to the age that each subject had at the time of the first dispensed medicine.

3.2.4.2 Psychotropic use

In general, the psychotropic use was defined as the annual prevalence per 1,000 paediatric inhabitants of Catalonia and of Greece. Stratifications by sex and age groups in total and per year were also performed.

It was expected that in our settings the number of children with dispensations of only hydroxyzine (N05BB01) would be substantial, as this medicine is used often in allergies despite

pertaining in the group of anxiolytics; thus, a deeper analysis was performed to exclude those dispensations and focus further on a target group, where the prevalence of use was specified.

In addition, the prevalence of psychotropic use stratified by ATC group and sex, in total and per year, as well as per age strata/year were defined. The prevalence of the ten most frequently used medicines was also calculated for both regions' populations, as well as per sex and age strata/year.

3.2.4.3 Age definition

Concerning the selected age groups, the Catalan data provider (*AQuAS*) delivered the data with the age of the individual been determined as the age group on which each subject pertained at the time of the medicine dispensation and not the exact age due to anonymisation purposes. Therefore, the age groups remained unchanged as they are broad enough to draw conclusions easier when determining the off-label use based on the age to which each medicine is authorised.

Although the Greek database contained the exact age of the individual at the time of the medicine dispensation, we decided to merge the individuals in the same age groups as in the Catalan database, in order to permit comparison of the results in the two regions.

Thus, the age groups used in this analysis were defined as: <1 year, 1-2 years, 3-5 years, 6-8 years, 9-11 years, 12-14 years, and 15-17 years of age.

3.2.4.4 Diagnostics

As described earlier, the Catalan database does not contain diagnostic data. However, the Greek database in general contains diagnostic codes and connects each dispensed medicine with a specific ICD-10 code assigned by the physician.

Initially an analysis of the most frequent diagnostics was performed by the higher ICD-10 code. We then analysed the ICD-10 codes F01-F98 which are specific for the mental, behavioural, and neurodevelopmental disorders grouped as per the Table 16 below.(116) The five most frequently dispensed medicines for each group of ICD-10 codes described above were identified and defined by the number of patients (P) and dispensations (D), as well as the ratio D/P. The same was also calculated for the three most frequently dispensed medicines of the most frequent and relevant single ICD-10 codes.

Table 16. ICD-10 codes: mental, behavioural and neurodevelopmental disorders.

ICD-10* Codes	Diagnosis
F01-F09	Mental disorders due to known physiological conditions
F10-F19	Mental and behavioural disorders due to psychoactive substance use
F20-F29	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders
F30-F39	Mood [affective] disorders
F40-F48	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders
F50	Eating disorders
F51	Sleep disorders not due to a substance or known physiological condition
F55	Abuse of non-psychoactive substances
F60-69	Disorders of adult personality and behaviour
F90-F98	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence

**ICD-10: International Classification of Diseases, 10th revision*

3.2.4.5 Psychotropic off-label use

We used the information included in the product's labelling -SmPC- to determine the authorisation status of an active substance. A medicine was considered authorised in children if in section 4.1 of the SmPC there was an indication specified for any paediatric age group. In addition, a medicine was also considered authorised for children if there was a posology recommended for any paediatric population in section 4.2 of its SmPC, since this was the way in which the paediatric indications were expressed before 2009 when the SmPC guideline revision was fully implemented.

The official national sites of both regions as well as other sources were used to check first if the concerned active substances included in the ATC groups of Table 15 were in general authorised in each country using the available SmPCs. Every available SmPC was checked to confirm if a paediatric use was stipulated; to avoid overestimation, if more than one formulation or strengths with different information on the authorisation status were found in the region, the active substance was categorised as authorised in the paediatric population if at least one SmPC contained paediatric information as described above.

As a second step, we defined the age for which each active substance was authorised; to avoid overestimation if more than one age cut-off was included in the SmPCs of the different formulations or strengths, the lowest labelled age cut-off was selected for the concerned active substances, since the determination of the formulation was not possible in the data provided for the Catalan paediatric population. For the active substances with no recommendation for use in the paediatric population, we set the minimum age cut-off at 18 years.

Based on this compiled information, a sub-study for the three last years of the Catalan data and for the whole period in Greece was performed to define the off-label use. In case of doubt the same strategy was followed to avoid again overestimation. The shorter period for the Catalan data was selected to limit the cofounders by any changes in the SmPC. If a change in the age cut-off has happened in a year during the study period, this change was considered in the analysis.

The psychotropic off-label use was defined in number of patients and of dispensations, as well as the D/P ratio. Regarding the patient number receiving a medicine as off-label, two analyses were done: 1. each patient was considered only once, so if a patient was in the group ´authorised´, means that he/she did not have any medicine dispensed as off-label; and 2. each patient was considered more than once, depending on the status of each dispensation. The off-label dispensations were also determined in total and by sex, as well as by each year and sex.

For the common annual period between the two datasets, viz 2017, the off-label dispensations were also analysed by age strata and sex. Moreover, the most frequently off-label dispensed medicines were identified.

3.2.4.6 Other variables

Data on the use of health services and other variables that were initially planned to be analysed, were not provided with the Catalan data.

For Greece, data on the specialty of the physician and the region were included in the received data package, and so they were analysed as per the number of prescriptions and per sex.

3.2.5 Statistical analysis

The extracted data were reviewed for its quality and completion. The linkage of the data and their review was done by a person independent than the principal investigators' group. No extra action was done for the missing data.

Before the actual analysis, the duplicate cases were detected and deleted. The analysis of the study was descriptive. Categorical variables were described using frequencies and percentages; prevalence was specified as number by 1,000 inhabitants.

The statistical analysis was performed using the statistical package SAS v9.4 (SAS Institute, Cary, NC, USA).

3.2.6 Study approvals and ethical considerations

The study protocol for the Catalan part was authorised by the Medicines Investigation Ethical Committee of the Parc Taulí Hospital (Reference number: 2016672). No further authorisation

needed by the Spanish Agency of Medicines and Medical Products (*Agencia Española de Medicamentos y Productos Sanitarios* - *AEMPS*) according to the regulations for observational studies. Signed informs of patient consent were not needed as the used data were encoded and anonymous. The part of the study referring to Greece, was approved by the Bioethics Committee of the School of Medicine of the Aristotle University of Thessaloniki (protocol number: 2/2.3.2019), while permission for use of these anonymised data was obtained by the administration of *EOPYY* following the national legislation. For this type of observational studies, no further authorisation by the Greek National Medicines Agency (*Ethnikos Organismos Farmakon* - *EOF*) is needed.

In accordance with the current regulations, the design of this study is among those in which it is not possible or appropriate to make an individual evaluation of the causal relationship between the clinical events and the medicines of interest. For this reason, individual reporting of suspected adverse reactions was not necessary.

3.3 Funding

A part of the study was partially funded with grants by the *Generalitat de Catalunya* (grant number SLT006/17/216), which main objective was to map the use of psychotropic drugs in the paediatric population in Catalonia.

4 RESULTS

4.1 Systematic reviews

4.1.1 Systematic review on the prevalence of psychotropic drug use in the paediatric population worldwide

Flowchart 17 below demonstrates the selection procedure followed of the reviewed articles, resulting in the final selection of 76 retrospective observational studies for further analysis.(117–192)

All the selected studies for this systematic review, reported the prevalence of psychotropics in general or of specific ATC groups, i.e. antiepileptics (N03A), antipsychotics (N05A), anxiolytics (N05B), hypnotics/sedatives (N05C), antidepressants (N06A) or psychostimulants (N06B), used in the paediatric population. For the articles where the information was not given directly in the text but was presented only in figures, program DigitizeIt was used to extract the prevalence rates. In those cases where the extraction was not feasible, we contacted the authors to provide us with the missing data. For one of the studies, the author provided more data covering a longer period than the one in the original published study.(148)

The extracted information concerning the reported prevalence is detailed in Table 96 that can be found in Annex I, where the following data are included: year of publication, country, database, timeframe, type of psychotropics, age of subjects, prevalence rates and sub-analysis type. The timeframe of the published studies was from 2000 to 2020 indicating an increasing interest along the years with the peak in 2016 (8 studies), followed by 2015 and 2012 (7 studies). Figure 18 below presents the fluctuation of the publications' timeframe.

In addition, as it can be seen in Figure 19 below, the vast majority of psychotropics' (or subcategories) prevalence rates were studied in the USA, followed by the Netherlands and Germany, as well as the Nordic countries in Europe (mainly Norway). Reference to Spanish data was done only in 3 studies, 2 of which concerned regional data for Catalonia of the whole county and of one region (Lleida). No reference found for Greece. Figure 20 demonstrates the distribution of available data in the European territory.

Two studies reported seven different categories of medicines, but the majority reported only one category. Half of the studies reported the use of antidepressants (N06A) in the paediatric population, followed by psychostimulants (N06B), antipsychotics (N05A), hypnotics/sedatives (N05C), anxiolytics (N05B) and antiepileptics (N03A) in descended order; only ten out of seventy-six studies reported the prevalence on psychotropics in general. Apart from reporting the main prevalence rate in children, several sub analyses were also reported, and this is summarised also in the detailed table in Annex I (Table 96).

Flowchart 17. Summary of literature search review of previous studies reporting paediatric use of psychotropics.

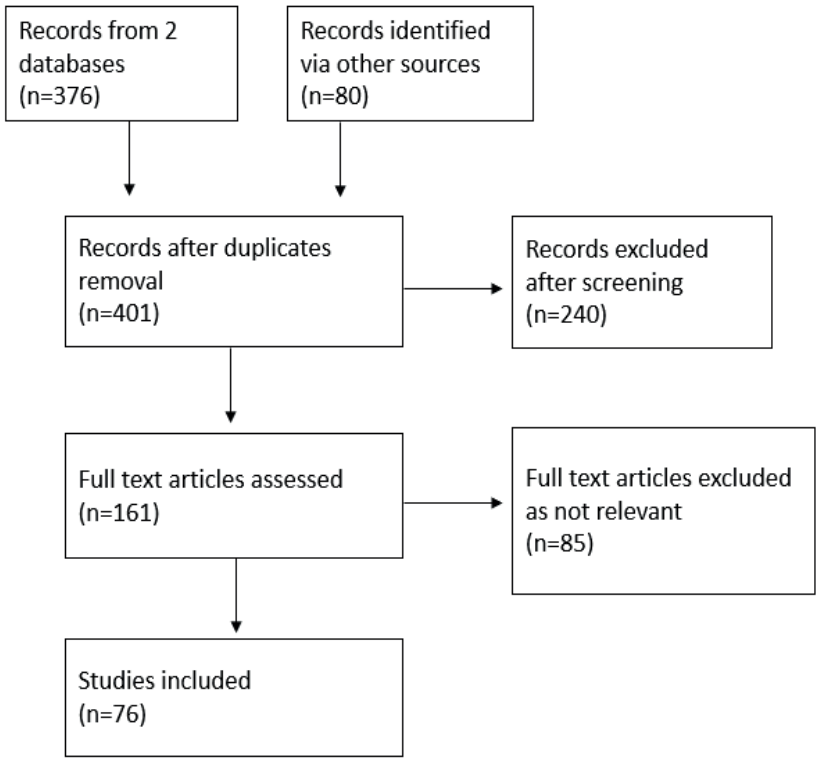


Figure 18. Studies reporting paediatric use of psychotropics per year of publication.

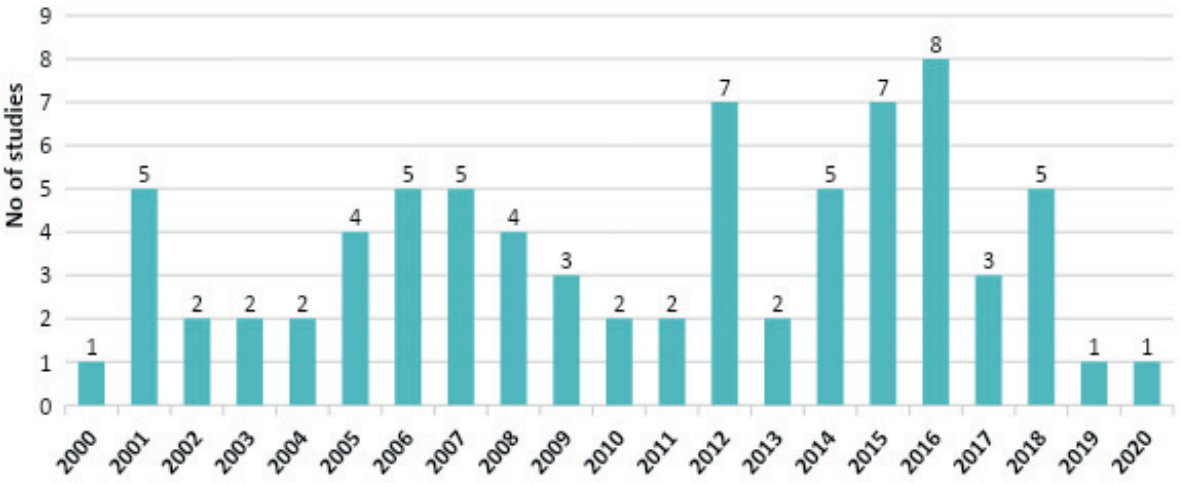
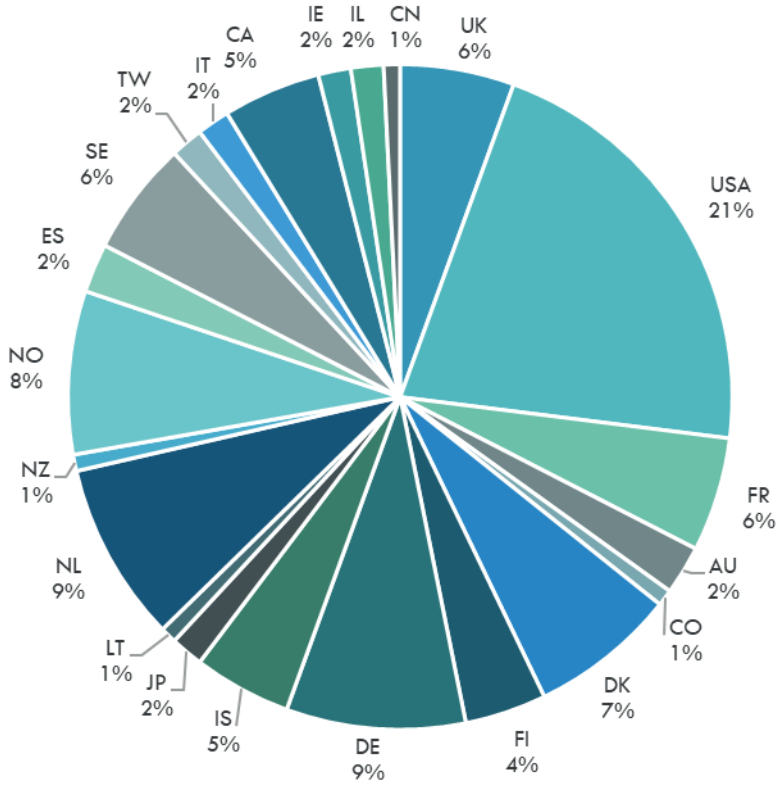


Figure 19. Countries reporting paediatric use of psychotropics in the selected studies (worldwide).



AU: Australia, CA: Canada, CN: China, CO: Colombia, DE: Germany, DK: Denmark, ES: Spain, FI: Finland, FR: France, IE: Ireland, IL: Israel, IS: Iceland, IT: Italy, JP: Japan, LT: Lithuania, NL: Netherlands, NO: Norway, NZ: New Zealand, SE: Sweden, TW: Taiwan, UK: United Kingdom, USA: United States of America

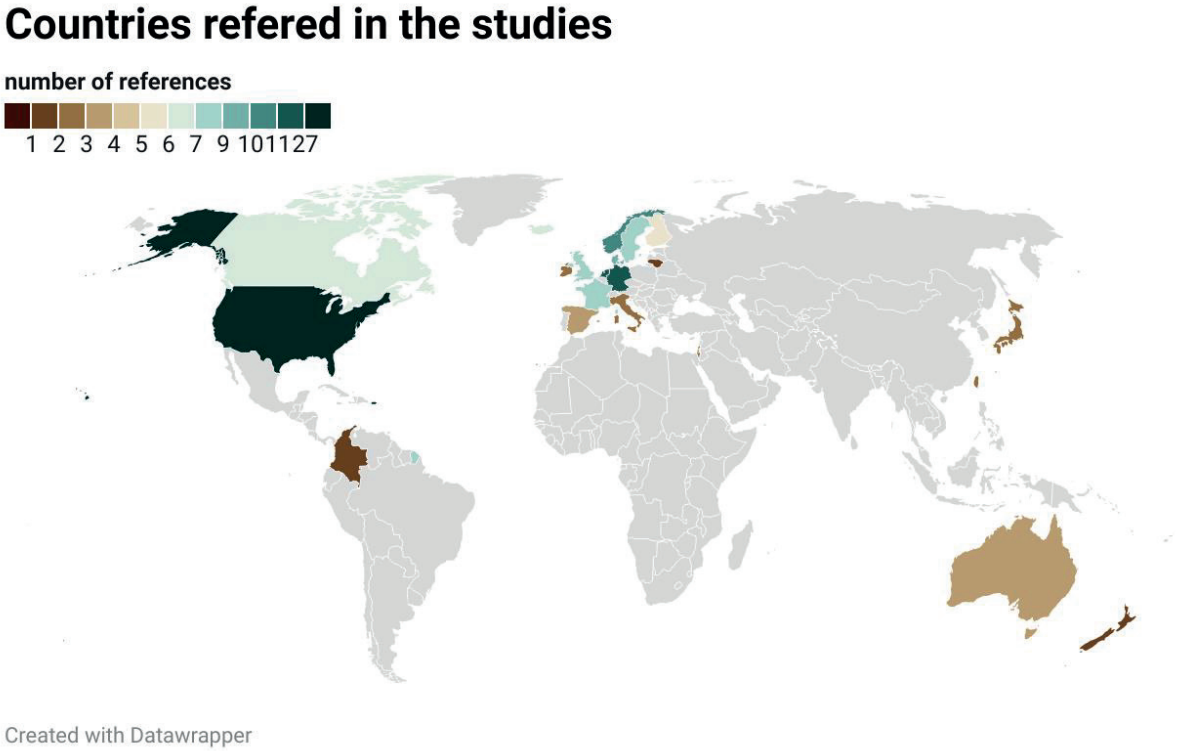
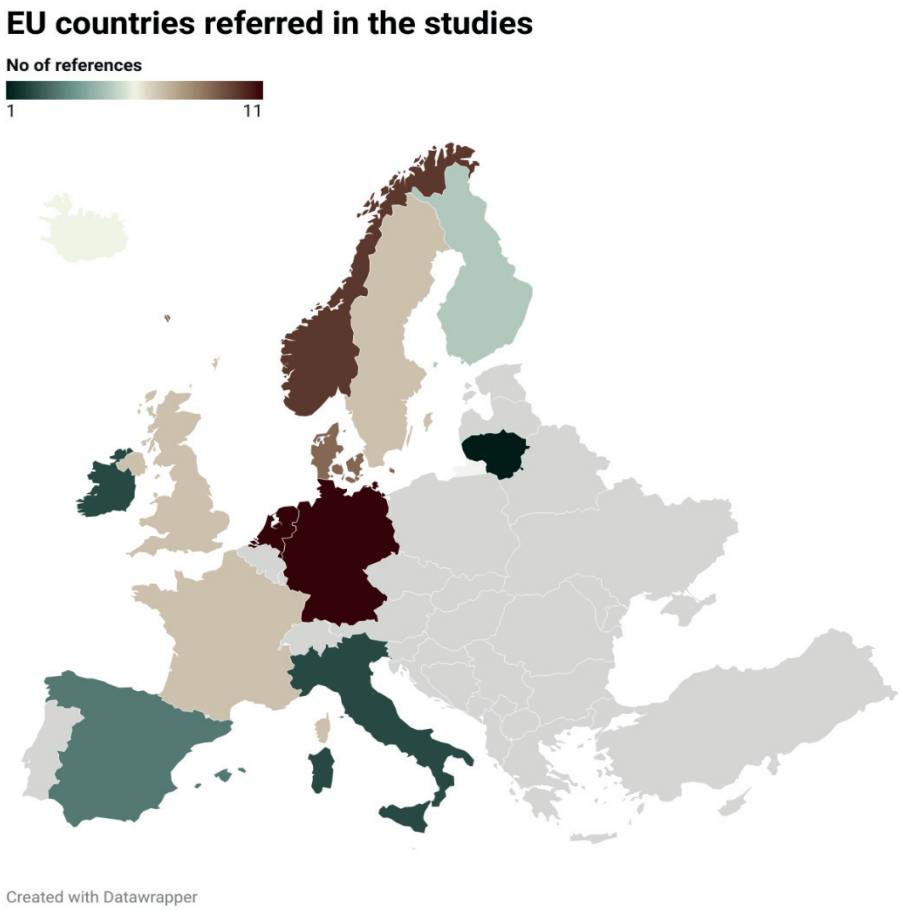


Figure 20. Countries reporting paediatric use of psychotropics in the selected studies (EU).



The prevalence of use of psychotropics in the USA was firstly reported by *Zito el al.* for the period 1987-1996 and fluctuated between 18.40-62.60 per 1,000 for the youths below 20 years of age (180), and since then the reported prevalence was increased depending on the source of data and the reported age group [0-19 years: 6.66% (2000); 1-17 years: 4.30(1998)-5.30%(1999), 0-17 years: 3.50-4.50%(2000); 6-17 years: 5.50(1996-1998)-8.90%(2010-2012); 2-4 years: 2.30% (2001)].(137,163,164,178) As regards Europe, it seems that countries in the north part reported higher prevalence. The reported prevalence was 2.00% in Germany and 2.94% in the Netherlands for the paediatric population 0-19 years old in 2000 (163), while in Iceland it fluctuated between 4.60-4.87% for the group 0-17 years of age in the period 2003-2007.(159) In Italy, the psychotropic use was lower and varied between 1.70% and 1.81% (2010 and 2009 respectively) for the population below 18 years of age (133), while in France it was 2.50% in 2010.(134) The prevalence for the Norwegian population between 0-17 years of age was reported only by sex and was between 30.60-37.00 (2004 and 2010 respectively) per 1,000 boys and 19.00-25.00 (2005 and 2014 respectively) per 1,000 girls, whereas for the 15-16year-olds for the period 2006-2010 it was between 13.90-21.50 per 1,000 boys and 19.70-24.70 per 1,000 girls respectively.(131,152)

Anticonvulsants'/antiepileptics' prevalence for the USA population aged ≤20 years varied depending on the data setting between 1.10-12.80 per 1,000 in the period 1987-1996, while in 2000 it was 2.00% for the ≤18year-olds and decreased into 0.77% for the ≤19year-olds using a different database (163,169); in the period 1994-2003 the prevalence was between 3.52-6.96 for the group of 5-17 years of age, whereas in 2001 it was 0.30% for children aged 2-4 years.(164,176,180) The prevalence for the group ≤18 years of age in the United Kingdom (UK) was between 7.30-8.69 per 1,000 in the period 1993-2005 (166), while *Hsia et al.* reported the rates only by age group for the period 1992-2001 (157), same as the reported data for the Danish youths aged ≤24 years in 1998.(187) In 2000, 0.38% of German population aged ≤19 years used antiepileptics, while for their Dutch peers it was 0.37% that slightly increased (4.00 per 1,000) in the study of *Van de Vrie-Hoekstra et al.* covering the period 1997-2005.(160,163) The most recent data came from Sweden, where 22,260 ≤17year-olds were exposed to antiepileptics with the prevalence varying by age and fluctuating between 2.22-6.35 per 1,000 in the ≤5year-olds and adolescents respectively.(122)

In the USA, antipsychotic rates for the ≤19year-olds were of 1.50 per 1,000 in 1996 (private), 0.76% in 2000, 15.50 per 1,000 (2001, southern), 20.50 per 1,000 in 2010 and 7.30 per 1,000 in 2014; in addition, other studies showed that the rates were between 0.20% in 1996-1998 and 1.20% in 2010-2012 that also changed depending on the age group and the setting [e.g. 2-4 years: 0.40% in 2001, 0.10 per 1,000 in 1991 and 1993 (HMO), 0.90 in 1995 per 1,000 (Medicaid, midwestern)].(124,137,138,163,164,177,180,183,189) In Italy, the antipsychotic use was of 0.60-0.69% in 2006 and in 2011 respectively concerning the ≤18year-olds.(133) In Canada, the use was increased with the time, fluctuating from 1.66 per 1,000 in 1996-1997 to 6.37 per 1,000 in 2010-2011 for the population ≤18 years of age, with boys been more exposed than girls during the period 1999-2008.(145,150) In Germany, different studies reported similar ranges, (0.34% in 2000, 0,21-0,32% in 2006-2012 and 3.40 per 1,000 in 2014) for the population ≤19year-olds, while one study reported that the prevalence for the ≤17year-olds was also similar (2.03 per 1,000 in 2006 and 2.61 per 1,000 in 2011).(124,127,141,163) Antipsychotics' prevalence in France was 0.30% for 0-17 years in 2010, with a similar number reported in 2014 for ≤19year-olds (3.80 per 1,000); *Montastruc et al.* reported that the prevalence for the population aged ≤16 years was between 1.80-2.50% (2007-2013), while *Verdoux et al.* reported the antipsychotic use in the youths ≤25 years to be between 4.55 per 1,000 in 2008 and 4.94 per 1,000 in 2009.(119,124,134,136) In Iceland, the antipsychotics' prevalence of use was higher and fluctuated between 8.70-10.60 per 1,000 in 2003-2007 for the population ≤17 years of age, which went up to 13.10 per 1,000 in 2014 for the ≤19year-olds.(124,159) Dutch population aged ≤19 years was reported also to be exposed to antipsychotics with an increasing rate over the years: in 1997 it was reported as 3.00 per 1,000,

0.51% in 2000, 6.80 or 7.20 per 1,000 in 2005 depending on the study, 9.80 per 1,000 in 2009 and finally 8.90 per 1,000 in 2014.(121,124,161,163,184) In Norway, the prevalence was of 0.18% in 2010 for the ≤18year-olds that went up to 2.70 per 1,000 in 2014 for the group aged ≤19 years; boys ≤17year-olds were more exposed than their female peers according to *Hartz et al*.(124,129,131) In the UK, the reported rate was between 0.39 per 1,000 in 1992 and 0.77 per 1,000 in 2005 for the ≤18year-olds, rates that also fluctuated by different age groups (0-2 years: 0.07 per 1,000 in 1998 for the ≤2year-olds and 3.15 in 2001 per 1,000 for the 16-18year-olds).(157,162) *Hálfdánarson et al.* reported that the prevalence of antipsychotics in Australian ≤19year-olds in 2014 was 3.80 per 1,000 similar to their Japanese (3.20 per 1,000) and Danish (4.00 per 1,000) peers, while it was lower in Lithuania (0.50 per 1,000), Colombia (1.30 per 1,000) and Sweden (2.50 per 1,000), and higher in New Zealand (5.00 per 1,000), Spain (6.60 per 1,000), Finland (8.00 per 1,000) and Taiwan (30.80 per 1,000 in 2013).(124)

Concerning the use of anxiolytics and hypnotics/sedatives, some studies reported the prevalence for these two groups together and it fluctuated for the ≤19year-olds in the Netherlands between 5.40 and 6.90 per 1,000 in the period 1995-1999, while in Iceland it was 1.40% during the period 2009-2012.(130,184) In France, 2.00% of the ≤17year-olds were exposed to these groups in 2010.(134) In the USA, data covering two different periods revealed that there was a slight increase in their use by children aged 6-17 years (0.30% in 1996-1998 and 0.50% in 2010-2012), while in 2001 0.30% of 2-4year-olds were exposed to these groups. (137,164) Data from the UK are available only by age group for the period 1992-2001, where adolescents found to be more exposed (13-15 years: 1.71-2.95 per 1,000; 16-18 years: 5.17-8.33 per 1,000).(157)

However, other studies reported the prevalence of these two groups separately. The prevalence of anxiolytics in the USA for the <20year-olds was 1.00-6.20 per 1,000 both rates observed in 1987 but in different settings, whereas in 2000 it was reported as of 0.49% for the ≤19year-olds. The same year and for the latter age group, the reported prevalence was 0.41% in Germany and 0.73% in the Netherlands.(163,180) In Iceland, the highest and lowest rate of anxiolytics' prevalence in the ≤17year-olds were observed in two consecutive years in the study investigating their use for the period 2003-2007 (1.50-2.00 per 1,000 in 2005 and in 2006 respectively).(159) In 2010, 1.92% of the French ≤17year-olds used anxiolytics; earlier than that, another study also showed a lower rate but only for the adolescents.(134,170) On the other hand, for Norway the only available data for the use of anxiolytics were by sex, with a similar rate observed in the whole paediatric population during 2004-2013, but adolescent girls (3.40-3.70 per 1,000) were more exposed than boys (2.30 per 1,000) in the studied period 2006-2010.(131,152)

For the use of hypnotics/sedatives, data are available for the same countries as described above for the anxiolytics, however the rates are different. In the USA, between 1987-1996, 0.28 (in 1987)-3.70 (in 1991) per 1,000 <20year-olds were exposed to this group of medicines, rates that were dependent on the setting (180); this rate decreased to 0.16% in 2000, while the same study reported that 0.09% of German and 0.33% of Dutch peers used hypnotics/sedatives.(163) Hypnotics/sedatives were present also in the paediatric population of Iceland, with a reported rate of 0.70-2.60 per 1,000 for the period 2003-2007.(159) Data from France revealed that the prevalence was 0.08% in 2010 (134), with adolescents been more exposed to hypnotics in 2002 (20.10 per 1,000) than to anxiolytics.(170) A study in 2004-2011 reported that the prevalence in the Norwegian paediatric population was between 8.94-12.32 per 1,000 and other studies provided only the rate by sex.(131,149,152)

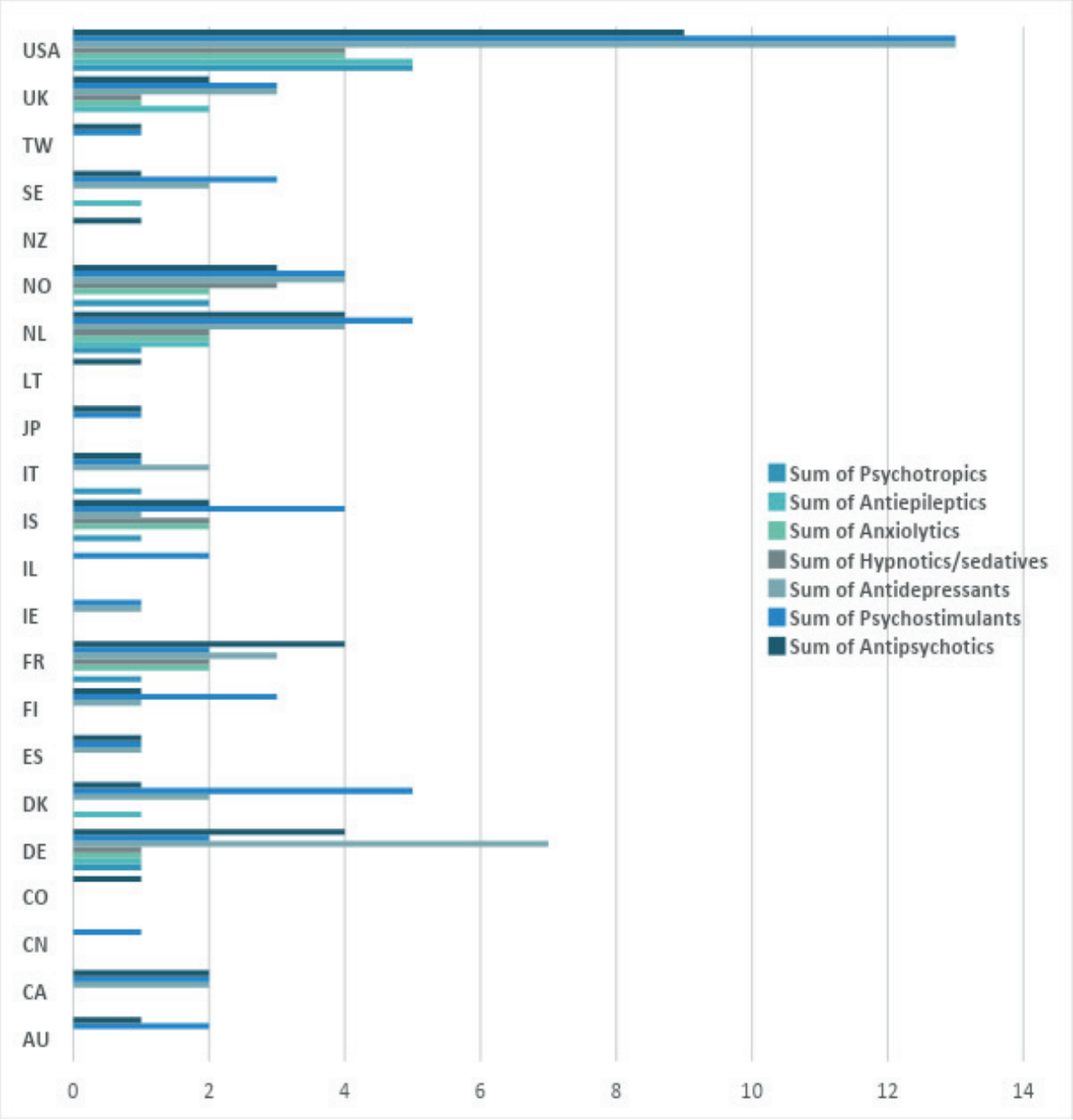
Antidepressants use was the most frequently reported subgroup of psychotropics and data for fourteen countries were reported in the selected studies. In the USA, the prevalence for the population aged <20 years was initially reported for the period 1987-1996 and varied depending on the setting from 1.90 to 20.5 per 1,000 (180); in 2000 the use of antidepressants was 2.71% while it dropped further in the period 2006-2012 (1.26-1.58%) for the same age group.(163,192) In other studies, the subjects pertained in the group ≤18 year of age, had a prevalence with the lowest rate in 1998 (1.1-1.59%) and the highest in 2002 (1.8-2.37%) (171,179); *Zito et al.* reported that the prevalence for the 2-19year-olds was 3.90-19.10 per 1,000 in the period 1988-1994, while different rates reported by *Olfson et al.* (6-17 years: 1.44-2.56% in 1996-2005) and by *Hunkeler et al.* (5-17 years: 9.68-21.30 per 1,000 in 1994-2003).(158,176,182) Three studies did not report the prevalence of antidepressants in the entire paediatric population, but only in age subgroups.(137,140,164) Canadian ≤18year-olds were exposed to antidepressants with rates of 5.10-15.40 per 1,000 during 1989-2007 and 4.50(1995)-10.70(2003) per 1,000 during 1995-2003.(143,165) In Europe now, the prevalence in Denmark was of 0.61-1.09% (2005-2010) for ≤19year-olds, whereas according to *Wesselhoeft et al.* the rate was of 7.52-12.86 per 1,000 in the group 5-19 years of age.(117,192) Three studies reported similar numbers for the prevalence of antidepressants in the German paediatric population aged ≤19 years (0.31-0.48% in the period 2005-2012, 3.37-3.74 per 1,000 in 2001-2003), whereas according to *Zito et al.* the rate was 0.17% in 2000; two studies reported the prevalence in the group of ≤17year-olds (1,57-1,84 per 1,000 for the period 2004-2006; 1.65-2.13 per 1,000 in 2005 and 2011 respectively), while *Ufer et al.* provided the prevalence data only per sex.(126,144,163,168,173,192) In Sweden, the prevalence for the youth aged ≤24 years was 1.40-2.10% and in a second study covering the period 2007-2017, the rate was of 8.98-18.03 per 1,000 (2017) for the 5-17year-olds.(117,118) The Norwegian 5-19year-olds were also exposed to antidepressants (5.08-7.60 per 1,000 during 2007-2017), and three studies reported

the rates only per sex and per smaller age groups, with adolescents having a higher exposure.(117,128,131,152) For the ≤19year-olds the prevalence was of 2,23-5,93 per 1,000 (1998-2005) in Finland (155), while in the Netherlands it was initially reported as of 3.80-4.70 per 1,000 in 1995-1998, later as 0.53% in 2000 and reached 0.48-0.60% in 2006-2012 (163,184,192); however, *Volkers et al.* reported that the prevalence for the group was 2.30 per 1,000 in 2001 and 2.00 per 1,000 in 2005.(167) In Iceland, the rates were the highest reported ones and varied between 23.40 and 28.30 per 1,000 (2003-2007) for the population aged ≤17 years.(159) In the UK, the studies reported different rates as the age groups included were not the same: 2.80-4.50 per 1,000 (1995-2009) and 0.66-1.05% (2006-2012), while the third study reported the prevalence per age subgroups only.(151,157,192) Similar data reported for the Irish patients aged ≤17 years, with the lowest rate in 2008 (2.61 per 1,000) and the highest in 2002 (4.74 per 1,000).(139) Concerning the southern part of Europe, data are available in France, Italy and Spain. 0.30% of French ≤17year-olds had been exposed to antidepressants in 2010, while previous study reported the prevalence of adolescents as 7.70 per 1,000 (134,170); according to *Revet et al.* the rate was around 0.50% of 6-17year-olds for the period 2009-2016.(120) The Italian paediatric population had a prevalence of 1.02-1.26% (2011 and 2006 respectively), whereas the rate for the ≤15year-olds was defined as 0.27 per 1,000 in a period of six months in 2000.(133,186) Finally, the only Spanish data on antidepressant use were reported by *Serna et al.* for the period 2002-2007, providing them as per age groups: 0.31-0.42% for ≤14year-olds and 2.32-2.74% for the 15-24year-olds.(156)

Psychostimulants and medicines used for ADHD were also reported in several studies, most of which coming from USA. The prevalence in the USA depended again on the setting and was between 3.60-38.40 per 1,000 for the population aged <20 years during 1987-1996, whereas in 2000 it was higher (4.29%).(163) Another study reported that this rate was 4.00% in 1996-1998 and 6.60% in 2010-2012 concerning the 6-17year-olds demonstrating a higher use with the years, but lower rates for the total paediatric population (137,147); for the group 2-4year-olds the use of stimulants was among 1.70 and 12.30 per 1,000 depending on the setting for the period 1991-1995, while in 2001 it was higher (1.50%).(189) In the Netherlands, lower rates were reported in the group of ≤19year-olds for approximately the same timeframe (1.50-7.40 per 1,000); in 2000 it was raised up to 1.18% and increased a bit more the following years. For their German peers the rate was lower in 2000, increased in the period 2005-2012 (1.30-2.20%), but was lower than the one observed in Denmark (0.40-1.50%) even in later studies considering the additional data provided by the author for 2018.(148,163,190) The exposure in the UK was lower reaching down to 0.30-0.50% for the period 2005-2012, and it seems that in previous years UK children older than 6 years of age used more stimulants than younger children.(190) Irish children aged less than 15 years had a prevalence of up to 8.63 per 1,000 in

2011.(135) Prevalence rates regarding the group <18 years of age, were also reported for France (0.20%), Iceland (21.70-28.40 per 1,000 in 2003-2007) and Italy (0.01% in 2006 and 0.19% in 2011).(133,134) In Norway, data only per sex were reported with boys been a lot more exposed than girls in the period 2004-2013; *Furu et al.* and *Zoëga et al.* presented the exposure data in several countries in the north of Europe for the adolescent groups which seem that older adolescents use less psychotropics.(125,159) Finally, in Australia, the prevalence of psychostimulants was of 1.24% in 2010 in children aged 5-17 years.(142) The distribution of the different psychotropic rates per country is presented in the following figure (Figure 21).

Figure 21. Psychotropic groups reported in the selected studies per country.



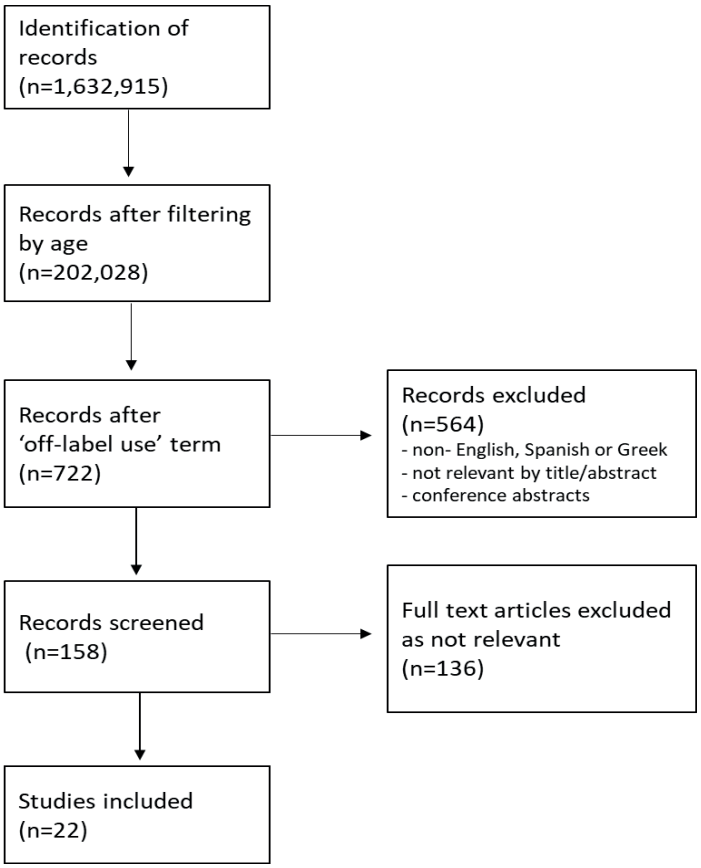
4.1.2 Systematic review on the off-label use of psychotropics in the paediatric population

With the search strategy for investigating the off-label use of psychotropics in the paediatric population (see Annex I), we initially retrieved 1,632,915 articles. After filtering the articles by age aiming to include only the paediatric relevant age groups, 202,028 articles remained. The search strategy string was then combined with a second one containing the term 'off-label use' and the proposed by the tool synonyms (i.e. *'off-label drug use'/exp OR 'off-label drug' OR 'off-label drug use' OR 'off-label prescribing' OR 'off-label prescription' OR 'off-label use' OR 'off-label use'*) and eventually 722 articles remained for further analysis. We excluded 45 articles because the language of the article was different than English, Spanish or Greek, and 475 were excluded as not relevant by the title and/or the abstract (e.g. study type not similar to the current one, duplicates, different disease, population or medicines, no reference to the off-label use). From the remaining 202, 44 were conference abstracts and therefore were excluded and 158 articles were further analysed by reading the full text. Finally, 22 articles were selected containing data relevant to the off-label use of psychotropics in paediatric outpatients (120,126,127,144,159,193–209), one of which referred to the use of antidepressants in Spain (194) but no relevant data for Greece. The following flowchart shows the process followed for the selection of the articles (see Flowchart 22) and a summary of the selected articles can be found in Table 97 in Annex I.

The studies, with all details in Table 97 in Annex I, describe different rates of off-label use and ATC groups, and they were published between 2003 and 2022. The data pool dates were different with a mean of 6.30 years (minimum 1 year, maximum of 22 years) and the last date or period included data up to 2018. Most of the studies presented the off-label use as prescriptions (or dispensed prescriptions) (54.50%), less than one third provided data on off-label use as users and prescriptions (or dispensed prescriptions) and a minority of them (18.20%) presented the data only as users of off-label medicines. Five of the selected articles contained off-label use data for more than one ATC group of psychotropics.(159,193,201,208,209) One article was dedicated only to melatonin where 3.40 to 11.00 prescriptions per 1,000 inhabitant boys and 1.50 to 7.70 prescriptions per 1,000 inhabitant girls were off-label (203), while two articles provided relevant off-label use data only for some medicines: topiramate and levetiracetam (anticonvulsants) (206), as well as for nortriptyline and escitalopram (antidepressants).(207) From the remaining selected studies, the majority of them refers only to the use of antidepressants (120,126,144,192,194,198,200,204,205), followed by antipsychotics (127,195,197,198,209) and two of them refer only to ADHD medication.(196,202) From the selected studies, half included all paediatric population (126,127,144,159,193,196–

199,201,207); the remainder included some paediatric age groups and two of them included data on young adults too, both of which conducted in the.(195,205) Finally, seven studies referred to German data, two to French children and two to Australian; for the remaining studies of one-country dataset, the data were mostly from European countries (Estonia, Denmark, Iceland, Netherlands, Norway, Spain and UK) and only two refer to East Asian territories (Japan and Korea). The age was the main criterion defining the off-label use in most of the studies, and for some of them, the indication was the second most frequent criterion.

Flowchart 22. Summary of literature search review of previous studies reporting paediatric off-label use of psychotropics.



Zoëga et al. study was the only one reporting the off-label prescriptions considering all psychotropics (24.60% in 2007) but also the unlicenced psychotropic prescriptions (0.60% in 2007).(159) Antidepressant off-label use was the most frequently reported psychotropic. Spanish children received 15.00-40.00% antidepressant off-label prescriptions, with the percentage to be increased with the age.(194) Data were also found for the off-label antidepressant prescriptions in the Netherlands (58.00%), Iceland (41.80%), and USA (>70.00%).(159,205,208) In Germany extensive studies revealed that, 58.00% of children received 52.66% or 64.20% prescriptions off-label in 2004, whereas this number dropped to 40.90% children with 36.30% of prescriptions in 2011; the numbers are changing depending on

the criterion defining the off-label use in 2011: 29.10% by age (reaching up to 80.50% for the group 12-17 years old and drops to 2.10% for <6 years of age), 15.30% by indication (up to 26.60% for hyperkinetic disorder) and 3.30% by contraindication.(126,144,198) In France, the data were presented as prevalence that fluctuated between 41.50% (2009) and 33.90% (2016) of children, and differentiated depending on the age: 48.40% (2009) and 34.80% (2016) for the 12-17year-old group, and 10.00% (2009) and 26.50% (2016) for children aged 6-11 years.(120) The Australian paediatric population below 5 years of age received all antidepressants as off-label prescriptions, whereas the number dropped to 74.40% for 6-11year-old group and 71.80% for the adolescents.(193) In Denmark, 94.60% of prescriptions were off-label, 98.40% when the criterion was the age and 1.50% when it was the indication.(201) Similarly, 95.00% of prescriptions were off-label in Korea which also differed depending on the indication: 72.30% in OCD treatment, 14.40% in enuresis treatment and 100.00% in all the other diagnoses (including depressive disorder).(200)

Antipsychotic off-label prescriptions were the second most frequently reported group of psychotropics and reported in similar numbers in the Netherlands (59.80%) and Iceland (52.00%).(159,208) In Germany the numbers were higher revealing initially an increase on the off-label prescriptions since 2004 (61.00%) up to a 69.50% in 2009, and then went down to 62.00% in 2011, corresponding to 52.30%, 71.10% and 62.70% of children respectively.(127,199) An increase was also observed in the USA from 44.40% to 47.30% in a five-year period (2014 and 2018 respectively).(195) According to Australian data, the off-label prescriptions were more than 99.00% for all age groups below 11 years of age, while 55.90% of medicines were prescribed as off-label to adolescents.(193) In France, the data were reported as prevalence and fluctuated between 7.90% (observed in 2009) and 16.10% (observed in 2007).(197)

Concerning the off-label use of hypnotics and sedatives, the reported percentages of off-label prescriptions were 83.50% in the Netherlands and 95.30% in Iceland, while in Denmark it was increased from 94.60% to 98.40% when the off-label criterion was the age (by indication: 1.50%).(159,201,208) Off-label anxiolytics' prescriptions were reported in the Dutch and Icelandic paediatric populations (16.80% and 10.40% respectively), while in Australia the percentage varied between 4.70% and 27.80% depending on the age (<1 year and 1-5 years respectively).(159,193,208) Antiepileptic data were reported only in Australian children, where the off-label prescriptions were between 1.60% (12-17 years) and 70.80% (<1 year), and separate data were available for the off-label use of topiramate (4.20%) and levetiracetam (3.60%).(206)

Stimulants/ADHD medication prescriptions were reported as off-label in the Netherlands (5.00%) and Iceland (1.20%); in Australia it was of 100.00% for the population aged 1-5 years and dropped to 0.10% in the group of 12-17 years.(159,193,208) In addition, data from the UK revealed that 4.00% of children below 6 years of age received an off-label ADHD medication, while the number of children in Germany was 12.70% and differentiated depending on the diagnosis while dropped to 1.20% in children below 6 years of age.(196,202)

Considering all the above, it is clear that broad studies on the off-label use of psychotropics is extremely limited, and the studied periods are mostly repeated, as we could see for the German data.

4.2 Retrospective observational population-based quantitative and qualitative study

4.2.1 Description of the reference and study populations

4.2.1.1 Reference populations

The average number of the paediatric inhabitants during the study period for each country was of 1,365,750 inhabitants in the region of Catalonia (from 2008 to 2017) and 1,872,219 in Greece (from 2016 to 2019), with the highest number observed in 2017 for both regions. Detailed data on the number of inhabitants per study year is given in the table below (Table 23). Data were retrieved from the official national statistic services of both regions: the National Statistics Institute of Spain and the Hellenic Statistical Authority.(114,115)

As regards the age distribution of the paediatric inhabitants in both regions, detailed information is provided in the following table (Table 24). The distribution of the paediatric population per age group was approximately the same in both regions with the lowest percentage been observed in the age group of children below 1 year old (≈5.00-6.00%) for both regions, and the highest percentage in the group from 3 to 5 years of age (18.00%) and 9 to 11 years of age (17.40%), respectively for Catalonia and Greece. Concerning the paediatric distribution per age and sex, girls roughly representing less of half of the population in all age groups and in both regions.

A comparison of the age strata is also presented in the figure below (Figure 25). Based on these observations, both paediatric populations were quite similar. In fact, there were less than ≈2.00% differences in representativeness by age and sex strata, and these differences observed only in some cases.

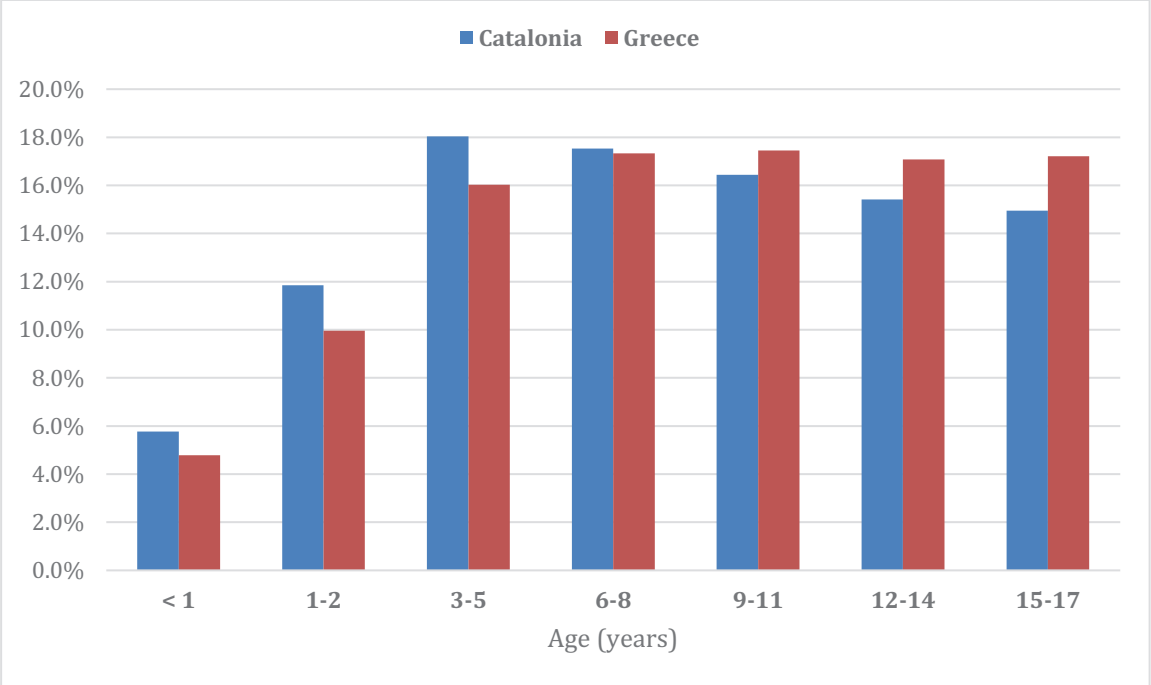
Table 23. Reference population for Catatonia (Spain) and Greece by year of study.

Year	Catalonia (Spain)	Greece
2008	1,281,777	-
2009	1,322,462	-
2010	1,346,516	-
2011	1,367,382	-
2012	1,384,978	-
2013	1,389,763	-
2014	1,386,458	-
2015	1,388,261	-
2016	1,391,507	1,876,718
2017	1,398,400	1,878,388
2018	-	1,872,031
2019	-	1,861,740
Average	***1,365,750***	***1,872,219***

Table 24. Description of the average reference population for Catatonia (Spain) and Greece by age strata.

	Catalonia (Spain)			Greece		
Age (in years)	**n**	**Stratum (%)**	**Girls/Stratum (%)**	**n**	**Stratum (%)**	**Girls/Stratum (%)**
< 1	78,815	5.57	48.30	89,580	4.80	48.50
1-2	161,773	11.84	48.30	186,494	10.00	48.60
3-5	246,395	18.00	48.30	300,011	16.00	48.60
6-8	239,352	17.50	48.40	324,369	17.30	48.70
9-11	224,624	16.40	48.50	326,616	17.40	48.70
12-14	210,561	15.40	48.40	319,850	17.10	48.60
15-17	204,231	15.00	48.20	322,310	17.20	48.60
<1-17		***100.00***	***48.40***		***100.00***	***48.60***

Figure 25. Comparison of age strata profiles for the Catalan (Spanish) and Greek reference populations.



In the following table (Table 26), the reference populations from both regions were analysed by age group and year of the study, presenting similarities in the distribution for the two study years in common (2016-2017). Catalonia's paediatric population was mostly represented by the group aged 3-5 years up to 2014, with the highest number observed in 2012 (259,109 paediatric inhabitants), and then the 6-8 years of age group was the most represented from 2015 to 2018. In Greece, from 2016 to 2018, the 6-8 years of age group was also in the first place, with the highest number been in 2017 (334,701 paediatric inhabitants), while the group from 9 to 11 years of age was the one mostly represented in 2019 with a slight smaller number of inhabitants, viz 334,187 paediatric inhabitants.

4.2.1.2 Study populations

During the study period (2008-2017) 449,196 subjects with at least one psychotropic medicine dispensed from the Catalan health reimbursement system were identified in the region of Catalonia; 137 patients were excluded as they were registered with a double sex, and therefore our initial sample was finally of 449,059 paediatric subjects. In Greece, no duplicates were identified and therefore the study population was of 63,782 subjects with at least one psychotropic dispensed from the Greek health reimbursement system for the study period (March 2016 to October 2019).

Table 26. Reference population description for Catalonia (Spain) and Greece by age stratum and year.

Catalonia (Spain)												
Age (years)	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
< 1	84,704	89,492	85,202	84,855	83,178	77,379	71,695	71,699	70,733	69,209	-	-
1-2	166,354	170,120	175,179	174,501	169,500	166,541	158,646	148,462	144,040	144,391	-	-
3-5	**232,715**	**242,585**	**248,705**	**253,238**	**259,109**	**257,027**	**253,642**	246,332	240,273	230,319	-	-
6-8	212,492	220,170	226,538	235,060	242,899	247,898	249,777	**254,292**	**252,728**	**251,663**	**-**	**-**
9-11	195,694	204,348	211,185	217,675	222,499	226,538	233,022	240,090	245,734	249,459	-	-
12-14	191,431	194,828	198,702	202,702	208,011	212,809	216,792	220,482	225,616	234,240	-	-
15-17	198,387	200,919	201,005	199,351	199,782	201,571	202,884	206,904	212,383	219,119	-	-
Total	***1,281,777***	***1,322,462***	***1,346,516***	***1,367,382***	***1,384,978***	***1,389,763***	***1,386,458***	***1,388,261***	***1,391,507***	***1,398,400***	**-**	**-**
Greece												
Age (years)	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
< 1	-	-	-	-	-	-	-	-	91,603	93,927	89,570	87,557
1-2	-	-	-	-	-	-	-	-	184,887	186,308	190,011	188,101
3-5	-	-	-	-	-	-	-	-	312,295	300,496	291,636	287,727
6-8	-	-	-	-	-	-	-	-	**331,628**	**334,701**	**329,067**	317,109
9-11	-	-	-	-	-	-	-	-	319,044	322,253	328,581	**334,187**
12-14	-	-	-	-	-	-	-	-	317,306	316,984	317,802	322,394
15-17	-	-	-	-	-	-	-	-	319,955	323,719	325,364	324,665
Total	-	-	-	-	-	-	-	-	***1,876,718***	***1,878,388***	***1,872,031***	***1,861,740***

In both settings, the first analysis revealed that there was a high number of study subjects receiving only hydroxyzine following a similar trend (68.30% in Catalonia and 66.60% in Greece) with the girls to be more exposed than the boys. Hydroxyzine is an active substance that, even though belongs in the group of anxiolytics, it is mostly used as antihistamine/antiallergic treatment. In our settings, the majority of children with 'hydroxyzine only exposure' belongs to the age subsets below 8 years old which are the groups of patients generally characterised by high percentage of allergic manifestations.(210) Hence, when the hydroxyzine-only dispensations were removed from the overall sample, the group was more homogeneous and representative concerning the use of psychotropics.

The final target group of our study consisted of 142,383 Catalan and 21,274 Greek paediatric study subjects exposed to at least one psychotropic and with or without hydroxyzine. When removing hydroxyzine-only subjects, the target population group representation by sex changed also in both settings, with boys been more represented than girls. Concerning the description of the population by age group, it seems that more than half of the Catalan subjects pertained in the adolescent group (12-17 years of age), the majority of which were girls (60.80%). Similar observation was done in the Greek target population with 27.70% pertained in the group of 15-17 years of age, mostly girls, but in this setting the group of younger children (1-5 years of age) was more than double than the one observed in Catalonia (26.70% vs 12.40% respectively). More details can be found in Table 27 below.

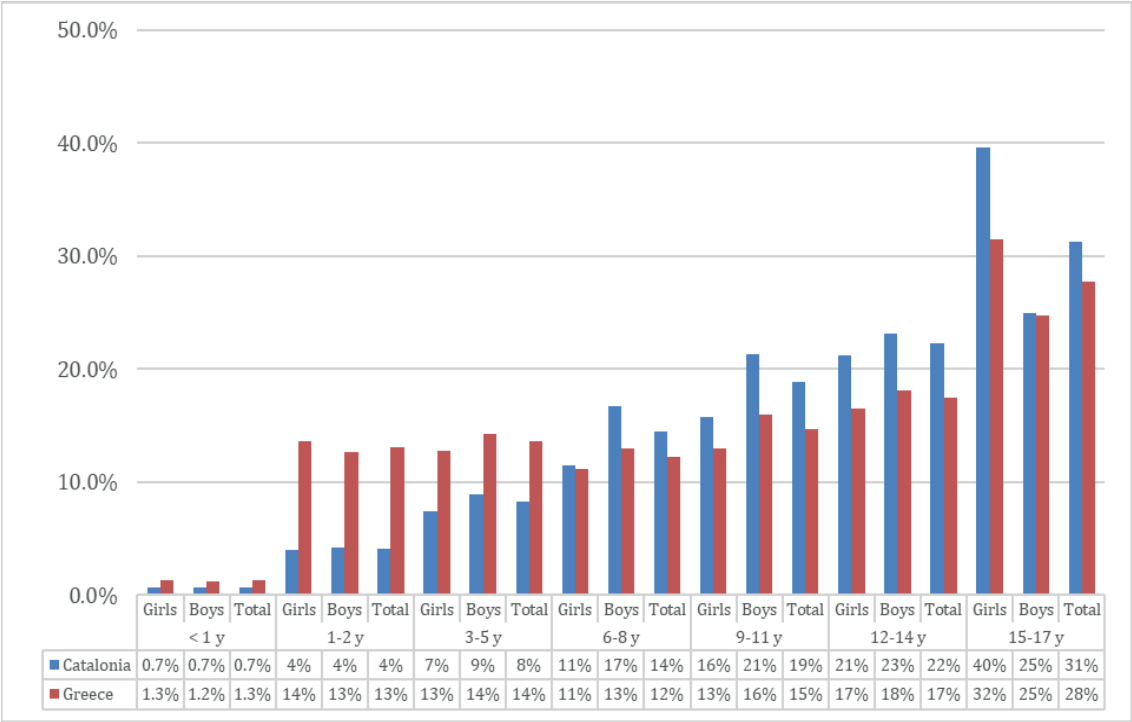
Table 27. Study population description – Catalonia (Spain) and Greece. Overall sample sizes.

	Catalonia (Spain) 2008-2017			Greece 2016-2019*		
	Girls n (%)	**Boys n (%)**	**Overall n (%)**	**Girls n (%)**	**Boys n (%)**	**Overall n (%)**
Only hydroxyzine dispensed$	150,247 (71.1)	156,429 (65.8)	306,676 (68.3)	19,793 (67.9)	22,715 (65.6)	42,508 (66.0)
Target exposed population&	60,926 (28.9)	81,457 (34.2)	142,383 (31.7)	9,357 (32.1)	11,917 (34.4)	21,274 (33.4)
Total	***211,173***	***237,886***	***449,059***	***29,150***	***34,632***	***63,782***

**: March 2016 to October 2019. $: population only exposed to hydroxyzine. &: population exposed at least to one psychotropic medicine (±hydroxyzine).*

According to the data from the national statistic authorities, it seems that the target study populations in both regions are similar as regards the sex (boys: 56.00% in Greece vs 57.00% in Catalonia) and the age distribution with the deviations described above. Figure 28 presents the

Figure 28. Comparative of the target exposed populations from Catalonia (Spain) and Greece by age and sex strata.



	Girls	Boys	Total	Girls	Boys	Total	Girls	Boys	Total	Girls	Boys	Total	Girls	Boys	Total	Girls	Boys	Total	Girls	Boys	Total
	< 1 y			1-2 y			3-5 y			6-8 y			9-11 y			12-14 y			15-17 y		
Catalonia	0.7%	0.7%	0.7%	4%	4%	4%	7%	9%	8%	11%	17%	14%	16%	21%	19%	21%	23%	22%	40%	25%	31%
Greece	1.3%	1.2%	1.3%	14%	13%	13%	13%	14%	14%	11%	13%	12%	13%	16%	15%	17%	18%	17%	32%	25%	28%

differences observed in the two target populations comparing per age and sex strata. The following Table 29 provide detailed information on the study population in both regions as overall and after exclusion of hydroxyzine (target group), as well as the distribution by sex and age strata.

4.2.1.3 Comparative of the reference and the target exposed populations

In the following table (Table 30), a comparison of the reference and the target exposed populations by age is presented separately for both study regions. The analysis revealed that in overall there is an infra-representation of subjects ≤8 years of age and over-representation of subjects ≥9 years of age in Catalonia. In Greece, there is an infra-representation of the paediatric population aged less than 11 years with the exception of the age group 1-2 years of age where an over-representation was observed. The same over-representation was found concerning the Greek adolescent group (≥12 years of age).

In Catalonia, the group of 15-17 years of age in our sample represented 31.20% of the total exposed population sample, while the corresponding percentage in the reference paediatric population be only 15.00%. Girls were more than half of the older adolescent (15-17 years of age) target exposed population, whereas the percentage of girls in the reference paediatric population was 48.20%. Similar observations were found between the Greek target exposed and reference paediatric populations, where 27.70% of the target exposed population was in the 15-

Table 29. Study population description for Catalonia (Spain) and Greece by age and sex strata.

Catalonia (Spain)																		
	Total exposed population						Population only exposed to hydroxyzine						Target exposed population					
Age (years)	Girls		Boys		Overall		Girls		Boys		Overall		Girls		Boys		Overall	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
< 1	5,080	2.40	6,602	2.80	11,682	2.60	4,681	3.10	6,038	3.90	10,719	3.50	399	0.70	564	0.70	963	0.70
1-2	39,840	18.90	44,671	18.80	84,511	18.80	37,394	24.90	41,256	26.40	78,650	25.60	2,446	4.00	3,415	4.20	5,861	4.10
3-5	57,457	27.20	62,945	26.50	120,402	26.80	52,964	35.30	55,674	35.60	108,638	35.40	4,493	7.40	7,271	8.90	11,764	8.30
6-8	35,635	16.90	42,061	17.70	77,696	17.30	28,674	19.10	28,425	18.20	57,099	18.60	6,961	11.40	13,636	16.70	20,597	14.50
9-11	24,707	11.70	31,638	13.30	56,345	12.50	15,125	10.10	14,306	9.10	29,431	9.60	9,582	15.70	17,332	21.30	26,914	18.90
12-14	20,287	9.60	26,411	11.10	46,698	10.40	7,373	4.90	7,533	4.80	14,906	4.90	12,914	21.20	18,878	23.20	31,792	22.30
15-17	28,167	13.30	23,558	9.90	51,725	11.50	4,036	2.70	3,197	2.00	7,233	2.40	24,131	39.60	20,361	25.00	44,492	31.20
< 1-17	***211,173***	***100.00***	***237,886***	***100.00***	***449,059***	***100.00***	***150,247***	***100.00***	***156,429***	***100.00***	***306,676***	***100.00***	***60,926***	***100.00***	***81,457***	***100.00***	***142,383***	***100.00***
Greece																		
	Total exposed population						Population only exposed to hydroxyzine						Target exposed population					
Age (years)	Girls		Boys		Overall		Girls		Boys		Overall		Girls		Boys		Overall	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
< 1	591	2.00	656	1.90	1,247	2.00	465	2.30	510	2.20	975	2.30	126	1.30	146	1.20	272	1.30
1-2	5,148	17.70	6,213	17.90	11,361	17.80	3,869	19.50	4,708	20.70	8,577	20.20	1,279	13.70	1,505	12.60	2,784	13.10
3-5	7,498	25.70	8,884	25.70	16,382	25.70	6,300	31.80	7,181	31.60	13,481	31.70	1,198	12.80	1,703	14.30	2,901	13.60
6-8	5,363	18.40	6,453	18.60	11,816	18.50	4,320	21.80	4,901	21.60	9,221	21.70	1,043	11.10	1,552	13.00	2,595	12.20
9-11	3,931	13.50	5,148	14.90	9,079	14.20	2,712	13.70	3,247	14.30	5,959	14.00	1,219	13.00	1,901	16.00	3,120	14.70
12-14	2,928	10.00	3,730	10.80	6,658	10.40	1,384	7.00	1,568	6.90	2,952	6.90	1,544	16.50	2,162	18.10	3,706	17.40
15-17	3,691	12.70	3,548	10.20	7,239	11.30	743	3.80	600	2.60	1,343	3.20	2,948	31.50	2,948	24.70	5,896	27.70
<1-17	***29,150***	***100.00***	***34,632***	***100.00***	***63,782***	***100.00***	***19,793***	***100.00***	***22,715***	***100.00***	***42,508***	***100.00***	***9,357***	***100.00***	***11,917***	***100.00***	***21,274***	***100.00***

17years of age group (50.00% girls), dropping to 17.70% in the reference population where the girls were in total the 48.60%. Similar observations were found between the Greek target exposed and reference paediatric populations, where 27.70% of the target exposed population was in the 15-17 years of age group (50.00% girls), dropping to 17.70% in the reference population where the girls were in total the 48.60%.

Table 30. Comparative of the reference and the target exposed populations in Catalonia (Spain) and Greece by age strata.

