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ORIGINAL ARTICLE

Central nervous system-active drug abused and overdose in children: a worldwide exploratory study using the WHO pharmacovigilance database

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Abstract

Recent epidemiological studies have reported an increase in central nervous system (CNS)-active drug abuse rates in paediatric settings, raising several public health concerns. No study to date has explored this issue worldwide. We performed an extensive analysis of drugs abuse/overdose reported for children in the last decade by using the largest pharmacovigilance database, i.e. the VigiBase, collecting adverse drug reaction reports that involved at least one suspect drug belonging to the Anatomical Therapeutic Chemical code "Nervous System" through the Standardised Medical Dictionary for Drug Regulatory Affairs Queries for Drug abuse. 8.682 reports matched our criteria. An increase in reporting activity was observed, starting from 2014; an intentional overdose was reported more frequently than an accidental one, with a difference between age groups. We retrieved 997 reports with death outcome. These referred more to adolescents ($n = 538$) than subjects of any other paediatric age group. Paracetamol and opioid analgesics were the most common suspect drugs in deaths across all age groups due to hypoxic-ischaemic encephalopathy, brain death, and cardio-respiratory arrest.

Conclusion: The number of reports associated with drug abuse and overdose is increasing (for opioid and paracetamol-containing products) and a considerable number of adverse drug reactions are serious. Data on the patterns of use of such medicines from each country may help in implementing strategies of risk-minimisation and renewing healthcare

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recommendations worldwide. An increased clinical awareness of drug abuse and overdose is warranted, while continuing to provide effective treatments.

What is Known:
- *The large increase in paediatric prescriptions for CNS-active drugs in the last 20 years has recently raised public health concerns about drug abuse and overdose.*
- *No study to date has examined this issue in paediatric patients worldwide.*

What is New:
- *The number of paediatric reports associated with CNS drug abuse and intentional overdose is increasing, including those with fatal outcome; over 4 years; more than 35% of the reports was entered from European countries.*
- *Opioid and paracetamol were most frequently suspected for ADRs with fatal outcome across all age groups, due to hypoxic-ischaemic encephalopathy and cardio-respiratory arrest, suggesting the need to implement strategies of risk-minimisation.*

Keywords Drug abuse · Overdose · Drug safety · Paediatrics · Pharmacovigilance · Spontaneous reporting system database

Abbreviations

ADRs	Adverse drug reactions
ATC	Anatomical Therapeutic Chemical
CNS	Central nervous system
FDA	Food and Drug Administration
ICSRs	Individual case safety reports
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MHPRA	Medicines and Healthcare Products Regulatory Agency
OTC	Over-the-counter
PT	Preferred term
USA	United States of America
WHO	World Health Organization

Introduction

The large increase in prescriptions for central nervous system (CNS)-active drugs in the last 20 years, although varying in percentages by nation and culture, has raised public health concerns about drug abuse, overdose, and misuse [8]. CNS-active drugs can cause a wide range of adverse drug reactions (ADRs); these can be serious and may imperil further both the physical and psychological state of health, also resulting in fatal outcomes [6, 20].

Drug abuse and overdose, while mostly prevalent in the United States of America (USA), are problems in many areas around the world including Europe, Southern Africa, and South Asia [7, 10, 11, 15, 34]. Reports from epidemiological studies indicate that the increase in CNS drug prescription rates occurs also in children, both adolescents and young adults, for a range of disorders in a variety of clinical settings [11, 25, 32, 35, 36]. Most importantly, epidemiological data suggests that the risk of inappropriate use of these drugs is high [4, 5, 17, 24], raising public health concerns also because the toxicity of medicines in children differs from that seen in adults [9, 14, 16, 51].

Despite the reduced available supply of prescription drugs for nonmedical use due to regulatory changes in recent years, the problem still persists. These regulatory changes were also possibly linked to an increasing abuse of illicit substances and also of over-the-counter (OTC) medicines such as stimulants, laxatives, sedatives, and dissociative substances such as dextromethorphan and codeine [18, 19, 27, 33, 37, 45].

No study to date has examined the association between the abuse and overdose of CNS-active drugs and their associated ADRs in paediatric patients worldwide. Although there are a number of national estimates from different countries that deal with substance abuse and overdose, studies so far have been limited in their scope and focussed specifically on few substances, one country and/or selected sub-populations of paediatric age groups.

This exploratory study was performed to improve the knowledge of CNS drug abuse and overdose patterns and their associated ADRs in children worldwide, as a first step towards implementing a routine screening of safety issues specifically related to paediatric drug abuse. By using the largest and most comprehensive pharmacovigilance database, i.e. VigiBase, we carried out analysis spanning a large period of data entry in the system. Further, we stratified our analysis by ADR reports with serious outcomes, drugs that were most frequently involved in overdoses (including intentional and accidental), and country wise, ADR-related death reports among different paediatric age-categories.