Catalonia (Spain)						
	Reference population			Target exposed population		
Age (years)	n	Stratum (%)	Female/Stratum (%)	n	Stratum (%)	Female/Stratum (%)
< 1	78,815	5.80	48.30	963	0.70	41.40
1-2	161,773	11.80	48.30	5,861	4.10	41.70
3-5	246,395	18.00	48.30	11,764	8.30	38.20
6-8	239,352	17.50	48.40	20,597	14.50	33.80
9-11	224,624	16.40	48.50	26,914	18.90	35.60
12-14	210,561	15.40	48.40	31,792	22.30	40.60
15-17	204,231	15.00	48.20	44,492	31.20	54.20
< 1-17	***1,365,750***	***100.00***	***48.40***	***142,383***	***100.00***	***42.80***
Greece						
	Reference population			**Target exposed population**		
Age (years)	**n**	**Stratum (%)**	**Female/Stratum (%)**	**n**	**Stratum (%)**	**Female/Stratum (%)**
< 1	89,580	4.80	48.50	272	1.30	46.30
1-2	186,494	10.00	48.60	2,784	13.10	45.90
3-5	300,011	16.00	48.60	2,901	13.60	41.30
6-8	324,369	17.30	48.70	2,595	12.20	40.20
9-11	326,616	17.40	48.70	3,120	14.70	39.10
12-14	319,850	17.10	48.60	3,706	17.40	41.70
15-17	322,310	17.20	48.60	5,896	27.70	50.00
< 1-17	***1,872,219***	***100.00***	***48.60***	***21,274***	***100.00***	***44.00***

4.2.2 Prevalence of psychotropic medicine use

4.2.2.1 Prevalence of use per year - total and target exposures

The prevalence of psychotropic use for the total exposed paediatric population fluctuated between 40.80 (2009) and 64.20 (2015) per 1,000 inhabitants under 18 years of age throughout the ten-year period in Catalonia, with boys been more exposed than girls during the whole period. The highest prevalence for boys was in 2015 (71.40 per 1,000 paediatric inhabitants) and for girls in 2008 (57.60 per 1,000 paediatric inhabitants). Excluding all patients with

hydroxyzine-only dispensations, the target exposed population analysis revealed that the prevalence almost halved and shifted from 26.40 to 29.60 per 1,000 paediatric inhabitants in 2008 and 2017 respectively, with the highest prevalence observed in 2014 (32.20 per 1,000 paediatric inhabitants). The pattern of boys being more exposed to psychotropics throughout the decade was not changed in the target exposed group analysis, with the highest prevalence for boys identified in 2013 and 2014 (39.90 per 1,000 paediatric inhabitants) and for girls in 2014 (23.90 per 1,000 paediatric inhabitants). The dispensing rates for the ten-year period in Catalonia are presented in Table 31 below and the evolution of prevalence per year, as well as per sex and year is given in Figure 32 for both groups (total and target exposed).

Concerning the Greek paediatric population prevalence analysis, we identified less variation with the prevalence between 13.40 and 14.60 per 1,000 paediatric inhabitants in 2019 and 2018 respectively, apart from 2016 where the prevalence was much lower (5.10 per 1,000 paediatric inhabitants). Boys had the highest prevalence of 15.60 per 1,000 male inhabitants in 2018, while the highest prevalence observed for girls was of 13.50 per 1,000 female inhabitants during the same year. When all paediatric patients with hydroxyzine-only dispensations were excluded, the prevalence for the target exposed population was more than halved and varied between 3.10 to 6.50 per 1,000 paediatric inhabitants in 2016 and, both 2018 and 2019 respectively, with the highest prevalence observed during the last two years of the study. Boys were still more exposed to psychotropics throughout the almost four-year period also in the target group analysis, with the highest prevalence for boys been observed in 2018 (7.30 per 1,000 male paediatric inhabitants) and for girls in both 2018 and 2019 (5.70 per 1,000 paediatric female inhabitants). Table 33 and Figure 34 below demonstrate the dispensing rates for the almost four-year period in Greece and the evolution of prevalence per year as well as per sex and year for both groups (total and target exposed) respectively.

4.2.2.2 Prevalence of use by age strata per year - target exposures

Concerning the analysis per age strata and per year, we identified that the group of adolescents had the highest exposure in both Greece and Catalonia paediatric populations throughout the respective study periods. As per the following tables (Table 31 and Table 33), all information of the differences observed during the study periods are presented in detail there.

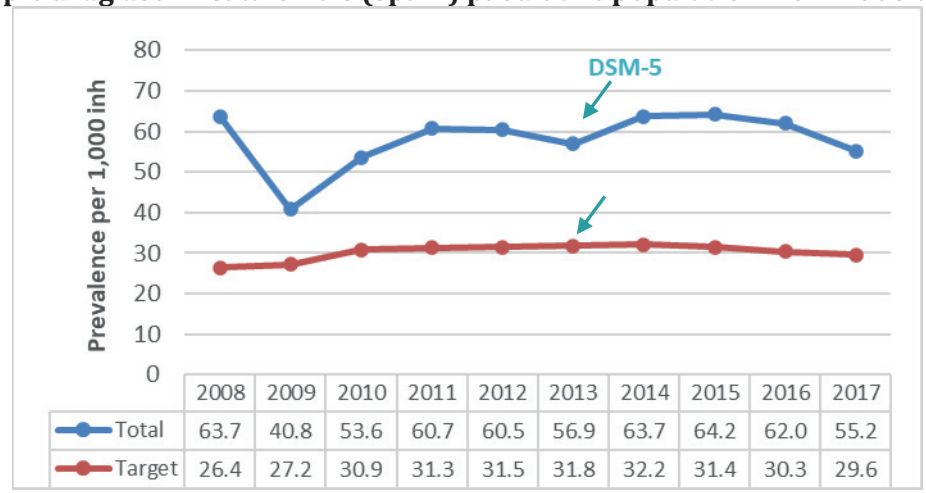
Focusing on the target exposures, the highest peak in prevalence was observed in 2012 in Catalonia's target exposed paediatric population (69.20 per 1,000 paediatric inhabitants). As it can be seen in Figure 35 below, throughout the ten-year period the prevalence was increasing with the age, with the highest prevalence been in the age groups of adolescents (12-14 and 15-17 years of age). A steady downward trend was observed in all age groups, but the starting point was different: for the groups <1 year, 6-8 years and 9-11 years of age it was during 2013, while

Table 31. Prevalence of psychotropic medicine use in Catalonia's (Spain) paediatric population from 2008 to 2017.

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Paediatric inhabitants	***1,281,777***	***1,322,462***	***1,346,516***	***1,367,382***	***1,384,978***	***1,389,763***	***1,386,458***	***1,388,255***	***1,391,507***	***1,398,400***
Any exposure										
All	***63.7***	***40.8***	***53.6***	***60.7***	***60.5***	***56.9***	***63.7***	***64.2***	***62.0***	***55.2***
Girls - Boys	57.6 - 69.5	33.5 - 47.6	46.5 - 60.3	52.4 - 68.4	52.0 - 68.4	48.7 - 64.7	55.8 - 71.1	56.4 - 71.4	54.5 - 68.9	47.7 - 62.1
Target exposures										
All	***26.4***	***27.2***	***30.9***	***31.3***	***31.5***	***31.8***	***32.2***	***31.4***	***30.3***	***29.6***
Girls - Boys	19.4 - 32.9	19.8 - 34.1	23.3 - 37.9	22.9 - 39.2	22.8 - 39.6	23.1 - 39.9	23.9 - 39.9	23.5 - 38.9	22.6 - 37.5	22.2 - 36.6
< 1 year	***0.0***	***0.0***	***1.3***	***1.1***	***1.7***	***2.4***	***2.2***	***2.1***	***1.7***	***1.9***
Girls - Boys	0.0 - 0.0	0.0 - 0.0	1.3 - 1.4	0.9 - 1.3	1.3 - 2.1	1.9 - 2.7	1.8 - 2.5	1.9 - 2.3	1.6 - 1.7	1.6 - 2.3
1-2 years	***1.0***	***4.4***	***8.3***	***7.0***	***5.3***	***5.0***	***4.7***	***4.8***	***4.9***	***4.6***
Girls - Boys	0.9 - 1.1	3.9 - 4.8	7.4 - 9.1	6.1 - 7.8	4.7 - 6.0	4.2 - 5.9	3.8 - 5.6	4.0 - 5.5	4.4 - 5.3	4.2 - 4.9
3-5 years	***14.9***	***11.4***	***12.0***	***11.0***	***8.9***	***7.9***	***6.7***	***6.2***	***5.8***	***5.6***
Girls - Boys	12.2 - 17.5	9.7 - 12.9	9.7 -14.2	9.0 - 12.8	6.8 - 10.9	6.0 - 9.7	5.5 - 7.9	5.1 - 7.3	4.6 - 6.8	4.4 - 6.8
6-8 years	***21.4***	***18.4***	***23.7***	***22.9***	***21.0***	***23.8***	***22.4***	***19.9***	***17.7***	***16.8***
Girls - Boys	17.2 - 25.5	13.5 - 23.1	16.1- 30.9	14.8 - 30.5	13.7 - 27.9	14.4 - 32.6	13.8 - 30.5	12.1 - 27.2	10.9 - 24.1	10.3 - 22.8
9-11 years	***37.0***	***38.9***	***44.4***	***45.5***	***43.7***	***45.4***	***43.2***	***40.5***	***37.5***	***34.8***
Girls - Boys	25.9 - 47.5	24.8 - 52.2	28.5 - 59.4	28.8 - 61.4	26.9 - 59.7	27.1 - 62.6	26.1 - 59.3	24.2 - 55.8	22.6 - 51.4	20.8 - 47.8
12-14 years	***45.6***	***47.8***	***50.9***	***54.2***	***55.8***	***57.2***	***58.8***	***58.0***	***55.3***	***53.2***
Girls - Boys	30.6 - 59.8	29.8 - 64.8	33.3 - 67.3	34.9 - 72.0	36.4 - 73.9	37.9 - 75.2	39.8- 76.8	39.3 - 75.6	37.0 - 72.6	35.9 -69.5
15-17 years	***48.5***	***55.3***	***60.4***	***62.8***	***69.2***	***63.5***	***66.8***	***66.1***	***65.2***	***63.7***
Girls - Boys	36.8 - 59.5	46.7 - 63.3	56.1 - 64.4	55.6 - 69.6	60.5 - 77.2	59.3 -67.3	63.5 - 69.7	62.9 - 69.0	61.1 - 69.0	59.5- 67.6

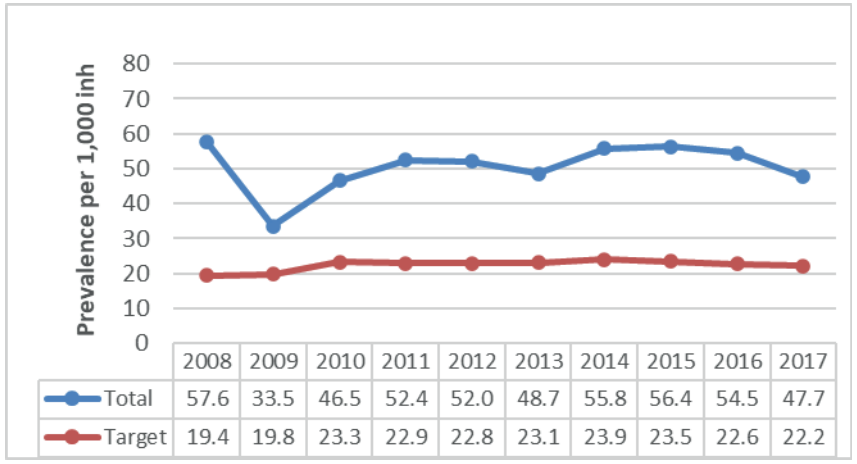
Prevalence of use expressed per 1,000 inhabitants.

Figure 32. Prevalence of psychotropic drug use in Catalonia's (Spain) paediatric population from 2008 to 2017 - total vs target exposures.



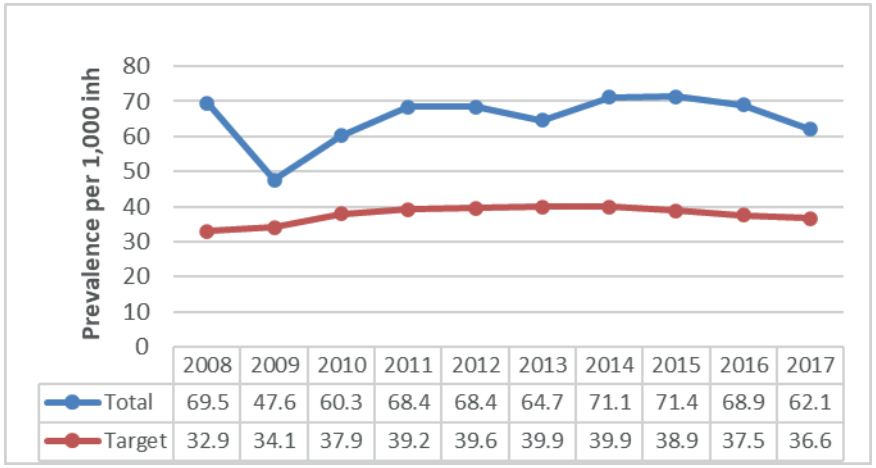
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total	63.7	40.8	53.6	60.7	60.5	56.9	63.7	64.2	62.0	55.2
Target	26.4	27.2	30.9	31.3	31.5	31.8	32.2	31.4	30.3	29.6

Overall



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total	57.6	33.5	46.5	52.4	52.0	48.7	55.8	56.4	54.5	47.7
Target	19.4	19.8	23.3	22.9	22.8	23.1	23.9	23.5	22.6	22.2

Girls



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total	69.5	47.6	60.3	68.4	68.4	64.7	71.1	71.4	68.9	62.1
Target	32.9	34.1	37.9	39.2	39.6	39.9	39.9	38.9	37.5	36.6

Boys

Table 33. Prevalence of psychotropic drug use in Greece's paediatric population from 2016 to 2019.

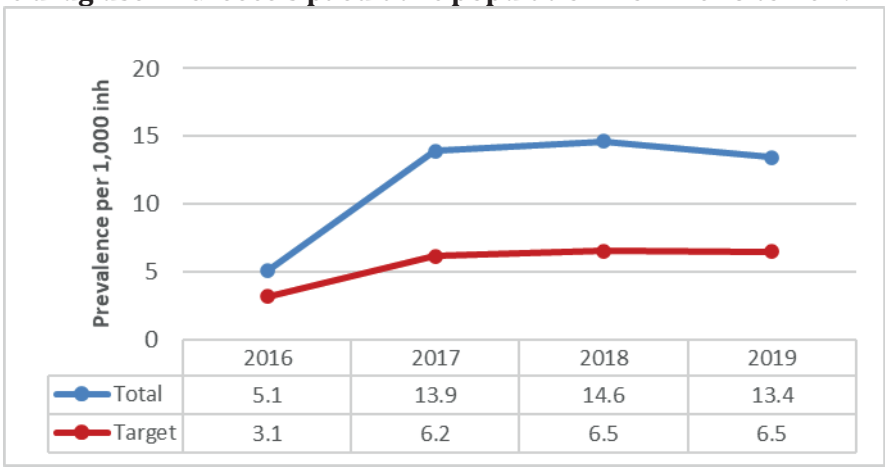
	2016*	2017	2018	2019+
Paediatric inhabitants	***1,876,718***	***1,878,388***	***1,872,031***	***1,861,740***
Any exposure				
Total	***5.1***	***13.9***	***14.6***	***13.4***
Girls - Boys	4.5 - 5.5	12.8 - 15.0	13.5 - 15.6	12.4 - 14.4
Target exposures				
Total	***3.1***	***6.2***	***6.5***	***6.5***
Girls - Boys	2.7 - 3.5	5.5 - 6.8	5.7 - 7.3	5.7 - 7.2
< 1 year	***0.0***	***0.9***	***1.1***	***1.0***
Girls - Boys	0.0 - 0.0	0.8 - 1.0	1.1 - 1.2	0.9 - 1.0
1-2 years	***1.4***	***6.0***	***5.6***	***5.6***
Girls - Boys	1.4 - 1.3	5.8 - 6.1	5.1 - 6.0	5.1 - 6.1
3-5 years	***1.5***	***4.8***	***5.4***	***5.7***
Girls - Boys	1.3 - 1.7	4.3 - 5.3	4.8 - 6.0	5.0 - 6.3
6-8 years	***2.3***	***4.5***	***4.7***	***4.5***
Girls - Boys	2.0 - 2.6	3.9 - 5.1	3.9 - 5.5	3.7 - 5.2
9-11 years	***3.7***	***6.1***	***6.1***	***6.3***
Girls - Boys	3.0 - 4.3	4.9 - 7.2	5.0 - 7.2	5.0 - 7.6
12-14 years	***4.4***	***7.1***	***7.5***	***7.2***
Girls - Boys	3.5 - 5.1	5.7 - 8.5	6.1 - 8.8	6.0 – 8.3
15-17 years	***5.7***	***9.9***	***10.7***	***10.6***
Girls - Boys	5.2 - 6.3	9.6 - 10.1	10.3 - 11.1	10.6 - 10.6

**: from March to December 2016, +: from January to October 2019. Prevalence expressed per 1,000 inhabitants.*

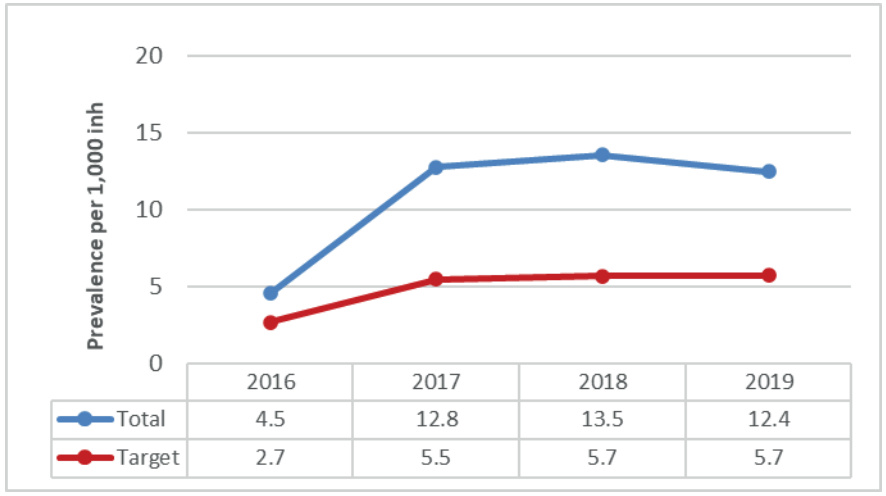
for the adolescent groups (12-14 and 15-17year-olds) was in 2014, and for the 1-2year-olds and 3-5year-olds was in 2010. Except for the 3-5year-old group that had in general a descending trend, prevalence in all other age groups was increasing since 2008 before reaching the point where the downward trend started.

In the following figures (Figure 36 and Figure 37), the differences in Catalonia's paediatric population prevalence by age group and sex during the study period are presented. In general, boys had higher exposures than girls. While girls seemed to follow the same pattern of increasing prevalence with the age (highest peak of 63.50 per 1,000 female inhabitants in 2014 for the 15-17year-olds), in case of boys we saw that the 12-14year-olds were in the first place, apart from 2012 (77.20 per 1,000 males) which was also the highest prevalence observed in the boys group. The prevalence in the 9-11year- and 12-14year-old groups was almost double in boys than the one observed in girls during the whole study period.

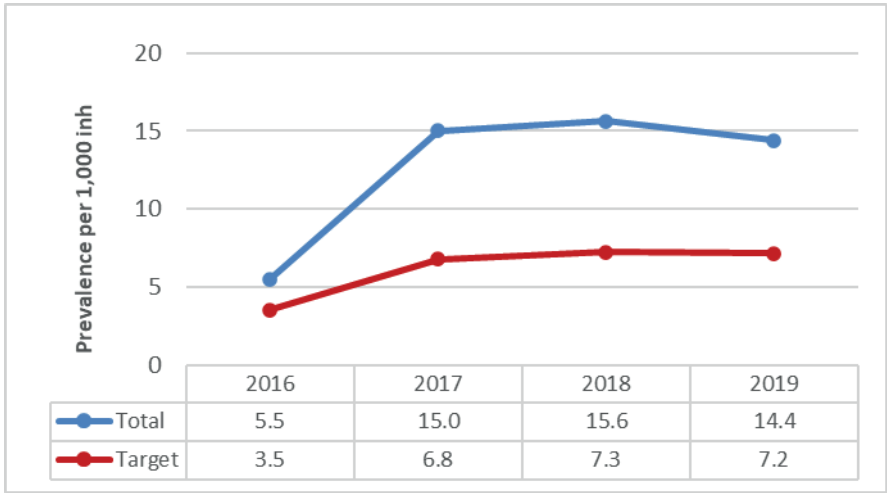
Figure 34. Prevalence of psychotropic drug use in Greece's paediatric population from 2016 to 2019 – total vs target exposures.



Overall

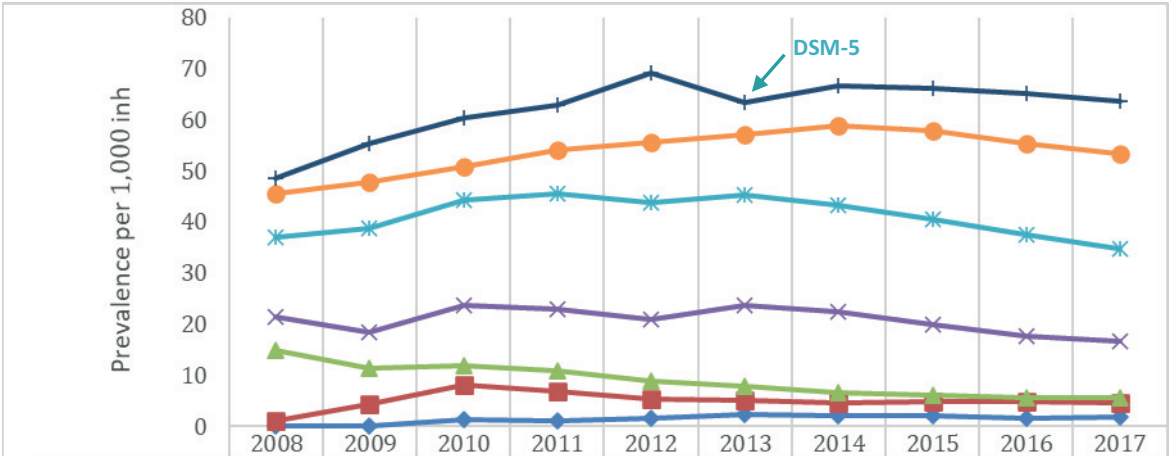


Girls



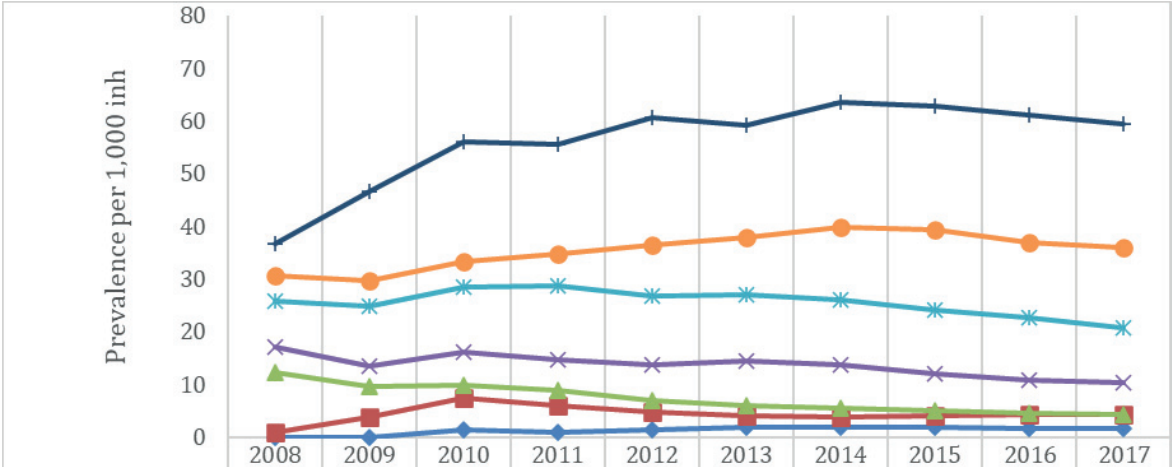
Boys

Figure 35. Prevalence of psychotropic drug use by age group in Catalonia (Spain) from 2008 to 2017 - target exposures.



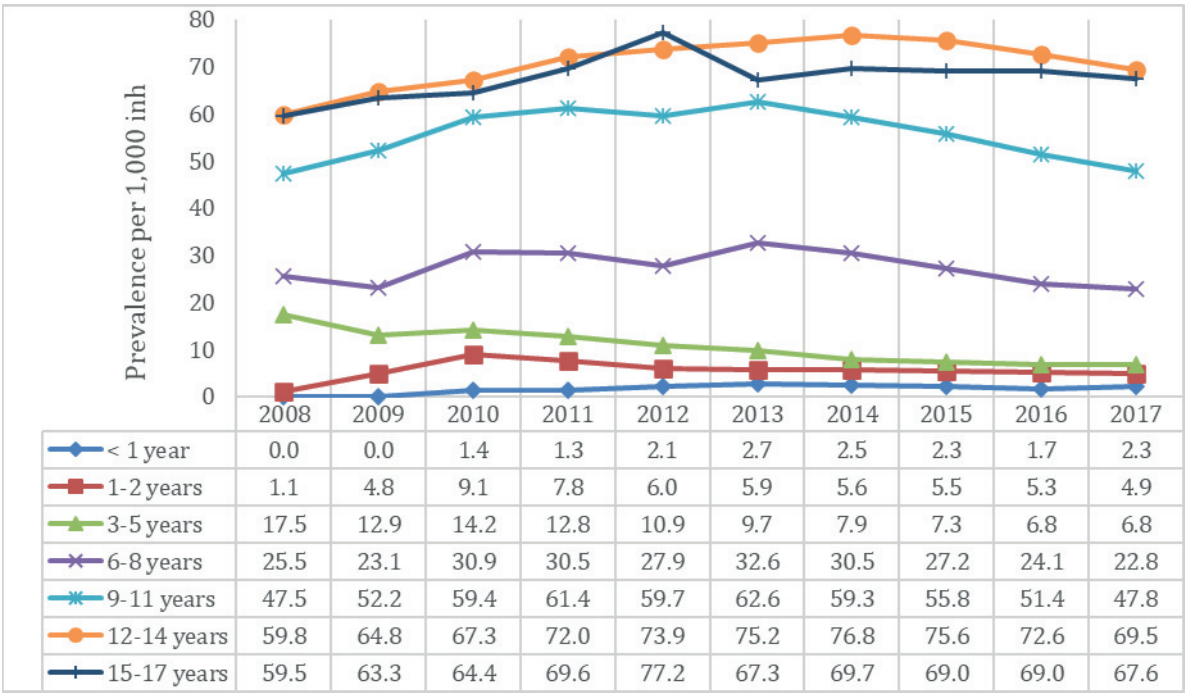
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
< 1 year	0.0	0.0	1.3	1.1	1.7	2.4	2.2	2.1	1.7	1.9
1-2 years	1.0	4.4	8.3	7.0	5.3	5.0	4.7	4.8	4.9	4.6
3-5 years	14.9	11.4	12.0	11.0	8.9	7.9	6.7	6.2	5.8	5.6
6-8 years	21.4	18.4	23.7	22.9	21.0	23.8	22.4	19.9	17.7	16.8
9-11 years	37.0	38.9	44.4	45.5	43.7	45.4	43.2	40.5	37.5	34.8
12-14 years	45.6	47.8	50.9	54.2	55.8	57.2	58.8	58.0	55.3	53.2
15-17 years	48.5	55.3	60.4	62.8	69.2	63.5	66.8	66.1	65.2	63.7

Figure 36. Prevalence of psychotropic drug use by age group in Catalonia (Spain) from 2008 to 2017 - target exposures (girls).



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
< 1 year	0.0	0.0	1.3	0.9	1.3	1.9	1.8	1.9	1.6	1.6
1-2 years	0.9	3.9	7.4	6.1	4.7	4.2	3.8	4.0	4.4	4.2
3-5 years	12.2	9.7	9.7	9.0	6.8	6.0	5.5	5.1	4.6	4.4
6-8 years	17.2	13.5	16.1	14.8	13.7	14.4	13.8	12.1	10.9	10.3
9-11 years	25.9	24.8	28.5	28.8	26.9	27.1	26.1	24.2	22.6	20.8
12-14 years	30.6	29.8	33.3	34.9	36.4	37.9	39.8	39.3	37.0	35.9
15-17 years	36.8	46.7	56.1	55.6	60.5	59.3	63.5	62.9	61.1	59.5

Figure 37. Prevalence of psychotropic drug use by age group in Catalonia (Spain) from 2008 to 2017 - target exposures (boys).



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
< 1 year	0.0	0.0	1.4	1.3	2.1	2.7	2.5	2.3	1.7	2.3
1-2 years	1.1	4.8	9.1	7.8	6.0	5.9	5.6	5.5	5.3	4.9
3-5 years	17.5	12.9	14.2	12.8	10.9	9.7	7.9	7.3	6.8	6.8
6-8 years	25.5	23.1	30.9	30.5	27.9	32.6	30.5	27.2	24.1	22.8
9-11 years	47.5	52.2	59.4	61.4	59.7	62.6	59.3	55.8	51.4	47.8
12-14 years	59.8	64.8	67.3	72.0	73.9	75.2	76.8	75.6	72.6	69.5
15-17 years	59.5	63.3	64.4	69.6	77.2	67.3	69.7	69.0	69.0	67.6

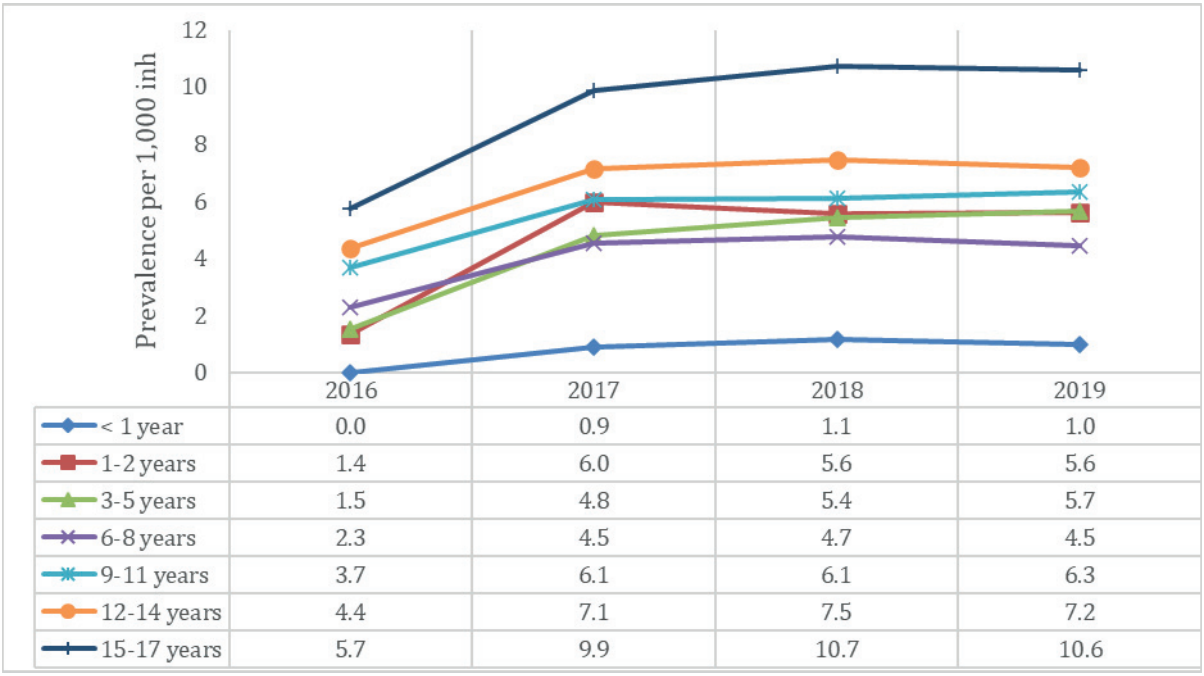
In Greece now, the analysis of the target exposures per age group showed that in each age group the prevalence of use was almost steady, except for 2016 where the prevalence was in general lower than in the other study years for all age groups. However, the prevalence of use was not following the same pattern of increase depending on the age as the one observed in Catalonia's paediatric data analysis.

Even though the Greek adolescent groups were exposed more in psychotropics than the youngest paediatric subset groups with the highest peak for both been in 2018 (7.50 per 1,000 inhabitants for the 12-14year old group and 10.70 per 1,000 inhabitants for the 15-17year old group), the age groups of the 1-2 years of age and of the 3-5 years of age had a higher prevalence than the 6-8 years of age group throughout the whole study period (Figure 38).

Concerning the analysis per age group and sex, Greek data revealed that boys were also more exposed to psychotropics in all age groups, even though the differences observed were not so high as in the ones observed in Catalonia's paediatric population. The highest prevalence was observed in the 15-17 years of age group with the peak been in 2018 for boys (11.10 per 1,000 male inhabitants) and in 2019 for girls (10.60 per 1,000 female inhabitants). The same trend as the one observed in the total Greek target paediatric population was also identified when analysing the data per sex too: groups of the 1-2 years of age and of the 3-5 years of age were more exposed than the 6-8 years of age group for both girls and boys, with 1-2 years of age

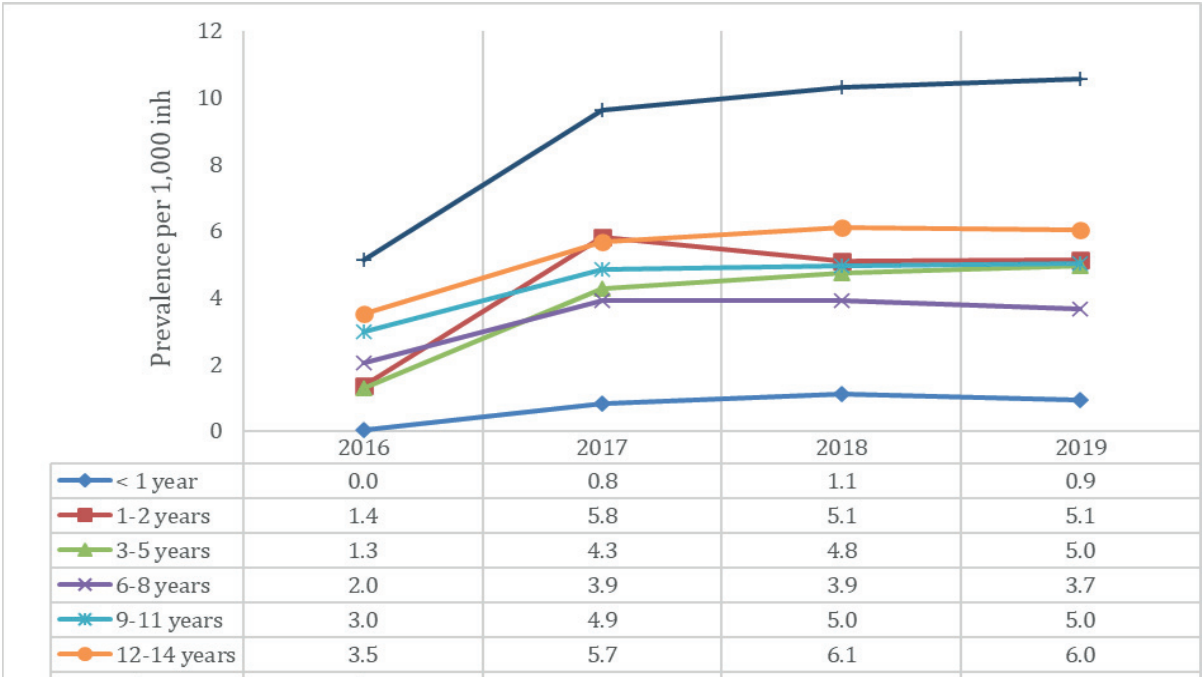
group surpassing the prevalence observed in the 12-14 years of age female group in 2017 (Figure 39 and Figure 40).

Figure 38. Prevalence of psychotropic drug use by age group in Greece from 2016 to 2019 - target exposures.



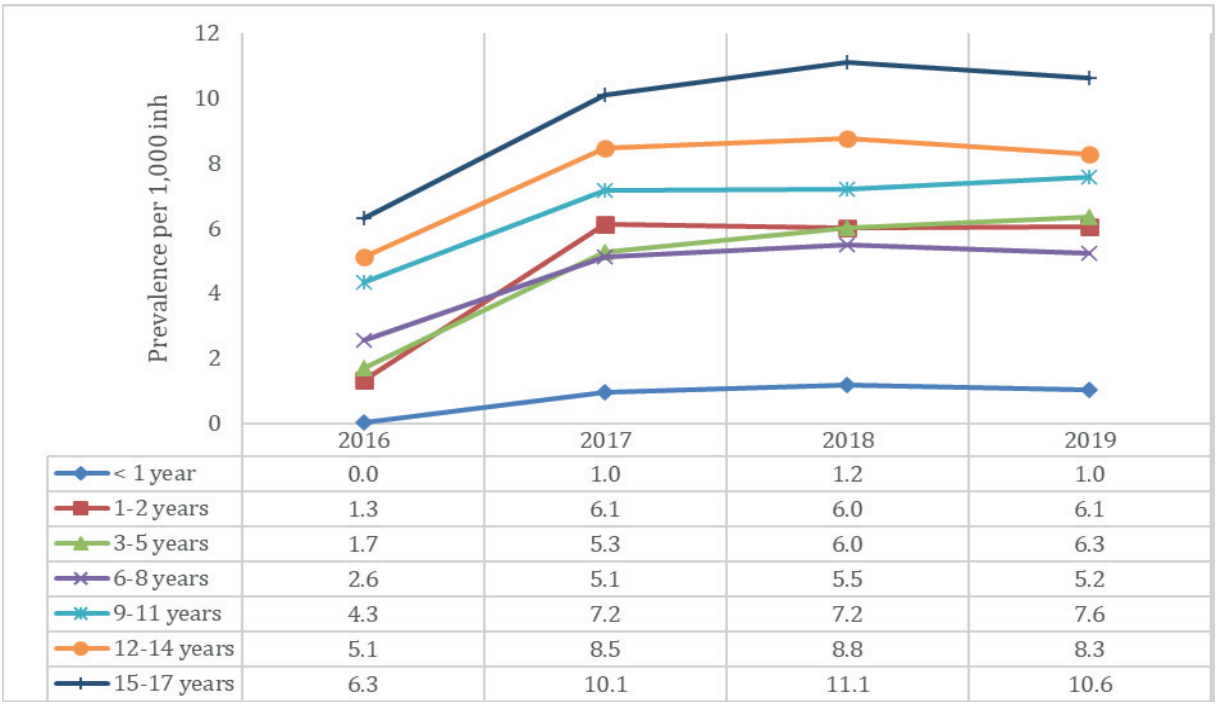
	2016	2017	2018	2019
< 1 year	0.0	0.9	1.1	1.0
1-2 years	1.4	6.0	5.6	5.6
3-5 years	1.5	4.8	5.4	5.7
6-8 years	2.3	4.5	4.7	4.5
9-11 years	3.7	6.1	6.1	6.3
12-14 years	4.4	7.1	7.5	7.2
15-17 years	5.7	9.9	10.7	10.6

Figure 39. Prevalence of psychotropic drug use by age group in Greece from 2016 to 2019 - target exposures (girls).



	2016	2017	2018	2019
< 1 year	0.0	0.8	1.1	0.9
1-2 years	1.4	5.8	5.1	5.1
3-5 years	1.3	4.3	4.8	5.0
6-8 years	2.0	3.9	3.9	3.7
9-11 years	3.0	4.9	5.0	5.0
12-14 years	3.5	5.7	6.1	6.0
15-17 years	5.2	9.6	10.3	10.6

Figure 40. Prevalence of psychotropic drug use by age group in Greece from 2016 to 2019 - target exposures (boys).



	2016	2017	2018	2019
< 1 year	0.0	1.0	1.2	1.0
1-2 years	1.3	6.1	6.0	6.1
3-5 years	1.7	5.3	6.0	6.3
6-8 years	2.6	5.1	5.5	5.2
9-11 years	4.3	7.2	7.2	7.6
12-14 years	5.1	8.5	8.8	8.3
15-17 years	6.3	10.1	11.1	10.6

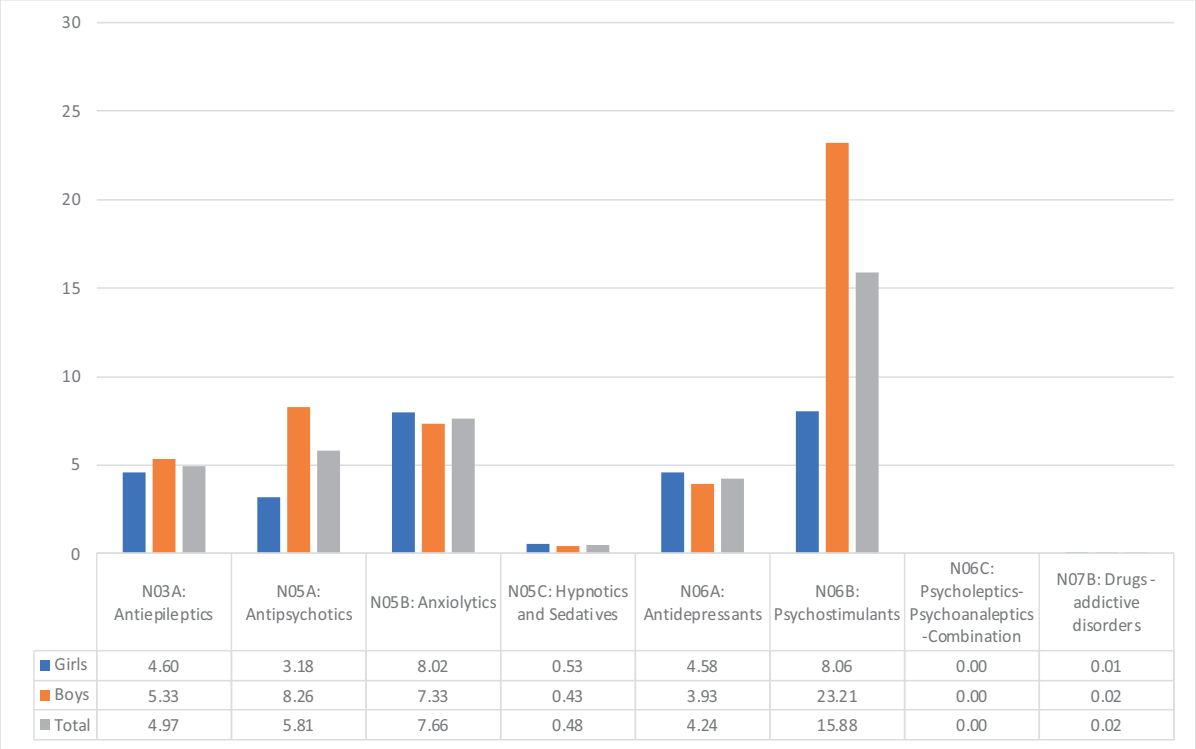
4.2.2.3 Prevalence of use by ATC groups - target exposures

When analysing the rate of the prevalence per ATC groups for the full study period, we observed some significant differences between the two regions for the target exposed populations.

In Catalonia's paediatric population, the highest exposure was found to be on the psychostimulants ATC group (N06B) with a prevalence of 15.88 per 1,000 paediatric inhabitants, followed by anxiolytics (N05B) and antipsychotics (N05A) with a prevalence of 7.66 and 5.81 per 1,000 paediatric inhabitants respectively. The prevalence for the other ATC categories drops further (see Figure 41), while N06C data were not available. Figure 41 also presents the differences in prevalence per ATC group that were observed among sex groups. Boys were much more exposed to N06B (23.21 per 1,000 male vs 8.06 per 1,000 female paediatric inhabitants) and N05A (8.26 vs 3.18 respectively). Although in other ATC groups the difference in prevalence between the sexes was not so significant, girls seemed to be slightly more exposed to anxiolytics (N05B), antidepressants (N06A) and hypnotics/sedatives (N05C) than boys.

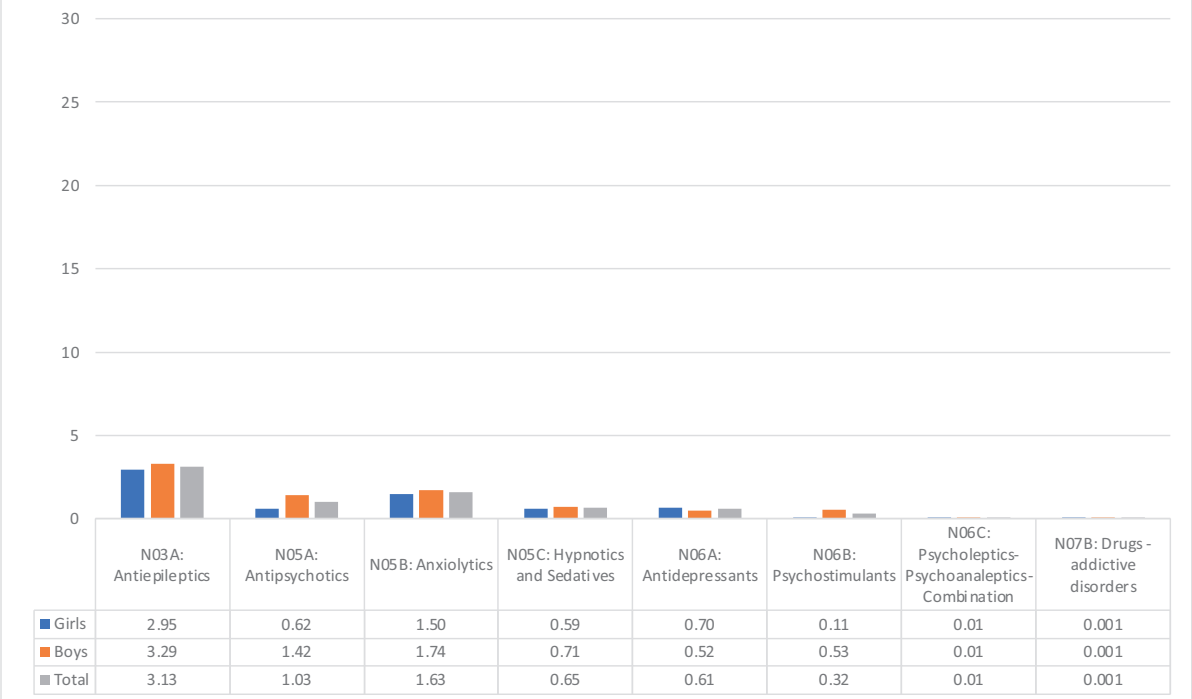
Regarding the ATC prevalence analysis in the Greek dataset, antiepileptics (N03A) had the highest prevalence rate (3.13 per 1,000 paediatric inhabitants), followed by anxiolytics (N05B) with more than the half prevalence rate (1.63 per 1,000 paediatric inhabitants) and antipsychotics with a rate of 1.03 per 1,000 paediatric inhabitants. Figure 42 below presents the prevalence rates per ATC group for Greece for the corresponding full study period.

Figure 41. Prevalence (per 1,000 inhabitants) of psychotropic drug use by ATC groups in Catalonia (Spain) - target exposures.



	N03A: Antiepileptics	N05A: Antipsychotics	N05B: Anxiolytics	N05C: Hypnotics and Sedatives	N06A: Antidepressants	N06B: Psychostimulants	N06C: Psycholeptics-Psychoanaleptics -Combination	N07B: Drugs - addictive disorders
Girls	4.60	3.18	8.02	0.53	4.58	8.06	0.00	0.01
Boys	5.33	8.26	7.33	0.43	3.93	23.21	0.00	0.02
Total	4.97	5.81	7.66	0.48	4.24	15.88	0.00	0.02

Figure 42. Prevalence (per 1,000 inhabitants) of psychotropic drug use by ATC groups in Greece - target exposures.



	N03A: Antiepileptics	N05A: Antipsychotics	N05B: Anxiolytics	N05C: Hypnotics and Sedatives	N06A: Antidepressants	N06B: Psychostimulants	N06C: Psycholeptics-Psychoanaleptics-Combination	N07B: Drugs - addictive disorders
Girls	2.95	0.62	1.50	0.59	0.70	0.11	0.01	0.001
Boys	3.29	1.42	1.74	0.71	0.52	0.53	0.01	0.001
Total	3.13	1.03	1.63	0.65	0.61	0.32	0.01	0.001

As reflected also in Figure 42 the Greek paediatric male population was more exposed to almost all ATC groups. The highest difference in rates was observed in antipsychotics (N05A) (1.42 per 1,000 male vs 0.62 per 1,000 female paediatric inhabitants) and psychostimulants (N06B) (0.53 per 1,000 male vs 0.11 per 1,000 female paediatric inhabitants), while girls were more exposed than boys only to antidepressants (N06A) with a prevalence of 0.70 per 1,000 female vs 0.52 per 1,000 Greek male paediatric inhabitants.

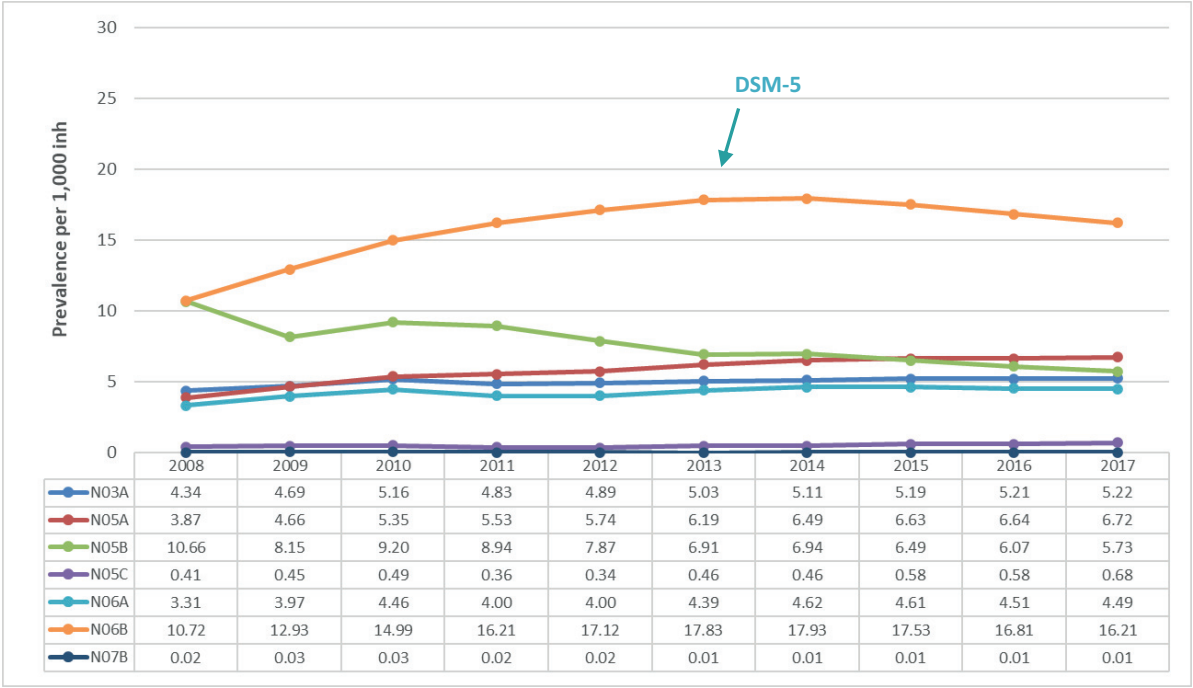
4.2.2.4 Prevalence of use by ATC groups per year - target exposures

The datasets were also analysed to identify the evolution of the prevalence by ATC group per study year and thereinafter per sex group. The following figures reflect the conducted analyses first for Catalonia's (Figure 43, Figure 44 and Figure 45) and then for Greece's (Figure 46, Figure 47 and Figure 48) target exposed paediatric population.

A constant higher exposure to psychostimulants (N06B) in comparison to all other ATC groups was observed in Catalonia during all study years, with a steady increase up to 2014 (17.93 per 1,000 paediatric inhabitants: boys 25.95 and girls 9.36 per 1,000 male and female paediatric inhabitants respectively). Anxiolytics (N05B) pertained in the second place, with following mostly a decreasing trend through the decade (10.66 and 5.73 per 1,000 paediatric inhabitants in 2008 and 2017 respectively). Antipsychotics (N05A) followed a steady increase and reached the second place in 2017 (6.72 per 1,000 paediatric inhabitants). The evolution for the other ATC groups remained generally more stable, with no clear trend of increase in their use along the study period (see Figure 43).

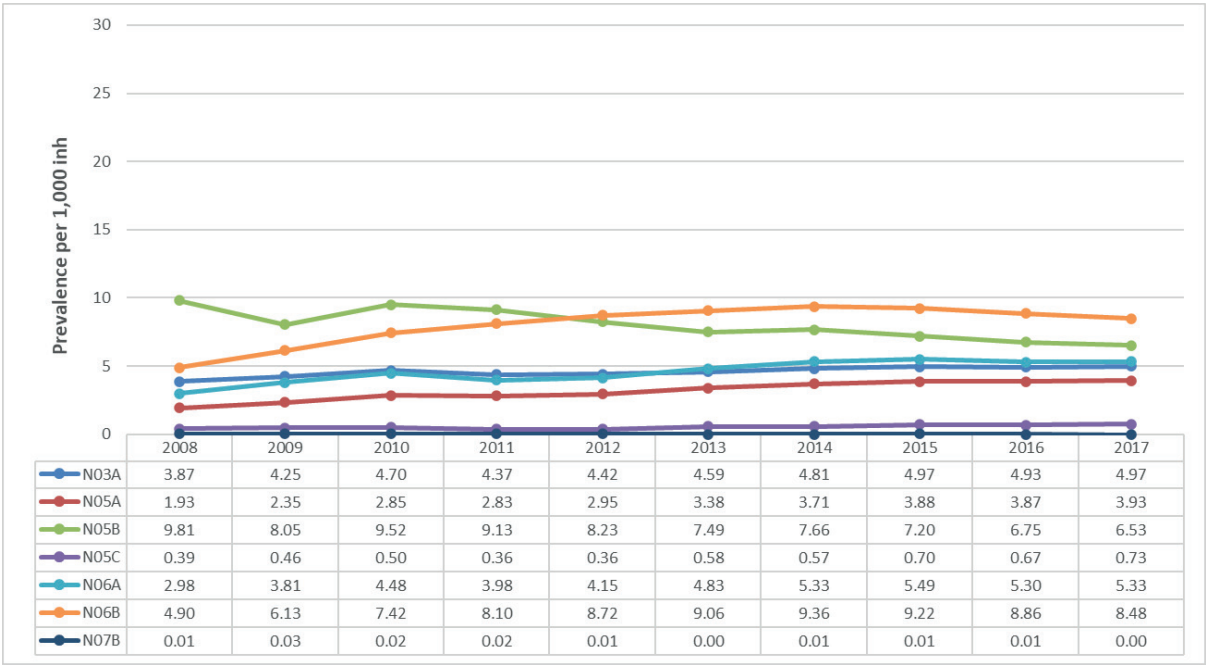
Boys were found to be more exposed to psychostimulants (N06B) along the years and then to antipsychotics (N05A) since 2012 (peak: 26.03 and 9.33 per 1,000 male paediatric inhabitants in 2013 and 2017 respectively), whereas girls were clearly more exposed to antidepressants (N06A) and hypnotics/sedatives (N05C) from 2012 onwards (peak: 5.49 and 0.73 per 1,000 female paediatric inhabitants in 2015 and in 2017 respectively) but with the observed differences in exposure not being so significant in comparison to the ones in boys. Anxiolytics (N05B) were moved from the second most exposed group to the third one since 2012 for both sex groups. Following the same pattern, the rest of the ATC groups had no clear trend in differences depending on the sex (see Figure 44 and Figure 45).

Figure 43. Prevalence of psychotropic drug use by ATC group in Catalonia (Spain) from 2008 to 2017 - target exposures.



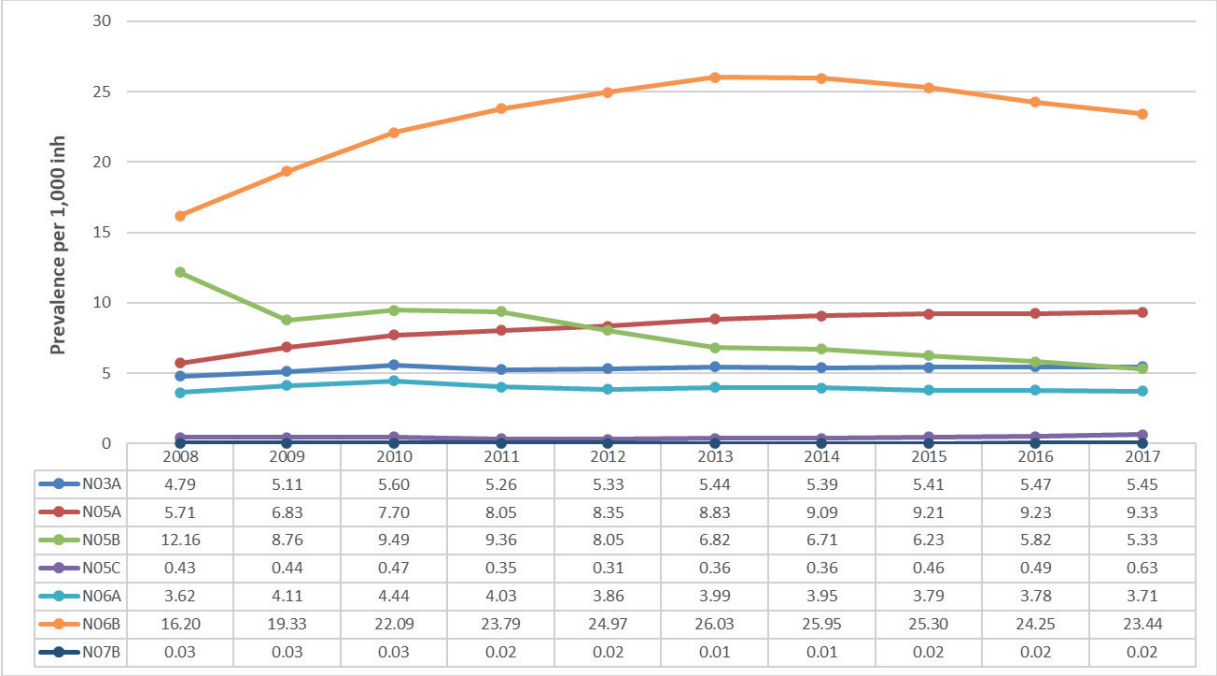
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
N03A	4.34	4.69	5.16	4.83	4.89	5.03	5.11	5.19	5.21	5.22
N05A	3.87	4.66	5.35	5.53	5.74	6.19	6.49	6.63	6.64	6.72
N05B	10.66	8.15	9.20	8.94	7.87	6.91	6.94	6.49	6.07	5.73
N05C	0.41	0.45	0.49	0.36	0.34	0.46	0.46	0.58	0.58	0.68
N06A	3.31	3.97	4.46	4.00	4.00	4.39	4.62	4.61	4.51	4.49
N06B	10.72	12.93	14.99	16.21	17.12	17.83	17.93	17.53	16.81	16.21
N07B	0.02	0.03	0.03	0.02	0.02	0.01	0.01	0.01	0.01	0.01

Figure 44. Prevalence of psychotropic drug use by ATC group in Catalonia (Spain) from 2008 to 2017 - target exposures (girls).



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
N03A	3.87	4.25	4.70	4.37	4.42	4.59	4.81	4.97	4.93	4.97
N05A	1.93	2.35	2.85	2.83	2.95	3.38	3.71	3.88	3.87	3.93
N05B	9.81	8.05	9.52	9.13	8.23	7.49	7.66	7.20	6.75	6.53
N05C	0.39	0.46	0.50	0.36	0.36	0.58	0.57	0.70	0.67	0.73
N06A	2.98	3.81	4.48	3.98	4.15	4.83	5.33	5.49	5.30	5.33
N06B	4.90	6.13	7.42	8.10	8.72	9.06	9.36	9.22	8.86	8.48
N07B	0.01	0.03	0.02	0.02	0.01	0.00	0.01	0.01	0.01	0.00

Figure 45. Prevalence of psychotropic drug use by ATC group in Catalonia (Spain) from 2008 to 2017 - target exposures (boys).

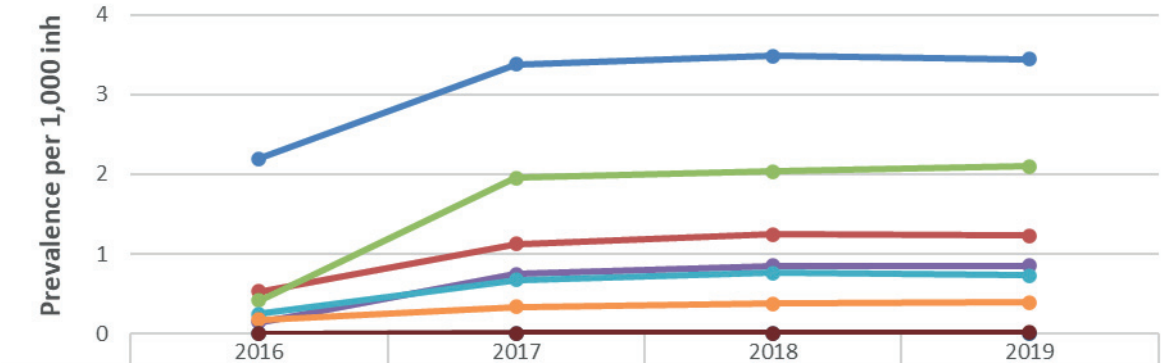


	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
N03A	4.79	5.11	5.60	5.26	5.33	5.44	5.39	5.41	5.47	5.45
N05A	5.71	6.83	7.70	8.05	8.35	8.83	9.09	9.21	9.23	9.33
N05B	12.16	8.76	9.49	9.36	8.05	6.82	6.71	6.23	5.82	5.33
N05C	0.43	0.44	0.47	0.35	0.31	0.36	0.36	0.46	0.49	0.63
N06A	3.62	4.11	4.44	4.03	3.86	3.99	3.95	3.79	3.78	3.71
N06B	16.20	19.33	22.09	23.79	24.97	26.03	25.95	25.30	24.25	23.44
N07B	0.03	0.03	0.03	0.02	0.02	0.01	0.01	0.02	0.02	0.02

Concerning Greece, antiepileptics (N03A) found to have the higher exposure during the whole period, followed by anxiolytics (N05B) and antipsychotics (N05A) with the highest rate of the observed prevalence been of 3.48 (in 2018), 1.25 (in 2018) and 2.10 (in 2019) per 1,000 paediatric inhabitants respectively. In general, the differences in the trend throughout the study period were stable for all ATC groups, where the lowest rate observed in 2016 for all of them (see Figure 46).

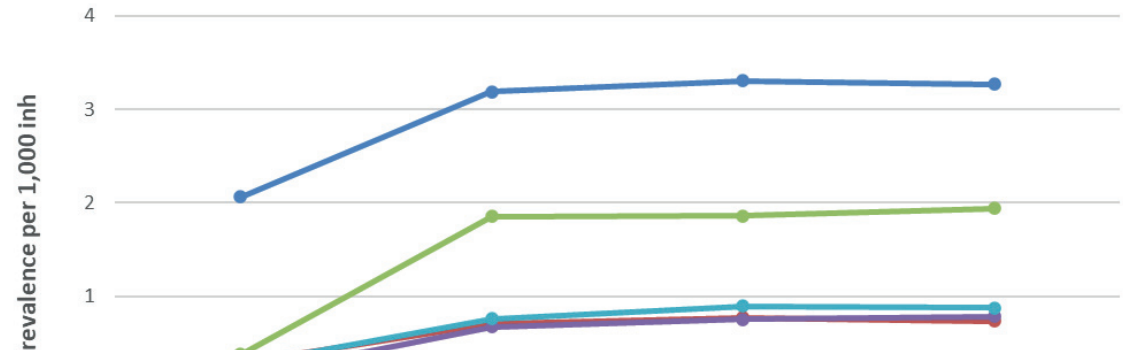
Boys' exposure to all psychotropic ATC groups was higher for the whole study period except for antidepressants (N06A) where girls had a higher exposure. The prevalence in psychostimulants (N06B) along the years (peak: 0.63 per 1,000 male paediatric inhabitants in 2018) was significantly lower compared to Catalan data, while girls were barely exposed to this ATC group (peak: 0.14 per 1,000 female inhabitants in 2019). The use of antipsychotics (N05A) in boys is more than double in all study years compared to girls (peak: 1.70 vs 0.77 per 1,000 male vs female paediatric inhabitants in 2019 and 2018 respectively). However, similar to the analysis for all sexes presented above, the fluctuations throughout the study period were stable for all ATC groups for girls and boys, with 2016 been identified as the year of the lowest rate (see Figure 47 and Figure 48).

Figure 46. Prevalence of psychotropic drug use by ATC group in Greece from 2016 to 2019 - target exposures.



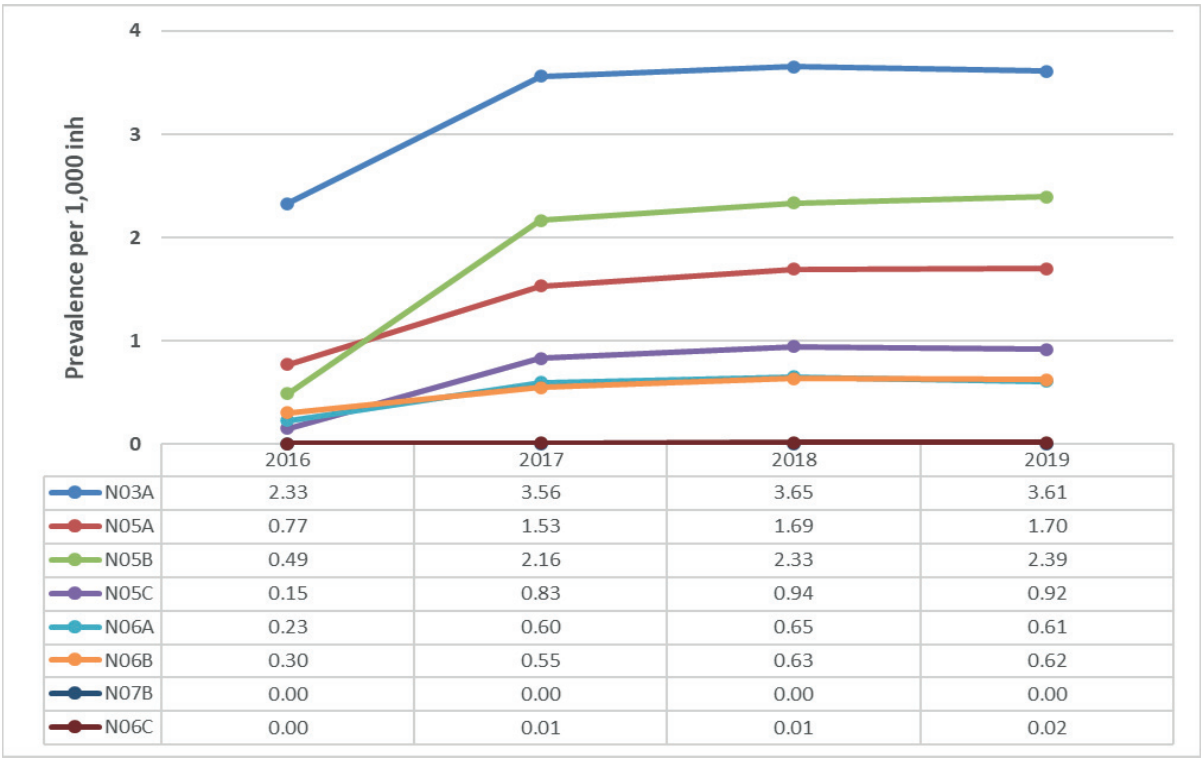
	2016	2017	2018	2019
N03A	2.20	3.38	3.48	3.45
N05A	0.54	1.13	1.25	1.23
N05B	0.42	1.95	2.04	2.10
N05C	0.15	0.75	0.85	0.85
N06A	0.25	0.68	0.77	0.74
N06B	0.18	0.34	0.38	0.39
N07B	0.00	0.00	0.00	0.00
N06C	0.00	0.01	0.01	0.02

Figure 47. Prevalence of psychotropic drug use by ATC group in Greece from 2016 to 2019 - target exposures (girls).



	2016	2017	2018	2019
N03A	2.06	3.19	3.31	3.27
N05A	0.29	0.70	0.77	0.73
N05B	0.38	1.85	1.86	1.94
N05C	0.14	0.67	0.75	0.78
N06A	0.27	0.76	0.89	0.87
N06B	0.06	0.11	0.11	0.14
N07B	0.00	0.00	0.00	0.00
N06C	0.00	0.01	0.01	0.01

Figure 48. Prevalence of psychotropic drug use by ATC group in Greece from 2016 to 2019 - target exposures (boys).



	2016	2017	2018	2019
N03A	2.33	3.56	3.65	3.61
N05A	0.77	1.53	1.69	1.70
N05B	0.49	2.16	2.33	2.39
N05C	0.15	0.83	0.94	0.92
N06A	0.23	0.60	0.65	0.61
N06B	0.30	0.55	0.63	0.62
N07B	0.00	0.00	0.00	0.00
N06C	0.00	0.01	0.01	0.02

4.2.2.5 Prevalence by ATC4 group per year and per age strata - target exposures

The following figures present the analysis of data done comparing the target exposed paediatric population as per the observed prevalence of psychotropic ATC use per year and age strata throughout the corresponding study periods in both Catalan and Greek territories.

Concerning the use of antiepileptics (N03A), the prevalence of use increases with the age in both countries, and in the analysis per sex as well. The evolution of antiepileptics (N03A) prevalence is given in Figure 49 below, where Greek children are less exposed than the ones in Catalonia with slight fluctuations.

The same pattern as in the antiepileptics (N03A) was observed also in the evolution of antipsychotics (N05A) prevalence of use for both country sets as it can be seen in Figure 50 below. Adolescent boys are in general more exposed than girls in both countries, but in Catalonia after the peak observed in 2012 for 15-17year-old boys, the youngest adolescent boys (12-14 years old) were more exposed until the end of the study period.

As regards the evolution of anxiolytics (N05B) prevalence per age strata throughout the study years, some differences were identified between the countries as it can be seen in Figure 51 below. In Catalonia, although anxiolytics (N05B) continued to increase with the age, a downward

trend from 2010 onwards was observed, and girls were more exposed than boys in all age strata. In Greece the exposure was lower compared to Catalonia and the prevalence in younger children was higher than in adolescents; the prevalence trend varied for younger children while it was more stable in adolescents.

Figure 52 below demonstrates the prevalence of hypnotics/sedatives (N05C) per age groups throughout the study periods. Catalonia's paediatric population exposure increases with the age, with older adolescents' (15-17 years old) prevalence in hypnotics/sedatives (N05C) to be almost double than in the other age groups; girls were more exposed and there was an upward trend for the 12-17year-olds. Greek younger children (apart from the <1year-olds) had a higher prevalence than the older adolescent subset with a lot of fluctuations during the study period.

Antidepressants (N06A) use was also increased with the age in both countries and adolescent girls had a significant higher prevalence than boys. Figure 53 below presents the evolution of antidepressants (N06A) prevalence per age strata, study year and sex, where the prevalence is higher in Catalonia as it has been observed in all other analyses so far.

The prevalence of use of psychostimulants (N06B) during the study periods in both countries is given in Figure 54 below. The difference in the rates is extremely significant among the countries, but the evolution of psychostimulants (N06B) prevalence in girls of all ages in both country sets was quite stable for the study periods. Boys of 12-14 years of age are more exposed to psychostimulants (N06B) in Catalonia, while the prevalence in other age groups (from 6 years of age and above) was fluctuated. In Greece, there were more instabilities in the evolution of prevalence analysed by sex and can be seen below.

Psycholeptics & psychoanaleptics in combination (N06C) data were not included in the initial data request for Catalonia hence no data were collected. Therefore, Figure 55 below presents only the limited data collected from the Greek territory.

Drugs used in addictive disorders (N07B) were also very limited and Figure 56 below demonstrates the prevalence of use per age group, sex and study year with several fluctuations.

Figure 49. Antiepileptics (N03A): prevalence of use per age strata and year - target exposures.

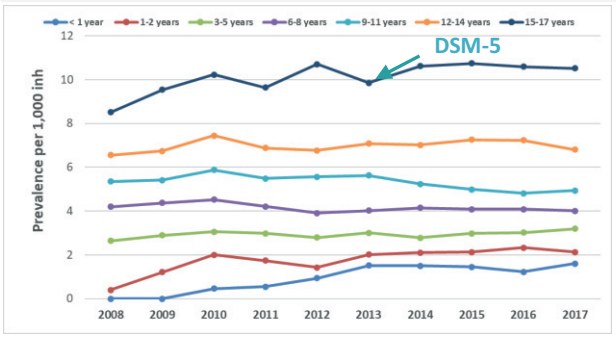
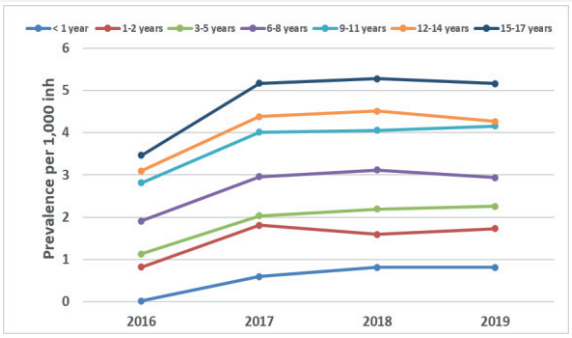
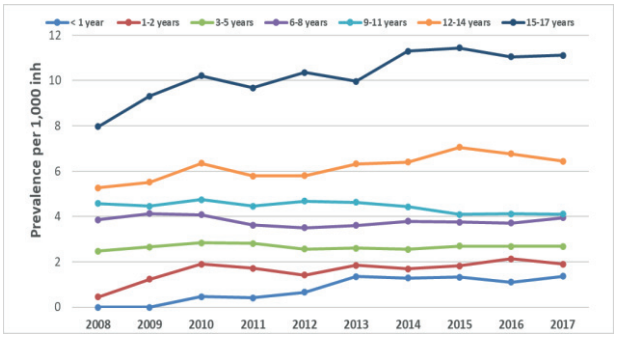
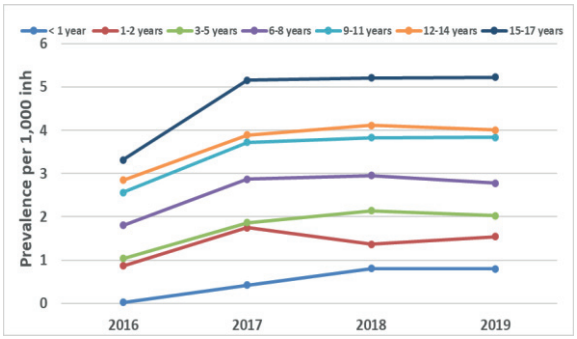
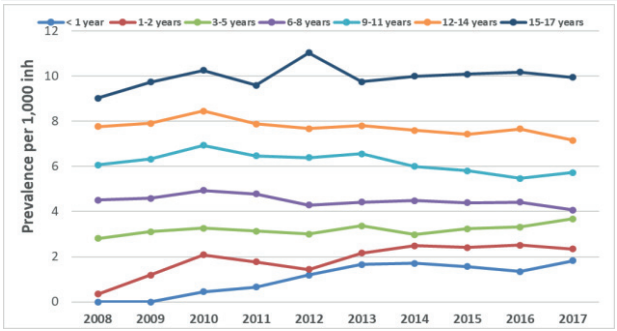
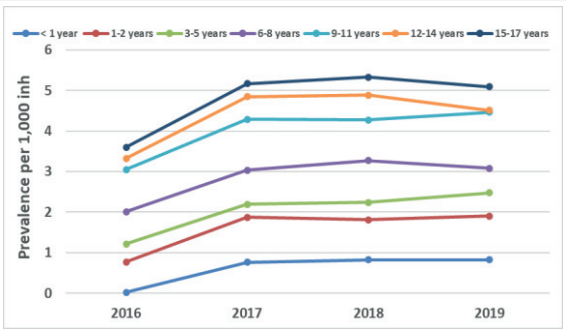
Catalonia (Spain)	Greece
Overall	
	
Girls	
	
Boys	
	

Figure 50. Antipsychotics (N05A): prevalence of use per age strata and year - target exposures.

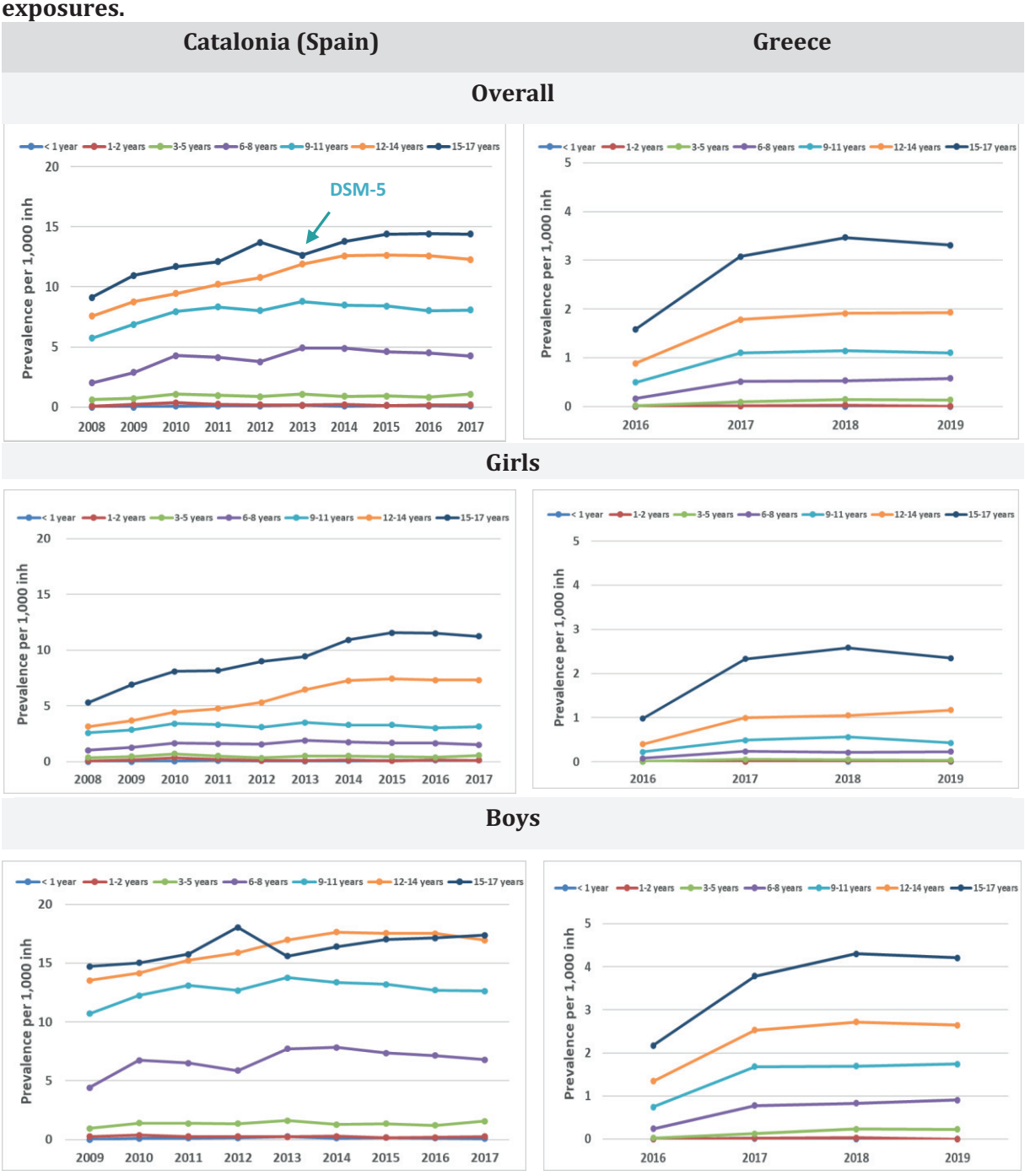


Figure 51. Anxiolytics (N05B): prevalence of use per age strata and year - target exposures.

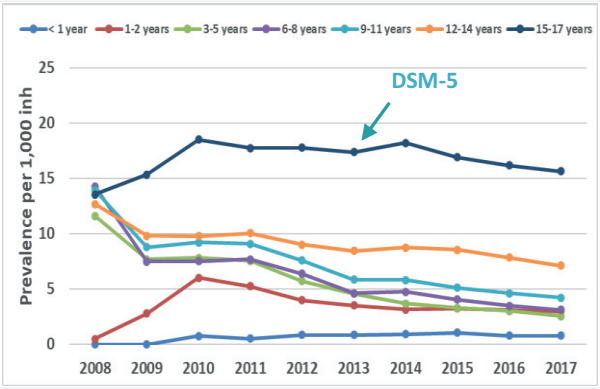
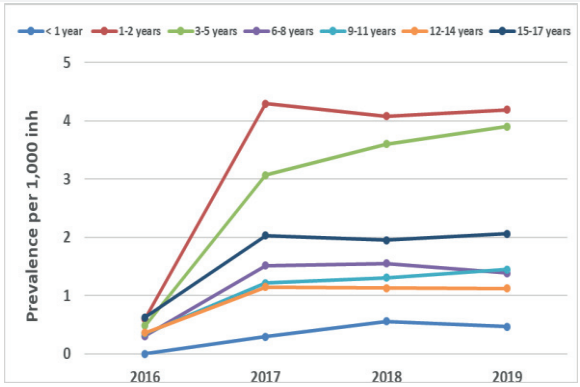
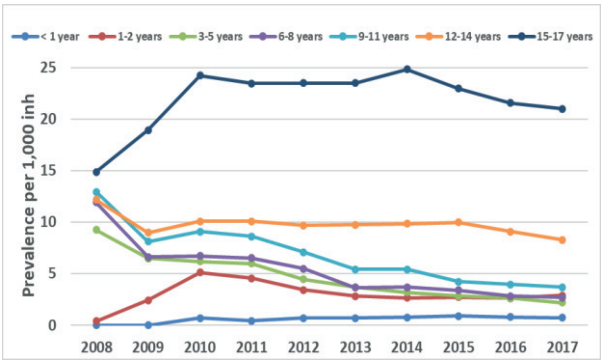
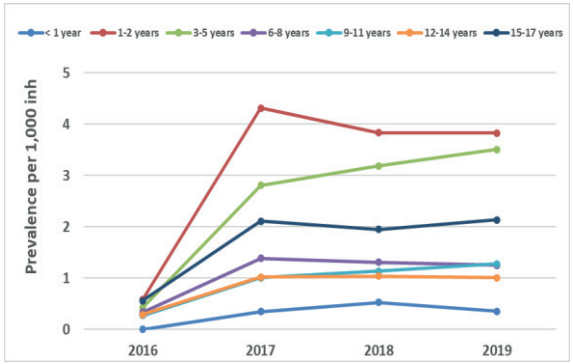
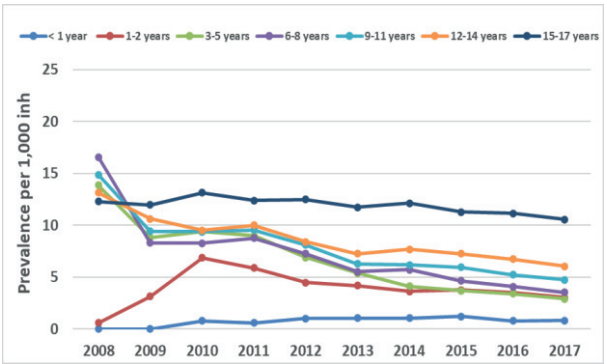
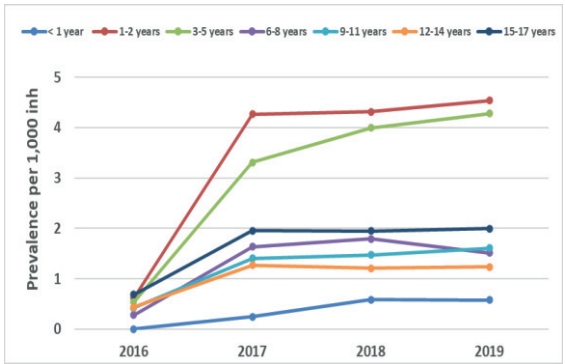
Catalonia (Spain)	Greece
Overall	
	
Girls	
	
Boys	
	

Figure 52. Hypnotics & Sedatives (N05C): prevalence of use per age strata and year - target exposures.

Figure 53. Antidepressants (N06A): prevalence of use per age strata and year - target exposures.

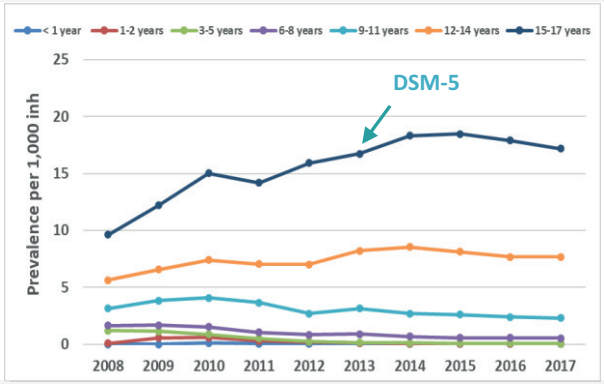
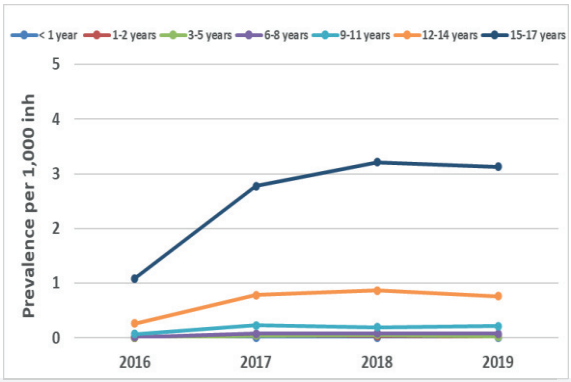
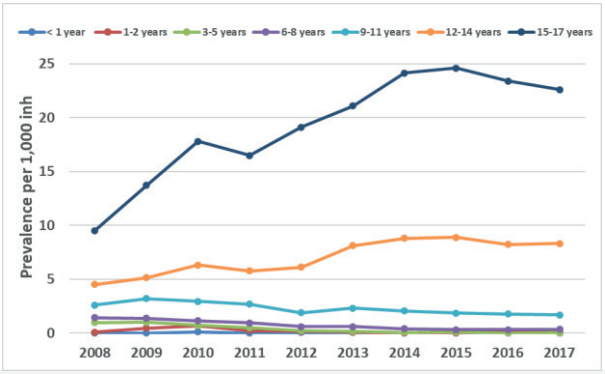
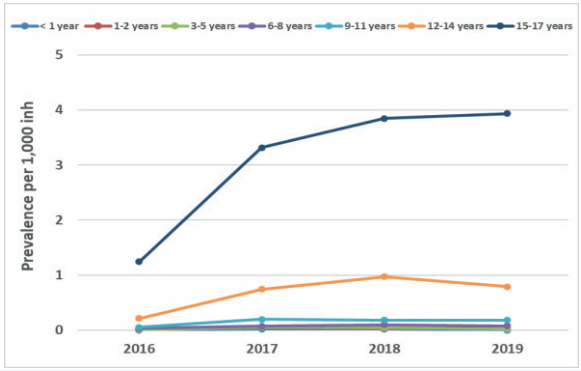
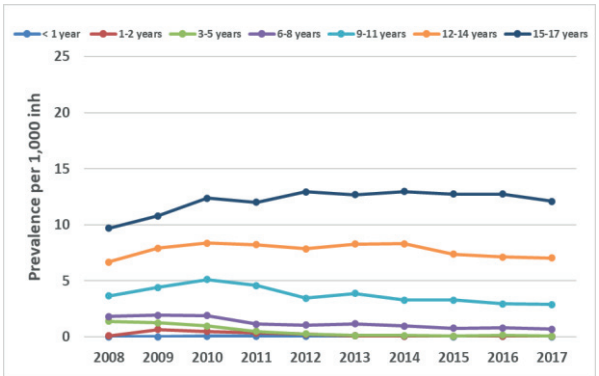
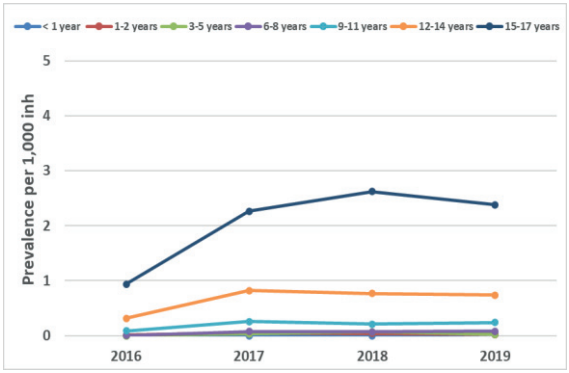
Catalonia (Spain)	Greece
Overall	
	
Girls	
	
Boys	
	

Figure 54. Psychostimulants, agents used for ADHD and nootropics (N06B): prevalence of use per age strata and year - target exposures.

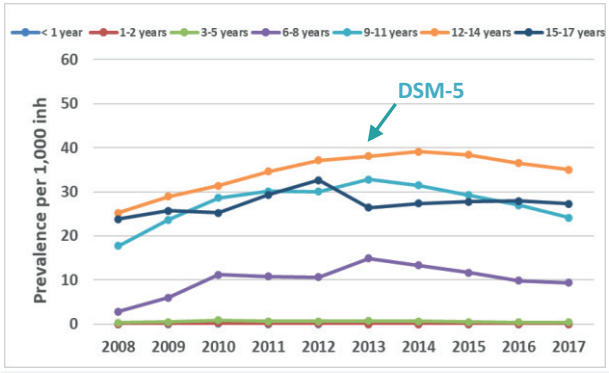
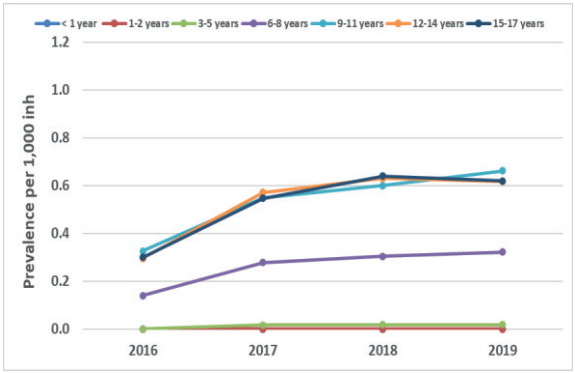
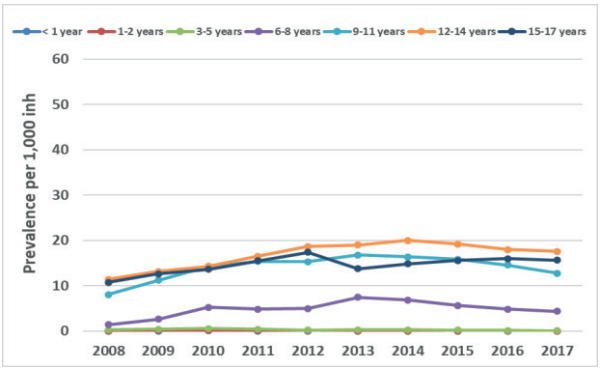
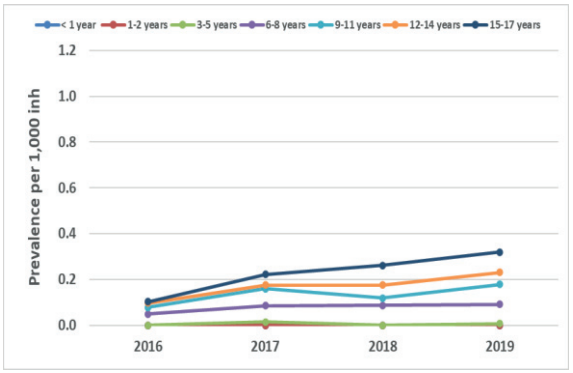
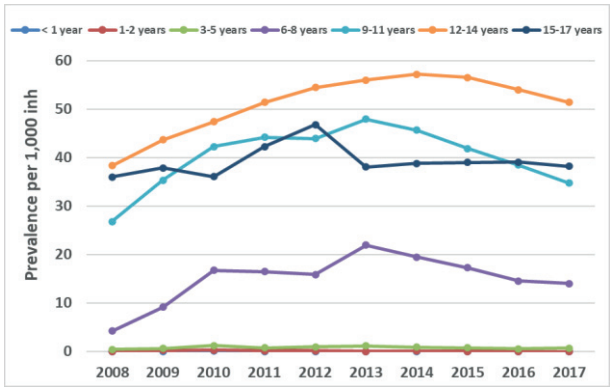
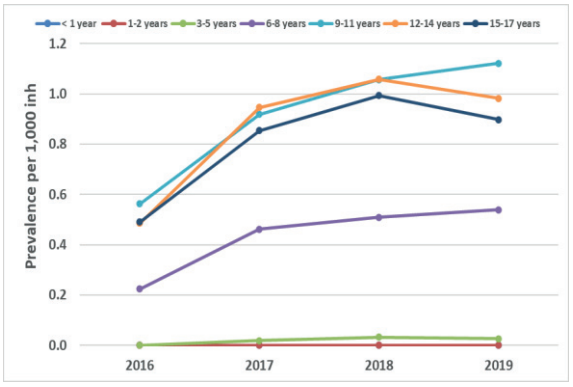
Catalonia (Spain)	Greece
Overall	
	
Girls	
	
Boys	
	

Figure 55. Psycholeptics & psychoanaleptics in combination (N06C): prevalence of use per age strata and year - target exposures.

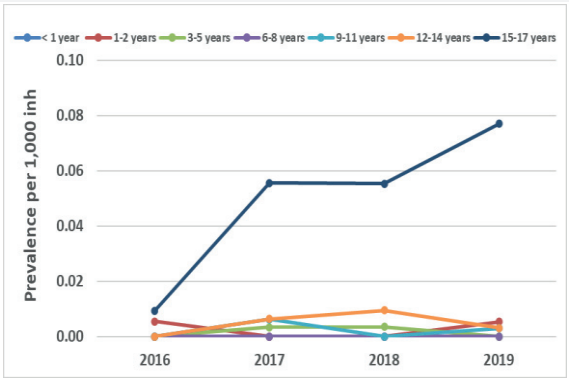
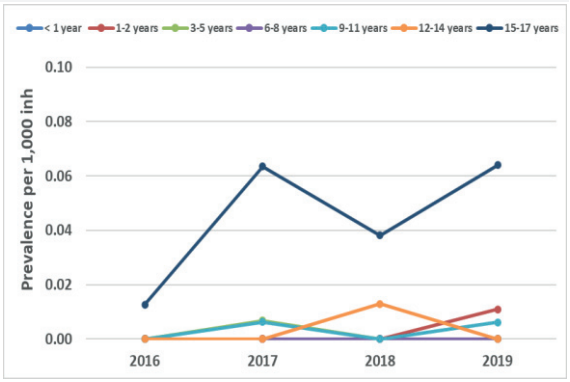
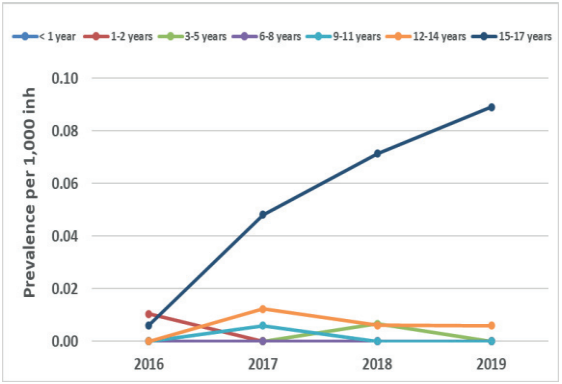
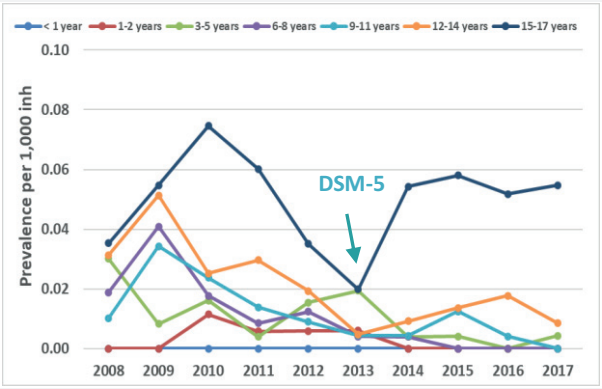
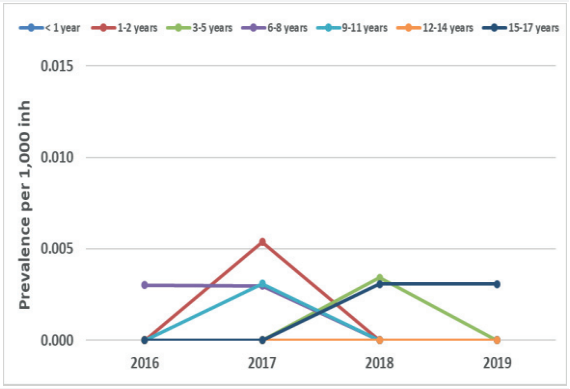
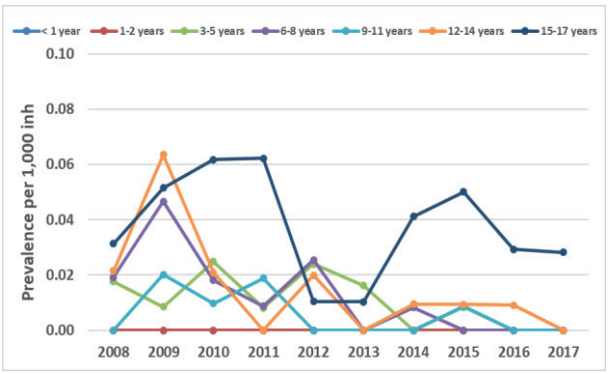
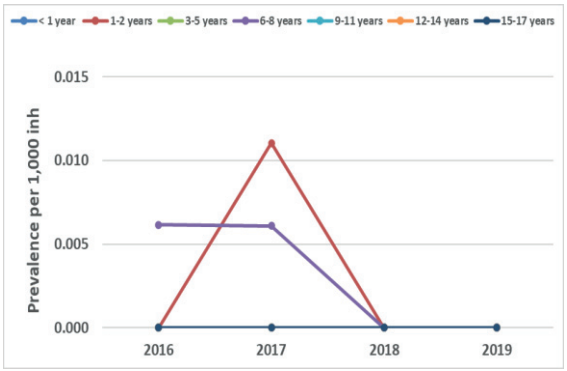
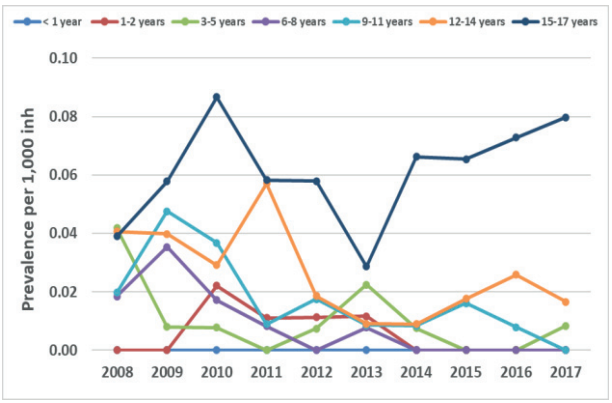
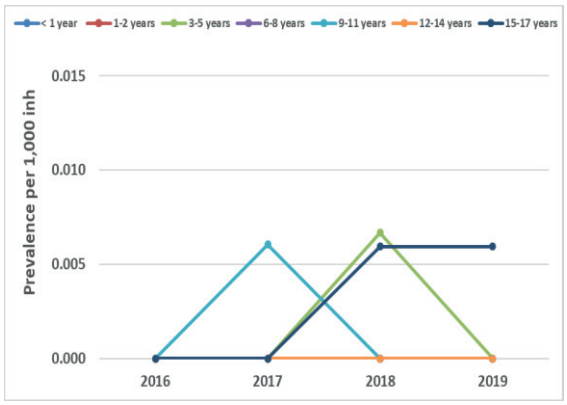
Catalonia (Spain)	Greece
Overall	
	
Girls	
	
Boys	
	

Figure 56. Drugs used in addictive disorders (N07B): prevalence of use per age strata and year - target exposures.

Catalonia (Spain)	Greece
Overall	
	
Girls	
	
Boys	
	

4.2.2.6 Medicines with higher prevalence of use - target exposures

The analysis of the most frequently used psychotropics in the target exposed populations was done combining both regions, as well as separately for Catalonia concerning the ten-year period and for Greece in the almost four-year period. All data are summarised in the following figures and tables. All data below refer to prevalence per 1,000 inhabitants.

After combining the data for both regions, methylphenidate (N06BA04) had the higher prevalence observed for both sexes, as well as for boys separately, of 41.50 and 59.50 respectively (girls: 22.20). Diazepam (N05BA01) was the second most frequent medicine (25.70) representing at the same time the highest prevalence observed in girls (girls: 29.10 vs boys: 22.50). Even though hydroxyzine-only dispensations were excluded from the analysis of the target study populations, a high frequency of hydroxyzine (N05BB01) used in combination with other psychotropics exists, reaching up to 17.70 (boys: 20.40 vs girls: 15.30), leaving risperidone (N05AX08) as the fourth most prevalent medicine (15.70; boys: 22.90 vs girls: 8.00) in our study samples. However, when analysing the data per sex, we saw that the use of risperidone was higher in boys than of hydroxyzine (22.90 vs 20.40 respectively). For the remainder medicines, the prevalence was below ten, except for fluoxetine (N06AB03) which in girls reached up to 11.60. The most frequent used medicines combined from both countries, for both sexes and separately for each sex, are given in Figure 57.

When analysing separately the data for each region, and subsequently per sex, there were several differences between the two regions which are detailed in Figure 58. In Catalonia, the paediatric patients had the greatest exposure to methylphenidate, with a prevalence of 41.00, followed by diazepam (22.20), hydroxyzine (17.70), risperidone (14.20), fluoxetine (9.20), valproic acid (7.50), sertraline (7.30), atomoxetine and clonazepam with the same rate (6.60), and aripiprazole (5.90). In boys we observed an even higher prevalence concerning the exposure to methylphenidate (58.70), risperidone (20.80), hydroxyzine (19.90), atomoxetine (9.70), valproic acid (8.30), aripiprazole (7.90), while for the remainder a lower exposure was identified (diazepam: 18.70, fluoxetine: 7.80, sertraline: 6.90, clonazepam: 6.40). On the other hand, girls had a higher prevalence in use of diazepam (26.00), fluoxetine (10.80), sertraline (7.70), clonazepam (6.80). Two new psychotropics were also in the top-10 list of most prevalent medicines used by girls, alprazolam (6.70) and lorazepam (6.30), while concerning methylphenidate (22.20), hydroxyzine (15.30), risperidone (7.20) and valproic acid (6.60) the exposure was lower than the ones observed in the whole population with both sexes. In Greece, the prevalence rates were in general much lower than the ones observed in Catalonia. Greek paediatric patients were found to be more exposed to diazepam (3.50), levetiracetam (2.40), valproic acid (2.10), midazolam (1.70), risperidone (1.50), oxcarbazepine (1.00), fluoxetine (0.70), and to aripiprazole, sertraline and methylphenidate each having the same rate (0.50). The differences observed between the sexes were slightly increased or

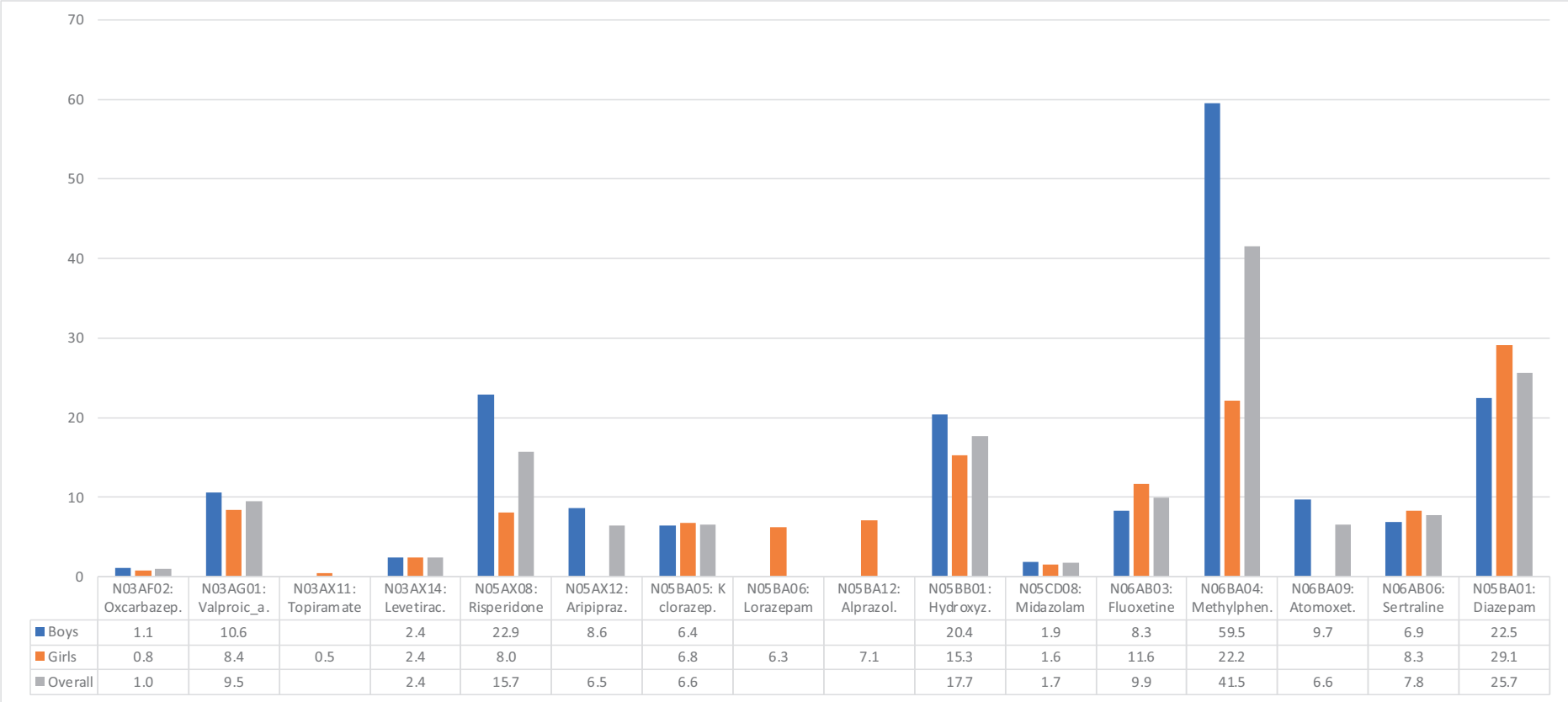
decreased when compared to the ones from both sexes, whereas no difference was observed for levetiracetam. Boys were slightly more exposed to all medicines in the above-mentioned list, apart from fluoxetine, with the highest difference between the sexes been found in the use of diazepam (boys: 3.80 vs girls: 3.10), valproic acid (boys: 2.30 vs girls: 1.80) and risperidone (boys: 2.10 vs girls: 0.90). In girls, the list is complemented by topiramate, alprazolam and sertraline, whereas in boys by the addition of aripiprazole, hydroxyzine and methylphenidate.

In the following tables (Table 59 and Table 60), two heatmaps present in detail the most prevalent psychotropics used by various age strata for each region in the target exposed paediatric population.

In Catalonia, the age group 12-14 years had higher exposures to methylphenidate, risperidone, atomoxetine, aripiprazole and potassium clorazepate, but the first exposure to the concerned psychotropics was in the age group of 3-5 years (methylphenidate and risperidone) and of 6-8 years (atomoxetine, aripiprazole and potassium clorazepate) respectively. The prevalence of use was higher in the age group 15-17 years for diazepam, valproic acid, fluoxetine, sertraline and alprazolam, where the first patients were of <1 year of age for the first two mentioned psychotropics, of 9-11 years for fluoxetine and sertraline, and of 3-5 years for alprazolam. Hydroxyzine had the highest prevalence rate in the 6-8year-old age group (first patients <1 years old), and any exposure to lorazepam and quetiapine was only detected in the 15-17year-olds. Details on the observed differences in the prevalence of psychotropics pertaining in the most frequent used for all Catalan target exposed paediatric population as well as the analysis by sex can be found below in Table 59.

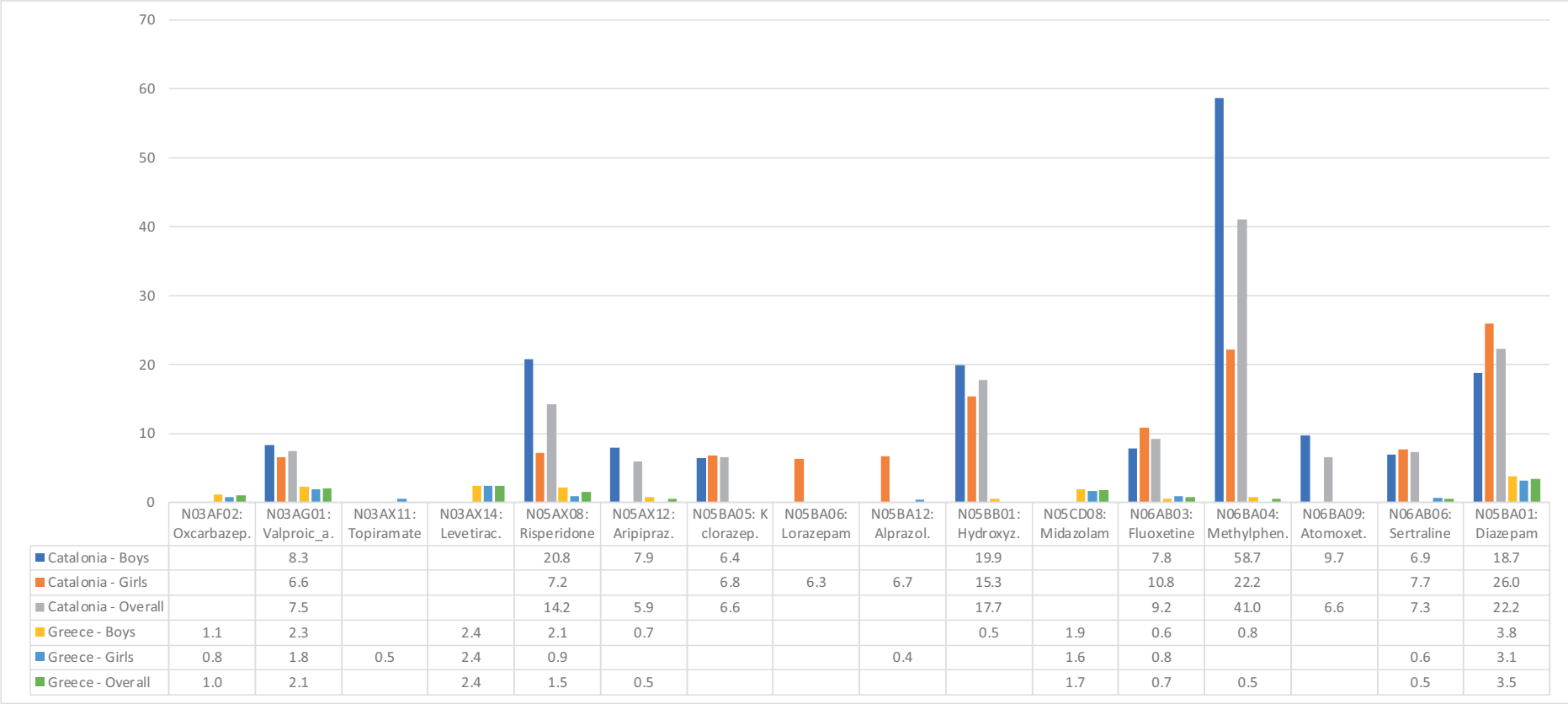
In general, the highest prevalence in Greece was observed in diazepam (11.30) and was in the group of 1-2year-olds with its exposure been only present in the groups aged <1year to 6-9 years. Levetiracetam and valproic acid were found in all age subsets with the highest prevalence been in 15-17year-olds and the first exposure to the concerned active substances been in the subset <1 year of age. Risperidone, aripiprazole and fluoxetine had also the highest prevalence in the group of 15-17year-olds, with risperidone's lower age group been the 3-5year-olds while for aripiprazole was the 6-8year-olds and for fluoxetine was the 12-14year-olds group. Sertraline, quetiapine and alprazolam were found dispensed only in the group of 15-17year-olds. All ages of the Greek target paediatric population were exposed to oxcarbazepine with the highest prevalence in the group of 12-14year-olds. Midazolam's highest prevalence was identified also in the group of 12-14year-olds, but midazolam was found in all other age groups except for the older adolescent subset (15-17year-olds). It is worth to highlight here that methylphenidate's prevalence per age group was lower in the Greek population compared to the other active substances, with the highest rate been in the group of 12-14year-olds and the youngest exposed age subset been of 6-8year-olds. The most frequent per age group active substances identified in the Greek paediatric study population are given below in Table 60, where also the differences observed by sex can be found.

Figure 57. Most prevalent (per 1,000) medicines used, Catalonia (Spain) (from 2008 to 2017) and Greece (from 2016 to 2019) combined - target exposures.



	N03AF02: Oxcarbazep.	N03AG01: Valproic_a.	N03AX11: Topiramate	N03AX14: Levetirac.	N05AX08: Risperidone	N05AX12: Aripipraz.	N05BA05: Klorazep.	N05BA06: Lorazepam	N05BA12: Alprazol.	N05BB01: Hydroxyz.	N05CD08: Midazolam	N06AB03: Fluoxetine	N06BA04: Methylphen.	N06BA09: Atomoxet.	N06AB06: Sertraline	N05BA01: Diazepam
Boys	1.1	10.6		2.4	22.9	8.6	6.4			20.4	1.9	8.3	59.5	9.7	6.9	22.5
Girls	0.8	8.4	0.5	2.4	8.0		6.8	6.3	7.1	15.3	1.6	11.6	22.2		8.3	29.1
Overall	1.0	9.5		2.4	15.7	6.5	6.6			17.7	1.7	9.9	41.5	6.6	7.8	25.7

Figure 58. Most prevalent (per 1,000) medicines used in Catalonia (Spain) (from 2008 to 2017) and Greece (from 2016 to 2019) - target exposures.



	N03AF02: Oxcarbazep.	N03AG01: Valproic_a.	N03AX11: Topiramate	N03AX14: Levetirac.	N05AX08: Risperidone	N05AX12: Aripipraz.	N05BA05: K clorazep.	N05BA06: Lorazepam	N05BA12: Alprazol.	N05BB01: Hydroxyz.	N05CD08: Midazolam	N06AB03: Fluoxetine	N06BA04: Methylphen.	N06BA09: Atomoxet.	N06AB06: Sertraline	N05BA01: Diazepam
Catalonia - Boys		8.3			20.8	7.9	6.4			19.9		7.8	58.7	9.7	6.9	18.7
Catalonia - Girls		6.6			7.2		6.8	6.3	6.7	15.3		10.8	22.2		7.7	26.0
Catalonia - Overall		7.5			14.2	5.9	6.6			17.7		9.2	41.0	6.6	7.3	22.2
Greece - Boys	1.1	2.3		2.4	2.1	0.7				0.5	1.9	0.6	0.8			3.8
Greece - Girls	0.8	1.8	0.5	2.4	0.9				0.4		1.6	0.8			0.6	3.1
Greece - Overall	1.0	2.1		2.4	1.5	0.5					1.7	0.7	0.5		0.5	3.5

Table 59. Heatmap table for the most prevalent medicines used by age strata in Catalonia (Spain) from 2008 to 2017 - target exposures.

		Overall	Prev. (‰)	Girls	Prev. (‰)	Boys	Prev. (‰)
< 1 year	1	N03AG01: Valproic acid	3.5	N05BA01: Diazepam	3.2	N03AG01: Valproic acid	4.1
	2	N05BA01: Diazepam	3.5	N03AG01: Valproic acid	2.9	N05BA01: Diazepam	3.8
	3	N03AX14: Levetiracetam	2.8	N03AX14: Levetiracetam	2.6	N03AX14: Levetiracetam	3
	4	N05BB01: Hydroxyzine	1.7	N03AG04: Vigabatrin	1.2	N05BB01: Hydroxyzine	2.1
	5	N03AG04: Vigabatrin	1.4	N05BB01: Hydroxyzine	1.2	N03AG04: Vigabatrin	1.6
	6	N03AA02: Phenobarbital	1.1	N03AA02: Phenobarbital	1	N03AA02: Phenobarbital	1.3
	7	N05AA02: Levomepromazine	0.5	N05AA02: Levomepromazine	0.4	N03AF02: Oxcarbazepine	0.5
	8	N03AF02: Oxcarbazepine	0.4	N05BA09: Clobazam	0.4	N05AA02: Levomepromazine	0.5
	9	N05BA09: Clobazam	0.4	N03AF02: Oxcarbazepine	0.3	N03AE01: Clonazepam	0.5
	10	N03AE01: Clonazepam	0.4	N03AE01: Clonazepam	0.3	N05BA09: Clobazam	0.4
1-2 years	1	N05BA01: Diazepam	17.8	N05BA01: Diazepam	16.1	N05BA01: Diazepam	19.3
	2	N05BB01: Hydroxyzine	11.1	N05BB01: Hydroxyzine	8.4	N05BB01: Hydroxyzine	13.7
	3	N03AG01: Valproic acid	7.4	N03AG01: Valproic acid	6.9	N03AG01: Valproic acid	7.8
	4	N03AX14: Levetiracetam	3.1	N03AX14: Levetiracetam	2.7	N03AX14: Levetiracetam	3.4
	5	N05BX92: Passiflora	2.7	N05BX92: Passiflora	2.4	N05BX92: Passiflora	3
	6	N03AG04: Vigabatrin	1.1	N03AG04: Vigabatrin	1	N03AA02: Phenobarbital	1.3
	7	N03AA02: Phenobarbital	1.1	N03AF02: Oxcarbazepine	1	N03AG04: Vigabatrin	1.2
	8	N03AF02: Oxcarbazepine	0.9	N03AA02: Phenobarbital	0.9	N05AA02: Levomepromazine	0.9
	9	N05BA09: Clobazam	0.8	N05BA09: Clobazam	0.8	N05BA09: Clobazam	0.9
	10	N03AF01: Carbamazepine	0.8	N05BA12: Alprazolam	0.7	N03AF02: Oxcarbazepine	0.8
3-5 years	1	N05BB01: Hydroxyzine	26	N05BB01: Hydroxyzine	19.6	N05BB01: Hydroxyzine	32.1
	2	N05BA01: Diazepam	14.4	N05BA01: Diazepam	13	N05BA01: Diazepam	15.8
	3	N03AG01: Valproic acid	9.6	N03AG01: Valproic acid	8.8	N03AG01: Valproic acid	10.4
	4	N05AX08: Risperidone	4.3	N05BX92: Passiflora	3.7	N05AX08: Risperidone	6.3
	5	N06BA04: Methylphenidate	4	N03AX14: Levetiracetam	3.4	N06BA04: Methylphenidate	5.8
	6	N05BX92: Passiflora	4	N06BA04: Methylphenidate	2.2	N05BX92: Passiflora	4.3
	7	N03AX14: Levetiracetam	3.7	N05AX08: Risperidone	2.1	N03AX14: Levetiracetam	3.9
	8	N03AF01: Carbamazepine	1.5	N03AF01: Carbamazepine	1.5	N05BA12: Alprazolam	1.6
	9	N05BA12: Alprazolam	1.5	N03AF02: Oxcarbazepine	1.4	N03AF01: Carbamazepine	1.6
	10	N03AF02: Oxcarbazepine	1.5	N05BA12: Alprazolam	1.3	N05BA05: Potassium clorazepate	1.6
6-8 years	1	N06BA04: Methylphenidate	53.1	N06BA04: Methylphenidate	27.2	N06BA04: Methylphenidate	77.3
	2	N05BB01: Hydroxyzine	29	N05BB01: Hydroxyzine	23	N05BB01: Hydroxyzine	34.7
	3	N05AX08: Risperidone	17.3	N03AG01: Valproic acid	10.7	N05AX08: Risperidone	27.4
	4	N03AG01: Valproic acid	11.7	N05BA01: Diazepam	10.1	N03AG01: Valproic acid	12.6
	5	N05BA01: Diazepam	10.8	N05AX08: Risperidone	6.5	N05BA01: Diazepam	11.5
	6	N06BA09: Atomoxetine	5.1	N03AX14: Levetiracetam	4.5	N06BA09: Atomoxetine	7.7
	7	N05BA05: Potassium clorazepate	4.8	N05BX92: Passiflora	4.2	N05AX12: Aripiprazole	7.5
	8	N05AX12: Aripiprazole	4.7	N05BA05: Potassium clorazepate	4	N05BA05: Potassium clorazepate	5.5
	9	N03AX14: Levetiracetam	4.7	N03AF01: Carbamazepine	2.7	N03AX14: Levetiracetam	4.9
	10	N05BX92: Passiflora	4.4	N06BA09: Atomoxetine	2.4	N05BX92: Passiflora	4.6

		Overall	Prev. (‰)	Girls	Prev. (‰)	Boys	Prev. (‰)
9-11 years	1	N06BA04: Methylphenidate	111.9	N06BA04: Methylphenidate	59.9	N06BA04: Methylphenidate	160.8
	2	N05AX08: Risperidone	30.4	N05BB01: Hydroxyzine	23.9	N05AX08: Risperidone	47.9
	3	N05BB01: Hydroxyzine	27.4	N05BA01: Diazepam	14.1	N05BB01: Hydroxyzine	30.6
	4	N06BA09: Atomoxetine	15.2	N05AX08: Risperidone	11.8	N06BA09: Atomoxetine	22.8
	5	N05BA01: Diazepam	14.1	N03AG01: Valproic acid	10.7	N05AX12: Aripiprazole	15.6
	6	N03AG01: Valproic acid	12.6	N05BA05: Potassium clorazepate	9.5	N03AG01: Valproic acid	14.4
	7	N05BA05: Potassium clorazepate	10.4	N06BA09: Atomoxetine	7.2	N05BA01: Diazepam	14.1
	8	N05AX12: Aripiprazole	10	N05BX92: Passiflora	5.7	N05BA05: Potassium clorazepate	11.3
	9	N06AB03: Fluoxetine	7.2	N06AB03: Fluoxetine	5.4	N06BA12: Lisdexamfetamine	9.5
	10	N06AB06: Sertraline	6.5	N06AB06: Sertraline	4.9	N06AB03: Fluoxetine	8.9
12-14 years	1	N06BA04: Methylphenidate	142.4	N06BA04: Methylphenidate	73.2	N06BA04: Methylphenidate	207.4
	2	N05AX08: Risperidone	39	N05BA01: Diazepam	34	N05AX08: Risperidone	57.8
	3	N05BA01: Diazepam	29	N06AB03: Fluoxetine	21.9	N06BA09: Atomoxetine	29.5
	4	N06AB03: Fluoxetine	20.5	N05AX08: Risperidone	19	N05BA01: Diazepam	24.3
	5	N06BA09: Atomoxetine	19.5	N05BB01: Hydroxyzine	18.9	N05AX12: Aripiprazole	22.5
	6	N05BB01: Hydroxyzine	18.9	N06AB06: Sertraline	16.3	N06AB03: Fluoxetine	19.1
	7	N06AB06: Sertraline	17.3	N05BA05: Potassium clorazepate	14.5	N06BA12: Lisdexamfetamine	18.9
	8	N05AX12: Aripiprazole	16.6	N03AG01: Valproic acid	12	N05BB01: Hydroxyzine	18.8
	9	N03AG01: Valproic acid	14.2	N05AX12: Aripiprazole	10.3	N06AB06: Sertraline	18.3
	10	N05BA05: Potassium clorazepate	14.2	N05BA06: Lorazepam	9.1	N03AG01: Valproic acid	16.3
15-17 years	1	N06BA04: Methylphenidate	119.8	N05BA01: Diazepam	98.3	N06BA04: Methylphenidate	172.5
	2	N05BA01: Diazepam	73.8	N06BA04: Methylphenidate	63.2	N05AX08: Risperidone	51.9
	3	N06AB03: Fluoxetine	39.4	N06AB03: Fluoxetine	52.3	N05BA01: Diazepam	51.1
	4	N05AX08: Risperidone	37	N06AB06: Sertraline	35.4	N06AB03: Fluoxetine	27.3
	5	N06AB06: Sertraline	29.6	N05BA12: Alprazolam	33.1	N06AB06: Sertraline	24.3
	6	N05BA12: Alprazolam	23.8	N05BA06: Lorazepam	29.5	N05AX12: Aripiprazole	23.7
	7	N05BA06: Lorazepam	22.1	N05AX08: Risperidone	21.1	N06BA09: Atomoxetine	22.4
	8	N05AX12: Aripiprazole	19.7	N03AX11: Topiramate	18.2	N03AG01: Valproic acid	18.4
	9	N05AH04: Quetiapine	16.8	N05AH04: Quetiapine	17.5	N05AH04: Quetiapine	16.3
	10	N03AG01: Valproic acid	16.4	N06AA09: Amitriptyline	16.7	N06BA12: Lisdexamfetamine	15.9

Table 60. Heatmap table for the most prevalent medicines used by age strata in Greece from 2016 to 2019 - target exposures.

		Overall	Prev. (‰)	Girls	Prev. (‰)	Boys	Prev. (‰)
< 1 year	1	N05BA01: Diazepam	1.2	N05BA01: Diazepam	1.1	N05BA01: Diazepam	1.3
	2	N03AA02: Phenobarbital	1.0	N03AX14: Levetiracetam	1.0	N03AA02: Phenobarbital	1.1
	3	N03AX14: Levetiracetam	0.9	N03AA02: Phenobarbital	0.8	N03AX14: Levetiracetam	0.9
	4	N05CD08: Midazolam	0.4	N05CD08: Midazolam	0.5	N05CD08: Midazolam	0.3
	5	N03AX11: Topiramate	0.3	N03AX11: Topiramate	0.3	N03AG01: Valproic acid	0.3
	6	N03AG01: Valproic acid	0.3	N03AG01: Valproic acid	0.3	N03AX11: Topiramate	0.2
	7	N03AF02: Oxcarbazepine	0.2	N03AF02: Oxcarbazepine	0.2	N05BB01: Hydroxyzine	0.1
	8	N05BB01: Hydroxyzine	0.1	N05BB01: Hydroxyzine	0.1	N03AF02: Oxcarbazepine	0.1
	9	N03AF01: Carbamazepine	0.1	N03AB02: Phenytoin	0.1	N03AF01: Carbamazepine	0.1
	10	N05BA09: Clobazam	0.1	N03AF01: Carbamazepine	0.1	N05BA09: Clobazam	0.1
1-2 years	1	N05BA01: Diazepam	11.3	N05BA01: Diazepam	10.7	N05BA01: Diazepam	11.7
	2	N03AX14: Levetiracetam	2.3	N03AX14: Levetiracetam	2.1	N03AX14: Levetiracetam	2.5
	3	N05CD08: Midazolam	2.1	N05CD08: Midazolam	2.0	N05CD08: Midazolam	2.2
	4	N03AG01: Valproic acid	1.4	N03AG01: Valproic acid	1.3	N03AG01: Valproic acid	1.6
	5	N05BB01: Hydroxyzine	0.8	N05BB01: Hydroxyzine	0.8	N05BB01: Hydroxyzine	0.8
	6	N03AA02: Phenobarbital	0.7	N03AA02: Phenobarbital	0.5	N03AA02: Phenobarbital	0.8
	7	N03AB02: Phenytoin	0.4	N03AB02: Phenytoin	0.5	N03AF02: Oxcarbazepine	0.4
	8	N03AF02: Oxcarbazepine	0.4	N03AF02: Oxcarbazepine	0.4	N03AX11: Topiramate	0.4
	9	N03AX11: Topiramate	0.3	N03AX11: Topiramate	0.3	N03AB02: Phenytoin	0.4
	10	N05BA09: Clobazam	0.3	N05BA09: Clobazam	0.3	N05BA09: Clobazam	0.3
3-5 years	1	N05BA01: Diazepam	8	N05BA01: Diazepam	7.1	N05BA01: Diazepam	8.9
	2	N03AX14: Levetiracetam	2.3	N03AX14: Levetiracetam	2.2	N03AX14: Levetiracetam	2.4
	3	N03AG01: Valproic acid	1.8	N03AG01: Valproic acid	1.6	N03AG01: Valproic acid	2.0
	4	N05CD08: Midazolam	1.6	N05CD08: Midazolam	1.5	N05CD08: Midazolam	1.7
	5	N05BB01: Hydroxyzine	0.7	N05BB01: Hydroxyzine	0.7	N05BB01: Hydroxyzine	0.8
	6	N03AF02: Oxcarbazepine	0.7	N03AF02: Oxcarbazepine	0.6	N03AF02: Oxcarbazepine	0.7
	7	N05BA09: Clobazam	0.4	N05BA09: Clobazam	0.4	N05BA09: Clobazam	0.4
	8	N03AX11: Topiramate	0.3	N03AX11: Topiramate	0.3	N05AX08: Risperidone	0.3
	9	N03AB02: Phenytoin	0.3	N03AB02: Phenytoin	0.2	N03AB02: Phenytoin	0.3
	10	N05AX08: Risperidone	0.2	N03AE01: Clonazepam	0.2	N03AX11: Topiramate	0.3
6-8 years	1	N05BA01: Diazepam	3.1	N03AX14: Levetiracetam	2.9	N05BA01: Diazepam	3.3
	2	N03AX14: Levetiracetam	2.9	N05BA01: Diazepam	2.8	N03AX14: Levetiracetam	2.9
	3	N03AG01: Valproic acid	2.6	N03AG01: Valproic acid	2.4	N03AG01: Valproic acid	2.7
	4	N05CD08: Midazolam	1.9	N05CD08: Midazolam	1.7	N05CD08: Midazolam	2.1
	5	N03AF02: Oxcarbazepine	1.2	N03AF02: Oxcarbazepine	1.1	N05AX08: Risperidone	1.6
	6	N05AX08: Risperidone	1.0	N05AX08: Risperidone	0.4	N03AF02: Oxcarbazepine	1.3
	7	N06BA04: Methylphenidate	0.5	N05BA09: Clobazam	0.4	N06BA04: Methylphenidate	0.8
	8	N05BA09: Clobazam	0.5	N03AX11: Topiramate	0.3	N05BA09: Clobazam	0.5
	9	N05BB01: Hydroxyzine	0.4	N05BB01: Hydroxyzine	0.2	N05AX12: Aripiprazole	0.5
	10	N05AX12: Aripiprazole	0.3	N03AX09: Lamotrigine	0.2	N05BB01: Hydroxyzine	0.5

		Overall	Prev. (‰)	Girls	Prev. (‰)	Boys	Prev. (‰)
9-11 years	1	N03AX14: Levetiracetam	3.5	N03AX14: Levetiracetam	3.5	N03AX14: Levetiracetam	3.6
	2	N03AG01: Valproic acid	3.3	N03AG01: Valproic acid	2.9	N03AG01: Valproic acid	3.6
	3	N05CD08: Midazolam	2.5	N05CD08: Midazolam	2.3	N05AX08: Risperidone	2.9
	4	N05BA01: Diazepam	2.3	N05BA01: Diazepam	1.9	N05CD08: Midazolam	2.7
	5	N05AX08: Risperidone	1.9	N03AF02: Oxcarbazepine	1.5	N05BA01: Diazepam	2.6
	6	N03AF02: Oxcarbazepine	1.8	N05AX08: Risperidone	0.8	N03AF02: Oxcarbazepine	2.1
	7	N06BA04: Methylphenidate	0.9	N05BA09: Clobazam	0.5	N06BA04: Methylphenidate	1.6
	8	N05BA09: Clobazam	0.5	N03AX09: Lamotrigine	0.4	N05AX12: Aripiprazole	0.8
	9	N05AX12: Aripiprazole	0.5	N05BB01: Hydroxyzine	0.3	N06BA09: Atomoxetine	0.6
	10	N03AX11: Topiramate	0.4	N03AX11: Topiramate	0.3	N05BA09: Clobazam	0.6
12-14 years	1	N03AX14: Levetiracetam	3.7	N03AX14: Levetiracetam	3.6	N05AX08: Risperidone	4.0
	2	N03AG01: Valproic acid	3.3	N03AG01: Valproic acid	2.9	N03AX14: Levetiracetam	3.8
	3	N05AX08: Risperidone	2.9	N05CD08: Midazolam	2.3	N03AG01: Valproic acid	3.6
	4	N05CD08: Midazolam	2.6	N05AX08: Risperidone	1.7	N05CD08: Midazolam	2.9
	5	N03AF02: Oxcarbazepine	1.9	N03AF02: Oxcarbazepine	1.5	N03AF02: Oxcarbazepine	2.2
	6	N05BA01: Diazepam	1.6	N05BA01: Diazepam	1.4	N05BA01: Diazepam	1.7
	7	N06AB03: Fluoxetine	1.1	N06AB03: Fluoxetine	1.1	N06BA04: Methylphenidate	1.7
	8	N06BA04: Methylphenidate	1.0	N03AX11: Topiramate	0.7	N05AX12: Aripiprazole	1.4
	9	N05AX12: Aripiprazole	1.0	N03AX09: Lamotrigine	0.6	N06AB03: Fluoxetine	1.1
	10	N03AX11: Topiramate	0.7	N06AB06: Sertraline	0.6	N03AX11: Topiramate	0.7
15-17 years	1	N05AX08: Risperidone	4.1	N03AX14: Levetiracetam	4.3	N05AX08: Risperidone	5.5
	2	N03AX14: Levetiracetam	4.1	N06AB03: Fluoxetine	3.5	N03AG01: Valproic acid	4.3
	3	N03AG01: Valproic acid	3.8	N03AG01: Valproic acid	3.3	N03AX14: Levetiracetam	3.9
	4	N06AB03: Fluoxetine	2.8	N06AB06: Sertraline	2.9	N06AB03: Fluoxetine	2.0
	5	N06AB06: Sertraline	2.3	N05AX08: Risperidone	2.6	N05AX12: Aripiprazole	2.0
	6	N05AH04: Quetiapine	1.9	N05BA12: Alprazolam	2.0	N03AF02: Oxcarbazepine	2.0
	7	N05AX12: Aripiprazole	1.7	N05AH04: Quetiapine	1.8	N05AH04: Quetiapine	1.9
	8	N03AF02: Oxcarbazepine	1.7	N05CD08: Midazolam	1.4	N05BA01: Diazepam	1.7
	9	N05BA12: Alprazolam	1.6	N03AX11: Topiramate	1.4	N06AB06: Sertraline	1.7
	10	N05BA01: Diazepam	1.6	N05AX12: Aripiprazole	1.4	N05CD08: Midazolam	1.6

4.2.3 Diagnosis data analysis

The analysis of the diagnosis data was only feasible in the Greek database and concerned the target exposed population. We identified 1,301 different ICD-10 codes, grouped into 607 different groups when the ICD-10 code was rounded up to the whole number.

In this exercise, a high number of patients were diagnosed with epilepsy (G40) or other convulsions (R56), but a high number of patients´ diagnosis captured as 'non-specified'. ADHD (F90), and PDDs (R56) were found as diagnostic codes in more than thousand patients each, while other mental health related disorders such as anxiety disorders (F41), OCD (F42), unspecified psychosis (F29) and depressive episode (F32) disorders were also identified but not so frequently. We also detected some non-related (directly or indirectly) to mental health disorders codes, with asthma and acute bronchitis being among the twenty most frequently diagnoses. The ten most frequently observed diagnostic codes are presented in the following table (Table 61).

Table 61. Analysis of the most frequently ICD-10 diagnostics grouped by the higher code - Greece.

ICD-10		Patients	
Code	**Diagnostic**	**All (n=21,274)**	**%**
G40	Epilepsy	8,420	39.58
-	Non-specified	4,177	19.63
R56	Convulsions*	3,607	16.95
F84	Pervasive developmental disorders (PDD)⁺	1,223	5.75
F90	Attention-deficit hyperactivity disorders (ADHD)	1,053	4.95
F41	Other anxiety disorders	583	2.74
F42	Obsessive-compulsive disorder (OCD)	486	2.28
F29	Unspecified psychosis not due to a substance or known physiological condition	413	1.94
F32	Depressive episode	359	1.69
G80	Cerebral palsy	287	1.35

Patients may have received more than one type of diagnosis; thus, the sum of percentages exceeds 100.
Abbreviations: ICD-10, International Classification of Diseases, version 10 (2020).
**: not elsewhere classified and febrile. ⁺: autism, Asperger syndrome, Rett syndrome, etc*

Concerning the codes related exclusively to mental health, we found that most of the Greek target paediatric exposed population had a diagnosis included in the category of 'anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders' (F40-F48); however, the 'behavioural and emotional disorders with onset usually occurring in childhood and adolescence' group (F90-F98) was the one identified to have the highest number of dispensed medicines per patient (ratio 6.6) followed very closely by the group 'schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders' (F20-F29). The diagnostic

group of 'mental and behavioural disorders due to psychoactive substance use' (F10-F19) was in the lowest position compared to other diagnostic groups concerning both the number of patients and of the dispensed medicines, while the diagnosis of 'abuse of non-psychoactive substances' (F55) was not found in our sample. Table 62 below presents in detail the results of this grouped analysis.