Materials and methods

Data source

We analysed the reports of suspected ADRs in VigiBase, the World Health Organization (WHO) global individual case safety reports (ICSRs) database [50], which contains the ICSRs from 156 countries over the five continents. Data is sourced from ICSRs from healthcare professionals, pharmaceutical companies, and patients. Relevant National Pharmacovigilance Center are responsible for collecting, processing, and evaluating the spontaneous ADR reports prior to their submission and registration in VigiBase, which contains

over 10 million ICSRs records to date. The reports contain reporter information, patient characteristics, ADRs (coded into the related Preferred Term or PT and System Organ Class, using the Medical Dictionary for Drug Regulatory Affairs [MedDRA] ADRs terminology [23]), seriousness, outcome, drug exposures with dates, dosages, and indications. Drugs are coded according to the WHO Drug Dictionary Enhanced and classified using the Anatomical Therapeutic Chemical (ATC) classification [49].

Data extraction

We collected ICSRs for paediatric patients (0 < 18 years old) that involved at least one suspect drug belonging to ATC code 'N'-Nervous system in the occurrence of ADRs submitted to VigiBase from 2007 to 2017. Of these, we extracted all reports in which these drugs have been designated as suspected/interacting agents in the onset of drug abuse/overdose-related ADRs. With the aim of increasing sensitivity of the search strategy, these reports were retrieved through Standardised MedDRA Queries for drug abuse, dependence, and withdrawal, applying a narrow search for the specificity of case retrieval.

The following information was collected: safety report ID code, age, gender, ADRs, outcome, seriousness, reporter qualification and country of primary source. ADRs were classified as serious or non-serious according to the WHO Critical Term List [22].

The data set was stratified into four different paediatric age-categories as defined by the International Conference on Harmonisation guideline on Clinical Investigation of Medicinal Products in the Paediatric Population [13]. Data was scrutinised manually and by using the Visual Basic Syntax system code (programming code) in Excel files for duplicate detection. Data was further screened for terminological errors, standardised, and drug names normalised. A descriptive analysis of the data was performed by using IBM SPSS Statistics® ver. 23 (Chicago, IL: SPSS Inc). Data was analysed with respect to the total number of reports of drug abuse per year (trend in reporting rate), demographic characteristics of the patients, classification of PT, seriousness, type of reporter, and country of primary source.

Results

904.681 ICSRs met the age criteria (0 < 18 years old); of these, 114.023 (12.6%) were related to ATC code N. In total, 8.682 ICSRs (7.6%) matched our inclusion criteria (Fig. 1). More than 50% of ICSRs were entered in the last 5 years (Fig. 2). The gender proportion was approximately even (45.9% female vs 47.6% male); in 6.5% of ICSRs, gender was not reported (data not shown). Nearly 50% ICSRs were about adolescent (2.392; 56.01% female and 1.729; 40.48% male adolescent), followed by ICSRs about children (767; 33.74% female and 1.348; 59.30% male), infants and toddlers (498; 40.13% female and 612; 49.32% male), and newborns (326; 36.34% female and 446; 49.72% male) (data not shown).

The reporter was a physician in 3.251 cases (37.45%), a consumer or a non-health professional in 2.189 (25.21%) and other health professionals in 1.609 (18.53%). In contrast, pharmacists account for only 7.6% of the total reports. Less than 1% ($n = 41$) of reports was issued by a lawyer and in 7% ($n = 616$) of reports, the reporter was unspecified.

The reporting of drug abuse and withdrawal ADRs varied substantially between different countries, with the North America having the highest reporting rates, i.e. 60.3% (USA accounted for 4.884 ICSRs, 56.3%; Canada for 349, 4% and Mexico for 4, 0.01%), followed by Europe accounting for 33.5% of ICRs (2.907 reports). The countries mostly involved were France with 829 ICSRs (9.5%); Germany with 803 ICSRs (9.2%,); the UK with 404 ICSRs; Italy; and Switzerland with 215 and 90 ICSRs, respectively (4.7% and 2.5%).

As shown in Table 1, half of the ICSRs involved at least one drug from the therapeutic subgroup N02: analgesics, whereas nearly 30% of the ICSRs contained at least one drug from N05: psycholeptics.

In total, there were 3.747 ICSRs retrieved with the following MedDRA PTs: accidental overdose, intentional overdose, and overdose; of these 3.178 were reported as serious. Table 2 lists the number of serious ICSRs in different paediatric age groups with the most commonly involved drugs and co-PTs.