Table 62. Analysis of the ICD-10 mental, behavioural and neurodevelopmental disorders diagnostics (F01-F99 codes) - Greece.

ICD-10 Codes	Diagnostics	Patients(P) n	Dispensations(D) n	(D/P)
F01-F09	Mental disorders due to known physiological conditions	541	2,520	4.7
F10-F19	Mental and behavioural disorders due to psychoactive substance use	32	92	2.9
F20-F29	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	1,067	6,862	6.4
F30-F39	Mood [affective] disorders	1,774	8,024	4.5
F40-F48	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	2,375	9,375	3.9
F50	Eating disorders	72	347	4.8
F51	Sleep disorders not due to a substance or known physiological condition	167	834	5.0
F55	Abuse of non-psychoactive substances	0	0	-
F60-F69	Disorders of adult personality and behaviour	64	268	4.2
F90-F98	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	1,728	11,330	6.6

4.2.3.1 Diagnosis related to the most frequent dispensed medicines

The most frequently dispensed medicines to patients having a diagnosis in the group mental, behavioural, and neurodevelopmental disorders (ICD-10: F01-F98) are shown below (Table 63).

Methylphenidate was the medicine mostly dispensed (5,500 medicines dispensed) to the highest number of patients (795 patients) with nearly seven dispensations corresponding to each patient diagnosed with behavioural and emotional disorders with onset usually occurring in childhood and adolescence (ICD-10: F90-F98). Even though valproic acid was the second medicine mostly dispensed by patient having a ratio slightly lower than the one of methylphenidate (6.8 vs 6.9 respectively), the total number of patients to which was dispensed was forty-four times lower than the methylphenidate's one, and risperidone was found as to be the second medicine with the highest number of dispensations.

Table 63. Most frequently dispensed medicines by ICD-10 mental, behavioural and neurodevelopmental disorders diagnostics (F01-F99 codes) - Greece.

ICD-10		ATC		Patients(P)	Dispensations (D)	
Code	Diagnostic	Name	Code	n	n	(D/P)
F01-F09	Mental disorders due to known physiological conditions	risperidone	N05AX08	243	1,220	5.0
		valproic acid	N03AG01	79	418	5.3
		quetiapine	N05AH04	53	187	3.5
		aripiprazole	N05AX12	51	193	3.8
		levetiracetam	N03AX14	50	260	5.2
F10-F19	Mental and behavioural disorders due to psychoactive substance use	risperidone	N05AX08	12	37	3.1
		quetiapine	N05AH04	9	14	1.6
		olanzapine	N05AH03	7	8	1.1
		diazepam	N05BA01	5	7	1.4
		sertraline	N06AB06	4	6	1.5
F20-F29	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	risperidone	N05AX08	587	3,265	5.6
		aripiprazole	N05AX12	258	1,408	5.5
		quetiapine	N05AH04	164	670	4.1
		valproic acid	N03AG01	120	663	5.5
		olanzapine	N05AH03	120	465	3.9
F30-F39	Mood [affective] disorders	fluoxetine	N06AB03	529	2,031	3.8
		sertraline	N06AB06	381	1,638	4.3
		risperidone	N05AX08	300	1,162	3.9
		quetiapine	N05AH04	287	1,029	3.6
		escitalopram	N06AB10	200	679	3.4
F40-F48	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	fluoxetine	N06AB03	632	2,552	4.0
		sertraline	N06AB06	494	2,391	4.8
		alprazolam	N05BA12	413	831	2.0
		risperidone	N05AX08	319	1,022	3.2
		escitalopram	N06AB10	190	542	2.9
F50	Eating disorders	fluoxetine	N06AB03	40	171	4.3
		risperidone	N05AX08	14	62	4.4
		sertraline	N06AB06	13	72	5.5
		alprazolam	N05BA12	10	12	1.2
		aripiprazole	N05AX12	5	25	5.0
F51	Sleep disorders not due to a substance or known physiological condition	melatonin	N05CH01	124	731	5.9
		valproic acid	N03AG01	18	122	6.8
		levetiracetam	N03AX14	13	75	5.8
		risperidone	N05AX08	13	32	2.5
		clobazam	N05BA09	12	76	6.3
F60-F69	Disorders of adult personality and behaviour	risperidone	N05AX08	20	62	3.1
		quetiapine	N05AH04	18	53	2.9
		aripiprazole	N05AX12	11	40	3.6
		valproic acid	N03AG01	9	30	3.3
		sertraline	N06AB06	8	32	4.0
F90-F98	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	methylphenidate	N06BA04	795	5,520	6.9
		risperidone	N05AX08	516	2,149	4.2
		atomoxetine	N06BA09	319	2,073	6.5
		aripiprazole	N05AX12	162	846	5.2
		quetiapine	N05AH04	115	533	4.6

Risperidone was dispensed 3,265 times in patients with a diagnosis of schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (ICD-10: F20-F29), but it was the only medicine ranked among the five most frequently dispensed medicines for all diagnostic groups related to mental health, where in four out of nine groups was in the first place. Among antidepressants, fluoxetine had the highest number of dispensations (2,552) in the diagnostic

group of anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (ICD-10: F90-F98).

For the more relevant and most frequent diagnostic single codes as presented in Table 61 previously, the three most frequently dispensed medicines in terms of patients and dispensations were identified. Most patients in this exercise were dispensed levetiracetam and to each patient corresponded more than 13 dispensations in the epilepsy group under ICD-10 code G40. However, valproic acid was found to have the highest rate of dispensations per patient (14.4). The same medicines and ranking pattern were also observed for all those paediatric patients related to a diagnosis that was non-specified.

As regards the diagnostic ICD-10 code F84 (PDDs), we identified that risperidone had the highest number of dispensations (7,720) and the highest number of patients to which the medicine was dispensed (1,205 patients). However, valproic acid is again the one having the highest rate of dispensations per patient (9.9 vs 6.4) in patients with this diagnostic code, while aripiprazole is really close to the dispensation rate observed for risperidone (6.4 vs 6.2).

For the Greek paediatric patients diagnosed with other anxiety disorders (ICD-10: F41), fluoxetine dispensations prevailed while sertraline was found to have the highest dispensation ratio per patient (3.4 vs 3.0). In the ADHD diagnosed study subjects, methylphenidate and atomoxetine were respectively in the first two positions of the most frequently used medicines in this diagnostic single group, both with quite a high rate of dispensations per patient (7.0 and 6.4 respectively).

In both the depressive episode (ICD-10: F32) and OCD (ICD-10: F42) diagnosed group of paediatric patients, fluoxetine (3.6 vs 5.2 respectively) and sertraline (4.0 vs 6.2 respectively) were the most frequently dispensed medicines with the highest rate of dispensations per patient been observed for both medicines in the latter single diagnostic group. For the patients with unspecified psychosis not due to a substance or known physiological condition (ICD-10: F29), the most frequently dispensed medicines were risperidone, aripiprazole and quetiapine. Table 64 below presents in detail all the relevant information regarding this sub-analysis.

Table 64. Most frequently dispensed medicines by the most frequent and relevant single ICD-10 code - Greece.

ICD-10		ATC		Patients (P)	Dispensations (D)	
Code	Diagnostic	Name	Code	n	n	(D/P)
G40	Epilepsy	levetiracetam	N03AX14	4,143	56,701	13.7
		valproic acid	N03AG01	3,353	48,179	14.4
		diazepam	N05BA01	2,392	5,102	2.1
-	Non specified	levetiracetam	N03AX14	1,079	6,522	6.0
		valproic acid	N03AG01	858	6,337	7.4
		diazepam	N05BA01	791	1,393	1.8
F84	Pervasive developmental disorders	risperidone	N05AX08	1,205	7,720	6.4
		aripiprazole	N05AX12	453	2,829	6.2
		valproic acid	N03AG01	179	1,769	9.9
F41	Other anxiety disorders	fluoxetine	N06AB03	375	1,120	3.0
		alprazolam	N05BA12	334	610	1.8
		sertraline	N06AB06	286	973	3.4
F90	Attention-deficit hyperactivity disorders	methylphenidate	N06BA04	780	5,423	7.0
		atomoxetine	N06BA09	313	2,012	6.4
		risperidone	N05AX08	214	940	4.4
F32	Depressive episode	fluoxetine	N06AB03	386	1,398	3.6
		sertraline	N06AB06	266	1,073	4.0
		escitalopram	N06AB10	149	470	3.2
F42	Obsessive-compulsive disorder	fluoxetine	N06AB03	247	1,286	5.2
		sertraline	N06AB06	200	1,248	6.2
		risperidone	N05AX08	171	674	3.9
F29	Unspecified psychosis not due to a substance or known physiological condition	risperidone	N05AX08	234	1,026	4.4
		aripiprazole	N05AX12	91	408	4.5
		quetiapine	N05AH04	63	304	4.8

4.2.4 Dispensed medicines' analysis per physician specialty

The Greek database directly connects the dispensed medicine with the prescriber physician and their specialty, while this is not the case for Catalonia; thus, we performed this analysis only for the Greek paediatric study population. We conducted the analysis in the target exposed population, where the total number of dispensed medicines was 222,352. Table 65 below presents in detail the list of most frequent specialties prescribing the dispensed medicines and the sub-analysis per sex (see Figure 66). The detailed list is found in Annex I.

Most of the dispensed medicines were prescribed by paediatricians reaching up to 42.17%. Dispensed medicines of more than 10.00% were prescribed by neurologists (16.31%), general practitioners (13.98%) and child-psychiatrists (13.58%) representing more than thirty thousand dispensed medicines for each speciality. More than ten thousand dispensed medicines were prescribed by physicians without a speciality (5.83%), and internists were responsible for

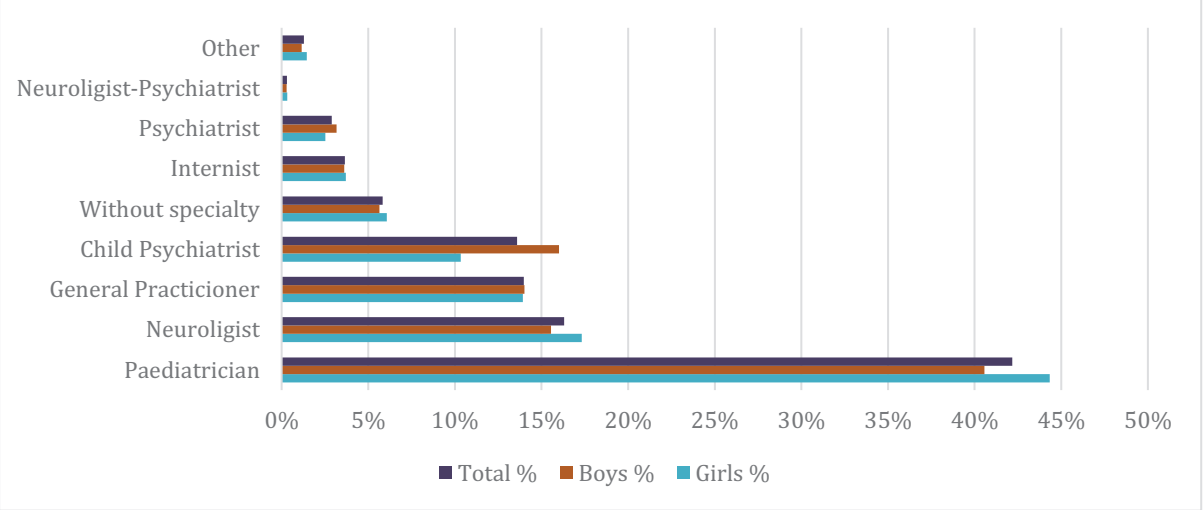
prescribing 3.66% of the dispensed medicines in our sample. Psychiatrists and neurologists/psychiatrists prescribed 2.89% and 0.30% respectively.

Table 65. Psychotropic dispensations in children per physician speciality - Greece.

Physician specialty	Girls		Boys		Total	
	n	%	n	%	n	%
Paediatrician	42,147	44.33	51,622	40.56	93,769	42.17
Neurologist	16,476	17.33	19,781	15.54	36,257	16.31
General Practitioner	13,234	13.92	17,847	14.02	31,081	13.98
Child Psychiatrist	9,837	10.35	20,365	16.00	30,202	13.58
Without specialty	5,768	6.07	7,187	5.65	12,955	5.83
Internist	3,529	3.71	4,598	3.61	8,127	3.66
Psychiatrist	2,394	2.52	4,032	3.17	6,426	2.89
Others*	1,697	1.79	1,838	1.45	3,535	1.61
Overall	***95,082***	***100***	***127,270***	***100***	***222,352***	***100***

**Data from 31 specialities with percentages <1% in the total column are aggregated in the 'Others' category. A complete detailed version is shown in Annex I.*

Figure 66. Psychotropic dispensations in children per physician speciality (top10) - Greece.



Analysing the data per sex, we have seen some differences compared to the aforementioned data for both sexes. Dispensed medicines to girls followed the same pattern as the ones for both sexes: 44.33% by paediatricians, 17.33% by neurologists, 13.92% by general practitioners and 10.35% by child psychiatrists. However, for boys the pattern was slightly changed as prescriptions by child psychiatrists were more prevalent: 40.56% by paediatricians, 16.00% by child psychiatrists, 15.54% by neurologists and 14.02% by general practitioners. Psychiatrists also prescribed a higher number of the dispensed medicines to boys compared to girls (3.17% vs 2.52% respectively), whereas neurologists/psychiatrists were more involved with medicines

dispensed to girls than boys (0.32% vs 0.29% respectively). As regards the physicians without specialty, medicines were prescribed more to girls than boys (6.07% vs 5.65% respectively).

For the ten most frequent physician's specialties, we also analysed the dispensations as per the ATC group (see Table 67). Concerning antiepileptics (N03A) slightly more than half was prescribed by a paediatrician (50.50%), followed by neurologists (20.30%) and general practitioners (15.60%), while the rest of the specialties prescribed less than ten percent each. Child psychiatrists prescribed almost half of the dispensed antipsychotics (N05A), while each specialty of general practitioners, paediatricians and psychiatrists prescribed in a descending order more than ten percent (12.70%, 11.60% and 10.70% respectively). 42.00% of anxiolytics (N05B) were prescribed by paediatricians, followed by general practitioners (14.00%), neurologists (12.70%) and physicians without specialty (11.70%). As regards the dispensed hypnotics/sedatives (N05C), more than half were prescribed by a paediatrician; neurologists had a share of 16.40% followed by physicians without specialty (12.10%). Almost 60.00% of antidepressants (N06A) were prescribed by child psychiatrists and 13.70% from a psychiatrist, while all other specialised physicians had a share of less than one tenth each. Child psychiatrists were also in the first place regarding psychostimulants'/ADHD medicines' (N06B) dispensations (64.00%), whereas paediatricians were in the second place having more than four times less (14.70%) prescriptions than the former specialty. Psycholeptics and psychoanaleptics in combination (N06C) were mostly prescribed by psychiatrists (37.70%) and then by general practitioners (14.50%), whereas 68.40% of drugs used in addictive disorders (N07B) were prescribed by paediatricians and then by psychiatrists (15.70%).

4.2.5 Dispensed medicines' analysis per prefecture

Among the available variables in the Greek database, the prefecture in which the patient resides is also included, whereas this information is not included in the pharmacy data provided for Catalonia. Hence, an analysis of the dispensed medicines per prefecture was performed only for the Greek paediatric subjects, and more precise for the target exposed population group (number of dispensed medicines: 222,352). Two prescriptions were excluded from the analysis due to the lack of information on the prefecture. Table 68 below presents in detail the list of most frequent prefectures with the dispensed medicines in descending order as well as the sub-analysis per sex, while a full list is available in Annex I.

Table 67. Psychotropic dispensations by ATC groups per physician speciality - Greece.

Physician Specialty	N03A *(n=153,630)*	N05A *(n=31,855)*	N05B *(n=25,955)*	N05C *(n=7,186)*	N06A *(n=16,232)*	N06B *(n=10,112)*	N06C *(n=159)*	N07B *(n=19)*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Paediatrician	77,580 (50.5)	3,703 (11.6)	10,905 (42.0)	3,989 (55.5)	750 (4.6)	1,485 (14.7)	-	13 (68.4)
Neurologist	31,178 (20.3)	2,071 (6.5)	3,308 (12.7)	1,177 (16.4)	726 (4.5)	805 (8.0)	15 (9.4)	1 (5.3)
Child psychiatrist	2,989 (1.9)	15,878 (49.8)	2,525 (9.7)	119 (1.7)	9,608 (59.2)	6,469 (64.0)	7 (4.4)	-
General practitioner	23,966 (15.6)	4,050 (12.7)	3,623 (14.0)	656 (9.1)	1,391 (8.6)	471 (4.7)	23 (14.5)	-
Without specialty	8,037 (5.2)	1,204 (3.8)	3,028 (11.7)	867 (12.1)	517 (3.2)	189 (1.9)	3 (1.9)	-
Internist	5,950 (3.9)	1,205 (3.8)	988 (3.8)	177 (2.5)	648 (4.0)	98 (1.0)	10 (6.3)	1 (5.3)
Psychiatrist	1,405 (0.9)	3,416 (10.7)	1,125 (4.3)	95 (1.3)	2,222 (13.7)	467 (4.6)	60 (3.0)	3 (15.8)
Neurologist-Psychiatrist	372 (0.2)	168 (0.5)	136 (0.5)	10 (0.1)	132 (0.8)	19 (0.2)	40 (25.0)	1 (5.3)
Haematologist	411 (0.3)	42 (0.1)	31 (0.1)	49 (0.7)	39 (0.2)	-	-	-

Table 68. Psychotropic dispensations in children (and by sex) per prefecture - Greece.

Prefecture	Girls (n=95,082)		Boys (n=127,268)*		Total (n=222,350)*	
	n	%	n	%	n	%
Attica	31,936	33.6	45,879	36.0	77,815	35.0
Thessaloniki	10,904	11.5	12,653	9.9	23,557	10.6
Heraklion	4,702	4.9	5,306	4.2	10,008	4.5
Achaea	3,093	3.3	4,544	3.6	7,637	3.4
Aetolia-Acarnania	2,680	2.8	2,689	2.1	5,369	2.4
Larissa	2,255	2.4	3,017	2.4	5,272	2.4
Chania	2,117	2.2	2,584	2.0	4,701	2.1
Ioannina	2,006	2.1	2,406	1.9	4,412	2.0
Euboea	1,748	1.8	2,601	2.0	4,349	2.0
Magnesia	1,589	1.7	2,050	1.6	3,639	1.6
Xanthi	1,326	1.4	2,155	1.7	3,481	1.6
Serres	1,344	1.4	1,896	1.5	3,240	1.5
Dodecanese	1,338	1.4	1,829	1.4	3,167	1.4
Karditsa	1,445	1.5	1,614	1.3	3,059	1.4
Messenia	1,220	1.3	1,711	1.3	2,931	1.3
Cyclades	1,421	1.5	1,403	1.1	2,824	1.3
Elis (Ileia)	1,009	1.1	1,812	1.4	2,821	1.3
Kozani	1,186	1.2	1,566	1.2	2,752	1.2
Imathia	1,168	1.2	1,568	1.2	2,736	1.2
Corinthia	1,070	1.1	1,643	1.3	2,713	1.2
Pella	1,287	1.4	1,402	1.1	2,689	1.2
Kavala	1,143	1.2	1,482	1.2	2,625	1.2
Pieria	960	1.0	1,615	1.3	2,575	1.2
Phthiotis	1,018	1.1	1,548	1.2	2,566	1.2
Rethymno	1,089	1.1	1,262	1.0	2,351	1.1
Others**	14,028	15.1	19,033	14.9	30,341	14.9

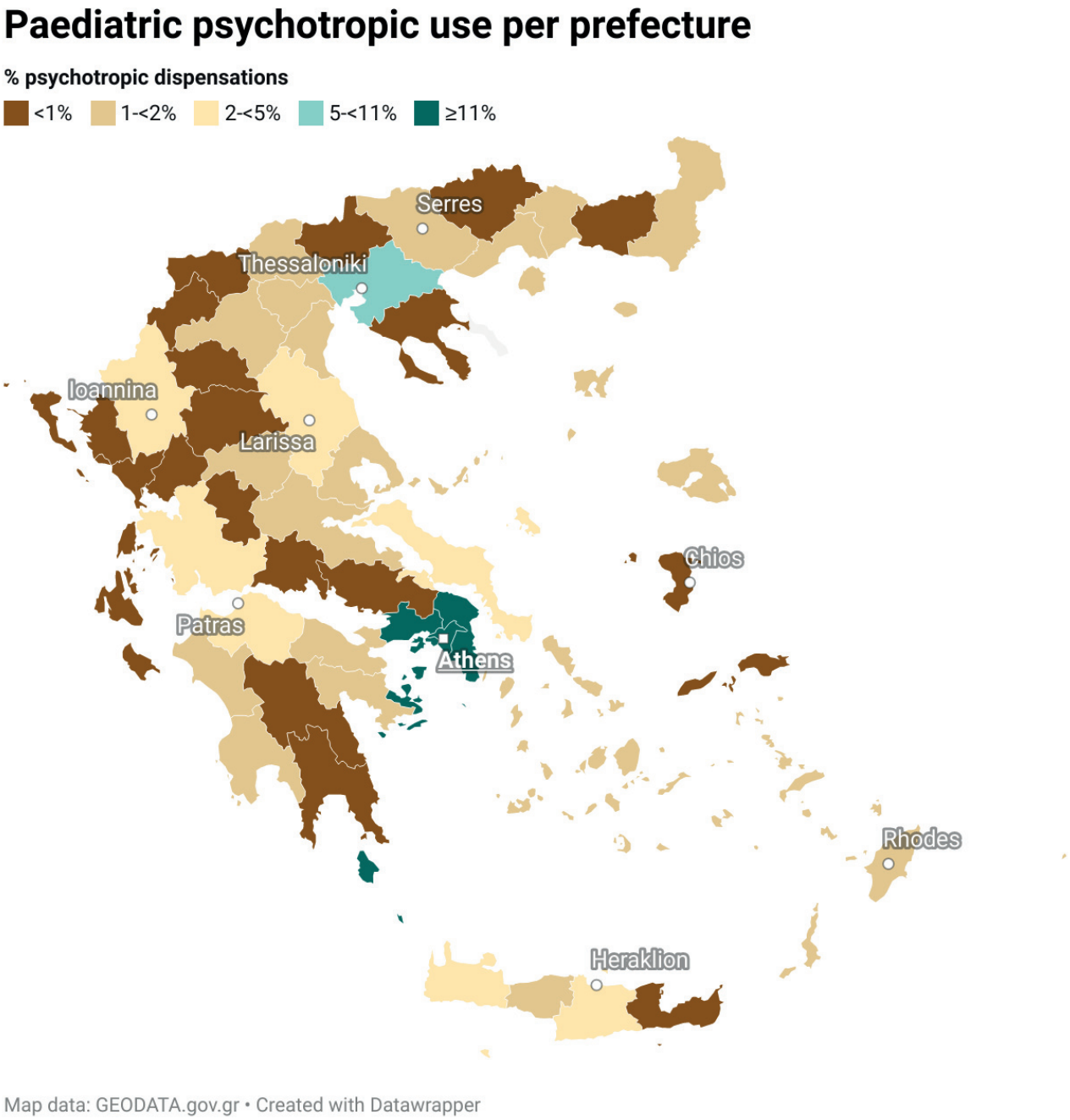
**No information for 2 dispensations.*

***Data from 26 prefectures with percentages ≤1% in the total column are aggregated in the 'Others' category. A complete detailed version is shown in Annex I.*

Most of the medicines were dispensed in children residing in Attica (35.00%), the biggest prefecture in Greece with a population of almost four million people. Thessaloniki as the second most populated prefecture of the country followed as the second region with 10.60% of the dispensations, while each of the remainder prefectures had a share of less than ten percent of the dispensed medicines. Heraklion (4.50%), Achaea (3.40%), Aetolo-Acarnania and Larissa (2.40%) and Chania (2.10%) were the only ones with a share of more than two percent while all others were below that threshold. Figure 69 below demonstrates the distribution of dispensed medicines in the map of Greece.

Similar trends were observed in the sub-analysis per sex. More girls than boys had a higher percentage of dispensations in Thessaloniki (11.50% vs 9.90%) and Heraklion (4.90% vs 4.20%), whereas for boys had a higher share in Attica (36.00% vs 33.60%) and Achaea (3.60% vs 3.30%).

Figure 69. Psychotropic dispensations in children per prefecture - Greece.



4.2.6 Off-label use analysis

4.2.6.1 SmPCs analysis

The active substances of the concerned for our analysis ATC groups were identified to be 348 based on data retrieved from WHO ATC index. According to data found in the *AEMPS* website (https://cima.aemps.es/cima/publico/lista.html) 38.50% of the concerned to this study active substances have an authorisation in Spain. An initial analysis of the SmPCs was done and a list was drafted as described in the following table (Table 70).

Table 70. Analysis of the number of SmPCs per ATC group - Catalonia (Spain).

ATC group		Active substances		Registries in *CIMA*		
Code	Name	WHO Index	Authorised	Total number	Without SmPC	SmPCs reviewed
N03A*	Antiepileptics	47	23	572	2	570
N05A*	Antipsychotics	68	29	721	1	720
N05B*	Anxiolytics	41	15	151	0	151
N05C*	Hypnotics and sedatives	72	17	90	5	85
N06A$	Antidepressants	64	26	578	3	575
N06B$	Psychostimulants, agents used for ADHD and nootropics	38	12	115	3	112
N06C$	Psycholeptics and psychoanaleptics in combination	3	2	3	0	3
N07B$	Drugs used in addictive disorders	15	10	96	0	96
Total		***348***	***134***	***2,326***	***14***	***2,312***

**: group checked by August 2019. $: group checked by August 2020.*

This list was the base to start drafting a similar list concerning the medicinal products authorised in Greece. However, the corresponding national authority in Greece (*EOF*) does not have such a comprehensive database and therefore the data were extracted from different sources: the available SmPCs found in *EOF*´s website, the last published prescription textbook of 2007 by the same competent authority, the Galinos.gr website (https://www.galinos.gr/) and the available in Greek SmPCs from the website of the relevant MAHs. In case of discrepancies, as some SmPCs were not updated or not available at all, information sought at EMA´s website and other EU NCAs. Therefore, the percentage of the active substances authorised in Greece was of 31.90%. The relevant comparative information between the two countries is presented in the following table (Table 71) where the percentage of all authorised active substances by ATC group was higher in Catalonia than in Greece, except for the antiepileptics group (N03A) that was even in both regions and the antipsychotics group where Greece preponderated.

Since a distinction based on the formulation or the strength of the dispensed medicine could not be performed for the Catalan data, every available SmPC was checked to confirm if a paediatric use was contemplated. The selected age cut-off was the lowest one found with the aim to limit overestimation of the off-label use; in case of doubt the same strategy was followed to avoid again overestimation. A comprehensive list with the official age cut-off for both regions can be found below in a comparative table included in Annex I (Table 100).

Table 71. Analysis of active substances per ATC group authorised in Catalonia (Spain) and Greece.

ATC group		Active substances				
Code	Name	WHO Index n	Catalonia (Spain)		Greece	
			n	(%)	n	(%)
N03A*	**Antiepileptics**	47	23	(48.90)	23	(48.90)
N05A*	**Antipsychotics**	68	29	(42.60)	32	(47.10)
N05B*	**Anxiolytics**	41	15	(36.60)	9	(22.00)
N05C*	**Hypnotics and sedatives**	72	17	(23.60)	11	(15.30)
N06A$	**Antidepressants**	64	26	(40.60)	19	(29.70)
N06B$	**Psychostimulants, agents used for ADHD and**	38	12	(31.60)	8	(21.10)
N06C$	**Psycholeptics and psychoanaleptics in**	3	2	(66.70)	1	(33.30)
N07B$	**Drugs used in addictive disorders**	15	10	(66.70)	8	(53.30)
	Total	***348***	***134***	***(38.50)***	***111***	***(31.90)***

**: group checked by August 2019. $: group checked by August 2020.*

Between the two regions some differences were identified based on the availability of the medicinal products and the availability of the same authorised formulations that sometimes affected the cut-off age in the SmPCs. Eight medicines were categorised with a different age cut-off level between the two regions for our analysis: valproic acid (N03AG01), levomepromazine (N05AA02), trifluoperazine (N05AB06), tiapride (N05AL03), lithium chloride (N05AN01), chlorodiazepoxide (N05BA02), potassium chlorazepate (N05BA05) and clomipramine (N06AA04).

During the analysis we also identified that the authorised lower age cut-off changed for two active substances in June 2018: brivaracetam (initially 16 years of age and then 4 years of age) and rufinamide (initially 4 years of age and then 1 year of age). This change in the age cut-off was taken into consideration when analysing the Greek data, whereas in the data from Catalonia this change did not have any effect on the analysis as the study period was before June 2018. In 2018, EMA approved melatonin for use in children from 2 years of age.(211) However, according to the *AEMPS* website the medicine was not approved and subsequently not commercialised in Spain before August 2019 (212) and since our study comprised of data up to 2017, melatonin was considered as approved only in adults; in Greece the age limit was also 18

years as the medicine was not on the market before 2021 (213) which is also outside of the limits of the period for which we had data for analysis.

In addition, two combinations of diazepam were available in Spain at the time of drafting Table 100 included in Annex I: a combination with sulpiride and one with pyridoxine; the former is not authorised in the paediatric population, but the latter is authorised from 6 months of age onwards. Since the identification of the exact combination dispensed to the paediatric population was not possible in the data analysis set of Catalonia, we considered the lower age cut-off as the default in order to avoid overestimations on the off-label use rates.

Despite the efforts to gather as much information as possible, there were still three products for which the status of paediatric authorisation could not be defined for Catalonia, and therefore those were marked as ´unknown´. In Greece, those active substances were not authorised.

4.2.6.2 Off-label use: study population analysis

For this sub-study period (2015-2017), 66,824 outpatient paediatric subjects with at least one psychotropic medicine dispensed from the Catalan health reimbursement system were identified in the region of Catalonia corresponding to 950,395 medicine dispensations. In Greece, since the period with available data was limited to approximately forty-four months, we have analysed the whole data package. Sixteen dispensations corresponding to 5 patients were excluded from this sub-analysis as the exact ATC code at level 7 could not be identified and thus the off-label status could not be defined. Hence, the Greek study population was of 21,269 subjects with at least one psychotropic dispensed from the Greek health reimbursement system corresponding to 223,307 medicine dispensations.

According to the available data, the target study subsets of subjects for the off-label use analysis in both regions were quite similar in regard to sex (boys: ≈56.00% in Greece vs ≈61.00% in Catalonia) while there was a higher discrepancy in the dispensed medicines per sex (boys: 57.20% in Greece vs 67.20% in Catalonia). We also observed that the total ratio of dispensations per subject was lower in Greece than in Catalonia (10.5 vs 14.2 respectively). Table 72 below present in detail the study subpopulation selected for the off-label use exercise comparing the two regions.

Table 72. Off-label study population description - Catalonia (Spain) and Greece. Overall sample sizes.

	Catalonia (Spain) 2015-2017					Greece 2016-2019*				
	Girls		Boys		Overall	Girls		Boys		Overall
	n	%	n	%	n	n	%	n	%	n
Patients	26,420	39.54	40,404	60.46	66,824	9,357	43.99	11,912	56.01	21,269
Dispensations	311,751	32.80	638,644	67.20	950,395	95,062	42.76	127,245	57.24	222,307
(D/P)	***11.8***		***15.8***		***14.2***	***10.2***		***10.7***		***10.5***

*: *March 2016 to October 2019.*

4.2.6.3 Off-label use per paediatric information and per age

The first step of our analysis was based on the categorical answer ´Yes/No´ as to whether any paediatric information was found in the SmPC of the concerned medicinal products to allow their use in this age subset. In the category 'No' we also included the few cases under the 'unknown' label found in the Catalan sample for glutamate (N05CM93): 67 patients (out of 66,824) and 168 dispensations.

The analysis of the number of subjects receiving medicines dispensed outside the authorised conditions for both regions is presented in the following table (Table 73). In this analysis, each patient was included only once using the following prioritisation method: if the subject received at least one medicine as off-label then he/she was included only in this category. Therefore, all the subjects categorised in the on-label group they had never received a medicine outside of the authorised conditions.

According to this first analysis, 12.02% of the study subjects in Catalonia received at least one medicine under an off-label status, and in Greece this figure is similar although slightly higher, reaching up to 14.04%. When investigating the rate of the off-label use based on sex, girls found to have a higher exposure in both sets compared to boys. Even though it was observed that boys in both regions had a lower exposure to the off-label use, Greek boys found to be more exposed to medicines under off-label status than their Catalan peers (11.85% vs 8.72%, respectively).

As a second step, we also performed an analysis where each subject could count more than once depending on the status of all the dispensed medicines corresponding to them. This analysis is presented in Table 74 below and is also comparing the number of dispensations. Here the off-label use was lower than the previous observation: 11.07% of the Catalan and almost 12.98% of the Greek subjects were taking medicines under off-label status corresponding to around 4.62%

Table 73. Off-label use as per paediatric information in the SmPC. Number of outpatients in Catalonia (Spain) and Greece (considered only once).

	Number of paediatric outpatients					
	Catalonia (Spain) 2015-2017			Greece 2016-2019*		
Medicines	**Girls n (%)**	**Boys n (%)**	**Total n (%)**	**Girls n (%)**	**Boys n (%)**	**Total n (%)**
Authorised	21,910 (82.93)	36,880 (91.28)	58,790 (87.98)	7,782 (83.17)	10,501 (88.15)	18,283 (85.96)
Not authorised	4,510 (17.07)	3,524 (8.72)	8,034 (12.02)	1,575 (16.83)	1,411 (11.85)	2,986 (14.04)
Overall	26,420	40,404	66,824	9,357	11,912	21,269

*: March 2016 to October 2019.

Table 74. Off-label use per paediatric information in the SmPC. Number of outpatients and dispensed psychotropics in Catalonia (Spain) and Greece.

	Catalonia (Spain) 2015-2017			Greece 2016-2019*		
	Girls n (%)	**Boys n (%)**	**Total n (%)**	**Girls n (%)**	**Boys n (%)**	**Total n (%)**
Authorised						
Patients (P)	25,002	39,547	64,549	8,632	11,380	20,012
	(84.72)	(91.82)	(88.93)	(84.57)	(88.97)	(87.02)
Dispensing (D)	289,375	617,129	906,504	146,853	203,886	350,739
	(92.82)	(96.63)	(95.38)	(94.37)	(94.63)	(94.52)
(D/P)	***11.6***	***15.6***	***14.0***	***17.0***	***17.9***	***17.5***
Not authorised						
Patients (P)	4,510	3,524	8,034	1,575	1,411	2,986
	(15.28)	(8.18)	(11.07)	(15.43)	(11.03)	(12.98)
Dispensing (D)	22,376	21,515	43,891	8,768	11,572	20,340
	(7.18)	(3.37)	(4.62)	(5.63)	(5.37)	(5.48)
(D/P)	***5.0***	***6.1***	***5.5***	***5.6***	***8.2***	***6.8***

*: March 2016 to October 2019.

and 5.48% of medicines dispensed as off-label respectively. Girls were observed to be the ones with the highest exposure in the off-label medication for both regions in this analysis set as well. Regarding the dispensed medicines per patient, our analysis revealed that 6.80 and 5.50 dispensations per patient were off-label in Greece and in Catalonia respectively, with boys having had a higher exposure to off-label medication per patient in both regions compared to girls. Greek boys were also more exposed to off-label dispensations per patient than their Catalan peers (8.20 vs 6.10, respectively).

Concerning the off-label use per year, the number of medicines dispensed were analysed per year of the selected period for each region. In Catalonia, there was no upwards trend. In fact, data seem to show a flat curve, or even a slight downward trend in both sexes and in the group of girls, with the highest peak in 2015, the first year of this sub-study (4.64% and 7.26% respectively). The peak of the off-label dispensed medicines was in 2016 (3.40%), but for the whole period of this study, their exposure was almost half of the one observed in girls. In Greece, the highest off-label use concerning the non-authorised medicines in paediatric population had an increasing trend with the peak detected in 2019 (5.74%). The same trend was followed when we analysed the data per sex where the medicines dispensed off-label to girls were more than the ones to boys with the peak for both sexes also in 2019 (6.11% and 5.47% respectively).

When comparing the data for 2017 which was the year in common for both regions in the current sub-study, we found that the proportion of medicines dispensed off-label in Greece was higher than in Catalonia (5.29% and 4.58% respectively); the same pattern was also in case of boys, while Catalan girls (7.09%) were more exposed to off-label use than their Greek peers (5.23%). Relevant data can be found below in Figure 75 (detailed data are shown in Table 101 in Annex I).

When the age criterion was also added to define the off-label use compared to the age in which the paediatric outpatient received a specific medicine, we identified that the off-label use increased in both settings and for both sexes. In both regions an upward trend was observed with the highest value in Greece been again in 2019 (8.10%), while in Catalonia this was observed this time in 2017 (7.73%); for both regions the highest trend found to be the last year for each set concerning this sub-study analysis. Catalan girls continued to be exposed to more off-label medicines than their Greek peers (9.34% and 8.20% respectively). In 2017, the trend identified before changed. The proportion of medicines dispensed off-label in Catalonia was higher than in Greece (7.73% and 7.30% respectively); the same pattern between the regions was also found concerning the girls, while Catalan boys (6.93%) were slightly less exposed to off-label use than their Greek peers (7.22%). Relevant data on this analysis can be found in Figure 76 (detailed data are shown in Table 101 in Annex I).

Regarding the differences identified between the regions on the off-label use based on age and the different age limit of some medicines detected during the SmPC analysis described previously, two out of these eight medicines (chlordiazepoxide and trifluoperazine) were not found in the Catalan database for the concerned sub-study period, whereas only one out of eight was not found in the Greek sample (tiapride).

Figure 75. Comparison of off-label use per year and sex - number of dispensed psychotropics in Catalonia (Spain) and Greece.

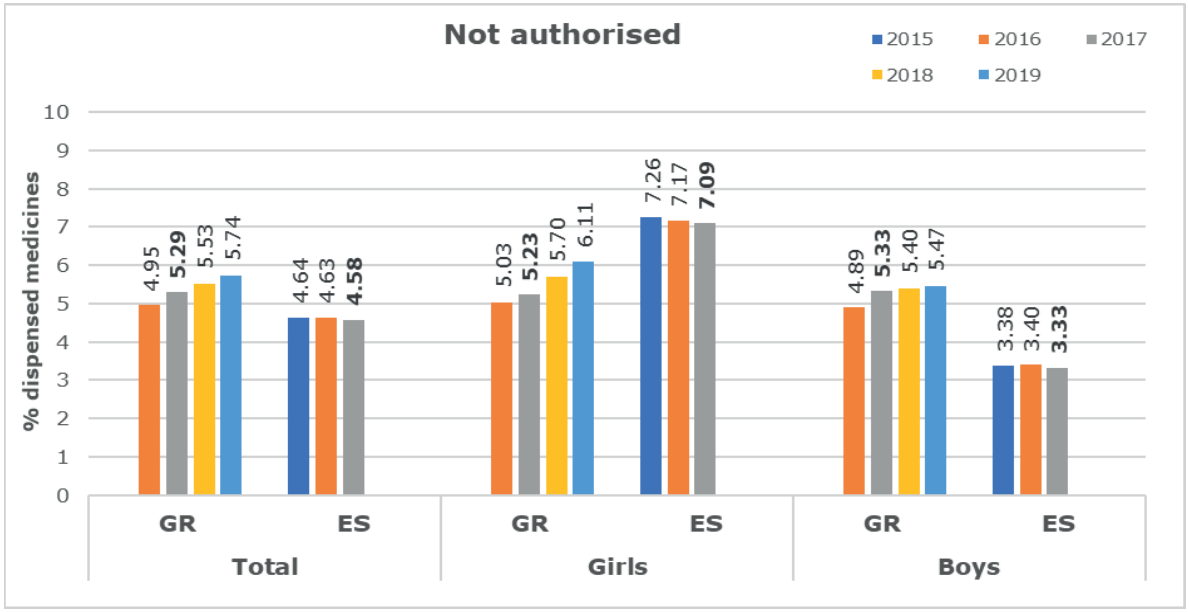
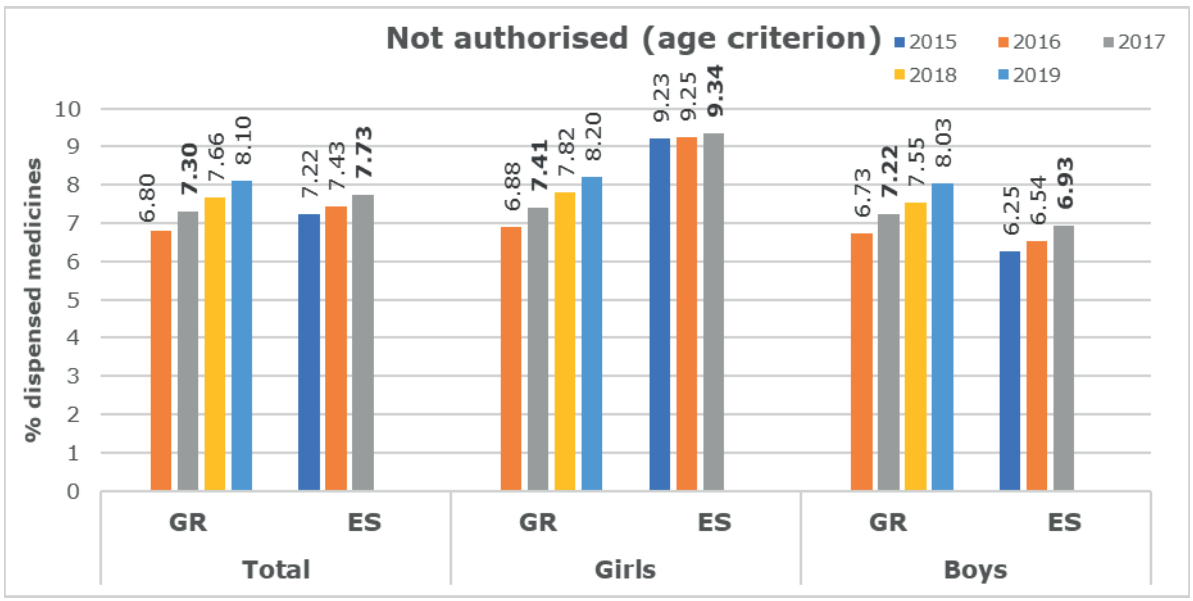


Figure 76. Comparison of off-label use (age criterion) per year and sex - number of dispensed psychotropics in Catalonia (Spain) and Greece.



4.2.6.4 Off-label use per age group

For the analysis of the off-label dispensations by different age groups, we selected the year 2017 as it is the common full annual period where both datasets are complete. The data analysis can be found as summarised in Figure 77 and Figure 78 below (detailed data are shown in Table 102 in Annex I).

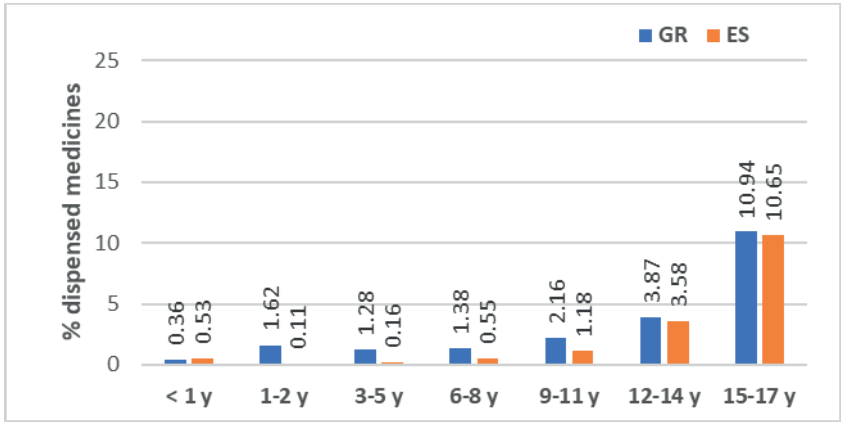
Concerning the dispensations administered as off-label based on the paediatric authorisation or not of the medicine, Greek paediatric population was more exposed to the off-label use for all age-groups. In both sets, the off-label use increased with the age, fluctuating between 0.36% to 10.94% in Greece and 0.11% to 10.65% in Catalonia. In Catalonia, the off-label use in the subgroups of 1-2 years of age and the 3-5 years of age was lower than in the group of <1 year of age (0.53%), while in children above 6 years of age the off-label use was increasing with the age. In Greece, the lowest point was observed in the subgroup of <1 year of age followed by the age groups 3-5 years and 6-8 years of age, while children aged between 1-2 years had a higher exposure to medicines dispensed off-label (1.62%); in children above 9 years of age the off-label use was increasing with the age. Catalan girl adolescents were in general more exposed to an off-label medicine than their Greek peers, whereas Greek boys of all ages had more dispensations than their Catalan peers.

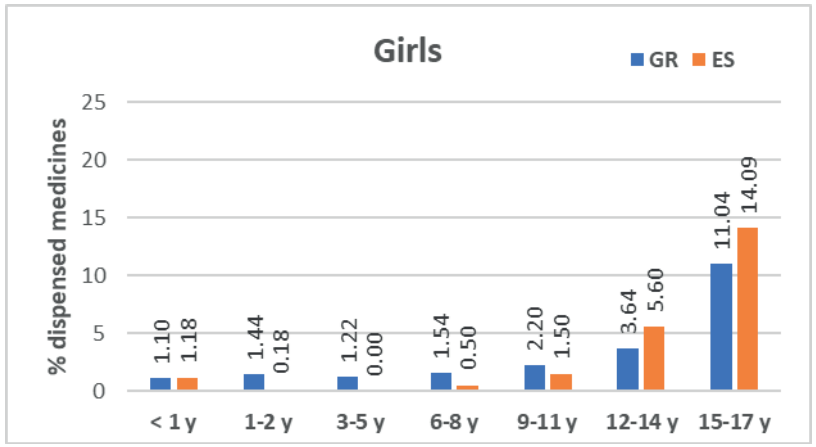
When the criterion of the authorised age was introduced into the off-label use analysis, a great increase in the off-label use was detected in both regions for the medicines dispensed in children below 5 years of age. In Catalonia, the off-label use trended among 4.51% and 19.14%, with the highest exposure in the group 3-5year-olds, followed by the children aged 1-2 years (16.30%); Catalan boys below 11 years of age had more off-label dispensations than girls, while adolescent girls were more exposed to off-label dispensations. The off-label use increased for all age groups in Greece and fluctuated between 2.75% and 18.48%, with the highest peak observed in the age group of <1 year old, followed by the group 3-5year-olds (14.38%); girls <1-5 years and 15-17 years of age had more off-label dispensed medicines than the boys, with the highest difference found in the group 3-5year-olds (16.40% vs 12.48%).

Comparing the two regions, Catalan girls had more off-label dispensations in all age groups as opposed to Greece, with the exception found in the group of <1 year of age; the same trend was observed also in the subset of boys, except for the age groups of <1 year and 15-17 years of age where Greek boys had more dispensations than their Catalan peers.

Figure 77. Off-label use per age group and sex in 2017 - number of dispensed psychotropics in Catalonia (Spain) and Greece.

Not authorised dispensed psychotropics





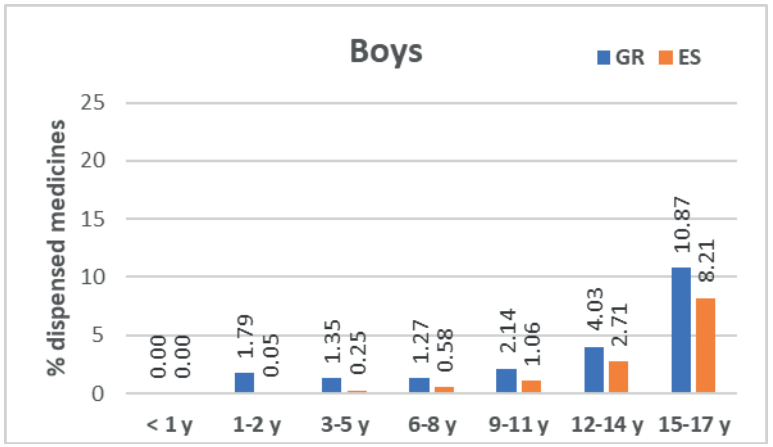
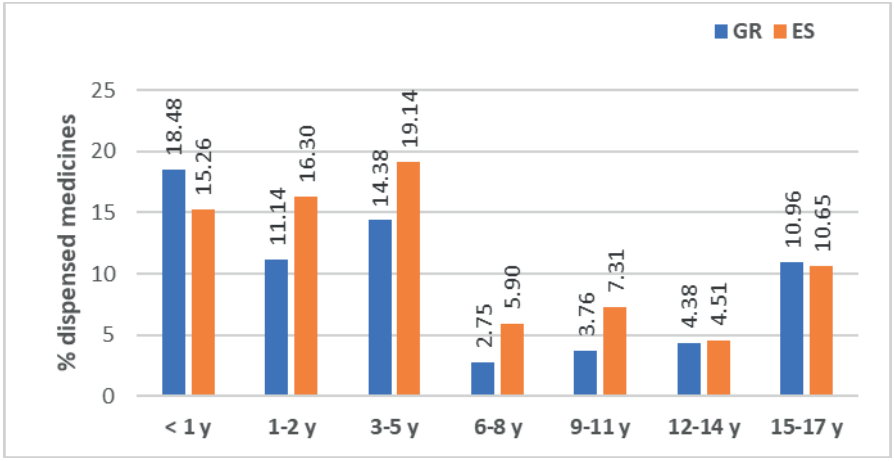
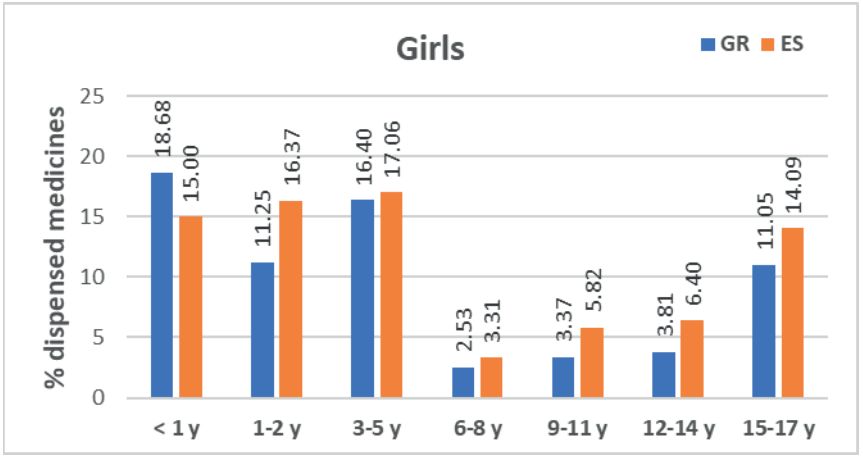
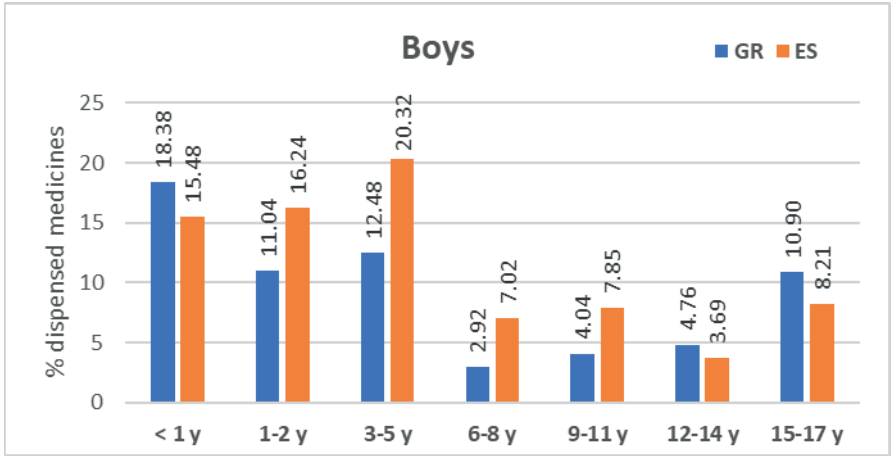


Figure 78. Off-label use (age criterion) per age group and sex in 2017 - number of dispensed psychotropics in Catalonia (Spain) and Greece.

Not authorised (age criterion) dispensed psychotropics







4.2.6.5 Most frequently off-label used medicines

The most frequent off-label used medicines according to the age to which a medicine is authorised, were identified for the year 2017 in both regions. Eight out of ten medicines dispensed as off-label were common in both regions; paliperidone and mirtazapine were the medicines ranking within the ten most frequently off-label used in Catalonia, whereas in Greece melatonin and pregabalin. The majority of the off-label medicines in this analysis pertained in the group of antipsychotics (N05A) followed by antidepressants (N06A), anxiolytics (N05B) and antiepileptics (N03A) in descending order in Catalonia; in Greece the distribution was equal among these same groups with a medicine in the group of hypnotics/sedatives (N05C) to complete the distribution among the various detected ATC groups. Table 79 below provides details on the analysis of the most frequently off-label dispensations.

As presented in the Table 79, aripiprazole was the most frequently dispensed off-label medicine in children residing in Catalonia with the off-label dispensations representing 1.77% of the total medicines dispensed in 2017, followed by quetiapine (1.44%). The percentage of the off-label dispensations for the rest of the medicines ranking here was below one percent where olanzapine was found in the third place (0.86%); nevertheless, it is worth mentioning that three of those medicines (paliperidone, clobazam and oxcarbazepine) had similarly the highest dispensation per patient (D/P) ratio corresponding to almost seven off-label dispensations per patient. Aripiprazole was the next in line with the highest D/P ratio (4.8) while for the remainder medicines ranked in this list, the D/P ratio was below four, with alprazolam been in the last place (D/P: 1.8).

When analysing the Greek data concerning the off-label dispensations for the year 2017, quetiapine was found in the first place (1.52%, D/P: 5.7), while the rest of the medicines had a percentage of off-label dispensations below one per cent with the lowest been observed for clobazam (0.29%, D/P: 5.1). Oxcarbazepine ranked as second (0.69%) with a high D/P ratio (6.2), but melatonin, which was in the third place (0.62%), had D/P reaching up to almost eight off-label dispensations per patient, making it the highest D/P among all medicines. Even though, the percentage of the off-label dispensations of olanzapine was low (0.40%), the D/P was high reaching up to six off-label dispensations per patient; aripiprazole had a D/P of 4.2, while the rest of the medicines included in the list had a D/P below four, with alprazolam been ranked in the last place (D/P: 2.7).

Table 79. Most frequent off-label used medicines in 2017 - number of dispensations in Catalonia (Spain) and Greece.

Catalonia (Spain)					Greece				
ATC		Dispensed psychotropics *(n=310,078)*			ATC		Dispensed psychotropics *(n=119,976)*		
Code	**Name**	**n**	**%**	**D/P**	**Code**	**Name**	**n**	**%**	**D/P**
N05AX12	aripiprazole	5,496	1.77	4.8	N05AH04	quetiapine	1,826	1.52	5.7
N05AH04	quetiapine	4,380	1.41	3.9	N03AF02	oxcarbazepine	832	0.69	6.2
N05AH03	olanzapine	2,654	0.86	3.6	N05CH01	melatonin	748	0.62	7.9
N06AB10	escitalopram	1,165	0.38	3.6	N05BA12	alprazolam	677	0.56	2.7
N05BA12	alprazolam	1,036	0.33	1.8	N05AX12	aripiprazole	538	0.45	4.2
N05AX13	paliperidone	1,024	0.33	6.7	N06AB10	escitalopram	514	0.43	3.7
N05BA09	clobazam	872	0.28	6.6	N05AH03	olanzapine	477	0.40	6.0
N06AB04	citalopram	743	0.24	3.5	N05BA09	clobazam	350	0.29	5.1
N06AX11	mirtazapine	659	0.21	2.9	N06AB04	citalopram	341	0.28	3.4
N03AF02	oxcarbazepine	622	0.20	6.5	N03AX16	pregabalin	312	0.26	3.7

Comparing the two region sets, we saw that there were some differences as well as similarities concerning the percentage of off-label dispensed medicines and the D/P. Oxcarbazepine and escitalopram in Greece had a higher percent of off-label dispensations than in Catalonia, but with a very similar D/P. Aripiprazole had a significant higher percentage in Catalonia compared to Greece, but again the D/P was similar. Quetiapine and clobazam had a similar percentage of off-label dispensations in both regions, but the D/P ratio in Greece was quite higher than in Catalonia for quetiapine, whereas D/P ratio in Catalonia was higher for clobazam. Off-label dispensations of olanzapine were more in Catalonia but the D/P ratio in Greece was higher. Alprazolam's off-label dispensations and D/P were higher in Greece, while citalopram had similar off-label dispensation's percentage and D/P ratio in both regions.

4.2.6.6 Off-label use per indication and existing evidence

Concerning the question if the psychotropics were dispensed according to the approved indications as reflected in their SmPC, we conducted a sub-analysis on the Greek data for the most frequently dispensed medicines by the most frequent and relevant single ICD-10 codes that was previously described in section 4.2.3.1 as per Table 64.

We found that levetiracetam, valproic acid and diazepam were dispensed under a non-specified diagnosis that could be counted as off-label use; valproic acid and aripiprazole were also dispensed for PDDs as off-label since both are not authorised for this indication. Risperidone was the active substance found to be dispensed with the highest number of the following off-

label indications as in children it is only authorised for the short treatment of persistent aggression in conduct disorder from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation: PDDs, ADHD, OCD and unspecified psychosis not due to a substance or known physiological condition. Fluoxetine is authorised in major depressive episodes and OCD but only in adults, constituting their identified in our sample use in children for these indications as an off-label use; fluoxetine was also used off-label in children with anxiety, an indication for which it does not have an authorisation. Sertraline is authorised in paediatric patients with OCD while in adults is also authorised in depression, panic disorder (with or without agoraphobia), social anxiety disorder and post-traumatic stress disorder (PTSD); thus, its use in paediatric patients of our sample suffering from anxiety or depression was considered off-label. Children suffering from anxiety and treated with alprazolam in our sample, as well as children with depression treated with escitalopram and children with psychosis treated with quetiapine, were also under an off-label status, considering that these active substances do not have authorised indications in the paediatric population. A summary of the identified off-label indications of the most frequent medicines per most frequent diagnosis can be found in the following table (Table 80).

Separate searches were conducted in PubMed from its inception to 17 August 2022 to find evidence on the identified off-label use by indication for the concerned active substances. This information is presented in the following pages.

Table 80. Off-label use per indication for the most frequently dispensed medicines of the most frequent ICD-10 code - Greece.

ATC		Patients (P)	Dispensing (D)		Indication (ICD-10)	
Name	**Code**	**n**	**n**	**(D/P)**	**Off-label**	**Authorised in paediatrics**
levetiracetam	N03AX14	1,079	6,522	6.0	Non specified	**Monotherapy**: treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. **Adjunctive therapy**: - treatment of partial onset seizures with or without secondary generalization in adults, adolescents, children, and infants from 1 month of age with epilepsy. - treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. - treatment of primary generalised tonic-clonic seizures in adults and adolescents from12 years of age with Idiopathic Generalised Epilepsy.
valproic acid	N03AG01	858	6,337	7.4	Non specified	Treatment of generalised, partial or other epilepsy in adults and paediatric patients.
		179	1,769	9.9	Pervasive developmental disorders	
diazepam	N05BA01	791	1,393	1.8	Non specified	- Control of tension and irritability in cerebral spasticity in selected cases. - As an adjunct to the control of muscle spasm in tetanus. - Oral premedication - Febrile convulsions and epileptic convulsions. *Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum. Safety and effectiveness of diazepam in paediatric patients below the age of 6 months have not been established.*
risperidone	N05AX08	1,205	7,720	6.4	Pervasive developmental disorders	Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in
		234	1,026	4.4	Unspecified psychosis not due to a substance or known physiological condition	
		214	940	4.4	Attention-deficit hyperactivity disorders	
		171	674	3.9	Obsessive-compulsive disorder	

ATC		Patients (P)	Dispensing (D)		Indication (ICD-10)	
Name	Code	n	n	(D/P)	Off-label	Authorised in paediatrics
						child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.
aripiprazole	N05AX12	453	2,829	6.2	Pervasive developmental disorders	- Treatment of schizophrenia in adults and in adolescents aged 15 years and older. - Treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.
fluoxetine	N06AB03	375	1,120	3.0	Other anxiety disorders	Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions in children and adolescents aged 8 years and above. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.
		247	1,286	5.2	Obsessive-compulsive disorder	
alprazolam	N05BA12	334	610	1.8	Other anxiety disorders	-
sertraline	N06AB06	286	973	3.4	Other anxiety disorders	Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years. Efficacy is not shown in paediatric major depressive disorder. No data are available for children under 6 years of age.
		266	1,073	4.0	Depressive episode	
escitalopram	N06AB10	149	470	3.2	Depressive episode	-
quetiapine	N05AH04	63	304	4.8	Unspecified psychosis not due to a substance or known physiological condition	-

Pervasive developmental disorders (PDDs)

PDDs include autistic disorders, Rett's syndrome, other childhood disintegrative disorder, Asperger's syndrome etc. ASDs are considered amongst the most common but varied disorders in paediatrics, where its management almost exclusively rely on behavioural therapies and social/educational programmes, with some non-specific pharmacotherapy options to be used to date for some associated symptoms but without targeting the core symptoms (214), and therefore there is a need to investigate further treatment options.(215) Approval by the US FDA was given to risperidone and aripiprazole for agitation and irritability in autism in the USA (216,217), but this is not the case in the EU. Some antiepileptics are also used in PDDs (218) with existing evidence on the use of valproic acid/valproate in PDDs as regards the core symptoms to be summarised in Table 81 below.

Table 81. Evidence on off-label use of valproic acid/valproate in paediatric patients with PDDs.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Plioplys	1994	Case reports	ASD	valproic acid	3	Positive
Hollander et al.	2001	Open label, retrospective	ASD	divalproex	14	Positive
Hellings et al.	2005	RCT	PDD	valproate	30	Negative
Hollander et al.	2006	RCT	ASD	divalproex	13	Positive
Hollander et al.	2010	RCT	ASD	divalproex	55	Positive
Hirota et al.	2014	Review, metanalysis	ASD	valproate/ divalproex[£]	76[$]	Negative
Fung et al.	2016	Review, metanalysis	ASD	valproate	56[†]	Negative
Siafis et al.	2022	Network metanalysis	ASD	valproate/ divalproex	41[+]	Positive*

*[£]: including other antiepileptics too, [$]: 4 studies (3 monotherapy), [†]: 2 studies, [+]: 3 studies, number of patients under treatment (no placebo), *: some indications of improvement, yet imprecise and not robust*

All studies for which the use of the antiepileptic focused on the epilepsy symptoms only (studies mainly referred to patients with Rett syndrome) with no reference to core symptoms of PDDs, were excluded. The only study for which the PDD was studied in general, was the one of *Hellings et al.*, where the RCT demonstrated that there was not statistically treatment difference between valproate and placebo group, a negative result that maybe caused by the large placebo response, subject heterogeneity and the small size of the groups.(219) All other evidence found was related to ASDs. According to *Plioplys*, the three case reports indicated that the use of valproic acid improved the language and social skills, and the patients were technically no longer qualified as autistic even though all autistic symptoms had not fully resolved.(220) *Holander et al.* in both the open label study and the two RCTs found a positive impact of the concerned

antiepileptic use in ASD.(221–223) The three metanalyses demonstrated conflicted results: *Hirota et al.* and *Fung et al.* found a negative result of valproate/divalproex use, while the most recent one by *Siafis et al.* showed some improvement but imprecise and not robust enough.(224–226) In all identified studies, the authors highlighted that further studies were warranted to obtain robust evidence on the use of this antiepileptic in PDDs.

Concerning the use of antipsychotics in patients with PDDs, separate searches in PubMed detected the studies summarised in the following table (Table 82). As previously mentioned, aripiprazole is one of the medications approved by the US FDA in 2009 for the treatment of ASD-associated irritability in children from 6-17 years of age, while some evidence exists from trials where its use was beneficial for managing aggression, explosive outbursts and self-injury. The identified evidence includes case reports (two for PDD and one for ASD) (227–229), open label studies (one for PDD, one for PDD not otherwise specified -NOS- and Asperger's syndrome, and six for ASD) (230–237), RCTs as well as post-hoc analysis and metanalyses (all for ASD).(224,238–245) The vast majority of the studies reported a positive effect of aripiprazole (224,226–231,233–241,243–245), while for some of them there was evidence of a slight improvement or not significantly effect (232,242), maybe because of the low number of subjects. It is worth to mention that after the US FDA approval in 2009 (216), the interest into identifying if there is a robust effect of aripiprazole in patients with ASD was increased.

Risperidone is also an antipsychotic for which in 2006 an approved indication by US FDA as per aripiprazole was given but covering children 5-16 years of age. The existing evidence from studies can be found in Table 83 below. The vast majority of the identified evidence was coming from open label studies or RCTs (226,244,246–278), complemented by few case reports (251,279) and five metanalyses.(224,226,245,274,280) The evidence seems to be positive with the exception of *McDougle et al.* where it was reported '*significant improvements in the restricted, repetitive, and stereotyped patterns of behavior, interests, and activities of autistic children but did not significantly change their deficit in social interaction and communication*' (265), as well as the RUPP Autism Network reported that in the first part of its study a negative effect was observed which was then changed to positive during the RCT.(262) Finally, four studies were conducted in preschool paediatric patients, for which there are limited data and no authorisation from the US FDA.

Table 82. Evidence on off-label use of aripiprazole in paediatric patients with PDDs.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Stigler et al.	2004	Case reports	PDD	aripiprazole	5	Positive
Stigler et al.	2009	Open label, prospective	PDD-NOS, Asperger's disorder	aripiprazole	25	Positive
Masi et al.	2009	Open label, retrospective	PDD	aripiprazole	34	Positive
Owen et al.	2009	RCT	ASD	aripiprazole	98	Positive
Marcus et al.	2009	RCT	ASD	aripiprazole	218	Positive
Huang et al.	2010	Case reports	PDD	aripiprazole	3	Positive
Aman et al.	2010	RCTs[£] (post-hoc analysis)	ASD	aripiprazole	265	Positive
Marcus et al.	2011	Open label, prospective	ASD	aripiprazole	330	Positive[$]
Marcus et al.	2011	Open label, prospective	ASD	aripiprazole	330	Positive[$]
Varni et al.	2012	RCTs[£] (post-hoc analysis)	ASD	aripiprazole	316	Positive[+]
Findling et al.	2014	RCT	ASD	aripiprazole	85	Negative[$]
Maloney el al.	2014	Open label	ASD	aripiprazole	14	Positive[*]
Fung et al.	2016	Review, metanalysis	ASD	aripiprazole	316[£]	Positive
Percinel et al.	2016	Case reports	ASD	aripiprazole	1	Positive
Ichikawa et al.	2017	RCT	ASD	aripiprazole	92	Positive
Ichikawa et al.	2017	Open label, prospective	ASD	aripiprazole	86	Positive[$]
Kim et al.	2018	Open label, prospective	ASD	aripiprazole	67	Positive
DeVane et al.	2019	RCT	ASD	aripiprazole	31	Positive
Fallah et al.	2019	Review, network metanalysis	ASD	aripiprazole	878[†]	Positive
Sugimoto et al.	2021	Observational, prospective	ASD	aripiprazole	510	Positive
Siafis et al.	2022	Network metanalysis	ASD	aripiprazole	399[&]	Positive

[£]: 2 RCTs, [$]: maintenance effect or long-term safety studies, [+]: improvement in QoL scales, [*]: slightly positive, not robust, [†]: 8 studies covering 3 interventions, [&]: 8 studies.