Among adolescents (12 < 18 years), PT 'intentional overdose' (n=1.014) was most frequently reported for serious ADRs followed by PT 'overdose' (n=897), and PT 'accidental overdose' ($n = 176$). Paracetamol was the suspect in most of the serious ICSRs indicating the PT 'intentional overdose' and 'overdose'. By contrast, oxycodone (10.6%) was recorded mostly as a suspect in serious ICSRs of 'accidental overdose'. The co-PT 'suicide attempt' was frequently reported with PT 'intentional overdose'.

Among children (2–11 years) and infants (28 days–23 months), the majority of serious ADR ICSRs were from accidental overdose, and mostly involved paracetamol as a suspected agent.

However, a considerable proportion of serious ADR ICSRs involving antidepressants (clonidine, sertraline, mirtazapine, and amitriptyline), antipsychotics (risperidone, olanzapine), antiepileptics (carbamazepine), and opioids (oxycodone, oxycodone, methadone, fentanyl) were detected among children and infants, respectively.

There were 40 ICSRs with the PT 'accidental overdose' and 43 ICSRs of 'overdose' that involved newborns. PTs: 'Medication error', 'seizure', and 'incorrect dose administered' were most frequently recorded terms. Serious ADR ICSRs from newborns also reported paracetamol as the most common suspect.

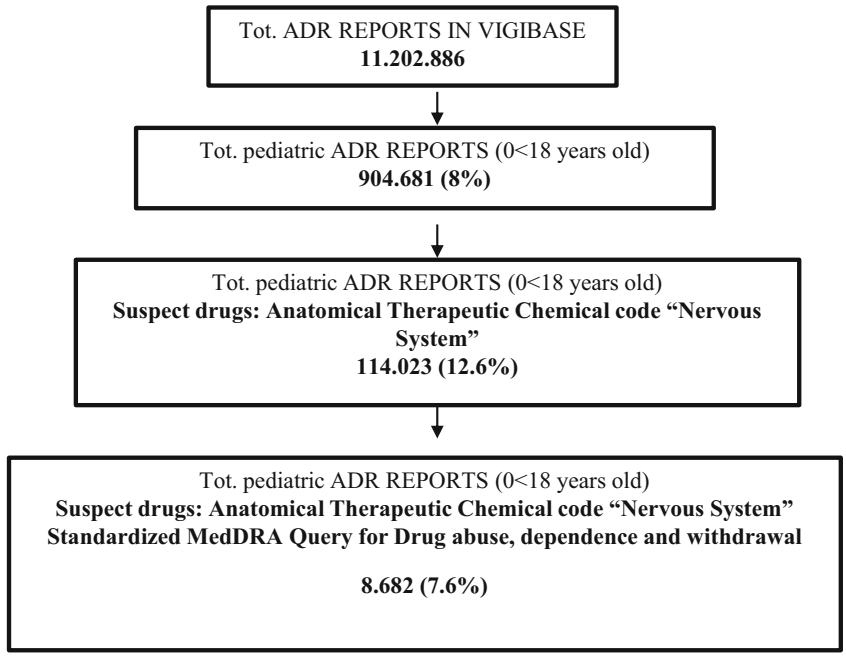

Fig. 1 Flow chart showing data extraction from VigiBase (Period: 2007–2017)

As reported in Table 3, a total of 997 ICSRs with death outcome were retrieved. There were more adolescents (n = 538) than subjects of any other paediatric age group. Opioid analgesics, or their combinations, were involved in the fatal ADRs, with oxycodone (27.5%) being the common suspect in all age groups. Paracetamol (26.3%) was recorded as the second prevalent drug implicated in ADR-related deaths in children of all age groups.

Consistent with the reported patterns of drug abuse, psychiatric ADRs were recorded only for the adolescents' age group including drug abuse, suicide attempt, suicidal ideation, depression, and insomnia.

Eight hundred and fifteen (82%) ADR-related deaths were reported from the USA, 73 (7.3%) from the UK, and 30 (3%) from Germany (Table 4). We stratified the ICSRs from these two drugs by country, age group, and ADRs as shown in Table 5.

Discussion

Drug abuse and overdose of CNS-active drugs have reached a critical level; they have been receiving international attention since the dramatic rise of this phenomenon due to the increased availability of these drugs and the perceived relative safety of the majority of them [29, 48].

Although this trend is more relevant for adults than children, widespread abuse and overdose (also unintentional) of such medications, with fatal outcome, have been reported among the paediatric population [13, 22, 29, 48, 49]. To our knowledge, this is the first study analysing patterns of ADRs reporting drug abuse/overdose in the paediatric setting worldwide.