Table 83. Evidence on off-label use of risperidone in paediatric patients with PDDs.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
McDougle et al.	1997	Open label, prospective	PDD	risperidone	18	Positive
Nicolson et al.	1997	Open label, prospective	ASD	risperidone	10	Positive
Findling et al.	1997	Open label, prospective	ASD	risperidone	6	Positive
Posey et al.	1999	Case reports	ASD	risperidone	2[y]	Positive
Zuddas et al.	2000	Semi-naturalistic, prospective	PDD-NOS, ASD	risperidone	11	Positive
Masi et al.	2001	Open label, prospective	PDD	risperidone	24	Positive
Masi et al.	2001	Open label, prospective	PDD	risperidone	10[y]	Positive
Vercellino et al.	2001	Open label	ASD	risperidone	9	Positive
McCracken et al.	2002	RCT	ASD	risperidone	101	Positive
Malone et al.	2002	Open label, prospective	ASD	risperidone	22	Positive
Boon-Yasidhi et al.	2002	Case reports	ASD	risperidone	5[y]	Positive
Masi et al.	2003	Open label	PDD-NOS, ASD	risperidone	53	Positive
Shea et al.	2004	RCT	PDD, ASD	risperidone	79	Positive
Gagliano et al.	2004	Open label, prospective	ASD	risperidone	20	Positive
Mukaddes et al.	2004	Open label, prospective	ASD	risperidone	19	Positive
RUPP Autism Network[+]	2004	I: Open label II: RCT	ASD	risperidone	I: 63 II: 32	Negative Positive
Rausch et al.	2005	Open label, prospective	Asperger	risperidone	13	Positive
Troost et al.	2005	I: Open label II: RCT	ASD	risperidone	36	Positive
McDougle et al.	2005	I: RCT II: Open label	ASD	risperidone	101	Positive
Williams et al.	2006	Open label	ASD	risperidone	48	Positive[$]
Luby et al.	2006	RCT	ASD	risperidone	24[y]	Positive[*]
Nagaraj et al.	2006	RCT	ASD	risperidone	40	Positive
Troost et al.	2006	RCT	PDD	risperidone	24	Positive
Pandina et al.	2007	RCT	ASD	risperidone	55	Positive
Gencer et al.	2008	Open label, prospective	ASD	risperidone	28	Positive[$^]
Sharma et al.	2012	Metanalysis	ASD	risperidone	608[†]	Positive
Kent et al.	2013	RCT	ASD	risperidone	96	Positive
Kent et al.	2013	Open label, prospective	ASD	risperidone	79	Positive[$]
Aman et al.	2014	Naturalistic, prospective	ASD	risperidone	84	Positive[$]
Fung et al.	2016	Review, metanalysis	ASD	risperidone	366[£]	Positive
DeVane et al.	2019	RCT	ASD	risperidone	30	Positive
Fallah et al.	2019	Review, network metanalysis	ASD	risperidone	878[&]	Positive
Mano-Sousa et al.	2021	Review, metanalysis	ASD	risperidone	2,377[#]	Positive
Siafis et al.	2022	Network metanalysis	ASD	risperidone	319[x]	Positive

[y]: pre-school patients, [+]: Research Units on Pediatric Psychopharmacology Autism Network, [$]: maintenance effect or long-term studies, [*]: slightly positive, [†]: 21 studies, [^]: compared to haloperidol, [£]: 5 studies, [&]: 8 studies covering 3 interventions, [#]: 41 studies, [x]: 20 studies

Attention deficit hyperactivity disorder (ADHD)

Paediatric patients with ADHD are frequently found also with symptoms of aggression which are difficult to distinguish if they come from hyperactivity, impulsivity or if there are symptoms related to a comorbid diagnosis.(281) Except for psychostimulants approved for ADHD, some atypical antipsychotics, risperidone included, are used off-label in these paediatric patients in particular when psychostimulants are failing.(282) Our search in PubMed revealed that evidence exists on risperidone use in patients with ADHD; identified studies are summarised in the following table (Table 84).

Most of the identified studies were RCTs (283–287), followed by open label studies (288–290), one extension study (291) and one single blind study (292), as well as one review/metanalysis.(293) Even though the positive results of all the retrieved studies were marked, there were several confounding factors to be able to extract robust evidence on the use of risperidone in ADHD: the majority was studying risperidone combined with psychostimulants, most of the times for treating aggression and not the core symptoms of ADHD, or for treating children with ADHD with or without comorbidities, or with intellectual impairment. The evidence was also limited by the short observational periods, as well as by the small number of children involved in the studies and the different primary endpoints.

Table 84. Evidence on off-label use of risperidone in paediatric patients with ADHD.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Aman et al.	2004	RCT	ADHD	risperidone	155	Positive
Correia et al.	2005	Single-blind CT	ADHD	risperidone[+]	45	Positive
Armenteros et al.	2007	RCT	ADHD[y]	risperidone	25	Positive[$]
Masi et al.	2007	Open label, prospective	ADHD	risperidone[+]	20	Positive
Günther et al.	2008	Open label, prospective	ADHD	risperidone	23	Positive
Aman et al.	2014	RCT	ADHD	risperidone	168	Positive*
Javelot et al.	2014	Open label, prospective	ADHD	risperidone	44	Positive
Pringsheim et al.	2015	Review, metanalysis	ADHD	risperidone	429[†]	Positive
Gadow et al.	2016	Extension CT	ADHD	risperidone	108	Positive
Jahangard et al.	2016	RCT	ADHD	risperidone	84	Positive
Blader et al.	2020	RCT	ADHD	risperidone	175[y]	Positive

[+]: vs methylphenidate, [$]: not convincing evidence, but good results in some scales, [*]: moderately positive, [†]: 4 studies, [y]: risperidone, divalproex sodium and placebo

Obsessive-compulsive disorder (OCD)

The treatment of paediatric patients diagnosed with OCD is initially limited to cognitive-behavioural therapy, serotonergic agents or a combination of the two, while risperidone is neither authorised for OCD in adults nor in children.(294) The literature search on the use of risperidone in children with OCD did not identify a lot of evidence and this is summarised in the following table (Table 85).

Most of the identified evidence was from case reports (295–298) one of which involving very young children.(299) In addition, only two articles described studies in this population: one open label study (300) and one naturalistic (301), both prospective. Despite the difference on the type of the identified evidence, the common point is that the use of risperidone in paediatric patients with OCD had positive results as augmentation of SSRIs/resistant cases.

Table 85. Evidence on off-label use of risperidone in paediatric patients with OCD.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Fitzgerald et al.	1999	Case report	OCD	risperidone*	4	Positive
Thomsen et al.	2004	Open label	OCD	risperidone*	17	Positive
Oner et al.	2008	Case report	OCD	risperidone*	2$	Positive
Nguyen et al.	2012	Case report	OCD	risperidone*	1	Positive
Masi et al.	2013	Naturalistic, prospective	OCD	risperidone*	35	Positive
Rosli et al.	2015	Case report	OCD	risperidone	1	Positive
Demirkaya et al.	2016	Case report	OCD	risperidone*	1	Positive+

**: as augmentation to SSRIs or resistant patients, $: 4-5 years of age, +: changed to ziprasidone due to weight gain*

In addition, fluoxetine was reported as to be used off-label in our sample in patients with OCD. In Europe, fluoxetine is authorised in the treatment of adults with OCD, but not for paediatric patients, while the package leaflet of the product includes warnings for its use in children as described previously. However, since 2003 fluoxetine is authorised in children with OCD aged more than 7 years in the USA.(302) The literature search then is necessary to demonstrate how much evidence exists concerning this difference between the regions. The identified evidence from the literature search is presented in the following table (Table 86).

One series of case reports (303), four RCTs (304–307), two open label studies of which one was prospective (308) and one retrospective (309), one study using retrospective chart reviews (310) and two metanalyses (311,312) were retrieved, all concluding with positive evidence on the use of fluoxetine in children with OCD. Several case reports were also found describing the use of fluoxetine in patients with OCD with other comorbid disorders as the main inclusion criterion, therefore were not reported in this analysis. In only one study, *Geller et al.* the number

of subjects was more than hundred, therefore the identified evidence was limited with regard the sample size.(305) The two metanalyses were based on the same three RCTs of *Riddle et al.* (304), *Geller et al.* (305) and *Liebowitz et al.* (306), but the most recent one of *Maneeton et al.* (312) included also the RCT of *Alaghband-Rad and Hakimshooshtary* (307) where the use of fluoxetine was compared to citalopram. *Fatori et al.* demonstrated that fluoxetine and group cognitive behavioural treatment (CBT) were similarly effective as initial treatments considering treatment failures over time.(313) *Coskun et al.* (309) and *Ercan et al.* (303) studied the efficacy and safety of fluoxetine use in pre-school patients, while the latter was also investigating this population which was resistant in previous non-psychopharmacologic treatment. Finally, the chart reviews study was the one investigating the long-term use of fluoxetine in patients with OCD.

Table 86. Evidence on off-label use of fluoxetine in paediatric patients with OCD.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Riddle et al.	1992	RCT	OCD	fluoxetine	13	Positive
Bouvard and Dougas	1993	Open label, prospective	OCD	fluoxetine	11	Positive
Geller et al.	1995	Chart reviews, retrospective	OCD	fluoxetine*	38	Positive
Geller et al.	2001	RCT	OCD	fluoxetine	103	Positive
Liebowitz et al.	2002	RCT	OCD	fluoxetine	43	Positive$
Alaghband-Rad and Hakimshooshtary	2009	RCT	OCD	fluoxetine+	29	Positive
Coskun et al.	2009	Open label, retrospective	OCD	fluoxetine	6†	Positive
Ercan et al.	2012	Case reports	OCDy	fluoxetine	4†	Positive
Skapinakis et al.	2016	Review, network metanalysis	OCD	fluoxetine	99x	Positive
Fatori et al.	2018	SMARTε	OCD	fluoxetine&	83	Positive
Maneeton et al.	2020	Review, metanalysis	OCD	fluoxetine	188k	Positive

**: long-term only, $: in a prolonged treatment period, +: vs citalopram, †: pre-school children, y: severe and resistant patients, x: 3 studies, ε: sequential multiple assignment randomised trial, &: vs group cognitive behavioural treatment (CBT), k: 4 studies*

Unspecified psychosis not due to a substance or known physiological condition

Psychotic disorders in paediatric patients have been recognised more frequently the past years. In the USA, risperidone is authorised in adolescents with schizophrenia since 2007 (217) and quetiapine since 2009 (314), while this is not the case in Europe. The performed literature search to identify evidence on the use of both medicines in children with unspecified psychosis did not result in finding any study, and therefore studies with a broader psychosis term were

included and summarised in the following tables (Table 87 and Table 88). References related to specified psychosis due to a substance or known physiological condition were excluded.

Regarding the use of risperidone in children, this is supported by three case report studies (315–317), one retrospective review of patients' chart (318), eight RCTs (319–326), three longitudinal studies (327–329) and two metanalyses.(330,331) The study of Haas et al. was a placebo-controlled one, but all other comparative studies were evaluating the use of risperidone compared to other antipsychotics of both first and second generation.(324) Sikich et al. (322) was the only RCT where the use of risperidone seems to not be superior to other agents, while according to *Jensen et al.* (321) and *Castro-Fornieles et al.* (327) the use of risperidone in psychotic situations was slightly positive or same as the other options; the latter was also supported by the two metanalyses. Two of the case reports also described a negative effect of risperidone in paediatric patients, but this may be due to the complexity of treating patients with comorbid disorders (see Table 87).

The same strategy was followed to identify the available evidence on the use of quetiapine in paediatric patients with psychosis and the information is summarised in Table 88 below. The use of quetiapine in paediatric patients is supported by two case report studies (316,332), four RCTs (321,325,326,333), three longitudinal studies (327,329,334), three open label prospective studies (335–337) and one metanalysis.(330) As described above for the use of risperidone, all the comparative studies were evaluating the use of quetiapine compared to other antipsychotics. The effective use of quetiapine was not the expected one in the studies from *Swadi et al.* (325) and *Cianchetti et al.* (329) compared to other antipsychotic agents, while according to *Jensen et al.* (321), *Castro-Fornieles et al.* (327), *Arango et al.* (337) and *Pagsberg et al.* (333) quetiapine use in patients with psychotic symptoms was described as slightly positive or similar to the others, while the metanalysis also supported the latter point.

Other anxiety disorders

Anxiety disorders are quite common in the paediatric population, and the treatment strategy includes psychotherapy and more concretely CBT as stand-alone or in combination with medication; off-label use of antianxiety medication was also observed in our sample as alprazolam, fluoxetine and sertraline are not authorised in the paediatric patients with other anxiety disorders.(338)

Table 87. Evidence on off-label use of risperidone in paediatric patients with psychosis.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Dryden-Edwards et al.	1996	Case report	Psychosis	risperidone	1	Positive
Grcevich et al.	1996	Charts review, retrospective	Psychotic disorders	risperidone	16	Positive*
Healy et al.	1999	Case report	Acute schizophrenia-like psychosis	risperidone	1	Negative
Sikich et al.	2004	RCT	Schizophrenia$	risperidone+	20	Positive
Mozes et al.	2006	RCT†	Childhood-onset schizophrenia	risperidone+	13	Positive$
Jensen et al.	2008	RCT†	Schizophrenia disorders	risperidone+	10	Positivey
Sikich et al.	2008	RCT	Early-onset schizophrenia and schizoaffective disorder	risperidone+	42	Negativex
Castro-Fornieles et al.	2008	Naturalistic, longitudinal	Early-onset schizophrenia	risperidone+	50	Positivey
Haas et al.	2009	RCT†	Schizophrenia	risperidone£	257	Positive
Haas et al.	2009	RCT	Schizophrenia	risperidone£	106	Positive&
Swadi et al.	2010	RCT	First-onset psychosis	risperidone+	11	Positive
Findling et al.	2010	RCT, longitudinal	Early-onset schizophrenia and schizoaffective disorder	risperidone+	21	Positive
Cianchetti et al.	2011	Open label, long-term follow-up	Early-onset schizophrenia and schizoaffective disorder	risperidone+	32	Positive
San et al.	2012	RCT†	First-episode psychosis (naïve)	risperidone+	25	Positive
Krause et al.	2018	Network metanalysis	Schizophrenia disorders	risperidone+	229#	Positivey
Xia et al.	2018	Metanalysis	Psychosis	risperidone+	232k	Positivey
Miller et al.	2020	Case report	Schizoaffective disorder	risperidone	1	Negative

**: negative for one subject, $: paranoid, disorganized, or undifferentiated subtype, +: vs other antipsychotics, †: open label or no comparator, y: slightly positive for risperidone or same as others, x: not superior to others, £: two doses, &: vs placebo, #: 7 studies, k: 8 studies.*

Table 88. Evidence on off-label use of quetiapine in paediatric patients with psychosis.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Healy et al.	1999	Case report	Acute schizophrenia-like psychosis	quetiapine	1	Positive
McConville et al.	2000	Open label, prospective	Chronic or intermittent psychotic disorders	quetiapine*	10	Positive
Shaw et al.	2001	Open label, prospective	Psychotic disorder	quetiapine	15	Positive
Hayden et al.	2001	Case reports	Schizophrenia	quetiapine	1	Positive$
McConville et al.	2003	Open label, prospective longitudinal	Schizoaffective disorder or bipolar disorder with psychotic features	quetiapine	10	Positive$
Jensen et al.	2008	RCT†	Schizophrenia disorders	quetiapine+	10	Positivey
Castro-Fornieles et al.	2008	Naturalistic, longitudinal	Early-onset schizophrenia	quetiapine+	18	Positivey
Arango et al.	2009	Open label, prospective	First-onset psychosis	quetiapine+	16	Positivey
Swadi et al.	2010	RCT	First-onset psychosis	quetiapine+	11	Negativex
Cianchetti et al.	2011	Open label, long-term follow-up	Early-onset schizophrenia and schizoaffective disorder	quetiapine+	8	Negativex
San et al.	2012	RCT†	First-episode psychosis (naïve)	quetiapine+	23	Positive
Pagsberg et al.	2017	RCT	Early-onset psychosis	quetiapine+	55	Positivey
Krause et al.	2018	Network metanalysis	Schizophrenia disorders	quetiapine+	223#	Positivey

**: two doses, $: long-term, †: open label or no comparator, +: vs other antipsychotics, y: slightly positive or same as others, x: not superior to others, #: 4 studies.*

Benzodiazepines are not authorised as to be used in the paediatric population; thus, psychiatrists and child psychiatrists are in general hesitant to prescribe this class of medicines mainly because of concerns on potential drug dependence and depressive side effects. The lack of data on benzodiazepine use was also confirmed by the scarce evidence found in the literature search for alprazolam and its use in the paediatric anxiety cases, where available evidence is summarised in the following Table 89.

The evidence found consists of two open label studies (339,340), one RCT placebo controlled (341) and one case report.(342) The two open label studies demonstrated a positive effect of alprazolam in paediatric patients with anxiety disorders, but the small sample size and the lack of placebo control do not render as robust evidence. On the other hand, the RCT did not show a difference between placebo and alprazolam arms, except for alprazolam's superiority only on

clinical global ratings but this difference was not statistically significant. In the single identified metanalysis where the authors were comparing various medications for childhood anxiety disorders, only the study of *Simeon et al.* (340) was included, therefore the authors could not conclude on the use of alprazolam.(343) As presented in the case report, alprazolam was discontinued in the adolescent patient with generalised anxiety disorder due to serious adverse events, i.e., suicidal ideation and self-destructive behaviour.

Table 89. Evidence on off-label use of alprazolam in paediatric patients with anxiety.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Pfefferbaum et al.	1987	Open label, prospective*	Anticipatory and acute situational anxiety$	alprazolam	13	Positive
Simeon et al.	1987	Open label, prospective, followed by post-drug placebo period	Anxiety disorders	alprazolam	12	Positive
Simeon et al.	1992	RCT† followed by post-drug placebo period	Overanxious or avoidant disorders	alprazolam	30	Negative
Türkoğlu et al.	2015	Case report	Generalized anxiety disorder	alprazolam	1	Negativeɣ

**: dose range study, $: cancer patients, †: vs placebo, ɣ: due to serious side effects*

SSRIs are frequently prescribed for the treatment of anxiety disorders in youth, even though fluoxetine and sertraline are not approved for paediatric patients. The identified evidence for both can be found below in Table 90 and Table 91 respectively.

The search for the fluoxetine resulted to several studies: three RCTs (344–346), two prospective open label (347,348), two open label extension studies (349,350) and two metanalyses (343,351); no case reports were included as there is abundant information for the use of fluoxetine in the different anxiety disorders. In all studies there was favourable evidence on the use of fluoxetine in paediatric patients suffering from anxiety. However, the RCT of *da Costa et al.* where fluoxetine was compared to CBT and clomipramine, an unusual high rate of placebo was observed: patients from all arms showed significant improvements, but fluoxetine had significant differences in some ratings of anxiety severity and impairment compared to placebo, and there was no difference observed compared to clomipramine.(346) The metanalyses showed that SSRIs had a favourable effect as treatment options (343,351), but head-to-head comparisons were sparse in the one performed by *Wang et al.*(343) The two extension studies showed good results in the maintenance of treatment, and it is also worth to mention that

fluoxetine seemed to also be effective and safe in patients that were previously unresponsive to other treatments.(349,350) For further details see Table 90 below.

Table 90. Evidence on off-label use of fluoxetine in paediatric patients with anxiety.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Birmaher et al.	1994	1. Chart review, retrospective 2. Open label, prospective	Overanxious disorders, SAD, SP*	fluoxetine	21	Positive
Fairbanks et al.	1997	Open label, prospective	Mixed anxiety disorders*	fluoxetine	16	Positive
Walkup et al.	2002	Open label, extension	GAD, SAD, SP*	fluoxetine	14	Positive
Birmaher et al.	2003	RCT	GAD, SAD, SP	fluoxetine$	37	Positive
Clark et al.	2005	Open label, extension	GAD, SAD, SP	fluoxetine	42	Positive
Beidel et al.	2007	RCT	SP	fluoxetine$+	33	Positive
da Costa et al.	2013	RCT	GAD, SAD, SP	fluoxetineɣ+	10	Positive†
Wang et al.	2017	Metanalysis, network	Anxiety disorders	fluoxetine	173#	Positive
Schwartz et al.	2019	Metanalysis	Anxiety disorders	fluoxetine	175x	Positive

GAD: generalised anxiety disorder, SAD: separation anxiety disorder, SP: social phobia/anxiety
**: unresponsive to previous psychopharmacological and/or psychotherapeutic interventions, $: vs placebo, +: vs CBT, ɣ: vs clomipramine, †: placebo response with unusual high rate, #: 6 studies, x: 3 studies.*

Table 91. Evidence on off-label use of sertraline in paediatric patients with anxiety.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Mancini et al.	1999	Case report	SP	sertraline	1	Positive
Compton et al.	2001	Open label, prospective	SP	sertraline	14	Positive
Rynn et al.	2001	RCT	GAD	sertraline*	11	Positive
Walkup et al.	2008	RCT	GAD, SAD, SP	sertraline*+	133	Positive
Strawn et al.	2012	Case report	GAD, SP	sertraline$	1	Negativeɣ
Huang et al.	2013	Open label, randomised, prospective	SP	sertraline†	36	Positive
Wang et al.	2017	Metanalysis, network	Anxiety disorders	sertraline	284#	Positive
Schwartz et al.	2019	Metanalysis	Anxiety disorders	sertraline	510x	Positive

GAD: generalised anxiety disorder, SAD: separation anxiety disorder, SP: social phobia/anxiety
**: vs placebo, +: vs CBT or vs CBT-sertraline, $: unresponsive to previous psychopharmacological and/or psychotherapeutic interventions, ɣ: partial response, †: tandospirone, #: 2 studies, x: 2 studies.*

Concerning the complied data for the use of sertraline which are presented in Table 91, we identified two case reports (352,353), two open label studies both prospective (354,355), two RCTs (356,357), and two metanalyses.(343,351) The evidence on the use of sertraline in children with anxiety disorders was found as favourable, with the exception for the case report

from *Strawn et al.* (353) where the subject found to be partially responsive to sertraline upon being previously unresponsive to treatments or psychotherapeutic interventions. The two RCTs compared sertraline to placebo demonstrating sertraline's superiority, while the combination of sertraline with CBT was also superior against placebo.(356,357) The two metanalyses also described a positive effect in the use of sertraline in children with anxiety disorders.(343,351) *Huang et al.* described the superiority of sertraline against tandospirone in social anxiety disorder upon randomisation in an open label study.(355)

Depressive episodes

Depression in paediatrics is routinely treated worldwide with psychotherapy as first-line, while antidepressants are often used for more severe disorder manifestations or when the patient is unresponsive to psychotherapy.(358) None of sertraline and escitalopram that were both identified as off-label in our sample, are authorised for depression in paediatrics in Europe and therefore their use is not recommended;(358) however, escitalopram is authorised in adolescents (12-17 years old) with major depressive disorder (MDD) since 2009 in the USA.(359)

The evidence found for the use of sertraline in paediatric patients with depression are summarised in the subsequent table (Table 92). Four RCTs support the use of sertraline in paediatric patients with symptoms of depression in short term,(360–362) with one of them providing evidence on long-term use too (363), four open label studies (364–367) and four network metanalyses.(368–371) All retrieved studies referred to outpatient data except for the open label study from *McConville et al*.(364) Most of the evidence proposes the effective use of sertraline apart from the metanalysis by *Zhou et al.* where the conclusion was that sertraline was not considered more effective than both pill placebo and psychological controls, and had more dropouts than the ones observed in the placebo group.(370)

Concerning the evidence supporting escitalopram use in depressive children and adolescents, the compiled information is presented in the following table (Table 93). We retrieved three RCTs (372–374) and four metanalyses.(368–371) All RCTs are placebo-controlled and only in the study of *Wagner et al.* no significant differences between escitalopram and placebo in the total population was detected, but some data suggest that escitalopram may had beneficial effects in adolescent patients as it was also well-tolerated.(372) The metanalyses have controversial conclusions on the use of escitalopram: from favourable to borderline in comparison with other treatment options, or not significantly more effective than placebo; however, the common point among those is that all had limitations and highlighted the low quality of the RCTs evidence.(368–371)

Table 92. Evidence on off-label use of sertraline in paediatric patients with depression.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
McConville et al.	1996	Open label, prospective	MDD	sertraline	13*	Positive
Ambrosini et al.	1999	Open label, prospective	MDD	sertraline	53	Positive
Nixon et al.	2001	Open label, prospective	MDD, DD	sertraline	21	Positive[+]
Wagner et al.	2003	RCTs[#]	MDD	sertraline[y]	189	Positive
Melvin et al.	2006	RCT	MDD, DD, DDNOS	sertraline[†]	51	Positive
Rynn et al.	2006	Open label, prospective	MDD	sertraline	216	Positive[+]
Cheung et al.	2008	RCT	MDD	sertraline[y]	13	Positive[+]
Ma et al.	2014	Metanalysis, network	MDD	sertraline	189[#]	Positive
Iftene et al.	2015	RCT	MDD	sertraline[†]	33	Positive
Cipriani et al.	2016	Metanalysis, network	MDD	sertraline	189[#]	Positive
Zhou et al.	2020	Metanalysis, network	MDD	sertraline	305[x]	Negative
Hetrick et al.	2021	Metanalysis, network	MDD	sertraline	189[#]	Positive

MDD: major depressive disorder, DD: dysthymic disorder, DDNOS: depressive disorder not otherwise specified
**: hospitalised for MDD, [+]: short and long-term treatment, [#]: two RCTs, [y]: vs placebo, [†]: vs CBT or CBT-sertraline combination, [x]: 5 studies.*

Table 93. Evidence on off-label use of escitalopram in paediatric patients with depression.

Studies identified in PubMed						
Author	**Year**	**Study**	**Disorder**	**Medicine**	**n**	**Evidence**
Wagner et al.	2006	RCT	MDD	escitalopram*	131	Negative
Emslie et al.	2009	RCT	MDD	escitalopram*	155	Positive
Findling et al.	2013	RCT	MDD	escitalopram*	83	Positive[+]
Ma et al.	2014	Metanalysis, network	MDD	escitalopram	286[#]	Positive
Cipriani et al.	2016	Metanalysis, network	MDD	escitalopram	131[x]	Positive
Zhou et al.	2020	Metanalysis, network	MDD	escitalopram	286[#]	Negative
Hetrick et al.	2021	Metanalysis, network	MDD	escitalopram	286[#]	Positive[y]

MDD: major depressive disorder
**: vs placebo, [+]: long-term, [#]: 2 studies, [x]: 1 study, [y]: partial favourable.*

4.2.1 Healthcare systems comparison

In general, the two systems have some similarities, and the most important information was compiled and presented below in Table 94.

4.2.1.1 Catalonia's (Spain) health system

In Spain, the governance of the national health system is decentralised, with regional healthcare authorities being payers and having certain autonomy into planning, but the overall coordination and monitoring of the health system performance resides under the central administration. The seventeen autonomous communities have a department of health, being as a health authority, which is responsible for topics such as local regulation, planning and financing; some regions have also a Health Technology Assessment (HTA) agency (Catalonia, Basque Country, Galicia, Aragon, Andalusia, Canary Islands and Madrid). In general, the national health system is almost universal and covers 99.10% of the population (since 2012), but private insurances exist along with private practices and private hospitals. The economic crisis resulted in austerity measures and reformation of the system with aim to reduce pharmaceutical expenditure; among the measures taken were also reductions on the budget as well as new regulations on the scope and depth of coverage.(375)

The pricing and the public reimbursement of pharmaceuticals is managed by the Inter-ministerial Commission on Prices of Medicines, a body of the Ministry of Health, following specific criteria and are updated annually. Three complementary measures increase the efficiency of the pharmaceutical care policy: reference prices, prescription by active substance and use of generics. The price and its reimbursement are decided based on the therapeutic significance of the medicine and the innovation grade on top of their impact on the budget, so that the selected for reimbursement products provide a significant therapeutic input for the patients. A maximum reference price at which a drug could be financed by the public sector is set as the average of the prices of the three cheapest products, creating also homogeneous groups to which this reference price applies. The physicians prescribe based on the active substance and the pharmacists dispense the cheapest drug within the group which is commonly a generic.

The autonomous communities are responsible to reimburse the pharmacies for any dispensed medicine following the pricing and co-payment who are regulated centrally and are included in the benefit scheme. The benefit package includes all medicinal products except for cosmetic formulae, dietary products, mineral water, elixirs, toothpaste and other health products, over-the-counter medicines, homeopathic remedies, or any item or accessory advertised aiming the general population. All residents of Catalonia are covered apart from patients with no

pharmaceutical coverage from the Catalan Health Service (*CatSalut)*, those with only private insurance, patients with prescription of a hyposensitising agents or vaccines, some magistral formulae and when the prescription is to be collected out of Catalonia. During the maximum one year duration of treatment prescription, the patient can go directly to the pharmacy with no need to go back to the physician.

The co-payment scheme, which was reformed and increased in 2012, is divided into two groups: pensioners and active workers. For the pensioners who have an annual income below €18,000 the co-payment is of 10% with a maximum ceiling of €8.23/month; the co-payment remains the same but with a monthly maximum ceiling of €18.52 when the annual income is between €18,000 and €100,000, while it goes up to 60% co-payment and a maximum ceiling of €61.70/month for an income above €100,000/year. Concerning the active workers, including unemployed or under unemployment benefit, there are similar groups based on the same annual income limits: 40%, 50% and 60% co-payment respectively with no ceilings for this group. These co-payment schemes apply to all reimbursed medicines except for any drugs prescribed to AIDS patients and to most chronic disease treatments: 10% co-payment limited to €4.26/prescription irrespective if the patient is pensioner or active worker.(376) There are several exceptions where the co-payment scheme is not applicable, e.g. due to incapacity or very low income.(377)

Since the pharmacy invoices are reimbursed by the autonomous communities, the database including all dispensed medicines are under the control of each region's health authority. Among the various autonomous communities, Catalonia was one of the most advanced, promoting the system of the electronic prescription (e-prescription), which came into effect in 2007 after a pilot phase in 2006 and reached 100% coverage two years later.(378,379)

4.2.1.2 Greece's health system

In Greece the health system is managed on a national level. Due to the economic crisis, the national health system had to be reformed, therefore the unification of the different social security providers into the National Healthcare Services Provider (*EOPYY in Greek spelling*) controlled by the Greek Ministry of Health was established in 2012 (Law 3918/2011) covering the healthcare costs for over 95-98% of the population including the vulnerable social groups since 2016 (e.g. unemployed, uninsured, refugees). Any healthcare service is provided via a network of public providers as well as contracted private providers for all primary, hospital and ambulatory healthcare; private providers presence is quite strong concerning the primary health by providing medical services from independent physicians and private clinics which are either contracted by *EOPYY* or not. The healthcare system is co-financed by the state,

contributions of social insurance and private payments. *EOPPY* is responsible for any negotiation, contraction and remuneration of public and private contracted healthcare providers. A patient can address to the public domains to receive any primary or hospital care, as well as to the private sector. Private healthcare professionals not contracted with *EOPYY* are paid entirely by patients, while contracted private physicians have a limit of 200 patients' visits per month which can be remunerated by *EOPYY*. Therefore, a patient will be required to pay out of pocket when visiting a contracted physician who reached the consultation ceiling for that month.(95,380)

The reformation of the system also introduced the electronic prescription in 2012, which contains several information regarding the patient, the treatment, the prescriber as well as the co-payment and as described in the introduction section, it is handled by *IDIKA*. All physicians, in public or private domains (contracted and not), have the right to use the e-prescription: during a visit, the physician can prescribe for more than one treatment period and up to 6 months in case of chronic health problems. The patient will then bring the prescriptions to the pharmacy which will dispense the prescribed medicines. Pharmacies are private and dispense all medicines, prescribed and over the counter, but there are some medicines that are dispensed by the *EOPPY*'s public pharmacies (e.g. expensive oncology treatments) or hospitals (e.g. hospital use treatments). Data reveal that the network of pharmacies in Greece is by far the densest in Europe (381), hence patients are covered in all regions despite the complicated geomorphology of the Greek territory (e.g. mainland and islands).

The pricing of the medicinal products has changed several times during the course of the past ten years and the competent authority for the pricing, evaluation and market authorisation of pharmaceuticals is *EOF*. The first price of a new, still on patent, medicine requires a previous allocation of a price in at least three (two for orphan products) other European countries and is defined as the average of the three lowest prices. To decrease the pharmaceutical expenditure, several austerity measures were adopted including repeated major pharmaceutical price reductions that resulted into increased pharmaceutical parallel exports and medicines shortages in the territory.(95) In addition, the reformation was responsible for the establishment of *EOPPY*'s current reimbursement system. A positive list with all medicinal products reimbursed by the social health insurance exists and the co-payment in Greece is in general 25%, whereas patients with life-threatening diseases, chronically ill, pregnant women, vulnerable groups and patients with a maximum taxable income of €1,200 are entitled to receive medicines free of charge or pay a reduced rate (10%).

Reference prices for each cluster of products are based on the prices of the less expensive products in the cluster and they are revised twice per year only for the positive list by the HTA

body established in 2018. In cases the patient gets a medicinal product with price higher than the reference one, he/she pays the difference between the reference and the actual price of the product on top of statutory rate co-payment. The final price is also affected if there are generics in the cluster and if the patient will eventually choose to take a generic one, while since 2014 a fixed fee of €1 is paid directly by the patient for each prescription with an exception for some categories of patients (e.g. unemployment, pregnancy). Finally, the use of therapeutic protocols for physicians, on the basis of international prescription guidelines, was also introduced as compulsory in 2012, aiming to control the excessive prescribing observed in the past and to guide into prescribing the cheapest medicines; however, not a lot of protocols are developed yet and therefore this is still a work in progress.(382)

All the above demonstrate that even though the coverage of the system in Greece is national, patients are a lot of times obliged to cover a big part of their health expenses with out-of-pocket payments including their medication; health expenditure has been growing faster than national income, contributing maybe to the recently reported low satisfaction of Greek citizens on the availability of quality health care in the territory.(380,381)

Table 94. Healthcare systems in Catalonia (Spain) and Greece.

Country	Date of e-prescription	Information included in the e-prescription	Coverage	Co-payment scheme
Catalonia (Spain)	2007	- Medicines (ATC code, name, dose, frequency, treatment duration, number of packages, co-payment) - Comment by prescriber to resolve any doubt - Prescriber details - Estimated cost of the treatment	All Catalonia residents with a social security number (except for undocumented immigrants)	Pensioners with annual income: - <€18,000: 10%, ceiling €8.23/month - €18-100,000: 10%, ceiling €18.52/month - >€100,000: 60%, ceiling €61.75/month Active workers with annual income: - <€18,000: 40% - €18-100,000: 50% - >€100,000: 60% Patients with AIDS patients and most chronic disease treatments: 10% co-payment, ceiling €4.26/prescription irrespective if the patient is pensioner or active worker. Reference prices. Exceptions do not have to contribute.
Greece	2012	- Patient information (full name, social security number, address, date of birth) - Medicines (ATC code, name, dose, frequency, treatment duration, number of packages, co-payment) - ICD-10 connected to the medicine - Date of prescription and dispensation - Prescriber details (name, specialty, any comment to solve any doubt)	All Greek population with a social security number	0%, 10% or 25%: - 25% is the general rule; - life-threatening diseases, chronically ill, pregnant women, vulnerable groups, patients with a maximum taxable income of €1,200 are entitled to receive medicines free of charge or pay a reduced participation (10%). A maximum price established for cluster of medicines. Positive list with all medicinal products that are reimbursed by social health insurance. Existence of therapeutic guidelines.

5 DISCUSSION

General Remarks

During childhood and adolescence periods, the brain growths and matures; cognitive and emotional skills, personality and coping strategies develop, to build a healthy and functional adult that will live a meaningful life. Paediatric patients with mental health issues exist and are more visible the past decades. However, defining the epidemiology of mental health disorders on national levels is not always an easy task especially for this vulnerable population. Mental disorders in childhood are frequent; the WHO considers that the prevalence of mental disorders amongst children and adolescents may be up to 10%, but also alerts that too often they do not receive proper help or care.(15)

Medicines are amongst the different therapeutic strategies available to treat mental health disorders. However, for decades medicines have been barely studied in children, making their use for long time mostly empirical based on extrapolation from adults, using formulations not suitable for children, and prescribing out of the authorised labelling, i.e. as off-label use.(82)

Considering how difficult is to study children healthcare, availability of paediatric data on drug use may be of high interest to academia, research or patient organisations and pharmaceuticals, resulting into a potential boost of studies and policies, leading to better healthcare planning and delivery, and thereinafter improving physical and mental well-being of paediatric patients and their families. The increasingly availability of RWE data allows generating evidence to support planning of health policies or strategies.(383-385) In particular, the use of data on dispensed medicines may serve as a starting point to approach the study of a medical condition and provides the basis for other projects or policies. Hence, drug utilization studies may be a useful tool to understand the medicine needs for paediatric patients suffering from mental health conditions.

Data on outpatient medicine use may help not only to describe the epidemiology of drug exposure, but also to approach appropriateness of therapeutic uses.(384) This is of special importance considering the restrictions and difficulties on conducting clinical trials in paediatrics. Outpatient data that are derived from routine care as well as their off-label use can contribute to increase the information on the safe and effective use of medicines for these patients.(385) In addition, adverse events related to medication not approved for use in children is also a reality and often related to an off-label use, so RWE data on drug use - and off-label drug use - in paediatrics renders a greater interest.(91) Furthermore, most literature is generated in northern European and Anglo-Saxon countries, but the substantial differences in the pattern of use of drugs in different parts of the world which depends on characteristics of healthcare systems and delivery, as well as cultural determinants and residential/environmental factors

(124,386), is considered as burden for extrapolation in other regions. Thus, analysing data coming from countries in the south of Europe, such as Spain and Greece, is of significant interest.

In view of the above, it was pertinent to obtain and analyse information on the epidemiology of exposure to psychotropic medicines in the paediatric population in Spain and Greece, as well as to approach the extent of the psychotropics' use outside of the authorised indications, viz their off-label use.

We hypothesised that the prevalence of psychotropic drug use in Catalonia's (Spain) and Greece's paediatric populations would be substantial, and that the psychotropic use in this part of the population would be often done out of the authorised conditions, viz in the absence of an authorised paediatric use as stipulated in the product labelling for each region. To this aim, we conducted a retrospective observational study with the objective of describing the consumption of psychotropic drugs in children, and to describe which were the most frequently used drugs and in which groups of patients.

In this study we described the use of psychotropics in the paediatric population in a Spanish region (Catalonia) and in Greece, with special emphasis on the quantitative assessment of the exposure to different therapeutic drug groups and to off-label products. Data were compared for extent of exposure and off-label use; however, it is important to consider that the comparison of the prescribing and reimbursement systems of the two regions revealed several similarities but also important differences that could affect the observed rates. Besides, local policies and clinical practice concerning the off-label use may also differ, leading to quantitative and qualitative differences in such use.

5.1 Summary of key findings

We analysed anonymised data on dispensed medicines covered by the national health systems of the region of Catalonia in the northeast part of Spain and from Greece. Both populations had a roughly similar age distribution but differed in the estimations of the extent of exposure. While the overall prevalence of psychotropic use was between 4.0% and 6.4% in Catalonia, it was lower in Greece with values between 0.5% and 1.5%. In both Catalonia and Greece, exposure was led by a high rate of use of hydroxyzine, an H1 antihistaminic which is used short-term for several acute indications, including skin allergies and itching. To allow a focused analysis on psychotropic use in mental conditions, the main analyses excluded patients who had hydroxyzine-only dispensations. In the resulting population, the prevalence was more than halved, but still with differences of one order of magnitude between both countries, ranging between 2.6% and 3.2% in Catalonia and 0.3% to 0.6% in Greece.

The highest prevalence of use of psychotropic drugs was observed in adolescents in both regions. In younger groups, the pattern differed so that the prevalence of use was higher with increasing age for the Catalan paediatric population, but in Greece the youngest groups (1-5 years old) were more exposed than older groups (6-8 years old). Boys were more exposed to psychotropics in both regions, in all age groups. The ATC group with higher prevalence of use were psychostimulants (N06B) in Catalonia, led by a high use of methylphenidate, while in Greece antiepileptics (N03A) were the most frequently ATC group and diazepam was the most prevalent active principle.

Greek data allowed to analyse indications, showing that most of the subjects receiving psychotropic drugs had an epilepsy diagnostic (ICD-10: G40), followed by diagnosis of mental, behavioural and neurodevelopmental disorders (ICD-10: F01-F99 codes). A 40% of prescriptions were issued by paediatricians, while 30% were issued by specialists, including neurologists, paedopsychiatrists, psychiatrists, and neurologists-psychiatrists. Antipsychotics (N05A), hypnotics/sedatives (N05C) and antidepressants (N06A) were prescribed by paedopsychiatrists, and mostly in big cities and urban areas, where most of the specialised physicians can also be found. It would be interesting to investigate if this observation may be reflecting differences in access to specialised paediatric or neuropsychiatric care in Greece.

Our study also confirmed that a significant amount of the dispensed psychotropic medicines was used out of the authorised conditions in similar extents for both regions. In the analysed subset, around 12% and 14% of paediatric subjects in Catalonia and Greece respectively had received at least one medicine that had no paediatric information in the product labelling. The percentage of the overall off-label dispensations based on lack of paediatric recommendation in the SmPC was

5.5% in Greece and 4.6% in Catalonia; if the range of the recommended age was fine-tuned, then the percentage increased into 7.6% and 7.5% respectively. Adjustment per sex and age for the available overlapping year for both cohorts (2017), revealed that the younger populations were mostly exposed to off-label dispensations, with boys been more exposed in Catalonia and girls in Greece.

The detailed analysis of prescriptions and indications for Greece showed that several psychotropics were used in indications for which they did not have an approval. Two antipsychotics, aripiprazole in Catalonia and quetiapine in Greece, were the most frequently dispensed off-label medicines, with aripiprazole been authorised for use in children older than 13 years of age and quetiapine been authorised only in adults. Antipsychotics (mainly risperidone), antidepressants (mainly fluoxetine), anxiolytics (alprazolam) and antiepileptics were found among the off-label psychotropics for which the available evidence potentially have merit in the concerned indications, but long-term studies are needed.

5.2 Suitability of methods

5.2.1 Design type

There are several methods in which the relationship between an intervention and an outcome can be assessed. Adequate selection of study design is essential for successfully executing a public health research, a selection that starts originally by the two big sets of studies: interventional and observational. Interventional studies, mostly prospective, are used to address direct impact of specific treatments or preventive measures on a specific disease. Observational type is selected for epidemiologic studies where the aim is to explore potential association in exposure-outcome relations and often they are retrospective.(387,388)

RCTs are considered to date the golden standard to obtain robust causative evidence. However, they are costly, often difficult and with feasibility hurdles, and to some extent may raise ethical limitations. In such cases, an observational study can be useful to provide supportive data on effectiveness in the real world although with caveats of potential biases. When the objective is to describe the actual use of a specific group of medicines in a specific part of the population, and to diagnose some specific issues or needs regarding rational use, such as off-label use, the preferred option are observational studies. Such studies provide valuable information that would eventually help to improve any preventive public health policies. Cross-sectional studies are used to assess a specific population at a single point in time, are retrospective in nature, and allow calculating the point prevalence/period prevalence and assessing of multiple outcomes at the same time.(387) As identified also in the literature reviews presented previously in the section of results, most of the available studies aimed to describe drug use and off-label use in paediatric mental health have applied cross-sectional designs and described retrospectively the prevalence of use, as well as the off-label use of psychotropics.

Observational studies of high quality can generate credible evidence especially when there are plenty of data. We had exhaustive information on drug dispensation for public healthcare in Catalonia for a ten-year period, which can be considered as almost complete population data since the electronic data from drug invoicing were fully available across the whole period.(389) For Greece, the data came from electronic prescriptions that were dispensed by the pharmacy and the coverage is considered complete; however, considering the possibility to purchase medicines without prescription in the country, the quantitative data have to be set in the context of a progressive deployment of the tool and may have some underestimation of the actual drug use.(390)

The limitations of our design need to be also mentioned. Cross-sectional studies investigate the presence of co-existing exposures and outcomes at a single point in time, so the outcome and

exposure variables are measured simultaneously, but besides form associations, it is prone to biases and is not suitable to establish causal relationships, therefore, it is not relatively easy to establish causality. However, our study had a descriptive objective and a full population approach, so that data and objectives did not aim to establish conclusions dependent on subjects' response, and in that sense the design was appropriate to fulfil its objectives.(391)

5.2.2 Data sources

Pharmacoepidemiologic studies may use data derived from different sources, which may include prospective or retrospective collection of data by investigators through interviews or structured questionnaires of all type, but also the use of already existing electronic registries and databases. While the former allow collection through anamnesis of a wider number of details on medication use, including characteristics of use and clinical consequences, the latter are often the preferred option; in particular, invoicing databases generally allow exhaustive population coverage, are devoid from recall bias and thus guarantee representativeness of the studied population and drug access.(392-394)

Digital databases containing information on the prescription or consumption of medicines, are helpful when there is a need to define the extent of the use of medicines in the whole population or at least to a sample that is highly representative. Since databases do not rely on reporting by subjects, they avoid potential biases of information by the subject towards missing, increased or inaccurate reporting of exposures or other variables. In addition, missing data, which may be a cause of concern in telephone administered interviews or written questionnaires, are also minimised. Using already available data minimise logistic complications, and thus may reduce the study cost and duration. Limitations include the predetermined type of variables with the collection of new variables to be generally not possible, as well as the difficulties derived from managing large databases with data structures that are not designed for research.(393)

We used the reimbursement data resulting from invoicing of medicines to the public health insurance in Catalonia (Spain) and Greece. Since both systems provide universal coverage, we may assume that in both cases we were covering almost all outpatient population in each concerned area. Prescription data might be a better option to describe the use of medicines since they may involve information on indication and in this way allow to link use of drugs and the disease, but invoicing information is closer to actual exposure, since involves the factor that patients have actually collected the prescribed treatment. Hence, data on reimbursement can define better the prevalence on the use of a medicine, even though one cannot still be reassured in absolute terms about the actual adherence to the dispensed medications.(388,393,394) While actual use may differ from acquisition of medicines, and eventually may change in time,

invoicing data are useful to define the trends and any relevant change throughout the evaluated period.

Another limitation from the source of data used is that databases of reimbursements are limited to prescription medicines.(389,390) Of note, the purchase of medication with no prescription is common practice in Greece and may lead to an underestimation of drug exposure. Similarly, private prescriptions may be purchased directly in the pharmacy with no public funding in Spain, and thus a certain degree of underestimation of drug exposure may occur. Furthermore, neither of the databases have data on medicines that are dispensed over the counter, but since all psychotropics are included as reimbursed drugs in both regions, this is not expected to be a big bias in our study. Since the reimbursement system does not collect inpatient data in neither Catalonia nor Greece, this study did not cover inpatient data; this seems acceptable as on one side our focus is to describe chronic use of drugs that is more relevant in terms of potential impact on children's development. On the other hand, we believe it is likely that most of the treatments including psychotropic drugs that were initiated in a hospital or institution would be continued after hospital or institution discharge, and thus they are captured in the study.

Catalan invoicing data did not include diagnosis or indication data related to each dispensed medication, so the prescription-indication part of the study aimed to measure adequateness of use, was not feasible. In addition, this represented a major limitation for the evaluation of the off-label use, which was limited to the assessment of whether the drug was used in a range of age included in the drug labelling. Data on the actual dispensed formulation were neither available, thus we used the lowest age limit that was included in the product label to assess if the product was within the actual authorised uses, which may have led to an underestimation of the extent of the off-label use. Finally, to avoid any risk of removing the de-identification, the data were aggregated by age categories, and in this way sometimes our data did not match the published ones for comparison purposes.

In contrast, the Greek data included information on the indication of the prescriptions, so that an analysis on the appropriateness of drug indications was feasible to some extent; hence, we have been able to do the first description on the indications with off-label use of psychotropics in the country's paediatric population. In addition, the Greek data included information on the specialisation of the prescribing physician, allowing identification of the source of prescriptions for the concerned medicines. However, the use per prefecture in Greece was at a certain point not possible to be evaluated, so we could not identify if psychotropics were used more in a rural or urban areas; yet, we could assume that the higher administration of psychotropics was connected with the centralised ubication of mental health specialists.

Finally, data from Catalonia and Greece derive from different health systems and models of drug access and reimbursement. Each region has its own prescribing restrictions, availability of treatments/alternative interventions and healthcare flows, so that the actual coverage of all potential pharmacological exposures may diverge. Besides, the coverage of the Greek database is of the entire country, while data from Catalonia are limited to the north-east region of Spain representing 16.00% of all Spanish population with some particular features. While Greece has an urban population of 82,50% similar to the 80,70% presented in Spain (395), Catalonia has a huge concentration of urban population, in a way that almost 95.00% of inhabitants are concentrated in three hundred urban districts of up to 2,000 inhabitants, and 71.00% live in cities of 20,000 inhabitants or more.(396) In addition, there are huge differences in the gross domestic product per capita (GDPc) between Greece (€16,235 in 2020) and Spain (€23,690 in 2020), as well as between the GDPc in Spain and in Catalonia (€29,111 in 2020) where the Catalan GDPc is closer to the average GDPc of the Eurozone (€29,910).(395,397) Since both urban lifestyle and GDPc have been related to the prevalence of mental health issues, the baseline status of the compared populations in regards to mental wellbeing and also in access to healthcare may have been quite different; hence, caution should be applied to conclusions from direct comparisons.

As a comparison of the two systems, in Spain the national health system is decentralised, with each autonomous community having its own regional healthcare authorities like *CatSalut* for Catalonia, while in Greece is managed nationally. However as already mentioned, both systems cover all residents with social security number in the concerned regions. Each region has implemented the electronic prescription, earlier in Catalonia (starting in 2006), justifying the longer period of the received data which were analysed in the present study. In addition, both regions have their own pharmacy billing database, but in Greece this database is more comprehensive than in Catalonia. Greek data are associating the dispensed medicine with patient demographic data, physician specialty, place of residence and diagnosis, while in Catalonia indication data are included only in prescriptions and not in billing data. Data on physician specialty and place of residence are collected in Catalan billing data, but the data supply to researchers for studies is restricted to the essential information required for the main study objectives. Only billing data were obtained for Catalonia, and the details on prescribers and place of residence of users were not within the initial study objectives; in contrast, full data were obtained from Greece billing database and so some sub-analysis in the present study could be performed only for this region.

According to recent data, Spanish government and regions cover most (70.00%) of the pharmaceutical expenses, leaving as out-of-pocket payments of users an average of 22.00% of

the cost. Greek governmental system is covering only a 51.00% of the pharmaceutical expenses, and out-of-pocket expenses of users averages 35.00%. The reason of the differences relies on differences in the healthcare systems and how they organise funding, prescribing, dispensing and billing of medicines.(381) The co-payment schemes establish in a different way the final paid amount by the patient, but both are taking into consideration vulnerable patient populations as well as the financial status of the insured subject.

Greece's scheme is more connected with the price of each medication, with a positive list and a maximum price that is covered for cluster of medicines by the social security, meaning that the patient will pay the difference if a non-generic or a more expensive medicine than the established maximum price is prescribed by the physician or selected by the patient itself at the time of its collection in the pharmacy. This factor increases the out-of-the pocket payments on top of the fixed fee per prescription and the money, so the patient does not prefer to visit the prescriber which most of the times is a private professional due to unavailability of public domains. In view of all these, many times the patients skip the visit to physician and buy the medicine directly from the pharmacy, even when the medicines are not over-the-counter and a prescription is needed.

The financial crisis in Greece also led to measures to reduce pharmaceutical expenses which was done through various cuts in the prices of reimbursed medicines, rendering more attractive to patients with chronic diseases to buy their treatment directly from pharmacies to protect their already shrunken incomes. The prices of most psychotropics were also decreased and can be directly obtained from the pharmacy with the exception of those under strict control from the state (e.g. benzodiazepines, opioids).

We observed lower rates of psychotropic use in Greece than in Catalonia (Spain) and this may be in part related to missed dispensed medicines that did not have an electronic prescription. Furthermore, Greece is very variable geographically with several remote areas in the mainland as well as small islands. These remote areas most probably have only a pharmacy, considering that Greece has the densest network of pharmacies in the whole Europe. Often, the pharmacy will work also as the primary healthcare point since in Greece there is a high concentration of physicians in national capital regions and a low availability of physicians in rural settings.(381) These specificities of Greece might have further contributed to not registered prescriptions.

In summary, the system of prescribing and reimbursing medicines in Greece could also affect the observed rates. Our argument is also supported by previous literature showing that reimbursement policies can indeed affect patient's treatment, e.g. policies targeting second generation antipsychotics led to reduced treatment adherence.(398)

5.3 Interpretation of the data

5.3.1 Studied populations and overall exposure

The data obtained for analysis referred to the overall population residing in both regions. The two populations are similar as regards the sex and age distribution for the study period, except for the subjects aged less than 5 years old with a higher number found in Greece; however, the two regions can be considered roughly comparable. In both, the contribution of the ≤14year-old girls is small, suggesting lower use of psychotropic drugs in younger girls.

While the overall reference paediatric population residing in Greece is 25.0% bigger than the one in Catalonia, the proportion of exposed subjects differed substantially, by one order of magnitude, with 449,059 paediatric subjects exposed in Catalonia (6.00% of overall population of any age) and 63,782 subjects in Greece (0,6% of overall population of any age). When we removed the hydroxyzine-only dispensations to avoid distortion due to potential uses in acute non-neuropsychiatric disorders, the exposed populations were reduced similarly to one third of the initial exposure, to 142,383 paediatric subjects exposed in Catalonia (2.0% of overall population of any age) and 21,274 paediatric subjects exposed in Greece (0,2% of overall population of any age).

In view of the above, it can be considered that the compared populations, both the reference and the study ones, are quite similar and comparable to each other in size, and distribution of age and sex, but differ substantially in the magnitude of overall exposure.

5.3.2 Drug utilization

5.3.2.1 Prevalence of use per year

Our data analysis revealed that the prevalence of psychotropic use in Catalonia varied between 40.8 and 64.2 per 1,000 paediatric residents for the period 2008-2017, while for Greece the prevalence rate was among 5.1-14.6 per 1,000 paediatric inhabitants for the period from March 2016 to October 2019. Excluding hydroxyzine-only dispensations, mostly used in children of school age and in adolescents with allergies, the rate of prevalence dropped for both regions: 26.4-32.2 per 1,000 paediatric inhabitants in Catalonia and 3.1-6.5 per 1,000 paediatric inhabitants in Greece.

In both regions there was a general increasing trend in exposure throughout the years. In Greece data from 2016 were not complete, so it may seem that the bigger growth was between 2016 and 2017, but this responded to a data artefact. In Catalonia, a low point in 2009 was coincident with the economic crisis, and some oscillations were observed thereafter, with a sustained

growing trend. In 2014 an increase in prevalence of use was coincident with the introduction of DSM-5 in 2013, where the changes on the diagnostic criteria compared to the previous version were reported to potentially impact on diagnosis of several patients mostly with ASD, ADHD and PTSD.(6,399-402) In addition, two new clinical guidelines were published in 2013 by National Institute for Health and Clinical Excellence (NICE) on: 1. psychosis and schizophrenia in children and young people where it clearly stated that an antipsychotic medication should not be offered to paediatric patients if they showed no sufficient symptoms to diagnose psychosis or schizophrenia, and on 2. social anxiety disorder indicating that children should be managed with CBT.(402,403) Finally, the publication of several Spanish clinical practice guidelines related to mental health in the period 2011-2012 (404-407) may have also influenced prescription habits, resulting in increased prescription of psychotropics.

There are no previous data on overall use of psychotropics in Greek and Catalan children and adolescents, so we cannot contrast them against our results. Available data on psychotropic use from other countries are mostly old and thus not easy to compare with our dataset; however, these studies report similarly increasing trends in the psychotropics use during the years. The only study somewhat overlapping the period of the Catalan data, was conducted in Italy where the prevalence ranged between 17.0-18.1 per 1,000 which is lower than the one reported in Catalonia but higher than the one reported in Greece.(133) Catalonia's rates were found to be within the ratio reported in other European countries as well as the USA, while this is not the case with the low rates of our study concerning Greece.(159,163,178,180) A study in France reported a lower prevalence for the year 2010 compared to Catalonia (25 vs 30.9 per 1,000 respectively).(134) The available data from the USA are heterogeneous: some studies report high estimations, higher than the ones from Catalonia, but others show lower rates; these differences in the USA data may be due to the use of different datasets with different characteristics.(163,178,180)

Changes in modern psychiatry where the emphasis was shifted from the psychosocial to a medical model, resulted into a greater use of pharmacological interventions. The increasing knowledge and mostly the awareness on the negative impact in the social life of the paediatric population due to a bad mental health, also contributed into motivating early management of these patients, leading to increased diagnosis and subsequently treatment of psychiatric disorders with a childhood onset. Simultaneously, parental and social acceptability, as well as the demand in using psychotropics in children and adolescents have grown. Furthermore, the limited access in some countries to nonpharmacological therapeutic resources or inpatient psychiatric services, has led to psychotropics being increasingly considered as a solution for a

more affordable and quick way to benefit the outpatient, and to also shorten hospitalisation days.(408)

Data covering the period after 2011 are not available from other studies, and in this way the comparison to our results must be done for asynchronous cohorts, and thus may be biased regarding the timing of dispensation: new medicines may have been introduced, old medicines may have been revoked, paediatric indications may have been granted for already authorised medicines, changes in therapeutic or diagnostic guidelines or evolve of new evidence. Apart from the factor concerning the time period of the studies, these discrepancies may be due to differences in psychotropic definitions among the regions, the study population range (nationwide, regional, insurance's coverage) or age/disease inclusion criteria.

Despite the similarity in our two studied populations, there is a big difference on the psychotropic use prevalence rates between the two regions. According to the data, both Greek boys and girls were found to be significantly less exposed than their Catalan peers. The low prevalence in Greece is considered also weird based on the reported psychotropics' prevalence by other countries when looking to the available data on years 2016 and 2017. The difference between the countries is approximately five and ten times respectively, and we must consider that for 2016 the Greek data did not cover the whole twelve month-period. Such a low prevalence of use rate in Greece may be related to differences in the health systems and reimbursement models, as well as geographical and societal factors.

It must be highlighted that Greece is considered among the European countries with the lowest depression rates and the one with the lowest suicide rate, although whether this may reflect certain degree of underdiagnose and stigma cannot be assessed.(30) However, while in Catalonia relevant data on the rates of paediatric population diagnosed with a mental health disorder are available through the national system (26), this is not the case in Greece; the system is not adequately prepared to provide data on the prevalence of mental disorders and the available information is mostly derived from surveys that are not covering the whole paediatric population.(29,34,35) In this way we cannot know how many diagnosed patients in need of medication exist in Greece, nor whether the current situation reflects appropriate use, underuse or overuse of psychotropics. In addition, mostly due to financial and geographical reasons, attention of patients by mental health specialists is limited to the big urban areas making harder for patients to receive their potential treatment if they need to move between regions, and thus they remain undiagnosed and subsequently without prescription that would feed the dataset.(36)

Another problem identified in the Greek community is the high stigma on mental health diseases.(409) The stigma is even higher when it comes to the paediatric population, and in

combination with the difficulties related to the financial crisis in the country, a lot of children remain undiagnosed and untreated. Even in cases where the mental illness is diagnosed, it is possible that some psychotropic medicines are taken under the name of the parents or bought directly in the pharmacy. Purchasing prescription-only medicines in Greece, apart from the ones controlled/restricted under the law for narcotics (i.e., benzodiazepines, opioids), is common knowledge among all inhabitants; therefore, the number of psychotropics dispensed through the national reimbursement system may be slightly lower than the actual consumed amount.

Consumption of antidepressants and hypnotics/sedatives in the general population of Greece has been found to be lower than the average of European countries (100); data that can confirm the observed high gap in the prevalence rates between Greece and other countries. However, Greek citizens seem to be more familiar with epilepsy (410) and therefore the high documentation of antiepileptics in our study is confirming this trend.

The current study also demonstrated that boys are more exposed to psychotropics than girls in both regions for the whole period, confirming the trend as reported in previous studies.(131,133,134,163,180) In Catalonia, an increasing trend with the years was identified for Catalan boys peaking in 2013-2014 (39.9 per 1,000 inhabitants), while for Catalan girls higher prevalence rates were seen in 2010 and then in 2014 (23.3 and 23.9 per 1,000 inhabitants respectively). According to available data from Norway covering the period 2004-2014, similar numbers for boys until 2010 are reported, but then the rate started to drop in contrast to the present study, and so the exposure of Catalan boys to psychotropics was higher. The reported prevalence in Norwegian girls had a constant increasing trend and was higher than the one seen in Catalonia.(131) Data from a southern European state for the year 2010 reported lower prevalence for both girls and boys than in Catalonia (134), while other studies with similar or higher prevalence rates in countries like the Netherlands and USA, or lower rates like in Germany, are older than the periods covered by our datasets. In general, the difference on the psychotropic use between the sexes that was observed in previous studies and reported also in our study, is supported by data indicating the higher prevalence in diagnosing more boys with certain mental health disorders which for a big part of the HCPs are considered over-diagnosed.(20) Both Greek boys and girls found to be significantly less exposed than their Catalan peers. Even though the difference between the sexes in Greece was not as high as in Catalonia - both sexes had a slight increase with the years except for 2016- but it seems that girls in Greece tend to have less treatment compliance.(411) Explanations on the Greek phenomenon given above apply also here and no other comparison can be done for Greek data as no study exists to cover the use of psychotropics in the paediatric population during the same period.

In view of the above, we may consider that our study had prevalence rates of use of psychotropic drugs which are within the range of those previously reported for other countries, with lower exposure in Greece than in Catalonia, and higher overall exposures for boys than for girls.

5.3.2.2 Prevalence of use by age

In both settings and in each year of the concerned studied periods, the prevalence was increasing with the age, rendering adolescents as the most exposed subgroup of the paediatric population. This finding is supported by the scarce published prevalence rates from other studies.(134,163,164,180) A trend of increasing prevalence by age has been reported in the USA concerning preschool children (164), while for until 2012 and for all children above 6 years of age, the observed trend of increasing with year prevalence rates also found reported there.(137) However, only three studies found to report the prevalence of psychotropics by age groups. Two of them cannot be compared to our study: the first one reports data from 2000 and the reported age groups are quite different than ours (163), while and the second one gives data only for the 2-4year-olds in 2001 which also renders difficult the comparison exercise as per the non-common period of time and the non-comparable age strata.(180) The third study has more similarities to our age groups, but the comparison is only partially feasible with data from Catalonia for the year 2010: children in Catalonia below 5 years of age are less exposed than their French peers, whereas older children are more exposed to psychotropics in Catalonia than in France (134); nevertheless, this difference might be due to the exclusion of antiepileptics in the French study.

In general, when comparing the different age groups between the two settings of the present study, the gap on the prevalence in the subsets below the age of 6 years seems to be smaller, whereas the difference between the older groups is significantly high with the Catalan population being more exposed. For the common year for which we have full data from both regions, viz 2017, only Greek children aged 1-2 years old found to be slightly more exposed to psychotropics than their Catalan peers, while the exposure in the remainder age groups is up to seven times more in Catalonia depending on the age groups.

As regards the psychotropic use per age strata and sex, boys kept being more exposed than girls independently of the age for both regions. The difference between the sexes was less in Greece than in Catalonia for all age strata. In Greece, the highest prevalence rates were found to be for the same age group (15-17year-olds), but in 2018 for boys and in 2019 for girls.

Six studies found to report data on the psychotropic use by age and sex.(131,134,137,152,163,164) As described also above, two studies in the USA demonstrated that there is an increase in the prevalence of psychotropics with the age along the period and it

was also confirming that boys were more exposed than girls.(137,164) Studies reporting data by age groups in Europe, reported in general higher prevalence rates in boys of all ages than girls, with rates to be increasing with the years, while three of them had comparable data to ours concerning the studied period. In 2010, French boys and girls had higher prevalence than their Catalan peers aged 3-5 years old; the same pattern was also observed when comparing the 15-17year-old girls between the regions, whereas Catalan boys had a higher share of psychotropics use than their French peers.(134) Even though a trend was detected about boys having a higher exposure than girls, this was not the case in the Netherlands and Germany for the group of older adolescents, but this cannot be compared to our data in absolute terms, due to the fact that their study period is eight years earlier than our first available data and the age strata includes subjects up to the age of 19 years.(163) Data reporting psychotropic use in Norway included some time periods that are common with the Catalan dataset: boys have more dispensations of psychotropics than girls with the exception of the average rate for 15-17year-olds in 2010, 2012 and 2014, but the average of the reported rates is lower than the ones identified in Catalonia in the present study.(131) Compared to another Norwegian study, the rates of Catalan prevalence were much higher but the group of subjects in the former study were from 15 to 16 years of age.(152)

In conclusion, there is scarce evidence worldwide referring to the use of psychotropics in the paediatric population by age groups. The published information in some cases was only partially comparable to our study due to differences in the time periods and the definition of the study variables like the age groups. Definition of paediatric age strata is an area of improvement, especially when it comes to research, so that relevant data can be later compared across studies and regions.(412) In our study, the data provided by the Catalan health authority were aggregated by pre-defined age groups, as part of the measures taken to reduce the risk of subjects' identification. Instead, the Greek data were facilitated with maximum granularity and no grouping. We grouped Greek data to match the Catalan structure to permit a comparative study between the two regions. Nevertheless, the age groups were adequate to further analyse the off-label status and allowed the analysis of the off-label use per subjects' age criterion.

5.3.2.3 Prevalence of use by ATC groups

For the concerned study periods psychostimulants (N06B), anxiolytics (N05B) and antipsychotics (N05A) had the highest share of children using psychotropics in Catalonia, whereas in Greece antiepileptics (N03A) were in the first place followed by the same ATC groups ranked as second and third in the Catalan set.

Psychostimulants use was 15.88 per 1,000 in Catalonia while in Greece 0.32 per 1,000 in Greece for the concerned study periods and for all target paediatric exposed population. The reported rate in Catalonia is within the range reported in the USA (3.6-42.9 per 1,000) which is also the region for which we have data reported for psychostimulants since 1987, but the reported rates in USA fluctuate as they depend on the dataset used in each study.(147,163,178,180,190) Compared to European countries, Catalan prevalence rates are also within the limits of the rates reported in Germany (7.1-22 per 1,000) (163,190), the Netherlands (1.5-39.0 per 1.000) (163,174,184,190) and Israel (7-25 per 1,000) (172), slightly higher than Denmark (0.87-15 per 1,000) (148,190), lower than the ones reported in Iceland (21.7-28.4 per 1,000) (159), whereas in France (2 per 1,000) (134), Italy (0.1-1.9 per 1,000) (133) and the UK (3-5 per 1,000) (190) the reported prevalence rates for psychostimulants were closer to the one identified in our study for Greece. The prevalence of psychostimulants being higher in boys in our study is also supported from other studies (125,131,163,190), as well as from the fact that the ADHD diagnosis is more prominent in boys than girls (413,414), considering that the symptoms in boys and girls are different and the former ones are easier detectable leaving in this way girls under-identified and untreated.(415,416) Data published by *CatSalut* for the period 2016-2019 showed that the prescriptions of centrally acting sympathomimetic agents invoiced for paediatric patients were in the second place in the group of ATC1 'N' with more than three-fold number of prescriptions compared to the group of medicines that follow in frequency.(94)

Antiepileptics were in the first place in Greece (3.13 per 1,000), while in Catalonia even though they ranked as fourth (4.97 per 1,000), the rate was higher than the one in the Greek territory. Antiepileptic use in Greece seems to be associated with a diagnosis of epilepsy considering that epilepsy was found as the most prevalent diagnosis in the sample. However, some antiepileptics were the most frequently dispensed medicines for the second most prevalent diagnosis (non-specified), which may relate to any off-label use including bipolar disorder, migraine or ADHD. Of note, epilepsy is a disorder that the symptoms are visible and easily spotted compared to other mental disorders, therefore it can be diagnosed early, the need for specialist supervision is necessary, and since the stigma from the community seems low (410), treating options are broadly acceptable by the parents. In this way, dispensed antiepileptics have less risk to remain undocumented especially since in Greece medication purchases directly from the pharmacy is a factual common knowledge among inhabitants. Compared to previously reported rates of antiepileptics' prevalence, Greece had similar ones to those reported in the Netherlands (3.7-4 per 1,000) (160,163) and Germany (3.8 per 1,000) (163), while in UK the reported rates were higher even from the Catalan ones (7.3-8.69 per 1,000).(166) Comparing to reported prevalence in the USA, there is a wide range in the reported rates (1.1-20 per 1,000) depending on the dataset (region, age range, source of data and year), but our rates were found to be within these

limits.(163,169,180) Our data in both regions revealed a slightly higher prevalence of antiepileptics' use in boys than in girls which is also the case previously reported in Germany (163) and the UK (166), while in the Netherlands girls were slightly more exposed to antiepileptics.(160,163) In general, the difference observed between sexes is minor except for the USA which was the only country where a double rate of use of antiepileptics in boys compared to girls was reported.(163)

Anxiolytics found to be in the second place on the most frequent use of psychotropics in both regions for the whole paediatric population and the concerned study periods: 7.66 per 1,000 in Catalonia and 1.63 per 1,000 in Greece. Comparing to already reported data from other countries we could see a difference with our data: Greece had the lowest rates among European countries (134,163), had prevalence rate close to the one reported in USA back in 1987 (180) as well as the data reported by Iceland (159), whereas the prevalence rate for anxiolytic use in Catalonia was the highest reported one among all these studies, apart from France where the exposure to anxiolytics was more than double compared to Catalonia.(134) Nevertheless, according to *Kovess et al*., French rate is high maybe due to country-specific attitudes and reimbursement policies as well as the potential use of some anxiolytics for non-psychiatric disorders.(134) In our case we have excluded the hydroxyzine-only dispensations to avoid overestimation of the prevalence rates due to its frequent use in allergies. In regards to the difference in anxiolytics' dispensations observed per sex, while in Greece there was a higher use by boys which is supported with a trend reported in Norway and USA (131,163), in Catalonia the opposite was detected which is also supported with the trend reported in France, Germany and the Netherlands.(134,163) The higher use of anxiolytics by girls could be also related to the higher prevalence of anxiety disorders in girls (413), considering also the contributing factors, such as the general lower baseline self-esteem, the higher possibility of experiencing interpersonal violence and the higher exposure to stressful situations associated with gender inequity in this group of patients.

Antipsychotic use is the most studied subgroup of psychotropics in the paediatric population as described in previous sections. Regarding the two regions of the current study, again Catalonia had a higher number of children and adolescents exposed to this ATC group compared to Greece (5.81 vs 1.03 per 1,000). The prevalence found in our study for Catalonia is lower than the one reported in a previous study using dispensing data from *CatSalut*, but this difference may be due to the inclusion of subjects up to the age of 19 years and that the study reports only data from 2014, so in absolute terms this comparison is not valid here.(124) No previous studies reported any data for Greece nor prevalence rates lower than the one defined in the current study for this region. However, compared to Catalan prevalence rate, antipsychotic use had a lower share in

paediatrics in Australia, Colombia, France, Germany, Iceland, Japan, Latvia, New Zealand, Norway, Sweden and the UK (124,127,134,141,162,163), whereas higher exposure was reported in Finland, Italy, Taiwan and the USA (124,163); rates reported in Canada and the Netherlands varied and Catalan prevalence as reported in the current study is sometimes within these limits (145,161,163), but others not.(124) Concerning the higher exposure of boys to antipsychotics observed in both the Greek and Catalan territories, this trend was also reported in several other countries (124,127,131,134,136,150,177), apart from the rates in New Zealand where no difference in the prevalence per sex was found, as well as the Taiwanese ones where girls were more exposed.(124)

Antidepressants were also reported broadly in the literature. In the present study, the prevalence rate was of 4.24 per 1,000 in Catalonia and 0.61 per 1,000 in Greece for the target paediatric exposed population and the total concerned study periods. No data from other countries are reported as low as the one reported in Greece in the current study, whereas Catalonia's paediatric population along with their French and German peers are the least exposed to antidepressants (126,134,144,163,173,191,192) as opposed to other countries around the globe.(133,137,143,155,159,163,165,171,179,180,184,192) The trend of a higher number of girls treated with antidepressants as identified in our study datasets, was also found in several other countries like Denmark, Germany, the Netherlands, Norway and the UK (126,131,163,191,192); in USA mixed results by sex were reported as they were depended on the region and the database used (163,171,179,180,192), whereas in France boys found to have a higher prevalence than their female peers.(134) The general trend of girls having a greater share on the dispensations of antidepressants is justified taking into consideration that this group of patients is generally more frequently diagnosed with depression than their male peers especially during adolescence.(417)

Concerning hypnotics/sedatives, these have higher prevalence in Greece than in Catalonia (0.65 vs 0.48 per 1,000) for the whole age groups of the paediatric population in the relevant study periods; however in both regions children are less exposed than other countries for which there is a reported prevalence: France, Germany, Iceland, Netherlands, Norway and USA.(134,149,159,163) In our datasets, Catalan girls have higher exposure to hypnotics/sedatives, while Greek boys had higher prevalence; this controversy is also supported by data from other countries with German and American girls been more exposed, and Norwegian and Dutch boys following the same trend as their Greek peers.(131,163)

No data were found from previous studies concerning the ATC groups of N06C-psycholeptics psychoanaleptics combination and N07B-drugs in addictive disorders. In our datasets these two categories had minimum or no data and therefore the comparison is impossible to be of value.

5.3.2.4 Prevalence of use by ATC groups per year

In our study, the evolution of the prevalence throughout the years of each study period has shown a different trend per ATC group in the two studied regions.

5.3.2.4.1 Antiepileptics

While in Greece antiepileptics were found to be the most frequently used ATC group in the paediatric population with a trend to an increased use throughout the years according to the present study, this is not the case in Catalonia where the increasing trend is reversed in the period 2011-2012. The short decrease in the antiepileptic use may be connected to the US FDA warning published in 2008 on the increased risk of suicidality for all antiepileptics, which was also followed by warnings issued in Europe.(418) This alert triggered several studies the upcoming years due to critics questioning this alert applied to the whole class, and therefore may affected again the use of antiepileptics due to controversial information.(419) In addition, this subsequent increase on the antiepileptic use may be related to the approval of perampanel in Europe for the first time in 2012 for focal seizures and primary generalized tonic-clonic seizures for children 12 years of age and over; perampanel being the first non-competitive AMPA receptor antagonist anti-seizure agent, with the once daily administration and the long half-life, was considered as an advantageous option especially since the medicine was proved to be also safe and tolerant.(420) Another explanation could be the publication in 2012 of a clinical guideline in Spain related to bipolar disorders for which antiepileptics are sometimes used as mood stabilisers; the guideline was indicating when valproic acid could be added in the treatment of paediatric patients (405) - recommendations that also followed EMA's recommendation in 2010 on the use of all products containing valproic acid in bipolar disorder in adults.(421)

In general, only two studies reporting the evolution of antiepileptics´ use in the whole paediatric population were found, both of which in periods before the ones covered in our study for the regions of Catalonia and Greece. In the UK an increase on antiepileptics has been reported with the years with the exception of the period 2000-2002, which may be connected to the prescribing restrictions for vigabatrin recommended in 1999 from the authorities (166); however, the rates reported in the UK are higher than the ones in Catalonia and Greece. A second study in the USA, which covered an even older period (1987-1996), reported a similar increasing trend in children using antiepileptics too, rates that included the ones from Greece and Catalonia, despite the limitations on the comparison due to the difference on the study years and the varied USA prevalence rates being dependent on the datasets used.(180)

Our data showed that boys are prone to use more antiepileptics than girls within the years in both studied regions, a trend which seems to be validated in a study from the UK where the male/female ratios seem to slightly favour the use by boys (157), considering also the fact that there are data supporting the higher ratio of epilepsy diagnosis in males as reported to-date.(422)

5.3.2.4.2 Antipsychotics

The use of antipsychotics in both regions covered by the current study revealed an upward trend, resulting into the second most frequently ATC group from 2015 onwards in Catalonia. The highest prevalence in Catalonia was seen in 2017 (6.72 per 1,000) while in Greece the highest rate observed in 2018 was more than five times smaller compared to Catalonia (1.25 per 1,000). In 2017, where we have full data for both regions, the difference in the prevalence rates was almost six times favouring the antipsychotic use in the Catalan paediatric patients.

The increasing tendency of antipsychotics' use in paediatrics has already been reported in previous studies with data from Canada (1.66-6.37 per 1,000) (145), Germany [(2.03-2.61 per 1,000) or (2.1-3.2 per 1,000)] (127,141), Iceland (8.7-10.6 per 1,000) (159), Italy (0.6-0.69 per 1.000) (133), the Netherlands [(1.6-3.4 per 1.000) or (3-6.8 per 1,000) or (7.2-9 per 1,000)] (121,161,184), the UK (0.39-0.77 per 1,000) (162) and USA [(3.4-15.5 per 1,000) or (7.63-19.88 per 1,000)].(177,183) Even though the reported rates may refer to different periods, we can see that our rates are within the previously reported ones in several countries. However, few are the studies with which Catalan data share a common time period in absolute terms, while no data are reported for the whole paediatric population after 2014 to be comparable to Greek data. The prevalence of antipsychotics in Catalan children and adolescents found to be almost six times higher than in Italy (133), almost twice as high in Germany (141), half compared to rates from Canada (145) and almost half from the Netherlands.(121) In other countries, a breaking point on the increasing rates was observed in 2009 (121,136), but this was not the case in Catalonia where the increase was constant. Concerning the prevalence rates reported in 2014 for several countries mostly from Europe, antipsychotic use was higher in Catalonia than Denmark, France, Germany, Lithuania, Norway and Sweden, while the rate reported from Catalonia was similar to the one reported in the present study.(124)

The same trend of increasing trend in boys and girls was also observed in some of these previous studies, where boys had a higher exposure than girls throughout the study periods (124,131,136,141,150,177,183), while for the available data in 2014 for Catalonia the same difference between boys and girls was also reported, validating in this way the robustness of our analysis.(124) Except for the higher percentage of diagnosed boys with schizophrenia (423), this

higher prevalence in boys may be connected to a longer exposure to antipsychotics compared to girls as previously reported.(121)

In general, a higher use of antipsychotics with the years in the paediatric population is well-documented around the globe, and several explanations have been raised: increased knowledge and awareness leading to increased acceptance from the side of parents, the rise of autism diagnosis which is often accompanied by aggression treated with antipsychotics, the limited access to non-pharmacologic treatments or treatment options for vulnerable populations (e.g. foster) or limited time invested by health care providers for alternative options due to non-reimbursement of these services.(408) In addition, the consumption of second-generation antipsychotics which initially were considered safer, has risen for several indications for which they are used off-label in children (424), specifically for disorders like autism or ADHD where the diagnosis is more frequent in boys. Our study reported a high use of psychostimulants and antipsychotics, but the limitation imposed by data on not permitting an analysis of concomitant use or of indication-dispensation cannot validate this theory in the Catalan sample. However, data reported from another Spanish region confirmed the high concomitant use of these two ATC groups.(425) The uptrend shown in Catalonia follows also the high investment of the pharmaceutical industry on new antipsychotics in the period 1993-2006 (426) and the further increase probably can be attributed to the paediatric authorisation of paliperidone in 2014 in Europe.(427) Of note, paliperidone is a drug having some pharmacokinetic/pharmacodynamic superiority compared to the parent drug risperidone (428), and despite its authorisation in adolescents above 15 years of age, it was found to be among the most frequent medicines used off-label in Catalonia.

5.3.2.4.3 *Anxiolytics*

The use of anxiolytics had in general a decreasing rate throughout the study period in Catalonia as opposed to Greece where a slight increase with the years was observed. Anxiolytics found to be the second most frequent group in Catalonia until 2012 where antipsychotics started to supersede them, while in Greece antipsychotics were slightly higher than anxiolytics only the first year of the study period. For the common year in both regions, we saw that the prevalence rate of anxiolytics in Catalonia (5.73 per 1,000) was almost three-fold higher than in Greece (1.95 per 1,000). The breaking point in 2014 from which we saw a steady decrease in the anxiolytics use in Catalonia for all paediatric subjects of the target exposed group, could be explained by the new published NICE guideline in 2013 on social anxiety disorder which was indicating that children should be preferably managed with CBT.(403)

Few previous studies reported the evolution of anxiolytics' use separately for the whole paediatric population, as some are presenting this use together with sedatives/hypnotics' use

(157,184) and there is no study with recently available data to be directly compared to Greece. The few studies reported prevalence data in Iceland (159), Norway (131) and USA.(163) Prevalence in Iceland seems to remain almost steady throughout the study period with the several ups and down to not permit a definition of a clear trend, and having rates to be surprisingly closer to the Greek ones reported in the present study despite the different reporting periods.(159) In the USA, a clear trend could neither been established, as the trend depended on the region of the data source, being sometimes closer to either Greek or Catalan data; however, the comparison cannot be considered correct in absolute terms, as it referred to a period of at least twelve years before the first available data in Catalonia and included the population below 20 years of age.(163) According to a study reporting the anxiolytic prevalence in 2010 in France, the rate found to be two-fold higher than the available data for the same year in Catalonia, but this difference could be probably explained by country-specific patterns and reimbursement policies or the use of hydroxyzine in non-psychiatric conditions, considering that in the present study we tried to control in a way this issue by eliminating the hydroxyzine-only dispensations.(134)

The same difference was observed in the analysis by sex, where in France the difference between the sexes was greater, favouring the use of anxiolytics by boys, while in Catalonia the difference was quite minimum favouring girls.(134) In general, Catalan girls were more exposed to anxiolytics from 2011 onwards, while in Greece a clear trend in favour of anxiolytics' use by boys was found. This trend on anxiolytics use is not reflected in 2017 data from *CatSalut* which reported that more boys had a diagnosis of anxiety disorders administered at special mental health centres directed to children and adolescents.(26) However, previous published data reported also a higher use of anxiolytics by girls in Germany and the Netherlands despite not been directly comparable to ours due to a difference on the study period (163), while in the USA there is no clear pattern of the use by sex since as this was changing again based on the region and the data source.(163,180) The only study that could directly be compared to our data for Catalonia, is a study from Norway reporting the anxiolytic use by sex for the period 2004-2014: similar trends in both sexes throughout the periods were observed but prevalence rates in Catalonia were always higher, while a slightly higher trend in anxiolytic use by Norwegian boys compared to their female peers was also reported.(131)

5.3.2.4.4 *Hypnotics/Sedatives*

The use of hypnotics in children and adolescents is considered controversial: children with sleep disorders or as secondary of other mental disorders (e.g., ADHD) exist and are in need of treatment; a treatment which even though approved for them is related to risks for serious

adverse events (429) and with a regulatory warning been also introduced back in 2013-2014 in the USA.(430)

In the present study an increasing overall use of hypnotics among children and adolescents throughout the study period was identified in Greece, while in Catalonia the trend was interrupted by a decrease phase between 2011-2012. The overall increase along the years in Catalonia can be also supported by published data from *CatSalut* on the increased use of benzodiazepines and diazepines.(94) This short-term decrease in the use of hypnotics/sedatives in Catalonia may be related to the publication of a clinical guideline on sleep disorders in childhood and adolescence in Spain in 2011, which recommended the use of sleep hygiene strategies and the use of short-term medication, such as melatonin, in cases where the non-pharmacological interventions were not effective (406); the subsequent increase in the use of hypnotics/sedatives could be related to the tendency in the use of electronic devices and social media the past years that led to rising cases of sleep deficiency (431) or of poor sleep quality among children and adolescents.(432) It was also surprisingly found that the prevalence of use for this ATC group was higher in Greece in the whole period, where in 2017 it was 0.75 per 1,000 vs 0.68 per 1,000 in Catalonia. Anxiety and depression in Greece seem to be more frequently diagnosed the past years attributed also to the deep financial crisis that could explain the elevation of cases on sleeping issues secondary to other mental health problems, along with the explanation on the increased use of social media and electronic devices.

Not many studies report the evolution of prevalence of hypnotics/sedatives along the years for all paediatric population. The existing evidence supports the increasing tendency observed in our study.(149,159,180) The low rates in Iceland mirroring mostly the rates in Greece can be probably explained by the ten-year difference in the reported period between the studies (159), if we consider that in general the use of psychotropics in Iceland was reported in higher rates compared to Greece. Data from France in 2011, showed a higher rate of hypnotics/sedatives (0.8 per 1,000) than in Catalonia (0.49 per 1,000).(180) A study that could be immediately compared to ours as it reports prevalence rates in a longer common period with Catalonia, is a study from Norway covering the period 2008-2011, where the prevalence of hypnotics/sedatives was at least ten times higher than the one in (149); according to the authors this rate was mostly due to the off-label use of melatonin (melatonin was approved for children later on by EMA) which was paralleled with the increase in the use of stimulant medication for ADHD.

Norwegian boys seem to have a higher exposure for the whole period from 2004-2014 than their female peers (131), which could also be explained by the increasing use of hypnotics/sedatives in boys that are more diagnosed with/treated for ADHD, especially after the

publication of several guidelines recommending the use of melatonin in these patients.(433) However, the rates are much lower in Catalonia and Greece where we saw a predominance of girls over boys that may be attributed to the established consensus of higher rates of adolescent girls to receive a diagnosis for insomnia, while the evidence for higher insomnia issues in pre-pubertal boys remains inconsistent.(434)

Despite the scarce evidence on the literature, our study managed to confirm the established increasing trend of hypnotics/sedatives in the paediatric population, as well as the predominance of female over male patients.

5.3.2.4.5 Antidepressants

A general trend in a high use of antidepressants along the years exists, especially after approval was granted for fluoxetine in Europe for children and adolescents aged more than 8 years with moderate to severe major depressive episode.(435) The use of antidepressants in the Catalan paediatric population had uptrends and downtrends with breaking points being in 2010 and 2015, and the highest rate observed in 2014 (4.62 per 1,000). The decrease followed the year 2010, may be due to the publication of a clinical guideline for depression in Spain (407); the decrease on the use of antidepressants from 2015 may also be due to the higher suicide rates in the previous years in adolescents (436), since antidepressants are connected with a higher risk of suicidal thoughts in this subset of the population and warnings are included in their labelling and the publication of the guidance on prevention of suicides.(404) In addition, following US FDA's safety communication on potential risk of cardiac arrhythmias due to citalopram use that led to restrictions in its use (437), a published cross-sectional study in 2013, identified more antidepressants with a similar risk.(438)

Concerning the Greek subjects, the breaking point of the uptrend was in 2018 when it was also the highest rate (0.77 per 1,000); the slight decrease in 2019 may be due to the non-full dataset covering the whole year. Comparing the two regions for the common study period in 2017, we could see that the rate in Catalonia is six-fold up than the rate reported in Greece, but this high difference is connected to the general low psychotropic use in Greece, as well as to the specificities of the system and the low depression levels reported in the country.(30) However, the upward trend can clearly demonstrate that the financial crisis had an impact on the mental health of Greeks and that some campaigns for eliminating the stigma related to mental health helped also towards the detection of depressive patients. Moreover, children of depressed parents have a 15% to 45% risk for suffering from MDD, and the depression rates in the general population in Greece due to the financial crisis may have contributed to the increased rates of children in need of antidepressants.(439)

The detected general upward trend on the use of antidepressants by paediatric patients in the current study has been observed globally too.(126,143,151,155,159,165,171,173, 179,180,184,191,192) However, in Italy the use of antidepressants follows a downtrend and for the same period of data with Catalonia, the prevalence rates reported as three-fold smaller, approaching more the rates in Greece.(133) French paediatric patients in 2010 had a lower rate of antidepressant use than their Catalan peers.(134) In Germany the upward trend (173) seems to have changed (144) maybe due to the warning published in 2003 for the antidepressants, but subsequently the uptrend recovered reaching similar rates as the ones reported in Catalonia for the same period.(191,192) The same downtrend reported in Iceland, which may be due to the introduction of the warning, and although we cannot compare these results with ours due to differences in the reported periods, we showed that the prevalence in Icelandic paediatric population is six-fold higher than in Catalonia and approximately thirty-seven times higher when compared to Greece.(159) Similar to the ups and downs reported in Catalonia have also be seen in the Netherlands, but for the common period the prevalence in the Dutch population was higher than in Catalonia, i.e. in 2012 the Dutch rate was of 6 per 1,000 while the Catalan one was of 4 per 1,000.(192) Denmark, UK and USA prevalence data compared to Catalan antidepressant rates for a common period of the studies were much higher.(192)

Girls had a greater share of antidepressants in Greece for the whole period while in Catalonia boys had a higher exposure only in the period from 2008-2009 and in 2011. This trend can be justified considering that girls have higher rates of depression diagnosis (417), but also from previous studies reporting the same general trend: for all years of the study periods higher rates in antidepressant use in girls were reported in several countries (131,191,192), apart from France where in 2010 no difference by sex was found.(134) It is worth to highlight that in Norway for the year 2014, antidepressants' prevalence in girls was almost double than the one in Catalonia.(131) The antidepressant use had an uptrend in girls but a downtrend in boys in Catalonia, while in Greece a small increase was identified for both sexes. In a more recent study published in 2022 using data from a primary care database with prescription data from ten autonomous communities in Spain, girls had higher exposure to antidepressants than boys in the period 2013-2018, and the same observation concerning the uptrend in girls and the downtrend for the boys was found; even though the reported rates were slightly lower than the ones identified in the present study in Catalonia, the difference seems to be not significantly greater, thus supporting the representativeness of our study.(194)

5.3.2.4.6 Psychostimulants, agents used for ADHD and nootropics

While in Greece we saw an increasing trend in psychostimulants use with the highest rate observed in 2019 (0.39 per 1,000), this increase was not high enough to reach Catalonia's rates. In Catalonia, we also saw a trend of higher use of psychostimulants along the years until 2014 where we identified the peak in our study period (17.93 per 1,000). Comparing the common year in both regions with available full data (2017), we have seen that there is almost a fifty-times difference between the regions, but this could be due to several specificities between the systems as explained in previous sections.

The increasing diagnosis of ADHD until 2011 was reported by others, suggesting at the same time that many untreated or non-compliant to treatment paediatric patients still exist.(440) Several studies reported the increasing use of psychostimulants along the years for the whole paediatric population in Denmark (148,190), Germany (190), Iceland (159), Italy (133), the Netherlands (174,184,190), the UK (190) and the USA.(147,180,190) However, few of these studies have comparable data to ours concerning the same study period. Compared to Denmark, Catalan psychostimulant rates are higher for the same period (148,190) with a similar constant increase till 2012, followed by a decrease till 2015 and then a second peak in 2018 which was also the highest rate for our dataset; concerning the comparison with the Greek data for the studied period, Danish paediatric population was much more exposed than their Greek peers.(148) The Italian paediatric population for the common study years had a lower rate than the Catalans, closer to the rates reported in the current study for Greece despite the non-common time period.(133) Compared to data available from previous studies concerning the year 2012, Catalan children and adolescents in the present study had a greater share in the use of psychostimulants (17.12 per 1,000) than their British peers (5 per 1,000), while their Dutch (39 per 1,000), German (22 per 1,000) and American peers (37 per 1,000) had higher prevalence rates.(190) Even though these differences may be due to the inclusion of subjects up to 19 years of age in the study of *Bachmann et al*., it has to be highlighted that the ADHD diagnosis is mostly done in younger adolescents, while the trend of a higher rate compared to USA is also supported by another study with data from 2008 having an almost triple rate higher than in Catalonia.(147)

The change in trend in 2014 for our data in Catalonia could relate to the introduction of the modified diagnostic criteria (DSM-5) in 2013 that also affected the diagnosis of paediatric patients with ADHD; critics of the updated DSM-5 version were highlighting that even though new criteria may result in more reliable diagnosis, it could also relate to an increased ADHD prevalence but to lower cases of diagnosed adolescents.(402) In addition, a series of metanalyses published by the European ADHD Guidelines Group (EAGG) in the same period,

suggested that non-stimulant interventions, such as behavioural or diet interventions and cognitive training, were efficacious in reducing ADHD core symptoms (441,442), and this could probably affect the use of stimulant medication which is also related to several serious adverse events especially in the long term.(443) *CatSalut* data covering the period 2016-2019 showed a decrease in the use of psychostimulants confirming our results detecting the downtrend.(94)

The same trend that the prevalence of psychostimulants throughout the years was higher in boys than girls, was also reported in other studies with common year periods, where the prevalence rates in Catalonia were lower like in Denmark, Germany, Netherlands (190), Norway (125,131) and the USA (147,190), or higher like in France (134) and the UK.(190) Data from *CatSalut* for 2017 confirm that ADHD was the most frequent diagnosis at the special mental health centres for children and adolescents, with a male to female ratio of 3:1.(26)

5.3.2.4.7 Psycholeptics & psychoanaleptics in combination - Drugs used in addictive disorders

As regards the group psycholeptics/psychoanaleptics combination, we had data only from Greece indicating a slight increase with the years, but this conclusion cannot be neither taken for granted due to the limitations imposed from the small prevalence rates.

Concerning the evolution of the use of drugs for addictive disorders, the prevalence rates were quite low. In Greece no trend could be identified along the years, while in Catalonia the decreased trend could not be taken for granted.

Finally, no comparison to other countries could be performed as, to our knowledge, there are no previously reported prevalence data on these two ATC groups.

5.3.2.5 Prevalence of use by ATC4 group per year and per age

5.3.2.5.1 Antiepileptics

The use of antiepileptics in epilepsy but also as mood stabilisers in patients with bipolar disorder is documented.(444) Antiepileptics were found to have an age-related increase in both regions of the current study. In 2017, Catalan patients of all age groups were more likely to be treated with antiepileptics than their Greek peers. Antiepileptics' use seems to have more or less a stable course through the concerned study period in Greece except for 2016; in Catalonia some fluctuations were detected along the decade for the age groups between 3-14 years old remaining though in similar rates, while there was an increasing trend with the years for children below 3 years of age and the older adolescents group. A study in the UK previously reported an increased use of antiepileptics in adolescents with the years as in Catalonia and Greece, but the period is not the same compared to our data.(157)

In the analysis per sex, Catalan boys aged 3-14 years old were more exposed in antiepileptics; younger girls were more exposed in the first years of the study and in the older adolescent's group girls had a higher exposure from 2013 onward. In Greece, 15-17year-old girls in 2019 and 1-2year-old girls in 2016 had slightly higher chance on being in treatment with antiepileptics. These tendencies have been previously reported in a USA study (176), but no recent data exist on the prevalence of antiepileptics by age group and sex. The higher use of antiepileptics by adolescent girls potentially as mood stabilisers, could be explained by the publication in Spain of the clinical guideline on bipolar disorder (405), as well as on the fact that bipolar disorder has a predisposition to females (445) and considering that epilepsy - mostly diagnosed in males - seems to decline when reaching closer to adolescence.(446) This is also supported by the fact that epilepsy is the most frequent diagnosis in the Greek sample, as well as that levetiracetam and valproic acid found to be the most frequently dispensed medicines in children with a non-specified diagnosis which was the second most frequently identified diagnosis in the sample. Of note, warnings published in 2014 and 2018 on the use of valproic acid in women and adolescents of child-bearing potential due to potential foetus malformations or developmental disorders after birth, could also have an impact on the antiepileptics prevalence along the study years.(447)

5.3.2.5.2 Antipsychotics

The use of antipsychotics in the paediatric population is rising worldwide (424,448) and can be also connected to the high investment of the pharmaceutical industry on new antipsychotics in the period 1993-2006.(426) In Europe, harmonisation processes on the labelling of several antipsychotics led to better information on the use of clozapine in patients above 16 years of age with schizophrenia in 2002 (449), of risperidone in children and adolescents older than 5 years of age with conduct disorder in 2008 (450), and of quetiapine which did not lead to an inclusion of indication in underaged patients in 2014 but to the inclusion of the results from paediatric studies in the labelling.(451) Several generics of olanzapine were also approved in Europe during the period of the Catalan study (452–454), but no authorisation is warranted for children. Aripiprazole was authorised in 2008 for mania in bipolar disease in adults, with an extension in adolescents aged 13 years and older in 2012, while in 2009 an extension of indication in adolescents aged 15 years and above with schizophrenia was also granted; however, the requested extension for younger adolescents in 2012 was rejected but led to the inclusion of paediatric studies in the labelling.(455) In the USA, risperidone is authorised in adolescents with schizophrenia since 2007 (217) and quetiapine since 2009 (314), while aripiprazole and risperidone are approved in ASD-associated irritability since 2009 and 2006 (216,217); however, this is not the case in Europe.

Antipsychotics' use is accompanied by increased serious adverse events, which raised some concerns regarding the benefit/risk ratio of their use in the paediatric population back in 2008 and 2009 (456,457) leading to the establishment of networks aiming to monitor their safe use, such as the SafEty of NeurolepTics in Infancy and Adolescence (SENTIA) network which was established in Spain in 2010.(458)

In the present study, the upward trend of antipsychotics use is related to the age: adolescents are more likely to have an antipsychotic dispensation than children. In Catalonia within a decade, the dispensed antipsychotics had a more than 1.5-fold increase in adolescents, while for the younger patients the difference reached up to a twofold increase in some cases; in Greece there was a slight increase in all age groups, so the short study period did not help to detect a clear trend within the years. This increase in groups above 5 years of age may be attributed to the authorisation of several antipsychotics in the period 2008-2009 for children with conduct disorder in Europe and for other indications in the USA as highlighted previously. In 2017, the younger and older adolescents in Catalonia were 4.6- and 6.8-fold more likely in receiving an antipsychotic respectively, as opposed to their Greek peers, whereas for the group of children the difference was from seven to eighteen times, favouring the Catalan paediatric patients.

The highest use by age group in Catalonia varied depending on the age strata. For the group of 1-2year-olds the peak was in 2010, for the younger adolescents was in 2015 and for their older peers was in 2016, whereas for the remainder strata (3-11 years) the highest rate was in 2013. This high mobility with ups and downs surrounding the year 2013 for almost all age groups could be attributed to the approved and declined in 2012 requests for extending the use of aripiprazole in adolescents above 13 years of age with bipolar disorder and schizophrenia respectively. The decrease in the use of antipsychotics by older adolescents observed in 2013 for Catalonia, could be also derived by a new NICE clinical guideline on psychosis and schizophrenia in children published in January of the same year, stating that an antipsychotic medication should not be offered to paediatric patients with no sufficient symptoms to diagnose psychosis or schizophrenia (459) or by the Spanish clinical guideline on bipolar disorders published the previous year (405), taking also into account that adolescents are more likely to get a diagnosis of schizophrenia or bipolar disorder.

Children under 5 years of age had negligible exposure compared to older children in both regions which has been reported in previous studies as well.(124,134,136,157) Data per age strata provided by *Hálfdánarson et al.* upon request, covered various age groups concerning the period 2005-2014 for almost all of the sixteen countries participating in this multinational study on antipsychotic use; these data demonstrated that the period surrounding 2013 marked also a point of change in the evolution of use in the groups 10-14 years and 15-19 years of age for a

significant number of the participant countries. Among these countries, data from *CatSalut* for the period 2011-2014 were included and despite the different age groups between the studies that limits the comparison in absolute terms, we could see that our results are similar to the rates reported by *Hálfdánarson et al.* for the groups of younger adolescents (10-14 years vs the average of 9-14 years); for the group of older adolescents more similar rates were found for the period 2014-2015 instead of the period 2011-2013, but the difference in the compared age group should be highlighted since *Hálfdánarson et al.* include data up to 19 years of age. In 2014, the reported prevalence rate for the Catalan 10-14year-olds was found to be higher than all countries apart from Iceland and the Netherlands.(124) Compared to France for the year 2010, the 15-17year-olds residing in Catalonia were 1.7-fold more likely to receive an antipsychotic than their French peers.(134) No previous data for Greece found, but the rates reported by age were the lowest ones observed.

The higher use of antipsychotics in boys of all ages with a significant difference in the groups of older children that was reported by other studies (121,136,138,145), is also confirmed by the current study for both regions and concerning each year of the studied periods. In Greece, a trend on the use of antipsychotics along the years was not found by sex but had a slight increase for both sexes. However, in Catalonia where the period was longer and the detection of any trend is considered easier, an increase of antipsychotics in the female adolescents followed a steeper road compared to children where a negligible increase was observed if any. Looking at the data in the boys' group, a negligible increase found for children below 5 years of age, whereas for the other age groups, greater fluctuations in the period 2012-2013 were identified. Interestingly, younger adolescents were more likely to receive an antipsychotic from 2013 to 2016 than the older adolescents. A study reporting the use of antipsychotics by sex for the period 2004-2014 reported a similar trend where the 14year-old boys had lower rate of use compared to the 13year-olds for all the years apart from 2010 and 2012, while it seems that older adolescent girls were more likely to be antipsychotic users except for the years 2008 and 2012.(131) One explanation for these strange observations might be the use of antipsychotics in ADHD and autism as off-label. In 2013 when the prevalence in older adolescent boys dropped significantly while the rate for the younger adolescents kept rising, the new DSM-5 was adopted. One of the concerns expressed with the new version of the diagnostic criteria for mental disorders was the expected lower cases of adolescents with ADHD (402) to whom might be more likely to administer antipsychotics which are used off-label as a second-line treatment for stimulant-resistant ADHD or for other ADHD comorbidities.(460)

Globally, the differences in our estimations compared to other countries might be related to the differences in the study periods, the study populations/age strata or methodological approaches.

However, since an uptrend of antipsychotic use in children and adolescents was identified, this merits attention, particularly if this trend might be significantly related to their off-label use and to increased related adverse events.

5.3.2.5.3 *Anxiolytics*

As presented in the SmPC analysis for the two regions in the present study, only a number of anxiolytics have an authorisation in children and for some of them this indication is not even related to psychiatry (e.g. hydroxyzine). There are limited data on anxiolytics use in the paediatric population analysed per age groups, as their limited use is most of the times reported together with the use of hypnotics/sedatives.

In our study, we decided to exclude hydroxyzine-only dispensations as they were related with non-psychiatric use, but dispensations of hydroxyzine were not excluded in children with at least one other psychotropic. Despite this exclusion, the number of children using anxiolytics in Greece and Catalonia continues to be high, but the distribution of the use between the regions is different and does not follow the same pattern.

In Catalonia, the pattern of increased use with advancing age was observed. Almost all age groups had a similar prevalence in 2008, except for children below 2 years of age. The evolution since then was a steep uptrend for older adolescent and children 1-2 years of age which then stabilised and decreased along the years respectively; a more steady and slighter uptrend observed for the <1year of age group, while for the remainder age groups, we could clearly see a downtrend. In all age groups we have seen that there was a downtrend after 2014-2015 which might be related to the confirmed potential risk of QT interval prolongation and cardiac arrhythmia events following the use of hydroxyzine that triggered new restrictions in its use in Europe, restrictions that were aiming to minimise the risks.(461) Studies highlighting these risks started to increase awareness since 2011 (462,463), so that this can also explain the starting point of prevalence decrease in children below 14 years of age as patients of similar age are more likely to receive hydroxyzine due to the increasing prevalence of allergic rhinitis in children of school age and young adolescents (464,465); another point supporting this theory is the identification of hydroxyzine ranked high among the most frequently dispensed medicines in this young subgroup of the paediatric population. Another explanation could be the use of benzodiazepines for the treatment of convulsions (e.g. diazepam) which was also ranked high. Moreover, the high increase of anxiolytics in adolescents might also be related to the higher diagnosis of anxiety disorders in this subpopulation.(92) The introduction of several changes in DSM-5 concerning anxiety disorders in 2013, seems to have an impact on further decrease on the anxiolytics use despite predicting that the changes would have no impact on youth's diagnosis (6); the new published NICE guideline the same year on social anxiety disorder

recommending that children should be preferably managed with CBT (403) could explain the observed rates too.

The use of anxiolytics in the Greek sample is lower compared to Catalan for all age groups except for children from 1 to 5 years of age. In 2017, Greek children aged 1-2 years were 1.4-fold more likely to be treated with anxiolytics than their Catalan peers, 3-5year-olds had similar possibility of anxiolytic use, while for the group of older adolescents Catalans were 7.7-fold more likely to use this ATC group. In addition, Greek data do not follow the same pattern per age group as observed in Catalonia: the higher rates of prevalence of anxiolytics' use were detected in the group of 1-2year-olds followed by children aged 3-5 years. When excluding the prevalence for 2016 due to the non-full year data, we saw a steady increase for children <1 year of age, 3-5 years and 9-11 years, while for the remainder the evolution of the prevalence along the years was stable or with a slight decrease in Greece. The high anxiolytics' use in this very young population in Greece, might be less connected to the use of hydroxyzine for non-psychiatric disorders, as hydroxyzine did not rank very high in the most frequently used medicines in the region; nevertheless, it is most likely to be connected to the use of diazepam in epilepsy, considering its high ranking and the diagnosis of epilepsy as the most frequently identified in the sample. Of note, other pharmacological options, such as antidepressants, are considered as first line options in the treatment of children with anxiety disorders (466,467), a fact that was also observed in the Greek sample: other anxiety disorders were among the most frequent identified diagnoses for which the most frequent dispensed medicines were two antidepressants (fluoxetine and sertraline) and one anxiolytic (alprazolam).

The common part when comparing the two datasets for the use of anxiolytics, was that girls had generally a two-fold exposure than boys for the group of older adolescents, whereas boys were more exposed to anxiolytics in the population aged less than 12 years. Similar observations have been reported also in other countries concerning benzodiazepine's use.(468,469) However, not many studies report the use of anxiolytics on national level and per age group, but the existing ones report similar trends per age and sex as the present study.(131,152,170) In Catalonia, the use of anxiolytics in younger adolescents had a preponderance in girls, but with a nearly two-fold decrease from the older adolescents in almost all years after 2008. In Greece, boys aged 12-14 years kept being more exposed than their female peers. These results are supported by the fact that girl adolescents are more likely to get a diagnosis of internalising disorders such as anxiety (92), while allergic disorders seem to be higher in younger boys and adolescent girls.(470) Epilepsy and convulsions are mostly diagnosed in younger ages and have a male predominance (446), which is also in line with the higher diagnosis of epilepsy in Greece as observed in the present study. As a final remark, it is worth to mention that diazepam was also

among the most frequently dispensed medicines to Greek paediatric patients with non-specified diagnosis which was ranked as the second most prevalent diagnosis in the sample.

5.3.2.5.4 Hypnotics/sedatives

The use of hypnotics/sedatives in the paediatric population is a controversial topic. The prevalence of insomnia in this population may reach up to 30%, but most of the times sleep problems are treated with sleep hygiene strategies and very rarely with a soporific agent.(471) Nevertheless, sleep problems may impact severely children and adolescents, as well as their families, considering that they can lead to increased visits to healthcare institutions, and therefore need to be treated adequately.(472)

The pattern of hypnotics/sedatives use in the two regions of the current study differs, despite the fact that the licensed indications for hypnotic use in children and adolescents are covering the same paediatric age groups in both regions, with one extra medicine (lormetazepam) approved in children to be found only on the Spanish market. Catalonia still presents an uptrend with advancing age while in Greece the most exposed group interchanged between 9-11year-olds and 12-14year-olds.

Breaking it further down, the prevalence rates for children below 12 years of age in Catalonia had a steady trend up to 2010, whereas there was a decrease up to the lowest point in 2012 where it started again to increase. This breaking point in 2012 and especially for the youngest groups could be attributed to the approval of midazolam in 2011 for the treatment of prolonged acute convulsive seizures from 3 months of age (473); even though midazolam was not identified in the most frequently used medicines in Catalonia, this explanation could be still valid considering that hypnotics/sedatives prevalence rates are much lower than the other psychotropics, and thus midazolam had to compete with active substances with a much higher frequency. Another explanation could be the Spanish clinical guideline on paediatric sleep disorders published in 2011 recommending the use of sleep hygiene strategies before any pharmacological intervention.(406) The same guideline was also recommending melatonin use from the age of 6 years, even though it was officially approved by EMA in children from 2 years of age with ASD several years later (in 2018). Melatonin was not ranked on the most frequently used medicines too, but the theory could still be valid following the same approach explained previously for midazolam.

In Greece, the lowest rate was observed for children below 1 year of age which after a peak in 2017 remain quite stable having a halved rate in 2019. After 2017, the rate decreased in the groups below 12 years of age, while for the remainder groups the rates were increased following a similar rhythm, except for a decrease seen in the groups aged 6-11 years from 2018 onwards.

The higher use in the younger patient populations may be ascribed to the use of midazolam in children with seizures, considering that this active substance was ranked among the most prevalent in children below 14 years of age who are mostly diagnosed with epilepsy.

Comparing the two regions in 2017, we saw that Greek children below 12 years of age were two-fold more likely to use a hypnotic/sedative, the 12-14year-olds had similar rates in both regions, while the older adolescents in Catalonia had a three-fold higher exposure. The high rates in adolescents may be related to sleeping issues due to electronic devices and social media as adolescents are more exposed to them.(431,432) In both regions, the stressful period of life leading to sleep disturbances in adolescents due to intensive study for their participation in national baccalaureate exams in order to entry university, could also serve as a valid explanation.(474,475) This high difference between the regions though, may be explained by the lack of special mental health centres for the paediatric population in Greece, that could diagnose and treat the stressed adolescent patients properly. On the other hand, and since in Catalonia these centres exist, the high rates may be attributed to the unsuccessful or limited use of the recommended non-pharmacologic interventions, considering that they are time-consuming healthcare procedures compared to standard medicine consultation.

As described above for the anxiolytics, data per age strata on the exposure of paediatric patients to hypnotics/sedatives are limited in the literature. Only one study was found, where adolescents in France were much more exposed than our study populations, but this might be explained by the fact that the French study refers to data from 2002.(170) Two studies reported the prevalence of hypnotics' use per age and sex in Norway, with girls and boys been much more exposed than their Catalan peers mainly due to the high use of melatonin which was not identified in our sample. Norwegian adolescent girls and younger boys were more likely to receive hypnotics/sedatives than their peers, a trend that was also observed in Catalonia. This can be justifiable considering that sleep disorders are more common in younger boys and older girls, or due to the varied sex and age at onset distribution for other mental health disorders, such as ADHD and ASD in younger boys (476), or depression and anxiety in older girls. The same pattern was not seen in Greece, where boys of all ages had higher exposure aligned with the higher chances on receiving a diagnosis for epilepsy or ADHD.

In conclusion, the rates of hypnotic/sedative use per age groups are low compared to other regions, which is also in line with the warnings to not use these medicines to paediatric patients considering the high dependence risk and several other serious adverse effects.

5.3.2.5.5 Antidepressants

Antidepressants are not a first-line option for the paediatric population due to a higher risk of serious adverse events and the risk for suicidality.(477) Nonetheless, in the present study, the use of antidepressants showed age-related increase in both regions, which has recently also been observed in another study from Spain but with data from primary care prescriptions.(194) The prevalence of use had an uptrend fluctuation in Catalonia leading to a two-fold rate in the older adolescents during the ten-year study period, with the peak observed in 2014 for the youngest adolescents (8.54 per 1,000) and in 2015 for the oldest adolescents (18.45 per 1,000). In Greece the almost three-fold increase between 2016 and 2019 may be explained by the non-full data for the first year of the study; excluding 2016, a slight increase has been observed during the study period with the peak in 2018 for both groups of adolescents (3.21 and 0.87 per 1,000 respectively). Comparing the trends between the two regions, we could see that for the period 2016-2017 Catalonia had a downtrend for the older adolescents, while in Greece there was an uptrend that could not be severely change even if the missing three months were included in the dataset received for this analysis. In 2017, Greek older adolescents were six times less likely to receive an antidepressant compared to Catalonia (2.78 and 17.19 per 1,000 respectively), while the difference for the 12-14year-olds was nine-fold favouring Catalonia (0.78 and 7.66 per 1,000 respectively). On the other hand, a downtrend was detected for the paediatric population below 12 years of age which can also be related to lower diagnosis rates or the selection of non-pharmacologic interventions before reaching adolescence.

The pharmacoepidemiology of antidepressants reported in previous studies does not always use the same age groups, therefore our study is limited to be compared in absolute terms with all these studies. In several previous studies, children under the age of 5 years were excluded as the use of antidepressants was considered negligible, a fact that was also found in the present study for both regions.(117,120,137,158,176) Furthermore, the prevalence rates reported in other studies for this age group identified very low numbers following a downtrend in the concerned study periods.(163,167,171,173,191,192) In 2010, French 3-5year-olds had a higher chance on receiving an antidepressant than their Catalan peers, while the 15-17year-olds had almost half the chance compared to Catalonia.(134) The uptrend along the years in the groups above 12 years of age and the downtrend in the younger groups were also seen in other countries.(120,167,173,191,192)

In the pre-puberty phase, the difference between boys and girls seems to be similar, whereas adolescent girls are twice as likely to be diagnosed with internalising disorders such as depression.(478,479) Previous studies also reported this sex difference between male and female adolescent patients receiving antidepressant treatment with an increased prevalence

with the years.(117,118,120,128,131,134,140,152) In the present study we also observed this trend where adolescent girls in both regions had significantly higher rates of receiving an antidepressant than boys, while in the youngest age groups, boys were slightly more or similar exposed than/as girls. These slightly higher rates in younger boys may also be attributed to their higher prevalence of suffering from a disorder comorbid to depression (i.e. aggressive disorders and anxiety).

Regulatory warnings on higher suicidality by the use of antidepressants impacted initially the decrease of their use in the paediatric population. This was also related to less diagnosis or followed by a strategy of 'not doing nothing' which led to concerns and debates in 2014, where some studies showed an inverse suicide rate in adolescents as per the number of antidepressants use.(480,481) Despite the fact that the cautious use of antidepressants in the paediatric patients was not retrieved with guidelines supporting it (482) and the report of a second warning in 2013 on higher arrythmias by the US FDA (437), antidepressant rates started raising in the age groups were the diagnosis of depression is more prevalent. In our sample this can be supported as among the most prevalent active substances for adolescents were several antidepressants.

5.3.2.5.6 Psychostimulants, agents used for ADHD and nootropics

Psychostimulants are considered the most commonly dispensed medicines among children with ADHD, but they sometimes are also used in other conditions.(483) The present study reported a higher exposure to psychostimulants in Catalonia compared to Greece and the same was also shown in the analysis per age groups. In 2017, no children below 2 years of age found as exposed to psychostimulants in both regions. For the remainder age groups, Catalan 3-5year-olds were almost 25-fold more likely to use a psychotropic compared to their Greek peers, while for the older groups the difference increased further: more than 33-fold, almost 44-fold, more than 61-fold and almost 50-fold in an age group ascending order.

Concerning the trends per study years, no patients below 2 years of age were exposed to a psychostimulant in Greece and patients scarcely were identified in the group 3-5 years of age. All other groups in Greece had an almost steady or slight increase along the years and all of them had similar rates except for patients aged 6-8 years whose prevalence rates were almost halved. Consequently, the low and almost similar exposure of children above 9 years of age to psychostimulants could be interpreted with the following theories: lower diagnosis rates, not easily accessible system with specialists, non-pharmacologic interventions initially that if failed will be accompanied with medication, or non-documented medicine dispensation. The present study identified ADHD among the most frequent diagnoses in Greece, leading to the point that the explanation of this low use to be more associated with the last two theories. Greek children

with ADHD seem to follow the documented path: diagnosed early, treated with stimulants if necessary due to the serious adverse events that their use may enclose (443) and their symptoms seems to improve with the age.(484)

In Catalonia, the highest prevalence rates were reported in the population between 9 and 14 years of age. Since the average age range of ADHD diagnosis alone seems to be 2.25-7.5 years in Europe (485), this finding may suggest that children in Catalonia have a late-onset ADHD or diagnosed later than their first symptoms, but this cannot be cross-checked as diagnosis data are not available. Another explanation could be attributed to an early diagnosis but to late introduction of a stimulant medication when other non-pharmacologic interventions have failed. Finally, the lower use in the older groups may be attributed to the improvement of ADHD symptoms with the age.(484) Concerning the evolution along the years in Catalonia, we identified different trends that depended on the age groups: scarce use in children aged less than 1 year with two peeks in 2010 and 2013, while zero rates after 2015; a steep increase up to 2010 for the 1-2year-olds, followed by a steady decrease which also led to zero rate in 2017; uptrend with two peeks in 2010 and 2013 followed by a downtrend that stabled in 2017 for the group of 3-5 years of age; an increase till 2010, then a steady period which led to a peek in 2013 and a subsequent steady decrease in 6-8year-olds; an uptrend with a slight decline in 2012 followed by the highest reported rate in 2014 and a subsequent constant reduction for the 12-14year-olds; and for the group of older adolescents there was a somewhat steady prevalence that started to rise more in 2010 up to the highest rate in 2012, followed by a decrease and a subsequently a steadier rate.

It seems that there are two significant periods for all age groups marked by the year 2010 (peek or uptrend started) and 2013 (peek or downtrend started) or their satellite years. The first timepoint especially for the younger age strata where the onset of ADHD is lying, is probably associated to the raising rates of ADHD diagnosis until 2011 as reported by others.(440) The publication of DSM-5 in 2013 accompanied with the changes in the diagnostic criteria for ADHD and ASD, likely played an important role on the psychostimulants use related to potential lower diagnosis rates, especially for the adolescent group for which concerns had been raised.(402) An alternative theory, which might be more related to the younger groups where ADHD has its onset, could be the sudden and severe cardiovascular adverse events associated with the use of psychostimulants that were observed and led to recommendations by the European ADHD Guidelines Group on cautious approaches before starting any stimulant medication.(486) The further drop might be also related to the approval of guanfacine by EMA in 2015 for the paediatric population aged 6-17 years old for whom stimulants are not suitable, not tolerated or ineffective, provided that this new medicine was not pertained in the stimulants and was free of

their concerned risks.(487) Even though no data on guanfacine use were included in the present study, data from another region in Spanish has identified its use among the paediatric population.(425) Misuse of psychostimulants and a preference to prescribe non-stimulant medicines may also contributed to the downtrend.(488)

The scarce use of psychostimulants in the population below 2 years of age, as well as the limited or none use in the group 3-5 years of age are confirmed from other studies.(134,146,157) In general, the consumption of psychostimulants in preschool children has been reported as limited compared to the higher exposure observed in older paediatric patients (134,146,147,153,157,163,175,184) with the exception of USA, where the prevalence of use for this young population was higher compared to other countries.(180,189,190) The trend of higher exposure in the population 10-14 years of age was reported previously in the literature. For the period 2008-2012, even though the age groups are not same in absolute terms, Catalonia's population from 9-14 years of age is in average more exposed than the 10-14year-olds in Denmark and in the UK, and almost half-rate exposed than in Germany and the Netherlands, while the USA peers were up to 4.3-fold more likely to use a psychostimulant.(190) In the USA a decrease in the stimulant's use started also in 2010, Germany had no major fluctuations, and in Denmark, the Netherlands and the UK always an uptrend along the years was reported; no data have been presented from 2013 onwards to permit detection of similarities in the trends identified in the present study. In Israel, the 9-11year-olds found to be twice more likely to receive treatment with psychostimulants than their Catalan peers.(132)

Our study demonstrated that boys had much higher consumption of psychostimulants than girls in all age groups, with similar uptrend and downtrend as the ones observed in the combined boys-girls population in Catalonia along the years, while in Greece boys had a clear uptrend until 2018 followed by a slight decline in all age groups afterwards. The difference between the sexes were reaching sometimes up to 7-fold in Catalonia (3-5year-olds in 2017) and almost 9-fold in Greece (9-11year-olds in 2018). This high difference in the consumption by sex was reported in several studies in the past (131,153), confirming the trend that boys are more diagnosed with ADHD of externalising symptomatology, which is much more apparent than the type of ADHD with no sign of hyperactivity, which is more prevalent in girls.(416) However, in both regions and for the population above 9 years of age, the girls faced a higher rise in the consumption of psychotropics from the first to the last year of the concerned study periods. Those trends were also reported in a study from another region of Spain.(425)

In view of the above, the present study managed to validate well-established trends concerning the use of psychostimulants in the paediatric population as per the age and sex along the years.

5.3.2.5.7 Psycholeptics & psychoanaleptics in combination - Drugs used in addictive disorders

Psycholeptics and psychoanaleptics in combination group was not requested from the Catalan data provider and in Greece the consumption was zero or scarce throughout the years. In Greece, no specific trend could be identified since the scarce data demonstrated that it was only slightly used in older adolescents, probably off-label, as these combinations are not authorised in the paediatric population. No relevant pharmacoepidemiology data were found to permit any comparison. In general, fixed combinations are avoided in children as the doses could not be easily defined especially in younger children. Based on that, the manufacturers are encouraged to replace them with child-friendly fixed-dose combinations, but these initiatives are mostly targeting more prevalent and life-threatening paediatric diseases (489)

Concerning the category 'drugs used in addictive disorders' similar observations as above have been seen: the medicines included in this category were scarce or zero in Greece and no trend could be defined as per the age group, while in Catalonia a higher consumption was seen compared to Greece, but it is still very low or zero in the very young population. The only data that could be extracted is that we could see a higher exposure during adolescence. Only nicotine is authorised in children above 12 years of age and it can be used to quit smoking considering that older adolescent smokers are more frequent. Since these medicines are in general used for detoxification from substances, their identified use from older adolescents can be considered a sign of increasing concern for substance abuse.

5.3.2.6 Medicines with higher prevalence of use

Children below 2 years of age were found mainly exposed to substances from the group of antiepileptics in both regions. Older children which started to consume more substances were included in the group of anxiolytics and psychostimulants, while after 6 years of age more antipsychotic agents appeared. The first antidepressants were first detected in the group 9-11 years of age in Catalonia and in 12-14year-olds in Greece, and after that their consumption was further increased. Combining the most frequently identified medicines from both regions, we have reached to four medicines pertaining in the group of antiepileptics, two antipsychotics, five anxiolytics, one hypnotic/sedative, two antidepressants and two psychostimulants as being the most prevalent in the current study. It has to be highlighted though that all prevalence rates were much higher in Catalonia compared to Greece, so the following analysis will be based on a qualitative comparison.

Methylphenidate, a medicine approved for the treatment of ADHD in children aged above 6 years as a part of a comprehensive treatment plan and when remedial measures alone proven insufficient, was the most frequently used medicine in the analysis combining data from both

regions and as per sex, with boys been much more exposed. The increased use of methylphenidate was also prevalent in Catalonia alone as it was ranked first, while in Greece even though not ranked first, was still among the most used medicines; however, the difference among the regions was significantly big (41.0 vs 0.5 per 1,000) and got even greater in the analysis per sex (boys: 58.7 vs 0.8 per 1,000). This high methylphenidate use seems to be the reason for which psychostimulants were the most prevalent ATC group in Catalonia with increased rates in the ages 9-14 years; similar trends reported also in another Spanish region (425), as well as methylphenidate was among the most frequently used medicines reported in previous studies around the globe with similar observations concerning the age and the sex.(133,148,159,172) The increasing rates of ADHD diagnosis are justifying methylphenidate's use (440) and it seems that the changes concerning ADHD diagnosis criteria had a significant impact on the prescription of methylphenidate.(490) A higher use in certain age groups and in boys is probably related to the epidemiology of ADHD, the potential serious adverse events connected to its use (443) or to the initial non-pharmacological interventions that are recommended.(441,442,486) Methylphenidate use first appear in Greece's list later as opposed to Catalonia, and its lower rates may be related to the above concerns or any precautionary measures taken by physicians, as the debate concerning ADHD and its treatment seems to be still controversial among prescribers.(491) The use of non-stimulants indicated for the treatment of ADHD that were identified in the current study among the most frequent active substances, could also influence the rates of methylphenidate. Atomoxetine, a non-stimulant option for the treatment of ADHD was also found in the present study following the same characteristics as methylphenidate for Catalonia but in very low rates compared to methylphenidate, whereas in Greece it was included only in the most frequent medicines used in boys aged 9-11 years; these findings are also supported by previous studies for the use of atomoxetine.(133,425) In general, the use of these two medicines in both regions do not seem to be off-label and prescribers are mainly following the recommendations. Other non-stimulant medications (e.g. guanfacine) are not included in the analysis to cross check if Greek physicians prefer it against any stimulant option, but recent data indicate that they do not often prescribe methylphenidate to diagnosed children, as they prefer to start with non-pharmacological interventions.(492) In general, the increased use of these two stimulant active substances may be also attributed to its increased use in paediatric patients with ADHD and ASD comorbidity (493) or for ASD alone.(494)

Children and adolescents with anxiety are not to use anxiolytics as first-line treatment.(466,467) However, in the present study several anxiolytics identified as most prevalent. Diazepam was the second most frequently consumed active substance based on the combined data from both regions. Diazepam is a long-acting benzodiazepine pertained in the group of

anxiolytics, but in children is approved for controlling tension and irritability in cerebral spasticity, as an adjunct to the control of muscle spasm in tetanus, for oral premedication before surgery, and in febrile and epileptic convulsions. Diazepam found to be also among the most frequently used medicines in paediatrics previously.(164,170,495) Since most of the approved indications of diazepam are for its use in hospitalised patients, its high use in our sample seems to be connected to diazepam's use mainly in epilepsy, considering that epilepsy was the most frequent diagnosis in Greece, and due to the fact that the use of diazepam was present in all age groups and ranked very high mostly for younger patients in both regions; it is to be highlighted here that all these observations are connected to the epidemiologic characteristics of epilepsy in the paediatric population. However, based on the off-label use of diazepam in Greece, as it was mostly prescribed in children with non-specified diagnosis and its short-term use deducted by the low ratio dispensation/patient, the possibility that it was also used in anxiety mainly in adolescent girls cannot be precluded. In Catalonia though, it may also be related to the high psychostimulant use, as anxiolytics can be used in ADHD comorbid disorders mainly diagnosed in young boys, or to anxiety disorders, as its use was most frequent in adolescent girls which are more prominent to be diagnosed with anxiety.(92)

Alprazolam was another anxiolytic detected among the most prevalent in older adolescents' group in both regions, as well as in children aged 1-5 years in Catalonia, and its use in paediatrics is reported previously in other observational settings.(170,495) This active substance is not authorised in the paediatric population, but in adults is used for anxiety, so in our sample it was likely used for its anxiolytic properties as off-label as it was indeed identified among the list of the off-label medicines in both regions; moreover, in Greece alprazolam was among the off-label medicines used in children diagnosed with anxiety. Two more benzodiazepines found in Catalonia were previously reported also in other studies: lorazepam, which is not indicated in anxiety or insomnia in children so its high use can be connected to an off-label use as it was found among the ten medicines dispensed in adolescent girls, and clorazepate, which is one of the anxiolytics for which the use in children with anxiety disorders is approved.(495) Benzodiazepines belong to the medicines that are under strict control from both states, as they need to be used for short-term to avoid addiction, and they cannot be dispensed without specific prescription, making the reported numbers a good reflection on their actual use.

A non-benzodiazepine agent ranked also as frequently used, was hydroxyzine that belongs to anxiolytics and is indicated in anxiety in adults, whereas in children is approved for its antiallergic properties. Despite removing the high number of patients with hydroxyzine-only dispensations, hydroxyzine remained high ranked in both settings: in children up to 11 years of

age in Greece, and in children up to 14 years of age in Catalonia; this high ranked use was also reported previously.(164,170) Hydroxyzine has been also reported as to be used off-label in children due to its somnolence properties. Children with ADHD are more prominent to have insomnia problems and hydroxyzine is reported as a treatment option.(496) Hydroxyzine was found to be more used in age groups where ADHD is mainly diagnosed, but this range of age is also within the limits of allergy diagnosis and the use of hydroxyzine in patients that have allergy on top of a mental health issue cannot be excluded. In Catalonia though, the higher hydroxyzine use compared to Greece could be explained as a remedy to reduce sleep problems caused by the high use of psychostimulants, but analyses of coadministration or of diagnosis identification were not feasible. Either way, hydroxyzine use is associated with serious adverse events and its potential high use, especially if off-label, is of great concern.(461,497)

Benzodiazepines in general should not be given to children and if used a careful assessment and a short duration is needed. Midazolam is also a benzodiazepine but pertains in the group of hypnotics/sedatives with the outpatient indications to be treatment of insomnia in children above 12 years of age and for convulsions above 3 months of age. Midazolam ranked high in almost all age groups in Greece, but in none group in Catalonia. Since in Greece the only available non-parenteral or non-rectally administered medicine used in hospitalised patients, is Buccolam - authorised only in paediatric patients with convulsions (473) - we can easily deduct that the high midazolam use is connected to the high diagnosis of epilepsy and the high use of antiepileptics in the country.

Several antiepileptics ranked among the most frequently used medicines in both regions and in all age groups, but their use was more restricted in older children and adolescents in Catalonia compared to Greece, probably due to the increasing use of other medicines like psychostimulants, antipsychotics, and antidepressants. This was shown in the use of levetiracetam and oxcarbazepine, whereas topiramate was mostly found in Greece in all age groups but in Catalonia only among the most prevalent medicines in older adolescent girls; their use was previously reported as increasing along the years and as to be used in almost all age groups.(160,166,498) Except for the obvious indication in epilepsy, valproic acid, carbamazepine and lamotrigine have also approved indication in adults with bipolar disorder (499) and were identified among the most frequent antiepileptics in the present study. Nevertheless, all antiepileptics that are on the Spanish and Greek market are approved for paediatric use apart from pregabalin, none of them is approved as mood stabiliser for this vulnerable patient population. In Greece, bipolar disorder was not among the most frequently identified diagnostic codes, and considering that this disorder is rarely diagnosed in children aged less than 10 years, their use as mood stabilisers in young patients in this setting study is

not likely. Valproic acid found to be highly prevalent in all age groups in Greece, but in Catalonia its use seems to be decreased with the age; this can be related to the warning for no use in any woman or girl in childbearing age due to potential foetus malformations or developmental disorders after birth (500), so valproic acid was not found among the most frequent used medicines in older adolescents in Catalonia. A study from the USA in 2000, showed that valproic acid and carbamazepine were leading the use in paediatric patients with seizure-only or psychiatric-only diagnosis (169) and this could be supported partially by our data: in Greece valproic acid was prescribed in epilepsy, in PDDs and in patients with unspecified diagnosis. The high use of valproic acid in children below 2 years of age was previously reported as well as its identification in the list with the most prevalent antiepileptics.(160,498)

Two antidepressants ranked among the most prevalent active substances in the combined data: fluoxetine and sertraline having had also higher consumption by girls, while amitriptyline entered the list only for older adolescent girls. Fluoxetine and sertraline entered in the list for the first time in children aged 9-11 years for Catalonia and 12-14 years for Greece. Sertraline and fluoxetine ranked in the first two places in a recently published study in Spain with prescription data (194), while the three above-mentioned antidepressants were among the most consumed antidepressants by the paediatric population, along with a higher use in girls, as observed in previous studies in other countries (120,126,133,144,151,159,170,501); this finding can be related to the fact that all three antidepressants are approved in the paediatric population. Fluoxetine is indicated in children and adolescents with moderate to severe depression unresponsive to non-pharmacologic interventions, while sertraline is only approved in children and adolescents with OCD. However, in the present study both have been used off-label in Greece. Some antidepressants are used off-label in anxious patients as depression and anxiety may appear simultaneously (502), as well as in anxiety disorders developed after ADHD diagnosis along with CBT interventions.(503) Their consumption by adolescents and girls is associated with the epidemiology of depression and anxiety disorders for which they are mainly prescribed.(92,478,479) No other antidepressants were ranked high, and this is probably related to the serious adverse events and the higher risk for suicidality accompanying their use.(477)

Finally, two second-generation antipsychotics had a high consumption and ranked into the most prevalent active substances in the combined data analysis with boys' predominance: risperidone and aripiprazole. Levomepromazine, the only first-generation antipsychotic in the list, was detected in use by children below 2 years of age in Catalonia; it is not indicated in such young ages, but it can be used in palliative care as antiemetic, anxiolytic and sedative drug.(504) Quetiapine, a second-generation antipsychotic, was added in both regions' list for the older

adolescent group despite not having an indication in children. In Europe and in regards to paediatrics, risperidone is only authorised for the short-term treatment of persistent aggression in conduct disorder from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation; however, risperidone ranked as the active substance with the most off-label indications in the Greek paediatric patient population. In Catalonia, risperidone's high consumption may be also associated to its off-label use as data exist for aggression in patients with PDD, ASD, ADHD or psychosis as well as based on the authorisations approved by the US FDA. Aripiprazole is indicated in schizophrenic paediatric patients older than 15 years of age, but in the present study its high consumption from younger patients constituted aripiprazole the most frequent off-label active substance in Catalonia and the fifth most frequent in Greece. The higher use of aripiprazole seems to be related to its off-label use in PDD, ADHD and ASD, as well as it seems to be recommended in risperidone-resistant schizophrenic adolescents (505) and in adolescents with moderate to severe manic episodes with bipolar I disorder.(506) Aripiprazole is authorised in the USA for ASD, and even though the MAH did not pursue this indication in Europe, the labelling is updated to include all relevant information for paediatrics.(455) All mentioned antipsychotics were previously reported in the literature as among the most prevalent antipsychotics in several countries, while one of them reported data from Catalonia confirming the results of the current study.(124,133,159) A study from another region of Spain detected risperidone as concomitant use with psychostimulants for children with ADHD (425), which could support the high use of antipsychotics in Catalonia due to the high prevalence of psychostimulants; however, the data received for analysis in the current study could not permit such type of analysis. The male predominance can be justified by the epidemiology of schizophrenia, ASD and ADHD. The potential high off-label use of antipsychotics is of concern, taking into account their serious adverse events and considering that the UK MHRA did not approve risperidone's indication in Europe as submitted by the MAH, due to concerns of the potential misuse as a form of long term chemical control and in particular of the most intellectually disabled paediatric patients who may also be the most likely to have adverse effects, despite that some efficacy had been demonstrated.(507)

5.3.2.7 Diagnosis data analysis

Diagnosing mental health disorders especially in paediatric patients is complicated: multi-informant approaches are needed since they cannot be detected by genetic, neuronal, or physiological correlates as opposed to somatic disorders. Misdiagnosis can lead to overdiagnosis or underdiagnosis, as normal development behaviours may be misinterpreted due to relative immaturity compared to peers (508,509) or because young patients may not be able to explain their feelings and parents'/care giver's perception may be misleading when reporting to the

diagnostician.(510,511) Some symptoms are overlapping in different disorders (e.g. ADHD and bipolar disorder), while in other cases symptoms differ depending on the age - like children expressing their depression via irritability rather than the expected depressive symptoms of adults - or on the sex, like in ADHD where males are more prominent to have externalising behaviours and thus are easier detectable, or like girls who are prominent to have diagnosis of depression or anxiety.(512) Thus, physicians have different points to be sceptical when they are called to diagnose mental disorders in children and adolescents, on top of their differential interpretation of/adherence to diagnostic criteria systems, or any concerns about how to help patients within the limits of health policies and systems.(513,514)

In the present study, we analysed the diagnosis connected to children and adolescents receiving any psychotropic in Greece, as the system in Catalonia is not structured in a way to permit associating the dispensations with diagnoses data.

As expected, epilepsy was the most frequent diagnostic code with almost four out of ten paediatric patients having it connected with their dispensations; taking together with convulsions which were ranked third, we have seen that more than half of the patients were diagnosed with a disorder for which an antiepileptic treatment would be needed. This finding indicates that in majority antiepileptics were dispensed for indications related to antiepileptics' main indication in the study population. This is also related to the characteristics of this type of disorder: the symptoms are apparent and easier detectable in order to determine the diagnosis as opposed to mental health disorders, as well as the low risk for stigmatisation from other Greek citizens.(410) Though, the high number of children and adolescents had a non-specified diagnosis which may be connected to a high risk to use psychotropics outside of the authorised indications. Non-specified diagnosis may be indicative of prescriber's struggle to correctly diagnose a patient which could be related to the specialty of the prescriber. However, it might also mean that the problem may lie on the difficulty to use the right diagnostic code or to use the code that will permit prescribing a medicine that could be reimbursed based on the established reimbursement schemes and prescribing.(95) Indeed in Greece, according to the results of the present study, a lot of psychotropic dispensations had been prescribed by physicians with no psychiatric specialty or with no specialty at all, who may not be permitted by the system to use specific codes while prescribing, and the non-specified code may give them the liberty to prescribe certain treatments.

The analysis on the more psychiatric-related diagnostic group codes revealed that the highest number of dispensations per patient was in the group of behavioural and emotional disorders with onset in childhood and adolescence; a group where ADHD, conduct or tic disorders are included. This finding is indicative that ADHD indeed exists in Greece as reported also in

previous studies (515-517) and seems to be actually treated despite being underdiagnosed. Methylphenidate and atomoxetine had the highest dispensation/patient rates in the group, but several antipsychotics were also dispensed considering that risperidone is approved for use in paediatric conduct disorders. According to a study conducted in a representative sample of Greek adolescents that they were followed-up from birth to adulthood, children and adolescents have higher risk of presenting behavioural and emotional disorders due to parental high stress.(518) The long economic crisis in Greece resulted in a more stressed population, and thus, the slight increase of psychostimulants and antipsychotics in the Greek paediatric population may be related to an increased diagnosis of behavioural and emotional disorders due to very stressed parents, and a stressful daily life due to family financial problems.(34) Several studies previously reported the prescription of antipsychotics in children with ADHD.(127,129,138,141,145,150,501,519)

The second most prevalent group of psychiatric-related diagnostic codes was 'schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders', where 6.4 dispensations corresponded to a patient under this diagnostic group; a finding that could explain the use of antipsychotics in Greece as it was one of the most dispensed ATC groups. Antipsychotics were used as previously reported in other countries.(127,129,138,141,145,150) However, we could see that medicines not indicated in the paediatric population with schizophrenia, were among the most frequently dispensed active substances: as an example valproic acid may be used in these patients because evidence exists on its use in psychotic uncontrolled adult patients (520) and antiepileptics were also previously reported to be used in children with psychiatric disorders.(122,164,521,522) Nevertheless, the highest number of patients with quite a high number of dispensations was related to a diagnosis of anxiety disorders. The lower rate of dispensations per patients compared to the other diagnostic groups though, can be explained by the fact that physicians might prescribed these treatment options (mostly antidepressants) respecting the short-term period for which they are intended when used in anxiety disorders; of note, antidepressants have also been reported in children with anxiety as off-label use.(126,144,167,185,501) In addition, antipsychotics were previously reported for anxious paediatric patients (129,138,141,145): risperidone was also dispensed in anxious patients in the present study, maybe due to its off-label use in OCD as it is recommended to adults for augmentation of SSRIs (523,524) and some evidence also exists regarding its use in paediatrics (301); however, no official recommendation for this use exists probably because it seems that OCD symptoms may be induced by risperidone.(525) Mood disorders had also a high number of dispensations mostly related to antidepressants and antipsychotics, a finding that has been previously reported in other studies.(126,127,129,138,144,145,150,526) From the antipsychotics, only aripiprazole is indicated in paediatric patients with bipolar disorder in

Europe, but evidence exist on other antipsychotics for treating these patients as some of these medicines have authorisation from the US FDA.(527) Finally, it is important to highlight that a small number of children and adolescents with eating disorders have been also diagnosed in Greece but with a high ratio of dispensed psychotropics. The epidemiology of eating disorders is not known in Greece, but studies showed that girls had higher predominance.(528) Guidelines do not recommend medication as first-line treatment in children and adolescents with eating disorders (529) and in Europe no approved medication to cover the needs of these patients exist, while fluoxetine is authorised in adults for the treatment of bulimia nervosa. Antidepressants seems to be used in children and adolescents with eating disorders (144), as well as antipsychotics.(138,141) Evidence on the use of antipsychotics and antidepressants is considered scarce and most of the times of low quality, and the use of benzodiazepines has been only reported as concomitant use (530), but an analysis of concomitant use was out of the scope of the present study. In general, antipsychotics were mostly prescribed in all groups with a diagnostic code related to psychiatry, and this finding could explain the slight uptrend of antipsychotics in the Greek paediatric community. Nonetheless, it is of concern that risperidone was ranked among the five most frequently dispensed medicines for almost all diagnostic groups, especially since in Europe it is only authorised in paediatrics for its use in conduct disorder, considering also its high rate of adverse events that can affect the life and development of children.(88,531)

Among the most frequently single diagnostic codes that were more related to psychiatry and were used for the dispensation of psychotropics in Greece, epilepsy and non-specified codes were in the first two places for which the same active substances were used: levetiracetam, valproic acid and diazepam. Diazepam seems to mostly be used for its anticonvulsive properties in the current study and not as anxiolytic. Even though not authorised in paediatrics, alprazolam was the other anxiolytic that was among the most frequently dispensed medicines as short-term treatment in patients with anxiety disorders as it can be deducted based on the low number of dispensations per patient. Antidepressants found to be used as per the recommendations given in the guidelines for the treatment of anxiety in adults (532), despite their use under an off-label status in children and as previously reported in other studies.(126,144,185,501,533) Generally, antidepressants (fluoxetine, sertraline and escitalopram) were mostly used also in patients with diagnosis of depression, for which only fluoxetine has approval in children and adolescents, and of OCD for which only sertraline has a paediatric authorisation. Depression and OCD were reported previously in the world for children and adolescents receiving antidepressants (126,144,167,185,501), as well as among adolescents in Greece.(534,535) The use of antidepressants in these patients could be a valid option, as some Greek children and adolescents diagnosed with OCD seem to have had higher symptomatology of anxiety and

depression as reported in a small study.(536) Antipsychotics (risperidone, aripiprazole and quetiapine) found to be dispensed in most of the other diagnostic codes: PDDs, ADHD, OCD and psychosis as per previous trends (138); only aripiprazole is authorised for one of these conditions, while quetiapine is not indicated in paediatrics at all. Finally, psychostimulants (methylphenidate and atomoxetine) were dispensed in children with ADHD, but both have an authorisation for this indication in paediatrics.

In view of the above, an inadequate diagnosis may lead to over treatment or undertreatment and of course in off-label or inadequate use that could subsequently lead to non-compliance with the treatment as previously observed.(537) Existence of evidence underlining that residents in Greece may not seek help for mental health problems early, indicates that patients may remain undiagnosed and therefore untreated, and thus awareness programs are of need.(538) The low numbers of psychiatric diagnosis compared to other countries, may be associated with cultural differences, health policies and systems. We could see that despite the warnings from regulatory authorities on the use of medications like antidepressants, these are still used to treat disorders for which they do or do not have an authorisation, most probably due to guidelines recommending their use in view of lack of authorised medicines in paediatrics. It would have been of interest to further investigate if this use has increased the serious adverse events associated to off-label use, but this is beyond the scope of the present study. Despite some promising initiatives to explore genetic, environmental and neurometabolic risk factors of psychotic disorders under minimal exposure to antipsychotics have recently been put in place including participation of adolescents (539), to date most of the studies concerning the prevalence of mental disorders in Greece refer to the adult population, while those referring to paediatrics are mainly regional or using questionnaires from small school samples. Therefore, the current study is considered to provide for the first-time evidence on the diagnostic codes used for dispensed psychotropics in paediatric patients on a nationwide level. In the future, a study of interest would be to obtain data with all diagnostic codes; then to analyse the medication prescribed and check any difference in the medication after Covid-19 pandemic as data show that the first lockdown did not result to an overall increase in symptoms in children with pre-existing psychiatric or developmental disorders.(540)

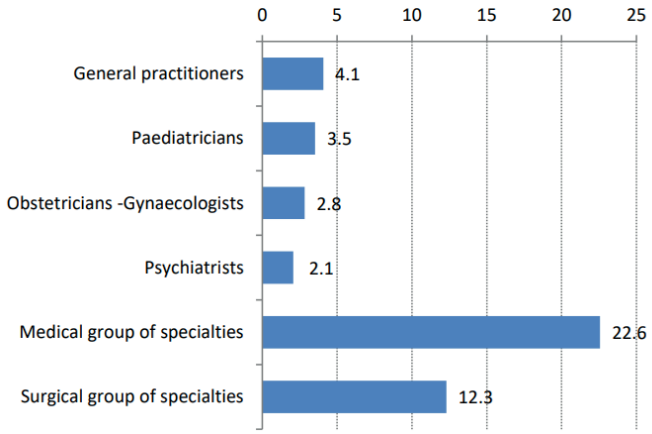
5.3.2.8 Dispensed medicines' analysis per physician specialty

Information on the prescriber is only available in Greek database, as this is connected to the dispensed medicine. Our study showed that there are children and adolescents in Greece using psychotropic medication, but the lowest rates that were found compared to other European countries may be indicative of underdiagnosis or undertreatment. Evidence exists that a big part

of adults in Greece with a serious mental health problem did not attend a physician or a psychiatrist, and from those under a psychiatrist supervision most had a serious disorder (541); hence, this may also be the case for paediatric patients.

The present study revealed that the majority of psychotropics were dispensed by paediatricians. Children are usually checked regularly from paediatricians only, to whom it is recommended to supervise also any behavioural and emotional issues. Despite the fact that paediatricians are fully trained to diagnose and treat usual paediatric disorders, data show that primary health care paediatricians and child psychiatrists believe that the former should be responsible to identify the majority of mental health issues and refer them to the latter who will be responsible to provide treatment.(542) In another study, the vast majority of paediatricians participating in the study, believe that they should have responsibility for identifying several mental disorders, such as ADHD, eating disorders, child depression, child substance abuse and behaviour problems, but they also reported that they should treat ADHD, whereas for the remainder they should refer the patient to a specialist.(543) The prescription of medication for ADHD was previously reported as to come mostly from primary care (544) or more specifically from paediatricians and general practitioners (545,546); others reported that the majority was initially prescribed by psychiatrists (154) confirming the results of the present study where child psychiatrists had the biggest share. Nevertheless, in Greece special mental health services and child psychiatrists are not equally distributed around the country or not readily available (33,36), a situation which was especially worsened during the financial crisis.(38,39) As reported by the national statistics institute, only 2.1 psychiatrists (including neurologist-psychiatrists and paedo-psychiatrists) correspond to 10,000 inhabitants, while general practitioners (including social medicine practitioners and rural medical physicians) and paediatricians have a greater share since they are the main entries for primary health care (see Figure 95).(547)

Figure 95. Number of physicians specialties per 10,000 inhabitants - Greece, 2020



***Source**: Hellenic Statistical Authority* (547)

In general, it has been previously reported that most of primary care providers are not extensively trained to identify and treat mental health disorders adequately, and the screening process is also limited due to time-constraints during the visit and/or reimbursement policies.(548) In Greece though, the deteriorated by the financial crisis mental health system resulted to inadequate public primary care and mental health services, while patients do not have access to treatment/interventions due to financial difficulties, as they need to refer to specialists that are paid out of their pocket.(36) The administration reforms have also played their role, which is also reflected on the educational plan of psychiatric specialty training, where several issues were identified on the acquired knowledge about mental disorders and their treatment, as well as in the part of clinical practice.(549) Along with psychiatrists, it seems that paediatricians play an important role in providing services related to mental health in Greek children and adolescents.(550)

Boys were found to have received more medicines than girls by all specialties, even though the order changes as boys are mostly treated by paediatricians and child psychiatrists, while girls from paediatricians and neurologists. According to data previously reported, boys were more related to prescriptions from specialised physicians while girls from general practitioners.(134)

Paediatricians seem to be responsible for most of the dispensed ATC groups too, except for antipsychotics, antidepressants and psychostimulants for which the highest rate was dispensed by child psychiatrists who are generally better trained to handle these high-risk medicines in order to treat disorders that are more complicated.(141,545,551) According to a previous study, the vast majority of benzodiazepines in children up to the age of 11 years were initiated by paediatricians, while for adolescents this was done by a psychiatric centre.(495) Previous studies are also consistent with our results that antidepressants were mostly prescribed by child psychiatrists, even though psychiatrists and paediatricians had also their share (118,126); in a similar setting the use of antipsychotics was found to be related to a higher prescription rate from paediatricians (127) as opposed to our results, which is consistent with other reported data that antipsychotics are in majority prescribed by child psychiatrists.(141) Neurologists have dispensed the second biggest share of antiepileptics after paediatricians, and this is justified by the fact that they are the most specialised to diagnose and treat epilepsy. Psychiatrists were also among the most frequent specialties treating paediatric patients and were mostly responsible for prescribing antidepressants and antipsychotics, as well as the majority of their combination. It seems that high antipsychotics prescription by psychiatrists (including child psychiatrists) has been previously described.(552)

In the current study, general practitioners have also prescribed a significant number of dispensed medicines. General practitioners and non-specialised physicians together seem to

have prescribed more medicines from groups like anxiolytics where hydroxyzine had a significant part, a finding consistent with data from other countries (553), and was unexpected. Physicians with no specialty, who are most of the times graduated medicine students in long waiting lists before entering their specialty career and are covering needs mainly in rural areas, are generally more reachable than mental health specialists, which are less accessible and found mostly in bigger cities. General practitioners in Greece, as in other countries, is not a preferred career option among undergraduate students despite country's high needs (554,555). A potential explanation of the share on psychotropics by general practitioners may be a result of refilling prescriptions that were initially given by specialists, rather than initiating new treatments for newly diagnosed mental disorders (556) especially in very young patients.(557) Previous studies also showed that general practitioners had a very high rate on prescribing all psychotropics and as per each ATC group (134,553), or antidepressants and antipsychotics separately (120,546,553,558), while it seems that these HCPs prescribe less off-label medicines compared to more specialised physicians.(144)

The low psychotropic dispensing rates in the Greek paediatric population as reported by the present study, may be explained by several factors: the deteriorated health system, the geographic constraints in order to access a specialist, the financial problems that patients are facing, amongst others. Nonetheless, a study reported that Greece has a high number of child psychiatrists compared to other countries in the region, and that there is no need for more paedo-psychiatrists and allied paediatric mental health professionals (559), but other data reveal that they are scarce when compared to west European countries paediatric specialist in mental health care.(38) Of note, two crucial points seem to be relevant to start a proper treatment in the paediatric population: problem recognition and adequate/timely referral from primary care physicians.(560) Insufficient self-recognition could be improved by minimising the stigma of mental disorders with campaigns targeting in increasing mental health awareness. Furthermore, underdiagnoses may be improved by proper physicians training; since the diagnosis requires certain abilities to interpret clinical presentation and symptom's weight, well-trained specialists are needed to avoid misdiagnosis or underdiagnosis, especially in those cases where symptoms are overlapping between mental disorders.(561,562) It is very important also to highlight that the perceptions of physicians about treatment options play a significant role on the final selection of the intervention (491) or the prevention of misuse of a treatment.(488)

In view of the above and due to the increased number of non-psychiatric specialists prescribing psychotropics in the current study, integration of mental health care programs in primary health care settings is necessary, which is also supported by psychiatrists.(36) This strategy will

improve screening and selection of treatment options for this vulnerable population avoiding any mis-/underdiagnosis and/or any potential off-label use or misuse, especially since in Greece it seems that the skeleton of services exists but has been deteriorated due to the economic crisis.(38,563,564) Several interventions targeting to improve mental healthcare services including plans for young patients, are addressed in the national health plan for 2021-2025, and therefore improvement is expected in this area.(565)

5.3.2.9 Dispensed medicines' analysis per prefecture

It is very important for a country to have a clear overview on the level of the citizens health, as this will probably affect country's health system and the implemented health policies. Differences have been observed as regards the access to health care facilities depending on the urbanisation of the place of residence, due to differences on demographics, socioeconomic indices and provision of health care services between rural and urban areas. In addition, stigmatisation seems to be greater in rural areas, especially in mental health (566), resulting into less frequent diagnosis (567) and subsequently lower or different treatment options.(568) Data on the place of origin were available only for Greece, so the present study performed an analysis only for this region and no comparison between the populations could be done.

It has been previously reported that adults residing in high general practitioner/population ratio and in municipalities with referral care services, were associated to higher probability of referral to a specialist.(569) Elderly people living in rural settings face several barriers concerning their health, as their access to relevant health services is more difficult; they are mostly residing in places with limited heath care facilities, they lack of autonomous means of transportation and they also face financial difficulties to afford transport.(570) These barriers can also be extrapolated to children and adolescents that are not independent and thus, the unmet medical care needs seem to be higher in paediatric populations residing in rural areas compared to their peers living in urban areas.(571)

In Greece, the place of residence seems to not have any impact on survival for children with life-threatening diseases (572), however the implication on mental health showed that rural residents have poorer mental health.(573) Several rural areas in Greece were previously reported to be less covered as regards mental healthcare facilities (574), and therefore other strategies like Mobile Mental Health Units (MMHUs) have been developed by nongovernmental organisations to provide services with success to remote areas, both in mainland and in some of the numerous Greek islands.(575) These initiatives cannot cover though another lack of the Greek health system, as mental health services for children and adolescents are even more limited especially in the more remote areas.(33)

Our study confirmed the above facts and showed that the vast majority of psychotropics were dispensed to children and adolescents residing in the greater area of Athens and subsequently to Thessaloniki, which are the two most populated and urbanised regions in the country. In fourteen prefectures, no difference on the dispensed psychotropics per sex was observed, but in Thessaloniki and some rural areas mostly in the north and the west, girls were more exposed to psychotropics, whereas in Athens's area boys led psychotropics dispensations. However, due to lack of data on the number of the paediatric population per prefecture, we could not properly calculate the population exposure by prefecture, and thus we can only describe rough numbers, which is inaccurate and of limited reliability. Yet, higher rates of psychotropics' dispensing in prefectures with higher density of population reflecting both a higher number of residents and a higher number of specialised physicians in the area.

In Greece, rural areas are in general poorer, and the economic crisis has worsened their previous financial status. This fact, together with the increased cost of out of the pocket payments for healthcare, may act as a barrier leading to inequities as regards the number of visits to physicians and to medicine purchases directly from the pharmacy, and thus to a lower adherence to treatments. Previous studies have reported different psychotropic rates based on the place of residence within the same country (133,141,148,519,545), but evidence on associations between exposure and urbanisation level is limited. Some others reported that children and adolescents in rural areas had higher probability to receive a psychotropic or ADHD medication per residents in each region (544), but others indicate that antipsychotic use is more frequent in suburban areas compared to rural or urban (576) or have no difference.(150)

Nevertheless, as previously highlighted, in Greece – and especially in smaller communities like in the rural areas – purchasing a medicine without prescription is possible. A low number of visits to physicians has been reported in Greece in 2019 (519 annual consultations per physician), the lowest among thirty-four countries (381); this would be consistent with a scenario of a part of the patients collecting their medicine directly from pharmacies with no prescription. If this is the case, these dispensed medications would be used by patients but would not appear in the national e-prescription database, so we would not be able to capture them. Hence, we cannot exclude some bias in our results towards an underestimation of the actual exposure in Greece per rural or urban areas.

Despite the potential bias, we may also assume that differences on psychotropic use per region exist. Other studies have reported regional differences in use of psychotropic drugs, and propose a number of explanations: differences in prescribing habits or clinical experience of single prescribers, differences in the availability of specialists, regional differences in disease

prevalence and/or socioeconomical factors, as well as potential cultural differences (e.g. behavioural disturbances less tolerated in urban areas, urban life more stressful). Considering that psychiatric diseases are increasing in the general Greek population in recent years, there is a need for further reformation of the system to improve accessibility and equity among the patients, especially for those living in rural/remote areas.(28,573)

Better health policies will play a significant role in improving mental health care in Greece avoiding the higher number of hospitalisations from areas lacking mental health services as previously observed in the country.(577) In this line, some strategies have been implemented like MMHUs (575); other options such as telemedicine and mobile apps may improve access to care in children and adolescents suffering from mental health disorders especially in the remote Greek territory.(578) Further campaigns aimed to eliminate the stigma of mental disorders combined with other actions could increase the willingness of these patients to seek help and subsequently to increase the success of any such strategy. Finally, it is worth to mention that the increasing number of immigrants and refugees residing in Greek remote islands are a relevant proportion of children and adolescents and this is a challenge that needs to be also addressed in the near future as data indicate that they have high mental morbidity and suicide rates.(579)

5.3.3 Off-label use analysis

Medication used under an off-label status is often considered a common practice in paediatric patients which imposes this vulnerable population into a high-risk situation due to uncertainties in the efficacy and safety of the concerned treatments. The off-label use in both Spain (and subsequently Catalonia) and Greece is somehow regulated. In Spain/Catalonia, there are legal measures in place to regulate requirements for off-label. A law established in 2009 states that a medicine could be given as off-label in both hospitals and primary care settings, provided that physicians justify the need, the absence of commercialised alternatives suitable for the patient, and obtain the consent from the patient after informing him or her on the benefits and risks. For repeated uses in certain circumstances, the physician's obligations may be waived if approved protocols are in place.(57) Reimbursement of medicines when off-label use is prescribed is not endorsed nor prohibited; in real life, off-label use of common medications is generally reimbursed by default, but it is decided at the regional level on a case by case basis for high impact innovative medicines. In Greece, a ministerial decree is required for physicians to permit off-label prescribing. This decree is established for reimbursement reasons (Official Gazette 545/B'/01-03-2012) and considers authorisation of off-label prescription in special cases if supported by international bibliographic references; the approval must be done before use. Furthermore, Greek law 4316/2014 states that any off-label use could be potentially reimbursed

if included in therapeutic protocols approved by the central council. In both Spain and Greece, as in the rest of Europe, promotion of any off-label use by the MAHs is forbidden, but MAHs remain responsible for reporting any side effects associated to this kind of use.(55)

The off-label use of psychotropics in paediatric populations has been previously reported in several countries. The extent of the off-label use depends on the setting and on definitions applied: small studies focused on a given indication or drug provide more detailed descriptions and include information on formulation, dose and indication that allow a more accurate definition of the off-label use, hence leading to higher reported rates of off-label use.(580,581,582)

In our study the data did not permit a very precise definition of off-label use in the Catalan database, since it did not allow linking dispensed medicines to a clinical indication, as well as the age of the subjects was aggregated into fixed groups for confidentiality purposes. We had to limit the analysis of the off-label use to the age range for which each active substance was approved. Thus, it is important to highlight that the off-label use rate described in the present study is only partial and it is driven by approval for the age group as it is not considering indication of the drug. Nonetheless, the exercise done with Greek data allowed to analyse the diagnosis included in the prescriptions and has shown that a big part of the psychotropics' off-label use is related to indications not approved in paediatrics.

In order to identify the approval status of psychotropics, the ATC codes in the database maintained by the WHO were used to search relevant databases publicly available in both regions. The current study showed that only 38.5% of psychotropics in the concerned ATCs were available in the Spanish market, while in Greece it was 31.9%. Formulations and labelling were reviewed to identify authorised uses in children. Depending on the marketed product (formulation or strength), the age cut-off could be different, but also depending on the indication for which a product was approved. Differences on the formulations or strengths commercialised in both regions led to the definition of a different cut-off age for eight active substances, but these were not widely used. In a pragmatic approach aimed to avoid overestimation of off-label use, we defined the age cut-off for each active substance as the lower of all marketed products with the same active substance. However, this strategy has likely resulted in underestimation of the actual off-label rates.

5.3.3.1 Off-label use due to non-authorised age range

Considering all the above limitations, we observed that approximately 12% of Catalan and 14% of Greek paediatric subjects received at least one psychotropic as off-label related to any paediatric approval of at least one product with the same active substance. The rates are slightly

lower when each subject was included more than once taking into consideration all dispensed psychotropics that they ever received during the concerned study periods (11% and ≈13% respectively); in this second analysis the number of off-label dispensed psychotropics was 4.6% in Catalonia and ≈5.5% in Greece. We have also seen that there was a slight downtrend in the off-label use in Catalonia along the years as opposed to Greece where an uptrend was observed. When the criterion of the minimal labelled age was introduced into the definition of the off-label use, the off-label rates of the dispensed psychotropics were increased, reaching to more similar rates between the regions (7.63% in Greece vs 7.46% in Catalonia), while an uptrend in both settings was seen along the years. The introduction of the age criterion though, resulted in higher off-label rate of dispensed psychotropics in 2017 in Catalonia compared to Greece (7.73% vs 7.30% respectively). In both settings and in both analyses, girls had a higher rate of off-label use compared to boys, but the boys had a higher rate of dispensed psychotropics per patient. Comparing the two regions we saw that Catalan girls were always more exposed to off-label psychotropics than their Greek peers.

Our study results are comparable to only one study previously reporting the off-label psychotropics' prescriptions in the Icelandic paediatric population where the authors report much higher off-label rates than the ones described in our sample (159); that can be explained by our methods based on age only, the study period, and the limitations described above.

The analysis of the off-label use of psychotropic drugs considering the age as criterion in 2017, as the only overlapping year between the Catalan and Greek datasets, showed off-label rates in the same order of magnitude and roughly similar in Greece and Catalonia, although nominally it was higher for almost all age groups in Greece as compared to Catalonia. In both, quantitatively most of the off-label use was in the group of older adolescents, paralleling the pattern of overall exposure to psychotropic drugs. Considering the proportion of off-label use in respect to the use in each age group, the youngest populations were those with higher proportions, especially in the group below 1 year of age in Greece (18.5%) and the 3-5year-olds in Catalonia (19.1%). These are the first estimations available for overall psychotropic off-label use, since published data exist only for separate psychotropic ATC groups like antidepressants (205) or antiepileptics (193), while in a study conducted in Spain the off-label prescriptions of antidepressants were found to increase with the age.(194) Actually, the literature has several reports focused on the off-label use of antipsychotics.(583)

Our analysis showed that in 2017 the most frequently active substances dispensed to children and adolescents out of the authorised age included antipsychotics (aripiprazole, quetiapine, olanzapine and paliperidone), antidepressants (escitalopram, citalopram and mirtazapine),

anxiolytics (alprazolam and clobazam), antiepileptics (oxcarbazepine and pregabalin) and hypnotics/sedatives (melatonin).

Off-label use of melatonin was previously reported in Norway (203), but our rates are not comparable as the Norwegian results were expressed per user and sex. In Greece a high rate of melatonin's off label use may be explained by the existing recommendations of melatonin use in paediatric insomnia in international guidelines (433), since during the study period the approved in paediatrics medicinal product was not on the market, meaning that children and adolescents were using the adult product with a higher strength. This is confirmed by the analysis of diagnosis which revealed that melatonin was used in the Greek paediatric population for sleep disorders. Off-label use of hypnotics/sedatives as an ATC group in paediatrics has also been previously reported.(159,201,208)

Regarding antipsychotics, not all were approved in paediatric patients. Of those approved, such as aripiprazole or paliperidone, some were authorised only in adolescents. Several studies have previously reported the off-label use of antipsychotics in the paediatric population.(127,159,193,195,197,208,209)

The antidepressants identified as off-label were neither authorised in paediatrics, however international guidelines recommend citalopram as alternative to fluoxetine when ineffective.(358) Several previous studies reported a high off-label use of antidepressants in the paediatric population (120,126,159,193,194,198,200,201,204,205,208,209), as well as of escitalopram alone.(207)

Alprazolam is authorised only in adults with anxiety, but in the prescription-indication analysis of the Greek sample it was observed that alprazolam was administered in children and adolescents with anxiety disorders. Benzodiazepines are not recommended in paediatric patients (with the exception of those used for their antiepileptic properties like clobazam) and the off-label use in paediatric patients has been previously described.(159,193,208)

Two antiepileptics had an off-label use in our settings. Oxcarbazepine is approved in paediatric patients, but the off-label use was observed in younger children, for whom no authorisation is approved. Pregabalin is authorised only in adults, but sometimes it is used in children as adjunctive treatment in seizures even though the efficacy and safety are not established.(584) In the literature, the off-label use of antiepileptics generally reported lower rates compared to other psychotropics (206) especially in older adolescents.(193)

It is worth to mention that in our datasets, no psychostimulants were identified among the most frequent off-label active substances in both databases even when the criterion was the age, nor when the indication was analysed using the diagnosis included in the prescription in the Greek

sample. Despite psychostimulant off-label use has been previously reported, low rates have been described as compared to other psychotropics, in line with our findings.(159,196,202,208)

5.3.3.2 Off-label use due to non-authorised indications

As highlighted in the analysis per diagnosis in Greece, several active substances were used for non-approved indications in paediatrics. Concerning PDDs, valproic acid, risperidone and aripiprazole were found to be used off-label, as none of these active substances are approved for this indication. As regards valproic acid, it seems that its use is mostly related to the treatment of convulsions comorbid to PDDs (like Rett syndrome) as the studies referred to the PDD core symptoms did not have any significant positive impact. In regards to the two antipsychotics, both have authorisation in the treatment of ASD-associated irritability in the USA (216), and abundance of information was found supporting their use. Despite the authorisation of risperidone in ASD by the US FDA, an authorisation for this indication was not eventually granted in Europe, as the submitted by the MAH proposal was not accepted by the UK MHRA due to concerns on the potential misuse of the medicinal product as a form of long term chemical control of this vulnerable population.(507) In addition, this off-label use entails that patients should be kept under close monitoring due to serious potential adverse effects, which in general have been investigated for a shorter period than the longer treatment schemes in real practice.(585-587) Due to the increasing interest of antipsychotic use in young patients, an initiative had started to investigate the serious lack of information on efficacy and safety of antipsychotics in this population; yet, the project could not provide the expected and promising results at its closure back in 2015 due to significant challenges.(588) However, the existing evidence demonstrates that medications prescribed to paediatric patients with PDDs, and mostly for ASD, are somehow heterogeneous and often rely only on clinicians' experience (589), while child psychiatrists seem to admit that they do prescribe risperidone for ASD in Europe even though off-label.(590) Thus, further studies are needed, and extra caution should be paid while treating these paediatric patients with medicines under an off-label status.

Risperidone was found also as to be off-label used in patients diagnosed with ADHD in our analysis. Information supporting its use in aggression related to ADHD was retrieved from the literature, but not for treating the core symptoms of ADHD; several confounding factors included in the studies (add on treatment to stimulants, ADHD with or without comorbidities) and the limited sample size of the studies or the different endpoints, are not rendered as robust evidence for its use in ADHD. In general, antipsychotics are used off-label as a second-line treatment for stimulant-resistant ADHD or for other ADHD comorbidities (460,590), while studies also report its concomitant use with stimulants.(425)

Risperidone and quetiapine were dispensed in Greece for psychosis for which none of them have an approval in the paediatric population in Europe, as they are only indicated in adults with schizophrenia. Abundant information was retrieved for both antipsychotics including several RCTs, some of which are connected to their approval by US FDA for the treatment of schizophrenia in adolescence (217,314), while other studies have investigated the serious adverse events connected to their use. The inclusion of an indication in underaged patients with schizophrenia in Europe was not granted in 2014 for quetiapine, but the labelling was updated to include the results from the paediatric studies (451), and the safety profile with some serious events, like extrapyramidal symptoms, is described in the labelling too.(450,451) Despite the concerns related to their safety, both active substances are used off-label in Europe for this particular patient population, while long-term data on efficacy and safety are still missing along with the uncertainties on their efficacy. Thus, treating physicians should take into consideration the serious adverse events and the missing information related to the use of these two antipsychotics in children and adolescents where several comorbid disorders could be responsible for complex cases as it happens with psychosis. Questionnaires to child psychiatrists also reveal that risperidone is indeed prescribed for psychosis in Europe even though off-label (590), as well for the treatment of OCD, where this indication for risperidone was also identified in the Greek sample.

In general, paediatric patients with OCD are initially treated with non-pharmacological interventions and subsequently serotonergic agents.(294) Robust evidence on the use of risperidone in underaged patients with OCD was not found, but it seems that risperidone has some positive results as augmentation to SSRIs or in resistant cases. Of note, risperidone was also identified to induce or exacerbate OCD symptoms in children (525,591,592) on top of the well-known serious adverse events reflected in its labelling. Hence, physicians using risperidone off-label to treat children with OCD should carefully monitor their patients as more research is needed on the short- and long-term efficacy and safety of antipsychotics in this patient population. Another active substance reported that is used from specialists for the treatment of OCD in children and adolescents even though off-label was fluoxetine (590), a finding also reflected in the Greek data. This off-label use is most probably due to fluoxetine's authorisation in adults with OCD in Europe and its authorisation in paediatric patients in the USA.(302) Due to the approval by the US FDA, several studies were conducted investigating the use of fluoxetine in children and adolescents with OCD, all demonstrating some positive response. However, the sample size was not high enough and one of the studies reported no difference compared to non-pharmacologic interventions. Despite the identified evidence and the already authorised in the USA use of fluoxetine in paediatric patients with OCD, the serious adverse events reported by the use of fluoxetine in children and adolescents should be considered when prescribing this agent.

At the same time, it is necessary to monitor fluoxetine use in these patients until more data are available, including those from long-term studies and pre-school patients that are still missing.

Fluoxetine and sertraline were used as off-label in patients with anxiety in Greece, as well as alprazolam. Generally, it is preferred to treat paediatric patients with anxiety disorder using initially non-pharmacologic interventions (338) and to date findings claim that that acute positive response to anxiety treatment might reduce the risk for chronicity.(593) As previously mentioned, benzodiazepines are not approved in paediatric patients due to their potential of causing dependence, abuse and depressive episodes described as side effects. The lack of robust evidence coming from controlled RCTs, along with the side effects and the possibility of drug dependence, should concern HCPs before prescribing and dispensing alprazolam to paediatric patients. Concerning the two antidepressants identified as off-label use for patients with anxiety in the present analysis, there is no medicine approved for these indications in paediatrics despite the existing evidence suggesting that a number of SSRIs are effective for underaged patients with different types of anxiety disorders. Hence, this lack of an approved specific indication is resulting into a significant barrier to physicians that are obliged to prescribe off-label treatments which may risk patient's well-being due to the serious adverse events accompanying SSRI use which may be still unknown.(594) Since the placebo effect is high in this indication (595), large RCTs and longitudinal evidence is needed. Future studies are expected to provide further data on the treatment sequence, including non-pharmacological interventions.(596) Until new evidence is gathered, prescribers should be cautious administering antidepressants in paediatric patients as the existing evidence is not convincing, and not use them off-label as previously reported as a common practice by child psychiatrists.(590)

Finally, sertraline and escitalopram were among those active substances for which an off-label use was also identified due to their use in non-approved indication of depressive episodes in paediatric patients residing in Greece. Depression is also one of the psychiatric disorders for which the first-line treatment in paediatrics is related to non-pharmacologic interventions. Antidepressants are recommended in non-responsive to psychotherapy cases or in more severe manifestations (358), which probably could justify their use by children and adolescents.(590) However, none of the above-mentioned antidepressants are authorised in paediatrics patients with depression in Europe, while only escitalopram is authorised in depressive adolescents in the USA. Retrieved information found controversial information on their use in this patient population. In general, the safety and effectiveness of SSRIs seem not to be established yet in the paediatric population for the treatment of depression, and the maintenance of the effect is uncertain.(369) Guidelines are more prone to propose the use of fluoxetine as a safer option in

case the psychotherapy is not effective.(358) Hence, the use of other SSRIs, like sertraline or escitalopram, should be prescribed with caution to children and adolescents, taking into consideration the existing warning on increased suicidality in this vulnerable population.

In general, off-label is deemed acceptable in case of a need and provided that reasonable evidence is available to support its use. RCTs are considered the best clinical evidence, and when no adequate RCTs are available, prospective open-label studies or retrospective chart reviews may provide useful information on safety and effectiveness, especially if the number of the sample size is large. Regarding the evidence from any case reports or series where the number of participants is small, it is considered less helpful, but might provide information on characteristics of a particular patient that may be relevant for the treating physician. The prescriber therefore has to decide an off-label use based on careful assessment of the patient's history and the potential risks balanced with the anticipated benefits of the selected medicinal product. Published guidelines are helpful when they summarise existing evidence and provide supportive information on the off-label use of certain psychotropics.

Considering all the above, it seems that several psychotropics could have a place to cover certain paediatric unmet needs in psychiatry, regardless of the persisting need for close monitoring of all psychotropics when used off-label in the paediatric population.(597-599) Guidelines are of an utmost importance, since safety and effectiveness uncertainties may sometimes result into physicians rejecting, delaying or underusing potentially effective psychotropics.(600) As an example, the use of antidepressants in underaged patients is restricted by the warnings imposed by regulatory authorities despite evidence on efficacy (601), due to observed high suicidality in this population, but a huge need exist and the safety finding has recently been questioned.(369,481,602) In addition, a recent publication concerning the safety profile of antidepressants and antipsychotics reports that the risk of serious side effects between paediatric patients is not significantly different.(91) These findings highlight further the opportunity to reflect RWE data into the labelling of already authorised psychotropics as a support to prescribers, should the alignment of the labelling around the world is not feasible.(603)

The paediatric regulation, which entered into force in 2007 in Europe, provisioned the need to update the labelling of old and off patent medicines that are not approved in children and adolescents.(81) Nonetheless, no major difference was observed concerning the regulatory information on psychotropics, and the unmet needs in neuropsychiatry continue.(604,605) Therefore, there is still a regulatory need for actions that should focus on reducing the uncertainties of the off-label use in paediatric patients in need of psychotropic treatment.(83)

5.4 Recommendations for implementation and future research

There is an increased interest in paediatric neuropsychiatric disorders and there is a growing number of clinical trials investigating this direction.(606) Despite this encouraging turn the past years, we still have a huge need of appropriate and consistent regulatory information for the use of available psychotropic drugs in children and adolescents. With this presented analysis, we have shown that such use of available medicines is far from being rare, but is currently done empirically through off-label use, in the absence of the regulatory guarantees that are granted through product labelling.(607)

The present study provides an overview on the psychotropic use that highlights several situations where paediatric patients are in need of special attention. The data generated in this study could be used as a basis to start working towards an improvement of the guarantees for medicines quality, safety and efficacy concerning paediatric patients in order to reach to the same level as the existing ones for adults. Besides, reflections on other mental health strategies and policies on how to holistically address the health of children and adolescents in the respective territories can also be done based on the observed use of drugs. As an example, it seems that inequities on access to mental health specialists of remote areas in Greece, and the effects of financial crisis had an impact on Greek citizens mental health (608) and could have also affected the underaged population. Therefore, the present analysis could serve as a tool to inform healthcare systems on the need to put in place and implement strategies to ensure universal access and equity of services to the whole population, even in remote areas (609), as well as to help reduce the mental health stigma that is considered more present in rural areas.(566)

Monitoring of the data analysed in this study may be of help to follow the effects of any implemented policy or plans. The goal of any intervention should be the early identification and intervention in paediatric patients with mental health issues, which will lead to healthier adults. This is of utmost importance considering that a significant number of mental disorders have their onset in childhood.(40)

The impact that Covid-19 pandemic and the multiple lockdowns had on the psychotropic use in the paediatric population could be a study of special interest. Preliminary data indicate a worse mental health status in both regions (381,610), and the use of drugs provided by billing data is a relatively easy and quite sensitive way to monitor activity and changes of the population needs. While it took long time to obtain the data for research, for health authorities this exercise is quite a straightforward action to access

and analyse their own data for purposes of management, eliminating the strict requirements of this research.

Large studies in mental health are uncommon and especially in the paediatric population, hence RWE data on the utilisation of psychotropics are offered as a continuum to randomised evidence. RWE data from routine clinical practice seem to generate a high interest mostly coming from regulatory authorities (611), since it is considered a way to reduce the gap in the knowledge on medicines already tested in a more restricted population than the one that they are actually administered, as well as to further define health policies.(13) Moreover, policies on dispensing and monitoring of the off-label use, and of any potential adverse events, could be improved based on real world data defining the real extent of psychotropic consumption by this vulnerable patient population. Of note, it would be important to find ways to systematically ascertain any potential adverse events in children and adolescents, and especially in the off-label setting, to generate valuable information for risk/benefit assessment in these populations where the extrapolation from adults in not reliable. A future study focusing on the off-label use considering diseases and separate psychotropic groups, as well as focusing on effectiveness and safety, could be of great importance.

Despite we may consider that our methods led to underestimation of off-label uses, our data confirm that off-label use is a frequent reality in paediatric patients. This fact supports the urgent need for harmonised guidelines on how to better use psychotropic medicines and in which indications. While in many countries clinical guidelines exist on the management of mental disorders in adults, such as those existing in Greece (612), the present study could provide a starting point for Greek and Catalan experts to identify the most frequent off-label uses in their settings. This could guide the roadmap to start drafting specific guidelines to minimise any off-label use of those psychotropics with no robust evidence in paediatric patients. These guidelines could be addressed to psychiatrists and neurologists but might also help primary care physicians that were found to play an important role on treating children and adolescents with poor mental health in Greece. In Catalonia (Spain), several guidelines exist so the findings of the present study could help in updating any previous versions.(613)

Furthermore, off-label use was identified for active substances that they do have an authorisation in concerned indications in regions outside of Europe. Hence, a deep impact analysis on the psychotropic use based on the different guidelines or the labelling between these two Mediterranean regions and countries in the north or those regions outside of the European territory, could provide an interesting point of view on how

systems work in the context of a different mental disease burden as previously reported.(614)

Finally, the information described in the current study could be also of help to regulatory authorities in order to define if there is still a need to further harmonise the requests for granting an authorisation in psychiatric indications for the paediatric population.(80) In addition, data may serve to highlight the need to commercialise the already authorised paediatric formulations that are not available on the markets, and thus improving the current situation. Furthermore, our data could support actions aimed to align the incentives for pharmaceutical industry with the needs to extend the labelling of existing psychotropics, many under an off patent status, and hence to regulate current established uses and patient age groups.(615)

CONCLUSIONS

1. Dispensation data from 449,059 paediatric patients who retrieved at least one reimbursed psychotropic prescription from pharmacies in Catalonia (Spain) between 2008 and 2017, and dispensation data from 63,782 subjects with at least one psychotropic drug reimbursed from the Greek health system between March 2016 and October 2019, were obtained.
2. The prevalence of psychotropic use in the paediatric population varied between 40.8 and 64.2 per 1,000 paediatric inhabitants in Catalonia (Spain), and between 5.1 and 14.6 per 1,000 paediatric inhabitants in Greece.
3. Both in Catalonia (Spain) and Greece, two thirds of the dispensations were due to short-term use of hydroxyzine. Subjects with no other psychotropic prescriptions than hydroxyzine were removed from the main analysis. Thereinafter, the prevalence of use ranged from 26.4 and 32.2 per 1,000 paediatric inhabitants in Catalonia (Spain) and from 3.1 to 6.5 per 1,000 paediatric inhabitants in Greece.
4. The prevalence of use of psychotropic medicines in children and adolescents was higher with the increasing age of the patients.
5. Boys were more exposed than girls to psychotropic drugs in both regions.
6. Psychostimulants, mainly methylphenidate, were the most frequently used ATC group in Catalonia (Spain), while in Greece antiepileptics were the most frequently used ATC group.
7. Information on diagnosis linked to prescriptions was available only for Greece, and the analysis showed that most patients exposed to psychotropic medicines had a diagnosis of epilepsy, paralleling the high use of antiepileptics in this country.
8. In Greece, paediatricians were responsible for more than 40% of the dispensed psychotropics, whereas neurologists, child psychiatrists, psychiatrists, and neurologists-psychiatrists together prescribed one third of the dispensed psychotropics. Most prescriptions of antipsychotics were issued by child psychiatrists.
9. A significant amount of the dispensed psychotropics was used outside the approved conditions: 12% and 14% of paediatric subjects in Catalonia (Spain) and Greece respectively had received at least one medicine that had no paediatric information in the product labelling.
10. Of all dispensed psychotropic medicines, 5.5% of those in Greece and 4.6% in Catalonia (Spain) had no paediatric information in their labelling, while 7.6% and 7.5% of them were dispensed in a non-authorised age range respectively. The rates of off-label use in

the current study found to be lower compared to other countries and are likely underestimated.

11. The prescribing and reimbursement systems of Catalonia (Spain) and Greece have several similarities but differences too, as well as their established policies for the off-label use which could partially explain the differences in the observed rates.
12. Aripiprazole in Catalonia (Spain) and quetiapine in Greece were the most frequently dispensed off-label psychotropics in 2017; this observation is consistent with a reported high off-label use of antipsychotics in the literature.
13. The prescription-indication analysis was feasible only with Greek data, and showed that antipsychotics and mainly risperidone, followed by antidepressants and mainly fluoxetine, were used for indications that did not have an authorisation at all, or were not authorised in paediatric patients specifically.
14. There is some available evidence supporting the observed off-label uses, but long-term studies are lacking.

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ANNEX I

a. Protocol for the systematic review on the prevalence of psychotropic drug use in the paediatric population worldwide

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Psychopharmacological treatment in paediatric populations across countries: a systematic review and meta-analysis

Citation

Ximena Goldberg, Marc Fradera, Stella Pesiou, Caridad Pontes, Narcís Cardoner, Ferrán Torres. Psychopharmacological treatment in paediatric populations across countries: a systematic review and meta-analysis. PROSPERO 2019 CRD42019128648 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019128648

Review question

To investigate current prevalence of use of psychoactive drugs in paediatric patients relative to country characteristics.

Searches

We will systematically search Web of Science (including MEDLINE) and Scopus since inception to December 31st, 2018. Only articles published in English language will be included.

Types of study to be included

Reports of nationwide prescription datasets or representative databases that cover over at least 5% of the population.

Condition or domain being studied

Rates of psycopharmacological treatment of young people aged 0 to 17 years across countries, time-related changes and potential off-label use.

Participants/population

The populations of reference are children and adolescents ages 0 to 17 years (both included).

Intervention(s), exposure(s)

Estimates of prevalence and incidence of psycopharmacological treatment of young people aged 0 to 17 years based on population-wide datasets

Comparator(s)/control

Group comparisons will be performed across countries and time points.

Main outcome(s)

Prevalence and incidence rates of the use of psychoactive drugs in paediatric populations globally, including (but not limited to) antidepressants, antipsychotics and sedatives.

Additional outcome(s)

Not applicable

Data extraction (selection and coding)

Data extraction will be done independently by at least two investigators. Any discrepancies will be resolved in consensus meetings.

From each individual study included in the eligible systematic reviews or meta-analysis, we will record several variables: study design, type of dataset, year of publication, type of psychoactive drugs, time frame, age of subjects, clusters, point prevalence and incidence.

Risk of bias (quality) assessment

The Hoy score tool will be used to assess the individual studies' quality. Two researchers will be involved and discrepancies will be resolved by a third researcher or consensus meetings. Agreement at each round for the quality of the selected articles between authors will be assessed by calculating the Kendall or Kappa coefficients, for the ordinal scores and the binary assessment, respectively.

Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65: 934-939.

Strategy for data synthesis

We will follow the recommendations given in the PRISMA guidelines. To provide a meaningful summary of prevalence/incidence across each age strata (and gender), meta-analysis will be considered only when the following conditions there is sufficient quantity of data and the included studies are sufficiently homogeneous. The heterogeneity of pooled prevalence/incidence estimates will be assessed using the I^2 (I^2) statistic (Der Simonian-Laird). Results will be pooled using random effects methods where statistical heterogeneity is moderate or high (I^2> 50%). When applicable and where meta-analysis is not appropriate, a narrative summary of findings will be performed.

Prevalence/Incidence from individual studies will be analysed to compute individual and pooled estimates and their 95% confidence intervals (95% CI) using the random-effects DerSimonian & Laird method. The decision on the use of random-effects models is based on a more conservative estimation in comparison to fixed-effects models. Between-studies heterogeneity will be evaluated by means of I^2 and the relation between the estimation of effects and their accuracy by means of funnel plots, using the standard error as estimation of accuracy. Values of I^2 of around 25%, 50% and 75% can be considered, respectively as: low, moderate and high levels of heterogeneity. A χ^2 test will be calculated to evaluate the statistical significance of the heterogeneity. A random-effects meta-regression is pre-planned on the baseline common covariates in cases with I^2 <50%, associated to statistical significance.

All statistical analyses will be conducted using the STATA software or equivalent validated software tool, and the level of significance is established at the standard two-sided 5% level, except for the heterogeneity testing where a two-sided 10% level is predefined.

Analysis of subgroups or subsets

Where statistical heterogeneity is high (I^2> 75%) this may suggest important differences between the included studies. It is not possible to state at this stage what could be the contributing factors to heterogeneity. However, we will collect study level information and check whether stratifying by one of the covariates may help to reduce unexplained variability. Meta-regression may also be used to examine the impact of such variables upon reported estimates size. If, following efforts to find the source of heterogeneity, statistical heterogeneity remains high, meta-analysis will not be attempted.

In any case, given the study objectives, we will conduct the analysis according to age-ranges (0-5, 6-11, 12-17), gender,

and type of psychoactive drug prescribed (antidepressants, antipsychotics and sedatives)

Contact details for further information

Ximena Goldberg

xlgoldberg@tauli.cat

Organisational affiliation of the review

Parc Taulí University Hospital

www.tauli.cat/tauli

Review team members and their organisational affiliations

Dr Ximena Goldberg. Parc Taulí University Hospital

Mr Marc Fradera. Parc Taulí University Hospital

Ms Stella Pesiou. Universitat Autònoma de Barcelona

Dr Caridad Pontes. Department of Pharmacology, Therapeutics and Toxicology. Universitat Autònoma de Barcelona

Dr Narcís Cardoner. Corporació Sanitària Parc Taulí

Dr Ferrán Torres. Biostatistics Unit. Faculty of Medicine. Universitat Autònoma de Barcelona

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

01 April 2019

Anticipated completion date

30 August 2019

Funding sources/sponsors

This team is involved in a project funded by the Generalitat de Catalunya (grant number SLT006/17/216, period: 2018-2019, PI: Dr. Ximena Goldberg), which main objective is to map the use of psychoactive drugs in the paediatric population in Catalonia. The systematic review of similar projects and their results is a key step and therefore completely funded by our project

Conflicts of interest

None known

Language

English

Country

Spain

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Child; Environment; Humans; Prevalence; Psychopharmacology

Date of registration in PROSPERO

15 April 2019

Date of first submission

18 March 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

15 April 2019

b. Search strategy for the systematic review of off-label psychotropics in the paediatric population

'psychotropic agent'/exp OR 'psychoactive agent' OR 'psychoactive drug' OR 'psychodynamic agent' OR 'psychopharmaceutic agent' OR 'psychopharmacon' OR 'psychotropic' OR 'psychotropic agent' OR 'psychotropic drug' OR 'psychotropic drugs' OR 'psychotropic treatment' OR 'psychotropics' OR 'anticonvulsive agent'/exp OR 'agent, anticonvulsive' OR 'anti convulsant agent' OR 'anti epileptic agent' OR 'anti epileptic drug' OR 'anticonvulsant' OR 'anticonvulsant agent' OR 'anticonvulsant drug' OR 'anticonvulsants' OR 'anticonvulsive agent' OR 'anticonvulsive drug' OR 'anticonvulsivum' OR 'antiepileptic agent' OR 'antiepileptic barbiturate' OR 'antiepileptic drug' OR 'antiepileptiform drug' OR 'antidepressant agent'/exp OR 'anti depressant agent' OR 'antidepressant' OR 'antidepressant agent' OR 'antidepressant drug' OR 'antidepressants' OR 'antidepressants, miscellaneous' OR 'antidepression drug' OR 'antidepressive agent' OR 'antidepressive agents' OR 'antidepressive agents, second generation' OR 'antidepressive agents, second-generation' OR 'antidepressive drug' OR 'neurothymoleptic agent' OR 'psychoenergizer' OR 'thymoleptic' OR 'thymoleptic agent' OR 'thymoleptic drug' OR 'thymolytic agent' OR 'neuroleptic agent'/exp OR 'antipsychotic agent' OR 'antipsychotic agents' OR 'antipsychotic agents, butyrophenone' OR 'antipsychotic agents, phenothiazine' OR 'antipsychotic drug' OR 'antipsychotics' OR 'butyrophenone tranquilizers' OR 'classical antipsychotic' OR 'classical antipsychotic agent' OR 'classical antipsychotic drug' OR 'long acting neuroleptic' OR 'major tranquilizer' OR 'major tranquillizer' OR 'neuroleptic' OR 'neuroleptic agent' OR 'neuroleptic drug' OR 'neurolepticum' OR 'phenothiazine tranquilizers' OR 'tranquilizer, major' OR 'tranquilizing agents, major' OR 'typical antipsychotic' OR 'typical antipsychotic agent' OR 'typical antipsychotic drug' OR 'typical neuroleptic' OR 'typical neuroleptic agent' OR 'typical neuroleptic drug' OR 'anxiolytic agent'/exp OR 'anti anxiety agents' OR 'anti anxiety agents, benzodiazepine' OR 'anti-anxiety agents' OR 'anti-anxiety agents, benzodiazepine' OR 'antianxiety agent' OR 'anxiolytic' OR 'anxiolytic agent' OR 'anxiolytic drug' OR 'anxiolytics' OR 'ataractic agent' OR 'ataractic drug' OR 'benzodiazepine tranquilizers' OR 'medium tranquilizer' OR 'minor tranquilizer' OR 'minor tranquilizing agent' OR 'minor tranquillizer' OR 'tranquilizer, minor' OR 'tranquilizing agents, minor' OR 'hypnotic sedative agent'/exp OR 'hypnosedative agent' OR 'hypnotic sedative' OR 'hypnotic sedative agent' OR 'hypnotics and sedatives' OR 'sedative hypnotic agent' OR 'sedatives/hypnotics' OR 'psychostimulant agent'/exp OR 'psychostimulant' OR 'psychostimulant agent' OR 'psychostimulating agent' OR 'attention deficit hyperactivity disorder'/exp OR 'adhd' OR 'attention deficit' OR 'attention deficit and disruptive behavior disorders' OR 'attention deficit and disruptive behaviour disorders' OR 'attention deficit disorder' OR 'attention deficit disorder with hyperactivity' OR 'attention deficit hyperactivity disorder' OR 'drugs used in the treatment of addiction'/exp OR 'alcohol deterrents' OR 'antialcoholics' OR 'drugs used in the treatment of addiction'.

c. Supplementary Tables

Table 96. Summary of previous studies reporting paediatric use of psychotropics.

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
Wesselhoeft et al.	2020	DK	Danish National Prescription Registry	2007-2017	Antidepressants	5-19 years	7.52 (2017) - 12.86 (2010) per 1,000	Age, sex, year & medicine
		NO	Norwegian Prescription Database (NorPD)				5.08 (2007) - 7.60 (2017) per 1,000	
		SE	Swedish Prescribed Drug Register				8.98 (2007) - 18.03 (2017) per 1,000	
Lagerberg et al.	2019	SE	Swedish Prescribed Drug Register	2006-2013	Antidepressants	0-24 years (subgroups)	1.40% (2006-2007) - 2.10% (2013) 0-11 years: ♂: 0.04% (2007-8) - 0.08% (2012-2013) ♀: 0.02% (2006-2009) - 0.04% (2012-2013) 12-17 years: ♂: 0.60% (2006) - 1.30% (2013) ♀: 0.70% (2006) - 2.10% (2013)	Age, sex & year
Kloosterboer et al.	2018	NL	Inter-Action Database (drugs dispensed by pharmacies in north & east)	2005-2015	Antipsychotics	0-19 years	7.2 (2005) - 9.8 (2009) per 1,000	Age, sex, year & medicine
Karlsson et al.	2018	SE	Swedish Prescribed Drug Register	2007-2014	Antiepileptics	0-17 years (subgroups)	0-17 years: 22,262 subjects 0-5 years: 2.22 per 1,000 12-17 years: 6.35 per 1,000	Age & year
Raman et al.	2018	AU	Australian Pharmaceutical Benefits Scheme (PBS)	2009-2014	ADHD medicines	3-18 years	1.39% (2009) - 1.74% (2014)	Age (data in figures)
		CA	Quebec Pregnancy Cohort	2001-2009			0.02% (2001) - 1.76% (2009)	
		CN	Hong Kong Clinical Data Analysis and Reporting System	2001-2015			0.04% (2001) - 1.45% (2015)	
		DK	Danish National Prescription Registry	2001-2013			0.15% (2001) - 1.52% (2013)	
		FI	Finnish Prescription Register	2005-2012			0.20% (2005) - 1.01% (2012)	
		FR	French National Health Insurance	2006-2014			0.19% (2006) - 0.39% (2014)	
		IS	Icelandic Medicines Registry	2003-2013			2.46% (2003) - 4.99% (2013)	
		JP	Japan Medical Data Center Database	2010-2015			0.29% (2010) - 0.65% (2014)	
		NO	Norwegian Prescription Database (NorPD)	2004-2013			0.97% (2004) - 1.77% (2010, 2012-2013)	

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
		ES	Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP)	2001-2014			0.19% (2001) - 1.93% (2014)	
		SE	Swedish Prescribed Drug Register	2006-2013			0.60% (2006) - 2.30% (2013)	
		TW	Taiwan National Health Insurance Research Database	2002-2010			0.31% (2002) - 1.54% (2010)	
		UK	The Health Improvement Network (THIN)	2001-2014			0.30% (2001) - 0.64% (2014)	
		USA	Truven Marketscan (private) Medicaid analytic extract (public)	2001-2014 2001-2010			3.87% (2001) - 5.67% (2013) 4.64% (2001) - 6.69% (2010)	
Montastruc et al.	2018	FR	Echantillon Généraliste de Bénéficiaires (EGB)	2007-2013	Antipsychotics	< 16 years	1.8% (2007) - 2.5% (2013)	Medicine
Revet et al.	2018	FR	Echantillon Généraliste de Bénéficiaires (EGB)	2009-2016	Antidepressants	6-17 years	0.50% (2011-2012) - 0.53% (2010, 2015-2016)	Age, sex, year & medicine
Hálfdánarson et al.	2017	AU	Australian Pharmaceutical Benefits Scheme (PBS)	2006-2014	Antipsychotics	0-19 years	3.8 per 1,000 (2014)	Age, sex, year & medicines
		CO	Two health insurance funds of the National Health Insurance System	2006-2014			1.3 per 1,000 (2014)	
		DK	Danish National Prescription Registry	2005-2014			4.0 per 1,000 (2014)	
		FI	Finnish Prescription Registry	2005-2014			8.0 per 1,000 (2014)	
		FR	French insurance healthcare system	2006-2014			3.8 per 1,000 (2014)	
		DE	BARMEK GEK	2005-2014			3.4 per 1,000 (2014)	
		IS	Icelandic Medicines Registry	2005-2014			13.1 per 1,000 (2014)	
		JP	Kraft Inc, AIN HOLDINGS INC, Sogo Medical Inc	2009-2014			3.2 per 1,000 (2014)	
		LT	National Health Insurance Fund database	2005-2014			0.5 per 1,000 (2014)	
		NL	Inter-Action Database (drugs dispensed by pharmacies in north & east)	2005-2014			8.9 per 1,000 (2014)	
		NZ	Pharms database	2005-2014			5.0 per 1,000 (2014)	
		NO	Norwegian Prescription Database (NorPD)	2005-2014			2.7 per 1,000 (2014)	

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
		ES	*CatSalut*	2011-2014			6.6 per 1,000 (2014)	
		SE	Swedish Prescribed Drug Register	2006-2014			2.5 per 1,000 (2014)	
		TW	National Health Insurance Research Database (NHIRD-TW)	2005-2013			30.8 per 1,000 (2013)	
		USA	United Health Database (private) Medicaid analytic extract (public)	2005-2014 2005-2010			7.3 per 1,000 (2014) 20.5 per 1,000 (2010)	
Furu et al.	2017	DK	Nationwide prescription databases	2008-2012	ADHD medicines	13-17 years	1 per 1,000	Age, sex & year
		FI					0.5 per 1,000	
		IS					3.3 per 1,000	
		NO					1.4 per 1,000	
		SE					1.2 per 1,000	
Bachmann et al.	2017	DK	Danish National Prescription Registry	2005-2012	ADHD medicines	0-19 years	0.4% (2005) - 1.5% (2012)	Age, sex & year
		DE	BARMER GEK				1.3% (2005) - 2.2% (2012)	
		NL	Inter-Action Database (drugs dispensed by pharmacies in north & east)				1.8% (2005) - 3.9% (2012)	
		UK	The Health Improvement Network (THIN)				0.3% (2005) - 0.5% (2012)	
		USA	Children's Health Insurance Program (CHIP), mid-Atlantic state	2006-2012			3.3% (2005) - 3.7% (2012)	
Hoshen et al.	2016	IL	Clalit Health Services	2006-2011	Psychostimulants	6-17 years	2.6% - 4.9%	Age
Hartz et al.	2016	NO	Norwegian Prescription Database (NorPD)	2004-2013	Antidepressants	13-17 years	5.66 - 9.1 per 1,000	Age, sex & year
Hartz et al.	2016	NO	Norwegian Prescription Database (NorPD)	2004-2013	Psychotropics Antidepressants Antipsychotics	0-17 years (subgroups)	♂: 30.6 (2004) - 37.0 (2010) per 1,000 ♀: 19.0 (2005) - 25.0 (2014) per 1,000 ♂: 1.7 (2005-2006) - 2.2 (2010-2012) per 1,000 ♀: 2.4 (2006) - 10 (2014) per 1,000 ♂: 1.6 (2004) - 2.4 (2011) per 1,000	Sex: age & year

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
					Anxiolytics Hypnotics/sedatives Stimulants		♀: 1.1 (2004-2010) - 1.6 (2014) per 1,000 ♂: 3.9 (2014) - 4.9 (2006-2007) per 1,000 ♀: 3.9 (2014) - 4.7 (2005-2007) per 1,000 ♂: 4.2 (2004) - 10.8 (2014) per 1,000 ♀: 2.6 (2004) - 8.8 (2014) per 1,000 ♂: 15.0 (2004) – 21.0 (2010) per 1,000 ♀: 3.8 (2004) - 8.5 (2014) per 1,000	
Schröder et al.	2016	DE	German Pharmacoepidemiological Research Database (GePaRD)	2004-2011	Antidepressants	0-17 years	1.65 (2005) - 2.13 (2011) per 1,000	Age, sex, year & medicines
Schröder et al.	2016	DE	German Pharmacoepidemiological Research Database (GePaRD)	2004-2011	Antipsychotics	0-17 years	2.03 (2006) - 2.61 (2011) per 1,000	Age, sex, year & medicines
Nesvåg et al.	2016	NO	Norwegian Prescription Database (NorPD)	2010	Antipsychotics	0-18 years	0.18%	Age, sex & medicines
Linnet et al.	2016	IS	Primary Health Care of the Capital Area	2009-2012	Hypnotics/Anxiolytics	<1-19 years	1.40%	Sex
Bachmann et al.	2016	DK	Danish Registry of Medicinal Products Statistics (RMPS)	2005-2012	Antidepressants	0-19 years	0.61% (2005) - 1.09% (2010)	Age, sex & year
		DE	BARMER GEK				0.31% (2006) - 0.48% (2011-2012)	
		NL	Inter-Action Database (drugs dispensed by pharmacies in north & east)				0.48% (2006-2007, 2009) - 0.60% (2012)	
		UK	The Health Improvement Network (THIN)				0.66% (2006) - 1.05% (2012)	
		USA	Children's Health Insurance Program (CHIP), mid-Atlantic state				1.26% (2006) - 1.58% (2012)	
Piovani et al.	2015	IT	Regional databases (administrative and reimbursement); north (71.2%), centre (49.9%), south (36.5%)	2006-2011	Psychotropics ADHD medicines Antidepressants Antipsychotics	0-<18 years	1.70% (2010) - 1.81% (2009) 0.01% (2006) - 0.19% (2011) 1.02% (2011) - 1.26% (2006) 0.60% (2006) - 0.69% (2011)	Year, medicine & region
Kovess et al.	2015	FR	Echantillon Généraliste de Bénéficiaires (EGB)	2010	Psychotropics Antidepressants Antipsychotics Anxiolytics Hypnotics	0-17 years	2.50% 0.30% 0.30% 1.92% 0.08%	Age, sex & medicine

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
					Hypnotics/Anxiolytics Stimulants		2.00% 0.20%	
Olfson et al.	2015	USA	Medical Expenditure Panel Surveys (MEPS)	1996/1998 2003/2005 2010/2012	Psychotropic Antidepressants Antipsychotics Anxiolytics or sedatives Stimulants	6-17 years	5.5% (1996/1998) - 8.9% (2010/2012) 1.5% (1996/1998) - 2.6% (2010/2012) 0.2% (1996/1998) - 1.2% (2010/2012) 0.3% (1996/1998) - 0.5% (2010/2012) 4.0% (1996/1998) - 6.6% (2010/2012)	Age, sex, year, disorder & medicine
Olfson et al.	2015	USA	IMS LifeLink LRx Longitudinal Prescription	2006, 2008 and 2010	Antipsychotics	1-18 years (subgroups)	1-6 years: 0.11% (2006) - 0.16% (2008) 7-12 years: 0.8% (2010) -0.87% (2008) 13-18 years: 1.1% (2006) -1.19% (2010)	Age, sex & year
O'Sullivan et al.	2015	IE	Irish Health Service Executive (HSE)	2002-2010	Antidepressants	0-15 years	2.61 (2008) - 4.74 (2002) per 1,000	Year & medicine
Verdoux et al.	2015	FR	Echantillon Généraliste des Bénéficiaires (EGB)	2006-2013	Antipsychotics	0-25 years (subgroups)	0-25 years: 4.55 (2008) - 4.94 (2009) per 1,000 0-5 years: 0.27 (2010) - 0.5 (2006) per 1,000 6-10 years: 1.77 (2007) - 2.59 (2013) per 1,000 11-15 years: 3.49 (2006) - 5 (2011) per 1,000 6-20 years: 6.72 (2006) - 8.04 (2013) per 1,000	Age, sex, year & medicine
Boland et al.	2015	IE	Irish General Medical Services (GMS) scheme pharmacy claims database	2002-2011	Psychostimulants	0-15 years	3,77 (2002) - 8,63 (2011) per 1,000	-
Hoffmann et al.	2014	DE	BARMER GEK	2005-2012	Antidepressants	0-19 years	0.31% (2006) - 0.48% (2011-2012)	Age, sex & year
Zhong et al.	2014	USA	Rochester Epidemiology Project (REP) medical records-linkage system Olmsted County, MN	2005-2011	Antidepressants	0-18 years (subgroups)	0-4 years: 1 (2009) - 5 (2010-11) subjects 5-13 years: 1% (2007, 2011) - 1.2% (2008) 13-18 years: 5.7% (2005-06) - 7.5% (2011)	Age, sex & year
Bachmann et al.	2014	DE	BARMEK GEK	2005-2012	Antipsychotics	0-19 years	0,21% (2006) - 0,32% (2012)	Age, sex, year, region & medicine
Prosser et al.	2014	AU	Pharmaceutical Drugs of Addiction System, New South Wales	1990-2010	Psychostimulants	5-17 years	1.24% (2010)	-

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
Meng et al.	2014	CA	Saskatchewan Ministry of Health	1983-2007 (9 triennial year)	Antidepressants	0-19 years	5.1 (1989) - 15.4 (2007) per 1,000	-
Dörks et al.	2013	DE	German Pharmacoepidemiological Research Database (GePaRD)	2004-2006	Antidepressants	0-17 years	1,57 (2005) - 1,84 (2004) per 1,000	Age, sex, year & medicine
Ronsley et al.	2013	CA	PharmaNet database and British Columbia Ministry of Health administrative data	1996/1997-2010/2011	Antipsychotics	0-18 years	1.66 (1996/1997) - 6.37 (2010/2011) per 1,000	Age, year & medicine
Brault et al.	2012	CA	National Longitudinal Survey on Children and Youth (NLSCY)	1994/1995 2000/2001 2006/2007	ADHD medicines	3-9 years	1,3% (1994/1995) - 2,1% (2006/2007)	Age, sex & year
Zuvekas et al.	2012	USA	Medical Expenditure Panel Surveys (MEPS)	1996-2008	Stimulants	0-18 years	2.4% (1996) - 3.5% (2008)	Age, sex & year
Pottegård et al.	2012	DK	Registry of Medicinal Product Statistics (RMPS)	1995-2011*	Psychostimulants, agents used for ADHD and nootropics	0-17 years	0.87 (1999) - 14.25 (2018) per 1,000	Year & medicine
Hartz et al.	2012	NO	Norwegian Prescription Database (NorPD)	2004-2011	Hypnotics and sedatives	0-17 years	8.94 (2004) - 12.32 (2011) per 1,000	Age, year & medicine
Alessi-Severini et al.	2012	CA	Manitoba Population Health Research Data Repository	1999-2008	Antipsychotics	0-18 years (subgroups)	♂: 2,5 (1999) - 10,2 (2008) per 1,000 ♀: 1,4 (1999) - 4,5 (2008) per 1,000	Sex & year
Wijlaars et al.	2012	UK	The Health Improvement Network (THIN)	1995-2009	Antidepressants	0-17 years	2.8 (1995) - 4.5 (2009) per 1,000	Medicine & year
Steffenak et al.	2012	NO	Norwegian Prescription Database (NorPD)	2006-2010	Psychotropics Antidepressants Anxiolytics Hypnotics	15-16 years (subgroups)	2,130 (2006) - 2,949 (2010) subjects ♂: 13.9 (2006) - 21.5 (2010) per 1,000 ♀: 19.7 (2006) - 24.7 (2010) per 1,000 769 (2006) - 903 (2010) subjects ♂: 4.3 (2006) - 5.2 (2010) per 1,000 ♀: 7.8 (2006) - 9 (2010) per 1,000 360 (2010) - 384 (2006) subjects ♂: 2.3 (all period) per 1,000 ♀: 3.4 (2010) - 3.7 (2006,2008) per 1,000 1,338 (2006) - 2,221 (2010) subjects ♂: 9.3 (2006) - 17.3 (2010) per 1,000 ♀: 11.7 (2006) - 17.4 (2010) per 1,000	Sex & year

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
Zoëga et al.	2011	DK	Nationwide prescription databases	2007	ADHD medicines	7-15 years	9.30 per 1,000	Age, sex & year
		FI					6.43 per 1,000	
		IS					47.03 per 1,000	
		NO					18.10 per 1,000	
		SE					9.58 per 1,000	
Hodgkins et al.	2011	NL	PHARMO medical record linkage system	2000-2007	ADHD medicines	6-17 years	110 (2000) - 210 (2007) per 10,000	Age, sex & year
Serna et al.	2010	ES	Spanish National Health System in the Health Region of Lleida (Catalonia)	2002-2007	Antidepressants	<24 years (subgroups)	0-14 years: 2.32% (2006) - 2.74% (2004) 15-24 years: 0.31% (2007) - 0.42% (2004)	Age & year
Foulon et al.	2010	FI	Social Insurance Institution of Finland (Kela) (all residents)	1998-2005	Antidepressants	≤19 years	2,23 (1998) - 5,93 (2005) per 1,000	-
Olfson et al.	2009	USA	Medical Expenditure Panel Surveys (MEPS)	1996, 2005	Antidepressants	6-17 years	1.44% (1996) 2.56% (2005)	-
Zoëga et al.	2009	IS	Icelandic Medicines Registry	2003-2007	Psychotropics Antidepressants Antipsychotics Anxiolytics Hypnotics & sedatives Stimulants & atomoxetine	0-17 years	46 (2003) - 48.7 (2007) per 1,000 23.4 (2007) - 28.3 (2003) per 1,000 8.7 (2003) - 10.6 (2007) per 1,000 1.5 (2005) - 2 (2006) per 1,000 0.7 (2006) - 2.6 (2007) per 1,000 21.7 (2003) - 28.4 (2007) per 1,000	Sex, year & medicine
Hsia et al.	2009	UK	General Practice Research Database (GPRD)	1992-2001	ADHD medicines	0-18 years (subgroups)	0-2 years: 0.01 (1992) per 1,000 3-5 years: 0.02(1995) - 0.22 (1998) per 1,000 6-9 years: 0.06 (1992) - 2.78 (2001) per 1,000 10-12 years: 0.06 (1992) - 6.14 (2001) per 1,000 13-15 years: 0.03 (1992) - 4.69 (2001) per 1,000 16-18 years: 0.008 (1992) - 1.65 (2001) per 1,000	Age, year & medicine (subjects' number)
					Antiepileptics		0-2 years: 2.74 (1999) - 4.41 (1992) per 1,000 3-5 years: 3.47 (1995) - 4.31 (2001) per 1,000 6-9 years: 3.71 (1995) - 5.26 (2001) per	

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
							1,000 10-12 years: 4.46 (1995) - 6.14 (2001) per 1,000 13-15 years: 5.13 (1995) - 7.34 (2001) per 1,000 16-18 years: 0.008 (1992) - 1.65 (2001) per 1,000	
					Antidepressants		0-2 years: 0.07 (1998) - 0.23 (1999) per 1,000 3-5 years: 0.32 (1999) – 1.1 (1992) per 1,000 6-9 years: 2.12 (2001) - 4.72 (1992) per 1,000 10-12 years: 2.12 (2001) - 4.15 (1992) per 1,000 13-15 years: 3.65 (1995) - 6.13 (2001) per 1,000 16-18 years: 8.52 (1992) - 23.9 (2001) per 1,000	
					Antipsychotics		0-2 years: 0.07 (1998) - 0.12 (1995) 3-5 years: 0.07 (1992, 1995, 1998) - 0.12 (1999) per 1,000 6-9 years: 0.15 (1992, 1999) - 0.24 (1998) per 1,000 10-12 years: 0.27 (1995) - 0.53 (1999, 2001) per 1,000 13-15 years: 0.54 (1995) - 0.91 (1999) per 1,000 16-18 years: 2.07 (1995) - 3.15 (2001) per 1,000	
					Hypnotics/Anxiolytics		0-2 years: 2.05 (1999) - 3.92 (1992) per 1,000 3-5 years: 1.14 (1999) - 1.89 (1992) per 1,000 6-9 years: 0.85 (1999) - 1.4 (2001) per 1,000 10-12 years: 0.97 (1992) - 1.37 (2001) per 1,000 13-15 years: 1.71 (1992) - 2.95 (2001) per 1,000 16-18 years: 5.17 (1992) - 8.33 (2001)	

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
							per 1,000	
Kalverdijk et al.	2008	NL	Inter-Action Database (drugs dispensed by pharmacies in north & east)	1997-2005	Antipsychotics	0-19 years	3.0 (1997) - 6.8 (2005) per 1,000	Age, year & medicine
Rani et al.	2008	UK	General Practice Research Database (GPRD)	1992-2005	Antipsychotics	0-18 years	0.39 (1992) - 0.77 (2005) per 1,000	Age, year & medicine
Zito et al.	2008	DE	GEK	2000	Psychotropics Anticonvulsants/mood stabilizers Antipsychotics Antidepressants Anxiolytics Hypnotics Stimulants	0-19 years	2.00% 0.38% 0.34% 0.71% 0.41% 0.09% 0.17%	Age, sex, year & medicine
		NL	Inter-Action Database (drugs dispensed by pharmacies in north & east)		Psychotropics Anticonvulsants/mood stabilizers Antipsychotics Antidepressants Anxiolytics Hypnotics Stimulants		2,94% 0,37% 0,51% 0,53% 0,73% 0,33% 1,18%	
		USA	state-Children's Health Insurance Program (s-CHIP), mid-Atlantic state		Psychotropics Anticonvulsants/mood stabilizers Antipsychotics Antidepressants Anxiolytics Hypnotics Stimulants		6,66% 0,77% 0,76% 2,71% 0,49% 0,16% 4,29%	
Zito et al.	2007	USA	7 state Medicaid programs	2001	Psychotropics Anticonvulsants Antipsychotics Antidepressants Anxiolytics/sedatives/ hypnotics Stimulants	2-4 years	2.3% 0.3% 0.4% 0.5% 0.3% 1.5%	Age, sex & medicine
Van de Vrie-Hoekstra et al.	2008	NL	Inter-Action Database (drugs dispensed by pharmacies in north & east)	1997-2005	Antiepileptics	0-19 years	4 per 1,000	Age, year & medicine

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
Raymond et al.	2007	CA	British Columbia PharmaNet system	1996-2004	Antidepressants	0-19 years	4.5 (1995) - 10.7 (2003) per 1,000	Year
Ackers et al.	2007	UK	General Practice Research Database (GPRD)	1993-2005	Antiepileptics	0-18 years	7,30 (1993) - 8,69 (2005) per 1,000	Year & medicine
Ufer et al.	2007	DE	AOK, Baden-Wuerttemberg	2000-2001	Antidepressants	0-19 years (subgroups)	4,178/898,964 subjects ♂: 0.35% ♀: 0.59%	Sex
Volkers et al.	2007	NL	Netherlands Information Network of General Practice (LINH)	2001, 2005	Antidepressants	0-17 years	2.3 per 1,000 (2001) 2.0 per 1,000 (2005)	Age, year & medicine
Mancini et al.	2006	FR	French General Health Insurance System (FGHIS), Bouches du Rhone (southern France)	2002	Antidepressants Anxiolytics Hypnotics	13-17 years	7.7 per 1,000 4.5 per 1,000 20.1 per 1,000	Age, sex & medicine
Zito et al.	2006	USA	Medicaid analytic extract, mid-Atlantic	2000	Anticonvulsants	<18 years	2%	Age & medicines with diagnosis
Vitiello et al.	2006	USA	Medical Expenditure Panel Survey (MEPS)	1997-2002	Antidepressants	0-18 years	1.1% (1998-1999) - 1.8% (2001-2002)	Age, sex & medicine
Fegert et al.	2006	DE	GEK	2000-2003	Antidepressants	0-19 years	3.37 (2001) - 3.74 (2003) per 1,000	Age, year & medicine
Vinker et al.	2006	IL	Central district of Clalit Health Maintenance Organisation (HMO)	1998-2004	Methylphenidate (the only registered stimulant)	0-18 years	0.7% (1998) - 2.5% (2004)	Age, sex & year
Patel et al.	2005	USA	3 Medicaid (midwestern, southern western) 1 private managed care organizations (MCOs in northeast and Pacific northwest)	1996-2001	Antipsychotics	0-19 years	1.5 (1996 in Private) - 15.5 (2001 in Public-Southern) per 1,000	Age, sex, year, database & medicine
Habel et al.	2005	USA	Northern California Kaiser Permanente Medical Care Program	1996-2000	Stimulants	2-18 years	1.86% (1996) - 1.93% (2000)	Age & year
Hunkeler et al.	2005	USA	Northern California Kaiser Permanente Medical Care Program	1994-2003	Antidepressants Anticonvulsants	5-17 years	9.68 (1994) - 21.30 (2003) per 1,000 3.52 (1994) - 6.96 (2003) per 1,000	Age, year & medicine
Faber et al.	2005	NL	Inter-Action Database (drugs dispensed by pharmacies in north)	1998-2002	Psychostimulants	0-19 years	0.6% (1998) - 1.2% (2002)	Age, year & co-medication
Safer et al.	2004	USA	State Children's Health Insurance Program (sCHIP) and private insurance datasets, mid-Atlantic State	1998-2000	Psychotropics Stimulants	0-17 years 1-17 years	<u>0-17 years (in 2000)</u> 3.5% (private) 4.5% (public) <u>1-17 years</u> 4.3% (private in 1998) 5.3% (public in 1999) 2.2% (private)	Age, year & insurance

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
							3.1% (public)	
Delate et al.	2004	USA	random sample of Express Scripts, Inc (ESI) database, children from all 50 states and the District of Columbia	1998-2002	Antidepressants	0-18 years	1.59% (1998) - 2.37% (2002)	Age, sex, year & medicine
Cox et al.	2003	USA	random sample of Express Scripts, Inc (ESI) database, children from all 50 states and the District of Columbia	1999	Stimulants	5-14 years	4.3%	Age, sex & region
Zito et al.	2003	USA	2 Medicaid: midwestern (MW) and mid-Atlantic (MA); 1 health maintenance organization (HMO), northwest (NW)	1987-1996	Psychotropics Anticonvulsants/mood stabilizers Antidepressants Anxiolytics Hypnotics Stimulants	<20 years	18.40 (1987 in MA) - 62.60 (1996 in MW) per 1,000 1.10 (1987 in NW) - 12.80 (1996 in MA) per 1,000 1.90 (1987 in MA) - 20.50 (1996 in MA) per 1,000 1.00 (1987 in MA) - 6.20 (1987 in MW) per 1,000 0.28 (1987 in MA) - 3.70 (1991 in MA) per 1,000 3.60 (1987 in NW) - 38.40 (1996 in MA) per 1,000	Age, year, database & medicine
Zito et al.	2002	USA	2 Medicaid: midwestern (MW) and mid-Atlantic (MA); 1 health maintenance organization (HMO), northwest (NW)	1988, 1991 and 1994	Antidepressants	2-19 years	MW: 6.66 (1988) - 19.10 (1994) per 1,000 MA: 3.90 (1988) - 17.78 (1994) per 1,000 HMO NW: 3.53 (1988) -12.85 (1994) per 1,000	Age, year, medicine & insurance
Patel et al.	2002	USA	Medicaid, Texas	1996-2000	Antipsychotics	0-19 years	7.63 (1996) - 19.88 (2000) per 1,000	Age, sex, year & medicine
Pietraru et al.	2001	IT	General practice database of Chivasso	Jan-Jun 2000	Antidepressants	0-15 years	0.27 per 1,000	Occasional/non-occasional users
Rochat et al.	2001	DK	Odense University Pharmacoepidemiologic Database (OPED), Funen County	1998	Antiepileptics	0-24 years (subgroups)	0-4 years: 0.15% 5-9 years: 0.48% 10-14 years: 0.54% 15-24 years: 0.54%	Age, sex & year
Rushton et al.	2001	USA	Medicaid, North Carolina	1992-1998	Stimulants	1-14 years (subgroups)	1-5 years: 0.6% (1992)-1.3% (1997-1998) 6-14 years: 4.4% (1992)-9.7% (1997)	Age & year
Schirm et al.	2001	NL	Inter-Action Database (drugs dispensed by pharmacies in north)	1995-1999	Antidepressants Antipsychotics	0-19 years	3.8 (1995) - 4.7 (1998) per 1,000 1.6 (1995) - 3.4 (1999) per 1,000	Age, year, sex & medicine

Author	Publication year	Country	Database	Timeframe	ATC group	Age groups	Reported prevalence	Sub-analysis by
					Hypnotics/anxiolytics Stimulants		5.4 (1995) - 6.9 (1999) per 1,000 1.5 (1995-6) - 7.4 (1999) per 1,000	
Zito et al.	2001	USA	2 Medicaid: midwestern (MW) and mid-Atlantic (MA); 1 health maintenance organization (HMO), northwest (NW)	1988, 1994	Antidepressants	2-19 years	MW: 6.6 (1988), 19.1 (1994) per 1,000 MA: 3.9(1988), 17.8 (1994) per 1,000 HMO NW: a rate similar to MA in 1988 but 28% lower than the Medicaid population by 1994	Year & insurance
Zito et al.	2000	USA	2 Medicaid: midwestern (MW) and mid-Atlantic (MA); 1 health maintenance organization (HMO), northwest (NW)	1991-1995	Antidepressants Neuroleptics/ Antipsychotics Stimulants	2-4 years	0.5 (1991 in HMO) - 3.2 (1995 in MW) per 1,000 0.1(1991 & 1993 in HMO) - 0.9 (1995 in MW) per 1,000 1.7 (1991 in HMO) - 12.3 (1995 in MW) per 1,000	Sex, year, database, & medicine

ATC group and age group are presented here as reported in the study.
AU: Australia, CA: Canada, CN: China, CO: Colombia, DE: Germany, DK: Denmark, ES: Spain, FI: Finland, FR: France, IE: Ireland, IL: Israel, IS: Iceland, IT: Italy, JP: Japan, LT: Lithuania, NL: Netherlands, NO: Norway, NZ: New Zealand, SE: Sweden, TW: Taiwan, UK: United Kingdom, USA: United States of America
**Article did not originally include the data separately for children, so the author provided them by including data on a longer period: 1999-2018.*

Table 97. Summary of previous studies reporting paediatric off-label use of psychotropics.

Author	Publication year	Country	Setting/ Database	Sample size (paediatric age groups)	Definition criterion of off-label use	Reported proportion of off-label use
Espín Martínez et al.	2022	ES	Outpatients Electronic Database for Pharmacoepidemiologic Studies in Primary Care (BIFAP) (2013-2018)	Not provided Antidepressant prescriptions: 894,129 (2013) 914,795 (2014) 915,409 (2015) 897,099 (2016) 878,751 (2017) 890,325 (2018) (<6-18 years)	Indication	N06A - Antidepressant off-label prescriptions: 15-40% (increased with age)
Schaffer et al.	2022	AU	Outpatients (all drug users) Pharmaceutical Benefits Scheme (PBS) (nationwide) (2013-2017)	840,190 children (49.3% females) with 8,219,772 dispensations (<1 year, 1-5 years, 6-11 years, 12-17 years)	Age (no dose recommendation for at least indication in the SmPC by age)	N03A - Antiepileptic off-label dispensations: <1 year: 70.8% 1-5 years: 21.1% 6-11 years: 14.3% 12-17 years: 1.6% N05A - Antipsychotic off-label dispensations: <1 year: 100% 1-5 years: 99.9% 6-11 years: 99.6% 12-17 years: 55.9% N05B - Anxiolytic off-label dispensations: <1 year: 27.8% 1-5 years: 4.7% 6-11 years: 5.3% 12-17 years: 12.3% N06A - Antidepressant off-label dispensations: <1 year: 100% 1-5 years: 100% 6-11 years: 74.4% 12-17 years: 71.8% N06B - Psychostimulant off-label dispensations: <1 year: 0% 1-5 years: 100% 6-11 years: 0% 12-17 years: 0.1% 6-11-year-old off-label dispensations: Risperidone: 13.2% Fluoxetine: 12.6% *Higher psychotropic off-label dispensations by specialists*

Author	Publication year	Country	Setting/ Database	Sample size (paediatric age groups)	Definition criterion of off-label use	Reported proportion of off-label use
						especially in younger children.
Candon et al.	2021	USA	Outpatients Medicaid (2014-2018)	~650,000 (2018) - all ages <u>Antipsychotic users</u>: 5,254 (2014) 2,688 (2018) (<21 years)	Indication	<u>Antipsychotic off-label prescriptions</u> 2014: 44.4% 2018: 47.3%
Scholle et al.	2021	DE	Outpatients German Pharmacoepidemiological Research Database (GePaRD) (representative data) (2015-2017)	~20% of the general population <u>ADHD drugs first-time users</u>: 18,703 (0-17 years)	(i) ADHD diagnosis (ii) second-line ADHD medication on the day of first use (iii) age <6 years	<u>ADHD off-label drug users</u> 12.7% (any one of the three off-label criteria) (i) 9.8% (no ADHD diagnosis) - 0.1% of patients with a diagnosis of narcolepsy without ADHD - 9.7% without either a diagnosis of ADHD or narcolepsy. (ii) 2.6% (second-line ADHD drugs as first treatment) (iii) 1.2% (< 6 years)
Bénard-Laribière et al.	2019	FR	Outpatients *Échantillon Généraliste de Bénéficiaires* (EGB) (2007-2014)	From 1/97th random sample of the French national healthcare reimbursement system (<18 years)	Age	<u>Antipsychotic off-label users (prevalence)</u> 2007: 16.1% 2009: 7.9%. 2014: 11.1-14.4% 2014, risperidone: 5.2-6.4% of children 2014 (2Q), cyamemazine: 1.1% 2014, SGAs (other than risperidone and aripiprazole): 60.0 to 85.7% of prescribing. aripiprazole: 15.0-29.4% of children FGAs (other than cyamemazine): 19.5-25.5% of children.
Tanemura et al.	2019	JP	Outpatients Prescription database of a company owning a nationwide chain of 697 pharmacies (with locations in 30 of the 47 prefectures in Japan) (1-Apr-2016 to 31-Mar-2017)	45,715 eligible patients with 331,920 prescriptions (all ages, specific antipsychotics and antidepressants) (<16 years)	Age	<u>Antipsychotic off-label users</u> Asenapine: 0.58%, P/P*: 3.5 Olanzapine: 0.85%, P/P*: 4.9 Paliperidone: 0.26%, P/P*: 1.0 Quetiapine: 0.72%, P/P*: 3.9 <u>Antidepressant off-label users</u> Duloxetine: 0.15%, P/P*: 3.9 Escitalopram: 0.53%, P/P*: 4.3 Sertraline: 1.1%, P/P*: 5.5 Total: 0.61%, P/P*: 4.6
Revet et al.	2018	FR	Outpatients	From 1/97th random sample of the French national	Age	<u>Antidepressant off-label users</u> <u>Prevalent</u>:

Author	Publication year	Country	Setting/ Database	Sample size (paediatric age groups)	Definition criterion of off-label use	Reported proportion of off-label use
			Échantillon Généraliste de Bénéficiaires (EGB) (2009-2016)	healthcare reimbursement system Antidepressant users: 75,717 (2009) - 3,962 (2016) (6-11 years, 12-17 years)		Overall: 41.5% (2009)-33.9% (2016) 12-17 years: 48.4% (2009)-34.8% (2016) 6-11 years: 10.0% (2009)-26.5% (2016) Incident: Overall: 40.9% (2009)-33.3% (2016) 12-17 years: 47.8% (2009)-34.5% (2016) 6-11 years: 12.3% (2009)-26.2% (2016)
Schröder et al.	2017	DE	Outpatients 3 statutory health insurance (SHI) providers, part of the German Pharmacoepidemiological Research Database (GePaRD) (2004-2011)	1,993,994 (2004) - 2,160,541 (2009) Antidepressant users: 3,561 (2005) - 4,456 (2011) (0-17 years)	Age Indication Contraindication (diagnosis)	Antidepressant off-label prescriptions 2004: 64.2% 2011: 36.3% Antidepressant off-label users 2004: 58% 2011: 40.9% *2011 – off-label* TCAs users: 17.5% SSRIs users: 37.7% Other antidepressants users: 69.3% *2011* Off-label users by age 12-17 years: 80.5% <6 years: 2.1% Off-label users by indication - hyperkinetic disorder (F90): 26.6% - reaction to severe stress and adjustment disorder (F43): 14.6% - emotional disorder with onset specific to childhood (F93): 11.4% - conduct disorder (F91): 9.5% - somatoform disorder (F45): 9.2%
Schröder et al.	2017	DE	Outpatients 3 statutory health insurance (SHI) providers, part of the German Pharmacoepidemiological Research Database (GePaRD) (2004-2011)	1,993,994 (2004) - 2,160,541 (2009) Antipsychotic users: 4,309 (2006) - 5,459 (2011) (0-17 years)	Age Indication Contraindication (diagnosis)	Antipsychotic off-label users: 2004: 52.3% 2009: 71.1% 2011: 62.7% Antipsychotic off-label prescriptions 2004: 61.0% 2009: 69.5% Off-label users by age 11.5% to 13.5% 2011: (3-5 years) 46.2%

Author	Publication year	Country	Setting/ Database	Sample size (paediatric age groups)	Definition criterion of off-label use	Reported proportion of off-label use
						Off-label users by indication 42.8% to 66.5% 2011: - hyperkinetic disorder (F90): 52.5% - pervasive developmental disorder (F84): 19.2% - tic disorder (F95): 15.7% - other behavioral and emotional disorders (F98): 15.4% - specific developmental disorders of speech and language (F80): 13.6% Off-label users by contraindication 2.5% to 1.4%
Chon et al.	2017	KR	Outpatients Health Insurance Review and Assessment Service-National Patient Sample (HIRA-NPS) comprising ~3% based on the National Health Insurance claims data (representative) (2013)	0.2 million children randomly extracted by age-gender stratification Antidepressant users: 2,190 (6–18 years)	Korean MFDS standards (indication)	Antidepressant off-label prescriptions 95% Off-label prescriptions by indication - OCD treatment: 72.3% - enuresis treatment: 14.4% - all the other diagnoses (including depressive disorder): 100%
Nielsen et al.	2017	DK	Outpatients Register of Medicinal Product Statistics (RMPS); Danish Civil Registration System; Danish National Registry of Patients (DNRP); National Health Insurance Service Registry (NHISR) (2006-2012)	1.2 million Sedatives, hypnotics, antidepressants users: 29,851 (186,831 prescriptions) (<18 years)	Age Indication	Sedative and hypnotic off-label prescriptions 94.6% - by age: 98.4% - by indication: 1.5% Antidepressant off-label prescriptions 94.6% - by age: 98.4% - by indication: 1.5% *Data also by sex and age*
Schröder et al.	2016	DE	Outpatients 3 statutory health insurance (SHI) providers, part of the German Pharmacoepidemiological Research Database (GePaRD)	1,993,994 (2004) - 2,160,541 (2009) 2,090,135 (2011) (0-17 years)	Age Indication Contraindication (diagnosis)	Antipsychotics (N05A and promethazine) off-label prescriptions 2004: 61.0 % 2006: 69.0 % 2007-2009: 68.1-69.5 % 2011: 62.0 %

Author	Publication year	Country	Setting/ Database	Sample size (paediatric age groups)	Definition criterion of off-label use	Reported proportion of off-label use
			(2004-2011)			Off-label risperidone users 2011: 52.1 % 2009: 61.8 % - with hyperkinetic disorder: 2004: 43.9 % 2011: 63.8 % - with pervasive developmental disorder: 2008: 21.9 % 2011: 27.0 % *Data stratified by gender and age too.*
Schröder et al.	2016	DE	Outpatients 3 statutory health insurance (SHI) providers, part of the German Pharmacoepidemiological Research Database (GePaRD) (2004-2011)	1,993,994 (2004) - 2,160,541 (2009) (0-17 years)	Age Indication Contraindication (diagnosis)	Antidepressant off-label prescriptions 2004: 64.2% 2006: 49.4% 2009: 40.6% 2011: 36.3% *2011* Off-label users by age: 29.1% Off-label users by indication: 15.3% Off-label users by contraindication: 3.3%
Beau-Lejdstrom et al.	2016	UK	Outpatients Clinical Practice Research Datalink (CPRD, formerly GPRD) ~8% of the population (representative) (1992-2013)	ADHD medication users: 14,748 (<6 years, 6–10 years and 11–15 years)	Age	ADHD medication off-label users <6 years: 4% Dexamphetamine off-label users <3 years: 2 out of 659
Hartz et al.	2015	NO	Outpatients Norwegian Prescription Database (NorPD); Norwegian Patient Register (NPR) (2004-2012)	Melatonin users: 1,489-4,913 boys 612-3,281 girls (4-17 years)	Age	Melatonin off-label 186,235 prescriptions corresponding to 3.4-11.0 per 1000 inhabitant boys and 1.5-7.7 per 1000 inhabitant girls *Data on diagnosis and data on figures*
Dörks et al.	2013	DE	Outpatients 4 statutory health insurance (SHI) providers, part of the German	2,599,685 Antidepressant users: 9,383	Age Indication	Antidepressant off-label prescriptions: 2004-2006: 49.11 % (13,035) 2004: 52.66 % 2005: 50.25 %

Author	Publication year	Country	Setting/ Database	Sample size (paediatric age groups)	Definition criterion of off-label use	Reported proportion of off-label use
			Pharmacoepidemiological Research Database (GePaRD) (2004-2006)	(26,543 prescriptions) (<2 years, 2–11 years and 12–17 years)		2006: 44.24 % <u>Off-label prescriptions by age</u>: Overall: 40.18 % SSRIs: 72.75 % St John's wort: 40.13 % TCAs: 3.68 % Other ADs: 100% <u>Off-label prescriptions by indication</u>: Overall: 16.63 % Other ADs: 20.54 % St John's wort: 19.17 % SSRIs: 17.86 % TCAs: 13.99 % <u>Off-label (both criteria):</u> Overall: 7.70 %
Hoffmann et al.	2012	DE	Outpatients Health insurance company Gmünder ErsatzKasse (GEK) (~2% of total population) (2009)	140,563 <u>Antidepressant users</u>: 821 (12–13 years, 14–15 years, and 16–18 years)	i) Licensed: approved or relatively contraindicated ii) Non-licensed: not approved or absolutely contraindicated iii) Licensing status indeterminate: not enough information given (Fachinformat)	<u>Antidepressant off-label prescriptions</u>: 45.5%
Czaja et al.	2012	USA	Outpatients PharMetrics (a unit of IMS Health) (85 US-based managed care plans, representing ~50 million) (1997–2009)	<u>Antidepressant users:</u> 290,816 (5-24 years) (5-8 years, 9–12 years, 13–18 years, 19–24 years)	30-day diagnosis-matching window - FDA-approved - Favorable evidence - Inconclusive evidence - No evidence	<u>Antidepressant off-label prescriptions</u>: >70% (overall) <u>Off-label (inconclusive evidence)</u>: *1997-2000* - 5-12 years: 10% - 13-18 years: 5% *2001-2003* - 5-12 years: 11% - 13-18 years: 6% *2004-2005* - 5-12 years: 13%

Author	Publication year	Country	Setting/ Database	Sample size (paediatric age groups)	Definition criterion of off-label use	Reported proportion of off-label use
						- 13-18 years: 7% *2006-2009* - 5-12 years: 15% - 13-18 years: 7% Off-label use (no evidence) *1997-2000* - 5-12 years: 76% - 13-18 years: 70% *2001-2003* - 5-12 years: 72% - 13-18 years: 56% *2004-2005* - 5-12 years: 67% - 13-18 years: 52% *2006-2009* - 5-12 years: 67% - 13-18 years: 51%
Cohen et al.	2012	AU	Outpatients Pharmaceutical Benefits Scheme (PBS) (nationwide) (July 2002-June 2009)	Anticonvulsant prescriptions: 155,051-157,945 (0-16 years)	Age - topiramate (>2 years) - levetiracetam (>4 years)	Anticonvulsant off-label *2008-2009* - 4.2% of the total prescriptions for levetiracetam - 3.6% of the total prescriptions for topiramate
Lass et al.	2011	EE	Outpatients Estonian Health Insurance Fund (EHIF) (2007)	277,265 All-dispensation users: 151,476 (0-23 months, 2-5 years and 6-11 years and 12-18 years)	Off-label: - no paediatric data - contraindication - age Unlicensed	Contraindicated Nortriptylline: 2 prescriptions/1000 subjects aged 6-11 years. Escitalopram: 6 prescriptions/1000 subjects aged 12-18 years.
Zoëga et al.	2009	IS	Outpatients Nationwide Medicines Registry (2003-2007)	All paediatric population Psychotropic users: 78,157 (2003) 78,542 (2004) 78,935 (2005) 79,450 (2006) 79,469 (2007)	Unlicensed Off-label: - age	*2007* Any psychotropic prescription: Off-label: 24.6% Unlicensed: 0.6% Antidepressant prescriptions: Off-label: 41.8% Unlicensed: 0.0% Antipsychotic prescriptions: Off-label: 52%

Author	Publication year	Country	Setting/ Database	Sample size (paediatric age groups)	Definition criterion of off-label use	Reported proportion of off-label use
				Psychotropic prescriptions: 21,986 (2007) (0-17 years)		Unlicensed: 5.2% Stimulant and atomoxetine prescriptions: Off-label: 1.2% Unlicensed: 0.0% Anxiolytic prescriptions: Off-label: 10.4% Unlicensed: 10.7% Hypnotic and sedative prescriptions: Off-label: 95.3% Unlicensed: 4.7%
Schirm et al.	2003	NL (north)	Outpatients InterAction database (2000)	All-dispensation users: 18,943 (0-16 years) (0-1 years, 2-5 years, 6-11 years, 12-16 years)	Age	Antipsychotic prescriptions Off-label: 59.8% Unlicensed: 2.8% Anxiolytic prescriptions Off-label: 16.8% Unlicensed: 2.9% Hypnotic and sedative prescriptions Off-label: 83.5% Unlicensed: 5.8% Antidepressant prescriptions Off-label: 58.0% Unlicensed: 4.4% Psychostimulant prescriptions Off-label: 5.0% Unlicensed: 5.6%

AU: Australia, DE: Germany, DK: Denmark, EE: Estonia, ES: Spain, FR: France, IS: Iceland, JP: Japan, KR: Korea, NL: Netherlands, NO: Norway, UK: United Kingdom, USA: United States of America
**P/P: Prescription/Patients*

Table 98. Psychotropic dispensations in children per physician speciality - Greece. Detailed complete version.

Physician specialty	Girls		Boys		Total	
	n	%	n	%	n	%
Paediatrician	42,147	44.33	51,622	40.56	93,769	42.17
Neurologist	16,476	17.33	19,781	15.54	36,257	16.31
General Practitioner	13,234	13.92	17,847	14.02	31,081	13.98
Child Psychiatrist	9,837	10.35	20,365	16.00	30,202	13.58
Without specialty	5,768	6.07	7,187	5.65	12,955	5.83
Internist	3,529	3.71	4,598	3.61	8,127	3.66
Psychiatrist	2,394	2.52	4,032	3.17	6,426	2.89
Neurologist-Psychiatrist	308	0.32	368	0.29	676	0.30
Haematologist	219	0.23	326	0.26	545	0.25
Neurosurgeon	148	0.16	258	0.20	406	0.18
Physiatrist	163	0.17	144	0.11	307	0.14
Cardiologist	157	0.17	124	0.10	281	0.13
Orthopaedic	63	0.07	60	0.05	123	0.06
Ophthalmologist	64	0.07	51	0.04	115	0.05
Pneumonologist - tuberculosis specialist	41	0.04	70	0.06	111	0.05
Surgeon	62	0.07	48	0.04	110	0.05
Internist-Oncologist	67	0.07	39	0.03	106	0.05
Nephrologist	91	0.10	14	0.01	105	0.05
Urologist	8	0.01	77	0.06	85	0.04
Anaesthesiologist	42	0.04	36	0.03	78	0.04
Otolaryngologist	40	0.04	28	0.02	68	0.03
Gynaecologist-Obstetrics	32	0.03	25	0.02	57	0.03
Endocrinologist	24	0.03	28	0.02	52	0.02
Rheumatologist	32	0.03	17	0.01	49	0.02
Radiotherapist-Oncologist	24	0.03	22	0.02	46	0.02
Gastroenterologist	17	0.02	22	0.02	39	0.02
Dermatologist-Venereologist	14	0.01	23	0.02	37	0.02
Public Health	28	0.03	9	0.01	37	0.02
Chest surgeon	18	0.02	8	0.01	26	0.01
Child surgeon	9	0.01	14	0.01	23	0.01
Nuclear medicine physician	14	0.01	4	0.00	18	0.01
Coroner	4	0.00	11	0.01	15	0.01
Allergist	6	0.01	4	0.00	10	0.00
Occupational safety and health	1	0.00	4	0.00	5	0.00
Radiodiagnosis	0	0.00	2	0.00	2	0.00
Histopathologist	0	0.00	1	0.00	1	0.00
Vascular surgeon	1	0.00	0	0.00	1	0.00
No info	0	0.00	1	0.00	1	0.00
Overall	***95,082***	***100.00***	***127,270***	***100.00***	***222,352***	***100.00***

Table 99. Psychotropic dispensations in children (and by sex) per prefecture - Greece. Detailed complete version.

Prefecture	Girls (n=95,082)		Boys (n=127,268)*		Total (n=222,350)*	
	n	%	n	%	n	%
Attica	31,936	33.6	45,879	36.0	77,815	35.0
Thessaloniki	10,904	11.5	12,653	9.9	23,557	10.6
Heraklion	4,702	4.9	5,306	4.2	10,008	4.5
Achaea	3,093	3.3	4,544	3.6	7,637	3.4
Aetolia-Acarnania	2,680	2.8	2,689	2.1	5,369	2.4
Larissa	2,255	2.4	3,017	2.4	5,272	2.4
Chania	2,117	2.2	2,584	2.0	4,701	2.1
Ioannina	2,006	2.1	2,406	1.9	4,412	2.0
Euboea	1,748	1.8	2,601	2.0	4,349	2.0
Magnesia	1,589	1.7	2,050	1.6	3,639	1.6
Xanthi	1,326	1.4	2,155	1.7	3,481	1.6
Serres	1,344	1.4	1,896	1.5	3,240	1.5
Dodecanese	1,338	1.4	1,829	1.4	3,167	1.4
Karditsa	1,445	1.5	1,614	1.3	3,059	1.4
Messenia	1,220	1.3	1,711	1.3	2,931	1.3
Cyclades	1,421	1.5	1,403	1.1	2,824	1.3
Elis (Ileia)	1,009	1.1	1,812	1.4	2,821	1.3
Kozani	1,186	1.2	1,566	1.2	2,752	1.2
Imathia	1,168	1.2	1,568	1.2	2,736	1.2
Corinthia	1,070	1.1	1,643	1.3	2,713	1.2
Pella	1,287	1.4	1,402	1.1	2,689	1.2
Kavala	1,143	1.2	1,482	1.2	2,625	1.2
Pieria	960	1.0	1,615	1.3	2,575	1.2
Phthiotis	1,018	1.1	1,548	1.2	2,566	1.2
Rethymno	1,089	1.1	1,262	1.0	2,351	1.1
Argolis	1,014	1.1	1,172	0.9	2,186	1.0
Lesbos	817	0.9	1,362	1.1	2,179	1.0
Evros	944	1.0	1,204	0.9	2,148	1.0
Trikala	932	1.0	1,139	0.9	2,071	0.9
Rhodope	800	0.8	1,143	0.9	1,943	0.9
Corfu (Kerkyra)	706	0.7	1,156	0.9	1,862	0.8
Lasithi	716	0.8	1,097	0.9	1,813	0.8
Boeotia	735	0.8	1,077	0.8	1,812	0.8
Laconia	572	0.6	1,025	0.8	1,597	0.7
Arcadia	662	0.7	898	0.7	1,560	0.7
Drama	718	0.8	776	0.6	1,494	0.7
Kilkis	528	0.6	827	0.6	1,355	0.6
Chalkidiki	731	0.8	617	0.5	1,348	0.6
Arta	531	0.6	629	0.5	1,160	0.5
Preveza	375	0.4	781	0.6	1,156	0.5
Chios	459	0.5	589	0.5	1,048	0.5
Cephalonia	480	0.5	418	0.3	898	0.4
Thesprotia	274	0.3	532	0.4	806	0.4
Florina	442	0.5	353	0.3	795	0.4
Kastoria	320	0.3	457	0.4	777	0.3
Zakynthos	238	0.3	521	0.4	759	0.3
Samos	241	0.3	415	0.3	656	0.3
Lefkada	259	0.3	304	0.2	563	0.3
Grevena	233	0.2	233	0.2	466	0.2
Phocis	190	0.2	239	0.2	429	0.2
Evrytania	111	0.1	69	0.1	180	0.1

**No information for 2 dispensations*

Table 100. Analysis of active substances authorised in Catalonia (Spain) and Greece with the age cut-off.

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
N03A	1	N03AA01	Methylphenobarbital	N/A	N/A	N/A	N/A
	2	N03AA02	Phenobarbital	Yes	0 years	Yes	0 years
	3	N03AA03	Primidone	Yes	0 years	Yes	0 years
	4	N03AA04	Barbexaclone	N/A	N/A	N/A	N/A
	5	N03AA30	Metharbital	N/A	N/A	N/A	N/A
	6	N03AB01	Ethotoin	N/A	N/A	N/A	N/A
	7	N03AB02	Phenytoin	Yes	0 years	Yes	0 years
	8	N03AB03	Amino(diphenylhydantoin) valeric acid	N/A	N/A	N/A	N/A
	9	N03AB04	Mephenytoin	N/A	N/A	N/A	N/A
	10	N03AB05	Fosphenytoin	N/A	N/A	N/A	N/A
	11	N03AB52	Phenytoin, combinations	N/A	N/A	Yes	0
	12	N03AB54	Mephenytoin, combinations	N/A	N/A	N/A	N/A
	13	N03AC01	Paramethadione	N/A	N/A	N/A	N/A
	14	N03AC02	Trimethadione	N/A	N/A	N/A	N/A
	15	N03AC03	Ethadione	N/A	N/A	N/A	N/A
	16	N03AD01	Ethosuximide	Yes	0 years	Yes	0 years
	17	N03AD02	Phensuximide	N/A	N/A	N/A	N/A
	18	N03AD03	Mesuximide	N/A	N/A	N/A	N/A
	19	N03AD51	Ethosuximide, combinations	N/A	N/A	N/A	N/A
	20	N03AE01	Clonazepam	Yes	0 years	Yes	0 years
	21	N03AF01	Carbamazepine	Yes	0 years	Yes	0 years
	22	N03AF02	Oxcarbazepine	Yes	6 years	Yes	6 years
	23	N03AF03	Rufinamide	Yes	4 years	Yes	4 or 1 years[&]

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	24	N03AF04	Eslicarbazepine	Yes	6 years	Yes	6 years
	25	N03AG01	Valproic acid	Yes	28 days	Yes	0 years
	26	N03AG02	Valpromide	No	18 years	N/A	N/A
	27	N03AG03	Aminobutyric acid	N/A	N/A	N/A	N/A
	28	N03AG04	Vigabatrin	Yes	0 years	Yes	0 years
	29	N03AG05	Progabide	N/A	N/A	N/A	N/A
	30	N03AG06	Tiagabine	Yes	12 years	Yes	12 years
	31	N03AX03	Sultiame	N/A	N/A	Yes	0 years
	32	N03AX07	Phenacemide	N/A	N/A	N/A	N/A
	33	N03AX09	Lamotrigine	Yes	2 years	Yes	2 years
	34	N03AX10	Felbamate	N/A	N/A	N/A	N/A
	35	N03AX11	Topiramate	Yes	2 years	Yes	2 years
	36	N03AX12	Gabapentin	Yes	6 years	Yes	6 years
	37	N03AX13	Pheneturide	N/A	N/A	N/A	N/A
	38	N03AX14	Levetiracetam	Yes	1 month	Yes	1 month
	39	N03AX15	Zonisamide	Yes	6 years	Yes	6 years
	40	N03AX16	Pregabalin	No	18 years	No	18 years
	41	N03AX17	Stiripentol	Yes	0 years	N/A	N/A
	42	N03AX18	Lacosamide	Yes	4 years	Yes	4 years
	43	N03AX19	Carisbamate	N/A	N/A	N/A	N/A
	44	N03AX21	Retigabine	N/A	N/A	N/A	N/A
	45	N03AX22	Perampanel	Yes	12 years	Yes	12 years
	46	N03AX23	Brivaracetam	Yes	16 years	Yes	16 or 4 years[&]
	47	N03AX30	Beclamide	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
N05A	48	N05AA01	Chlorpromazine	Yes	1 years	Yes	1 years
	49	N05AA02	Levomepromazine	Yes	3 years	Yes	2 years
	50	N05AA03	Promazine	N/A	N/A	No	18 years
	51	N05AA04	Acepromazine	N/A	N/A	N/A	N/A
	52	N05AA05	Triflupromazine	N/A	N/A	N/A	N/A
	53	N05AA06	Cyamemazine	N/A	N/A	N/A	N/A
	54	N05AA07	Chlorproethazine	N/A	N/A	N/A	N/A
	55	N05AB01	Dixyrazine	N/A	N/A	N/A	N/A
	56	N05AB02	Fluphenazine	Yes	12 years	N/A	N/A
	57	N05AB03	Perphenazine	N	18 years	No	18 years
	58	N05AB04	Prochlorperazine	N/A	N/A	N/A	N/A
	59	N05AB05	Thiopropazate	N/A	N/A	N/A	N/A
	60	N05AB06	Trifluoperazine	Yes	6 years	Yes	12 years
	61	N05AB07	Acetophenazine	N/A	N/A	N/A	N/A
	62	N05AB08	Thioproperazine	N/A	N/A	N/A	N/A
	63	N05AB09	Butaperazine	N/A	N/A	N/A	N/A
	64	N05AB10	Thioproperazine	N/A	N/A	N/A	N/A
	65	N05AB11	Perazine	N/A	N/A	N/A	N/A
	66	N05AC01	Periciazine	Yes	3 years	Yes	3 years
	67	N05AC02	Thioridazine	N/A	N/A	Yes	0 years
	68	N05AC03	Mesoridazine	N/A	N/A	N/A	N/A
	69	N05AC04	Pipotiazine	No	18 years	No	18 years
	70	N05AD01	Haloperidol	Yes	6 years	Yes	6 years
	71	N05AD02	Trifluperidol	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	72	N05AD03	Melperone	N/A	N/A	N/A	N/A
	73	N05AD04	Moperone	N/A	N/A	N/A	N/A
	74	N05AD05	Pipamperone	N/A	N/A	Yes	0 years
	75	N05AD06	Bromperidol	N/A	N/A	N/A	N/A
	76	N05AD07	Benperidol	N/A	N/A	N/A	N/A
	77	N05AD08	Droperidol	Yes	2 years	Yes	2 years
	78	N05AD09	Fluanisone	N/A	N/A	N/A	N/A
	79	N05AE01	Oxypertine	N/A	N/A	N/A	N/A
	80	N05AE02	Molindona	N/A	N/A	N/A	N/A
	81	N05AE03	Sertindole	No	18 years	No	18 years
	82	N05AE04	Ziprasidone	Yes	10 years	Yes	10 years
	83	N05AE05	Lurasidone	No	18 years	No	18 years
	84	N05AF01	Flupentixol	No	18 years	No	18 years
	85	N05AF02	Clopenthixol	N/A	N/A	N/A	N/A
	86	N05AF03	Chlorprothixene	N/A	N/A	N/A	N/A
	87	N05AF04	Tiotixene	N/A	N/A	N/A	N/A
	88	N05AF05	Zuclopentixol	No	18 years	No	18
	89	N05AG01	Fluspirilene	N/A	N/A	N/A	N/A
	90	N05AG02	Pimozide	Yes	12 years	Yes	12 years
	91	N05AG03	Penfluridol	N/A	N/A	Yes	12 years
	92	N05AH01	Loxapine	No	18 years	No	18 years
	93	N05AH02	Clozapine	Yes	16 years	Yes	16 years
	94	N05AH03	Olanzapine	No	18 years	No	18 years
	95	N05AH04	Quetiapine	No	18 years	No	18 years

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	96	N05AH05	Asenapine	No	18 years	No	18 years
	97	N05AH06	Clotiapine	No	18 years	N/A	N/A
	98	N05AL01	Sulpiride	No	18 years	No	18 years
	99	N05AL02	Sultopride	N/A	N/A	N/A	N/A
	100	N05AL03	Tiapride	Yes	0 years	Yes	7 years
	101	N05AL04	Remoxipride	N/A	N/A	N/A	N/A
	102	N05AL05	Amisulpride	No	18 years	No	18 years
	103	N05AL06	Veralipride	N/A	N/A	N/A	N/A
	104	N05AL07	Levosulpiride	No	18 years	No	18 years
	105	N05AN01	Lithium chloride	No	18 years	Yes	12 years
	106	N05AX07	Prothipendyl	N/A	N/A	N/A	N/A
	107	N05AX08	Risperidone	Yes	5 years	Yes	5 years
	108	N05AX10	Mosapramine	N/A	N/A	N/A	N/A
	109	N05AX11	Zotepine	N/A	N/A	N/A	N/A
	110	N05AX12	Aripiprazole	Yes	13 years	Yes	13 years
	111	N05AX13	Paliperidone	Yes	15 years	Yes	15 years
	112	N05AX14	Iloperidone	N/A	N/A	N/A	N/A
	113	N05AX15	Cariprazine	N/A	N/A	No	18 years
	114	N05AX16	Brexpiprazole	N/A	N/A	N/A	N/A
	115	N05AX17	Pimavanserin	N/A	N/A	N/A	N/A
N05B	116	N05BA01	Diazepam	Yes	6 months	Yes	6 months
	117	N05BA02	Chlorodiazepoxide	Yes	0 years	Yes	6 years
	118	N05BA03	Medazepam	N/A	N/A	N/A	N/A
	119	N05BA04	Oxazepam	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	120	N05BA05	Potassium Chlorazepate	Yes	0 years	Yes	9 years
	121	N05BA06	Lorazepam	Yes	6 years	Yes	6 years
	122	N05BA07	Adinazolam	N/A	N/A	N/A	N/A
	123	N05BA08	Bromazepam	No	18 years	No	18 years
	124	N05BA09	Clobazam	Yes	6 years	Yes	6 years
	125	N05BA10	Ketazolam	No	18 years	N/A	N/A
	126	N05BA11	Prazepam	N/A	N/A	No	18 years
	127	N05BA12	Alprazolam	No	18 years	No	18 years
	128	N05BA13	Halazepam	N/A	N/A	N/A	N/A
	129	N05BA14	Pinazepam	No	18 years	N/A	N/A
	130	N05BA15	Camazepam	N/A	N/A	N/A	N/A
	131	N05BA16	Nordazepam	N/A	N/A	N/A	N/A
	132	N05BA17	Fludiazepam	N/A	N/A	N/A	N/A
	133	N05BA18	ethyl loflazepate	N/A	N/A	N/A	N/A
	134	N05BA19	Etizolam	N/A	N/A	N/A	N/A
	135	N05BA21	Clotiazepam	N/A	N/A	N/A	N/A
	136	N05BA22	Cloxazolam	N/A	N/A	N/A	N/A
	137	N05BA23	Tofisopam	N/A	N/A	N/A	N/A
	138	N05BA24	Bentazepam	No	18 years	N/A	N/A
	139	N05BA51	Diazepam, combinations	No or Yes[$]	18 years or 6 months[$]	N/A	N/A
	140	N05BA55	Chlorazepate dipotasicum combinations	N/A	N/A	N/A	N/A
	141	N05BA56	Lorazepam combinations	N/A	N/A	N/A	N/A
	142	N05BA91	Oxazolam	N/A	N/A	N/A	N/A
	143	N05BB01	Hydroxizine	Yes	1 year	Yes	1 year
	144	N05BB02	Captodiame	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	145	N05BB51	Hydroxizine, combinations	No	N/A	N/A	N/A
	146	N05BC01	Meprobamate	N/A	N/A	N/A	N/A
	147	N05BC03	Emylcamate	N/A	N/A	N/A	N/A
	148	N05BC04	Mebutamate	N/A	N/A	N/A	N/A
	149	N05BC51	Meprobamate, combinations	N/A	N/A	N/A	N/A
	150	N05BD01	Benzctamine	N/A	N/A	N/A	N/A
	151	N05BE01	Buspirone	N/A	N/A	No	18
	152	N05BX01	Mephenoxalone	N/A	N/A	N/A	N/A
	153	N05BX02	Getocarnil	N/A	N/A	N/A	N/A
	154	N05BX03	Etifoxine	N/A	N/A	N/A	N/A
	155	N05BX04	Fabomotizole	N/A	N/A	N/A	N/A
	156	N05BX05	Lavandulae aetheroleum	N/A	N/A	N/A	N/A
	157	N05BX92	Passiflora, crataegus monogyna and salyx alba	Yes	12 years	N/A	N/A
N05C	158	N05CA01	Pentobarbital	N/A	N/A	N/A	N/A
	159	N05CA02	Amobarbital	N/A	N/A	N/A	N/A
	160	N05CA03	Butobarbital	N/A	N/A	N/A	N/A
	161	N05CA04	Barbital	N/A	N/A	N/A	N/A
	162	N05CA05	Aprobarbital	N/A	N/A	N/A	N/A
	163	N05CA06	Secobarbital	N/A	N/A	N/A	N/A
	164	N05CA07	Talbutal	N/A	N/A	N/A	N/A
	165	N05CA08	Vinylbital	N/A	N/A	N/A	N/A
	166	N05CA09	Vinbarbital	N/A	N/A	N/A	N/A
	167	N05CA10	Cyclobarbital	N/A	N/A	N/A	N/A
	168	N05CA11	Heptabarbital	N/A	N/A	N/A	N/A
	169	N05CA12	Reposal	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	170	N05CA15	Methohexital	N/A	N/A	N/A	N/A
	171	N05CA16	Hexobarbital	N/A	N/A	N/A	N/A
	172	N05CA19	Thiopental	Yes	0 years	Yes	0 years
	173	N05CA20	Etallobarbital	N/A	N/A	N/A	N/A
	174	N05CA21	Allobarbital	N/A	N/A	N/A	N/A
	175	N05CA22	Proxibarbal	N/A	N/A	N/A	N/A
	176	N05CB01	Barbiturates, combinations	N/A	N/A	N/A	N/A
	177	N05CB02	Barbiturates in combination with other drugs	N/A	N/A	N/A	N/A
	178	N05CC01	Cloral hydrate	N/A	N/A	N/A	N/A
	179	N05CC02	Chloralodol	N/A	N/A	N/A	N/A
	180	N05CC03	Acetylglycinamide chloral hydrate	N/A	N/A	N/A	N/A
	181	N05CC04	Dichloralphenazone	N/A	N/A	N/A	N/A
	182	N05CC05	Paraldehyde	N/A	N/A	N/A	N/A
	183	N05CD01	Flurazepam	No	18 years	N/A	N/A
	184	N05CD02	Nitrazepam	N/A	N/A	N/A	N/A
	185	N05CD03	Flunitrazepam	N/A	N/A	No	18 years
	186	N05CD04	Estazolam	N/A	N/A	N/A	N/A
	187	N05CD05	Triazolam	No	18 years	No	18 years
	188	N05CD06	Lormetazepam	Yes	2 years	N/A	N/A
	189	N05CD07	Temazepam	N/A	N/A	No	18 years
	190	N05CD08	Midazolam	Yes	3 months	Yes	3 months
	191	N05CD09	Brotizolam	No	18 years	N/A	N/A
	192	N05CD10	Quezapam	No	18 years	N/A	N/A
	193	N05CD11	Loprazolam	No	18 years	N/A	N/A
	194	N05CD12	Doxefazepam	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	195	N05CD13	Cinolazepam	N/A	N/A	N/A	N/A
	196	N05CE01	Glutethimide	N/A	N/A	N/A	N/A
	197	N05CE02	Methyprylon	N/A	N/A	N/A	N/A
	198	N05CE03	Pyrithyldione	N/A	N/A	N/A	N/A
	199	N05CF01	Zopiclone	No	18 years	No	18 years
	200	N05CF02	Zolpidem	No	18 years	No	18 years
	201	N05CF03	Zaleplon	N/A	N/A	N/A	N/A
	202	N05CF04	Eszopiclone	N/A	N/A	N/A	N/A
	203	N05CH01	Melatonin	No	18 years	No	18 years
	204	N05CH02	Ramelteon	N/A	N/A	N/A	N/A
	205	N05CH03	Tasimelteon	N/A	N/A	N/A	N/A
	206	N05CM01	Methaqualone	N/A	N/A	N/A	N/A
	207	N05CM02	Clomethiazole	No	18 years	No	18 years
	208	N05CM03	Bromisoval	N/A	N/A	N/A	N/A
	209	N05CM04	Carbromal	N/A	N/A	N/A	N/A
	210	N05CM05	Scopolamine	N/A	N/A	N/A	N/A
	211	N05CM06	Propiomazine	N/A	N/A	N/A	N/A
	212	N05CM07	Triclofos	N/A	N/A	N/A	N/A
	213	N05CM08	Ethchlorvynol	N/A	N/A	N/A	N/A
	214	N05CM09	Valerianae radix	Yes	12 years	Yes	12 years
	215	N05CM10	Hexapropymate	N/A	N/A	N/A	N/A
	216	N05CM11	Bromides	N/A	N/A	N/A	N/A
	217	N05CM12	Apronal	N/A	N/A	N/A	N/A
	218	N05CM13	Valnoctamide	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	219	N05CM15	Methylpentynol	N/A	N/A	N/A	N/A
	220	N05CM16	Niaprazine	N/A	N/A	N/A	N/A
	221	N05CM18	Dexmedetomidine	No	18 years	No	18 years
	222	N05CM19	Suvorexant	N/A	N/A	N/A	N/A
	223	N05CM93	Glutamate magnesium hydrobromate	Unknown	Unknown	N/A	N/A
	224	N05CX01	Meprobamate, combinations	N/A	N/A	N/A	N/A
	225	N05CX02	Methaqualone, combinations	N/A	N/A	N/A	N/A
	226	N05CX03	Methylpentynol, combinations	N/A	N/A	N/A	N/A
	227	N05CX04	Clomethiazole, combinations	N/A	N/A	N/A	N/A
	228	N05CX05	Emepronium, combinations	N/A	N/A	N/A	N/A
	229	N05CX06	Dipiperonylaminoethanol, combinations	N/A	N/A	N/A	N/A
N06A	230	N06AA01	Desipramine	N/A	N/A	N/A	N/A
	231	N06AA02	Imipramine	Yes	5 years	N/A	N/A
	232	N06AA03	Imipramine oxide	N/A	N/A	N/A	N/A
	233	N06AA04	Clomipramine	Yes	5 years	Yes	17 years
	234	N06AA05	Opipramol	N/A	N/A	N/A	N/A
	235	N06AA06	Trimipramine	No	18 years	No	18 years
	236	N06AA07	Lofepramine	N/A	N/A	N/A	N/A
	237	N06AA08	Dibenzepin	N/A	N/A	N/A	N/A
	238	N06AA09	Amitriptyline	Yes	6 years	Yes	6 years
	239	N06AA10	Nortriptyline	Yes	6 years	N/A	N/A
	240	N06AA11	Protriptyline	N/A	N/A	N/A	N/A
	241	N06AA12	Doxepin	No	18 years	No	18 years
	242	N06AA13	Iprindole	N/A	N/A	N/A	N/A
	243	N06AA14	Melitracen	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	244	N06AA15	Butriptyline	N/A	N/A	N/A	N/A
	245	N06AA16	Dosulepin	N/A	N/A	N/A	N/A
	246	N06AA17	Amoxapine	N/A	N/A	N/A	N/A
	247	N06AA18	Dimetacrine	N/A	N/A	N/A	N/A
	248	N06AA19	Amineptine	N/A	N/A	N/A	N/A
	249	N06AA21	Maprotiline	No	18 years	No	18 years
	250	N06AA23	Quinupramine	N/A	N/A	N/A	N/A
	251	N06AB02	Zimeldine	N/A	N/A	N/A	N/A
	252	N06AB03	Fluoxetine	Yes	8 years	Yes	8 years
	253	N06AB04	Citalopram	No	18 years	No	18 years
	254	N06AB05	Paroxetine	No	18 years	No	18 years
	255	N06AB06	Sertraline	Yes	6 years	Yes	6 years
	256	N06AB07	Alaproclate	N/A	N/A	N/A	N/A
	257	N06AB08	Fluvoxamine	Yes	8 years	Yes	8 years
	258	N06AB09	Etoperidone	N/A	N/A	N/A	N/A
	259	N06AB10	Escitalopram	No	18 years	No	18 years
	260	N06AF01	Isocarboxazid	N/A	N/A	N/A	N/A
	261	N06AF02	Nialamide	N/A	N/A	N/A	N/A
	262	N06AF03	Phenelzine	N/A	N/A	N/A	N/A
	263	N06AF04	Tranylcypromine	N/A	N/A	N/A	N/A
	264	N06AF05	Iproniazide	N/A	N/A	N/A	N/A
	265	N06AF06	Iproclozide	N/A	N/A	N/A	N/A
	266	N06AG02	Moclobemide	No	18 years	No	18 years
	267	N06AG03	Toloxatone	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	268	N06AX01	Oxitriptan	N/A	N/A	N/A	N/A
	269	N06AX02	Tryptophan	N/A	N/A	N/A	N/A
	270	N06AX03	Mianserin	No	18 years	N/A	N/A
	271	N06AX04	Nomifensine	N/A	N/A	N/A	N/A
	272	N06AX05	Trazodone	No	18 years	No	18 years
	273	N06AX06	Nefazodone	N/A	N/A	N/A	N/A
	274	N06AX07	Minaprine	N/A	N/A	N/A	N/A
	275	N06AX08	Bifemelane	N/A	N/A	N/A	N/A
	276	N06AX09	Viloxazine	N/A	N/A	N/A	N/A
	277	N06AX10	Oxaflozane	N/A	N/A	N/A	N/A
	278	N06AX11	Mirtazapine	No	18 years	No	18 years
	279	N06AX12	Bupropion	No	18 years	No	18 years
	280	N06AX13	Medifoxamine	N/A	N/A	N/A	N/A
	281	N06AX14	Tianeptine	No	18 years	N/A	N/A
	282	N06AX15	Pivagabine	N/A	N/A	N/A	N/A
	283	N06AX16	Venlafaxine	No	18 years	No	18 years
	284	N06AX17	Milnacipran	N/A	N/A	N/A	N/A
	285	N06AX18	Reboxetine	No	18 years	N/A	N/A
	286	N06AX19	Gepirone	N/A	N/A	N/A	N/A
	287	N06AX21	Duloxetine	No	18 years	No	18 years
	288	N06AX22	Agomelatine	No	18 years	No	18 years
	289	N06AX23	Desvenlafaxine	No	18 years	N/A	N/A
	290	N06AX24	Vilazodone	N/A	N/A	N/A	N/A
	291	N06AX25	Hyperici herba	No	18 years	N/A	N/A
	292	N06AX26	Vortioxetine	No	18 years	No	18 years

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	293	N06AX27	Esketamine	N/A	N/A	N/A	N/A
N06B	294	N06BA01	Amfetamine	N/A	N/A	N/A	N/A
	295	N06BA02	Dexamfetamine	N/A	N/A	N/A	N/A
	296	N06BA03	Metamphetamine	N/A	N/A	N/A	N/A
	297	N06BA04	Methylphenidate	Yes	6 years	Yes	6 years
	298	N06BA05	Pemoline	N/A	N/A	N/A	N/A
	299	N06BA06	Fencamfamin	N/A	N/A	N/A	N/A
	300	N06BA07	Modafinil	No	18 years	No	18 years
	301	N06BA08	Fenozolone	N/A	N/A	N/A	N/A
	302	N06BA09	Atomoxetine	Yes	6 years	Yes	6 years
	303	N06BA10	Fenetylline	N/A	N/A	N/A	N/A
	304	N06BA11	Dexmethylphenidate	N/A	N/A	N/A	N/A
	305	N06BA12	Lisdexamfetamine	Yes	6 years	N/A	N/A
	306	N06BA13	Armodafinil	N/A	N/A	N/A	N/A
	307	N06BA14	Solriamfetol	N/A	N/A	N/A	N/A
	308	N06BC01	Caffeine	Yes	0 years	Yes	0 years
	309	N06BC02	Propentofylline	N/A	N/A	N/A	N/A
	310	N06BX01	Meclofenoxate	N/A	N/A	N/A	N/A
	311	N06BX02	Pyritinol	N/A	N/A	N/A	N/A
	312	N06BX03	Piracetam	No	18 years	No	18 years
	313	N06BX04	Deanol	No	18 years	N/A	N/A
	314	N06BX05	Fipexide	N/A	N/A	N/A	N/A
	315	N06BX06	Citicoline	No	18 years	N/A	N/A
	316	N06BX07	Oxiracetam	N/A	N/A	N/A	N/A

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	317	N06BX08	Pirisudanol	Unknown	Unknown	N/A	N/A
	318	N06BX09	Linopirdine	N/A	N/A	N/A	N/A
	319	N06BX10	Nizofenone	N/A	N/A	N/A	N/A
	320	N06BX11	Aniracetam	N/A	N/A	No	18 years
	321	N06BX12	Acetylcarnitine	N/A	N/A	N/A	N/A
	322	N06BX13	Idebenone	N/A	N/A	Yes	12 years
	323	N06BX14	Prolintane	N/A	N/A	N/A	N/A
	324	N06BX15	Pipradrol	N/A	N/A	N/A	N/A
	325	N06BX16	Pramiracetam	N/A	N/A	N/A	N/A
	326	N06BX17	Adrafinil	N/A	N/A	N/A	N/A
	327	N06BX18	Vinpocetine	No	18 years	No	18 years
	328	N06BX21	Tetramethylglycoluril	N/A	N/A	N/A	N/A
	329	N06BX22	Phenibut	N/A	N/A	N/A	N/A
	330	N06BX54	Deanol, combinations	No	18 years	N/A	N/A
	331	N06BX95	γ-Amino-β-hydroxybutyric acid (GABOB)	Unknown	Unknown	N/A	N/A
N06C	332	N06CA01	Amitriptyline and psycholeptics (medazepam)	No	18 years	No	18 years
	333	N06CA02	Melitracen and psycholeptics (Flupentixol)	No	18 years	N/A	N/A
	334	N06CA03	Fluoxetine and psycholeptics	N/A	N/A	N/A	N/A
N07B	335	N07BA01	Nicotine	Yes	12 years	Yes	12 years
	336	N07BA03	Varenicline	No	18 years	No	18 years
	337	N07BA04	Cytisine	N/A	N/A	N/A	N/A
	338	N07BB01	Disulfiram	No	18 years	No	18 years
	339	N07BB02	Calcium carbimide	N/A	N/A	N/A	N/A
	340	N07BB03	Acamprosate	No	18 years	N/A	N/A
	341	N07BB04	Naltrexone	No	18 years	No	18 years

ATC group code	n	ATC code	Active substance	Paediatric information in the SmPC			
				Catalonia (Spain)		Greece	
				Authorised in children?	Age cut-off	Authorised in children?	Age cut-off
	342	N07BB05	Nalmefene	No	18 years	No	18 years
	343	N07BC02	Methadone	No	18 years	No	18 years
	344	N07BC51	Buprenorphine	Yes	15 years	Yes	15 years
	345	N07BC03	Levacetylmethadol	N/A	N/A	N/A	N/A
	346	N07BC04	Lofexidine	N/A	N/A	N/A	N/A
	347	N07BC05	Levomethadone	No	18 years	N/A	N/A
	348	N07BC06	Diamorphine	N/A	N/A	N/A	N/A
	349	N07BC51	Buprenorphine, combinations	No	18 years	Yes	15 years

[&]: the change in the age cut-off was in June 2018. [$]: "No" for combination with sulpiride, "Yes" for combination with pyridoxine

Table 101. Off-label use: analysis of number of dispensed psychotropics per year and sex in Catalonia (Spain) and Greece.

Catalonia (Spain)														
Year	All dispensed psychotropics			Not authorised medicines						Not authorised medicines - age criterion					
	Girls	Boys	Overall	Girls		Boys		Overall		Girls		Boys		Overall	
	n	n	n	n	%	n	%	n	%	n	%	n	%	n	%
2015	105,549	218,278	323,827	7,668	7.26	7,372	3.38	15,040	4.64	9,738	9.23	13,644	6.25	23,382	7.22
2016	103,573	212,917	316,490	7,427	7.17	7,236	3.40	14,663	4.63	9,581	9.25	13,925	6.54	23,506	7.43
2017	102,629	207,449	310,078	7,281	7.09	6,907	3.33	14,188	4.58	9,585	9.34	14,379	6.93	23,964	7.73
Total	***311,751***	***638,644***	***950,395***	***22,376***	***7.18***	***21,515***	***3.37***	***43,891***	***4.62***	***28,904***	***9.27***	***41,948***	***6.57***	***70,852***	***7.46***
Greece															
Year	All dispensed psychotropics			Not authorised medicines						Not authorised medicines - age criterion					
	Girls	Boys	Overall	Girls		Boys		Overall		Girls		Boys		Overall	
	n	n	n	n	%	n	%	n	%	n	%	n	%	n	%
2016*	8,047	11,260	19,307	405	5.03	551	4.89	956	4.95	554	6.88	758	6.73	1,312	6.80
2017	50,512	69,464	119,976	2,643	5.23	3,700	5.33	6,343	5.29	3,744	7.41	5,015	7.22	8,759	7.30
2018	51,590	72,951	124,541	2,943	5.70	3,943	5.40	6,886	5.53	4,033	7.82	5,507	7.55	9,540	7.66
2019*	45,472	61,783	107,255	2,777	6.11	3,378	5.47	6,155	5.74	3,727	8.20	4,962	8.03	8,689	8.10
Total	***155,621***	***215,458***	***371,079***	***8,768***	***5.63***	***11,572***	***5.37***	***20,340***	***5.48***	***12,058***	***7.75***	***16,242***	***7.54***	***28,300***	***7.63***

**: March 2016 to October 2019.*

Table 102. Off-label use: analysis of number of dispensed psychotropics per age group and sex in 2017 in Catalonia (Spain) and Greece.

Catalonia (Spain)																
Age group (in years)	All dispensed psychotropics			Not authorised medicines						Not authorised medicines - age criterion						
	Girls	Boys	Overall	Girls		Boys		Overall		Girls		Boys		Overall		
	n	n	n	n	%	n	%	n	%	n	%	n	%	n	%	
< 1	340	420	760	4	1.18	0	0.00	4	0.53	51	15.00	65	15.48	116	15.26	
1-2	1,704	2,081	3,785	3	0.18	1	0.05	4	0.11	279	16.37	338	16.24	617	16.30	
3-5	3,588	6,308	9,896	0	0.00	16	0.25	16	0.16	612	17.06	1,282	20.32	1,894	19.14	
6-8	10,148	23,565	33,713	51	0.50	136	0.58	187	0.55	336	3.31	1,654	7.02	1,990	5.90	
9-11	19,476	53,030	72,506	293	1.50	562	1.06	855	1.18	1,134	5.82	4,164	7.85	5,298	7.31	
12-14	30,184	69,540	99,724	1,689	5.60	1,882	2.71	3,571	3.58	1,932	6.40	2,566	3.69	4,498	4.51	
15-17	37,189	52,505	89,694	5,241	14.09	4,310	8.21	9,551	10.65	5,241	14.09	4,310	8.21	9,551	10.65	
Total	***102,629***	***207,449***	***310,078***	***7,281***	***7.09***	***6,907***	***3.33***	***14,188***	***4.58***	***9,585***	***9.34***	***14,379***	***6.93***	***23,964***	***7.73***	

Greece																
Age group (in years)	All dispensed psychotropics			Not authorised medicines						Not authorised medicines - age criterion						
	Girls	Boys	Overall	Girls		Boys		Overall		Girls		Boys		Overall		
	n	n	n	n	%	n	%	n	%	n	%	n	%	n	%	
< 1	91	185	276	1	1.10	0	0.00	1	0.36	17	18.68	34	18.38	51	18.48	
1-2	2,223	2,454	4,677	32	1.44	44	1.79	76	1.62	250	11.25	271	11.04	521	11.14	
3-5	4,444	4,742	9,186	54	1.22	64	1.35	118	1.28	729	16.40	592	12.48	1,321	14.38	
6-8	6,765	9,149	15,914	104	1.54	116	1.27	220	1.38	171	2.53	267	2.92	438	2.75	
9-11	8,942	12,831	21,773	197	2.20	274	2.14	471	2.16	301	3.37	518	4.04	819	3.76	
12-14	11,369	16,891	28,260	414	3.64	680	4.03	1,094	3.87	433	3.81	804	4.76	1,237	4.38	
15-17	16,678	23,212	39,890	1,841	11.04	2,522	10.87	4,363	10.94	1,843	11.05	2,529	10.90	4,372	10.96	
Total	***50,512***	***69,464***	***119,976***	***3,744***	***5.23***	***5,015***	***5.33***	***8,759***	***5.29***	***3,744***	***7.41***	***5,015***	***7.22***	***8,759***	***7.30***	