Overall, there was an increase in the reporting trend from the year 2009 until 2011, which then declined. A similar increase was observed starting from 2014. This may in part be

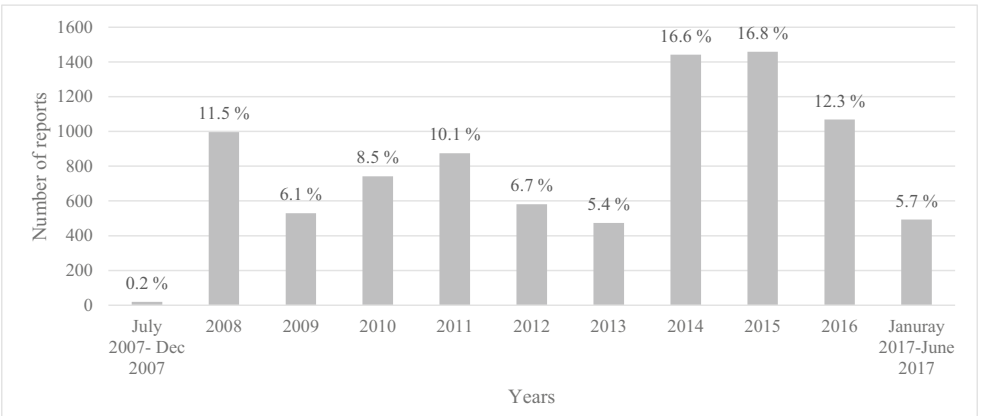

Fig. 2 Number and percentage of reports entered over a period of 10 years

Table 1 Reports by second-level (therapeutic subgroups) ATC classification and the most frequently reported drugs

ATC N therapeutic subgroup	Count	Percentage (%)	Most frequent drugs [name (frequency, *n*)]
ATC: N01 anaesthetics	528	6.1	Cocaine (72), propofol (39), ketamine (39), sufentanil (36), and bupivacaine (26)
ATC: N02 analgesics	4.372	50.4	Paracetamol (1.579), oxycodone (556), methadone (416), morphine (331), and fentanyl (292)
ATC: N03 antiepileptics	1.455	16.8	Valproic acid (354), lamotrigine (284), levetiracetam (180), carbamazepine (171), and vigabatrin (159)
ATC: N04 anti-Parkinson drugs	37	0.4	Benzatropine (16), trihexyphenidyl (8), tropatepine (5), and pramipexole (4)
ATC: N05 psycholeptics	2.592	29.9	Quetiapine (462), risperidone (313), alprazolam (269), bupropion (224), clonazepam (200), aripiprazole (170), lorazepam (162), midazolam (160), diazepam (157), and olanzapine (151)
ATC: N06 psychoanaleptics	2.586	29.8	Methylphenidate (882), fluoxetine (275), atomoxetine (271), sertraline (260), lisdexamfetamine (238), paroxetine (178), citalopram (157), venlafaxine (154), escitalopram (147), and duloxetine (99)

explained by the fact that a new definition of ADR had been adopted by European countries, according to Regulation No 1235/2010 and Directive 2010/84/EU [44]. This change may have a positive impact on reporting activity: over 4 years (2014–2017), 35.6% of total ICSRs were entered from European Countries. There has also been an exponential increase of ICSRs reporting 'abuse', 'overdose', and 'misuse' in the Italian National database for Pharmacovigilance following the implementation of the new Pharmacovigilance legislation, in line with our observations [40].

The observation that drug abuse in children was reported across all five continents confirms the need to improve the efficacy of strategies to manage this global safety issue. There has been an international trend of an increasing use of these medications in children and adolescents, in the recent past [43].

Fifty-two countries reported at least one CNS drug abuse/overdose report in our analysis. Underreporting may impact on the reporting activity of countries less used to reporting, such as those from Asia, Africa, South America, and Oceania [38]. The reporting activity varied substantially across countries, with the USA having reporting rates of more than 50%. In Europe, countries contributing the highest number of reports were France (9.5%), Germany (9.2%), and the UK (4.7%), possibly because these countries have been members of the WHO Programme for International Drug Monitoring for a long time [1]. The extensive use of CNS agents among children in these countries is probably another explanation for the higher numbers of reports of analgesics, psycholeptics, and psychoanaleptics overdoses we detected [43].

Overall, "intentional overdose" was reported more frequently than "accidental overdose", with a difference between age groups in that ICSRs concerning adolescent females were higher in number than in male children, infants, and newborns. The data is consistent with other studies on the general population, which have similarly shown that female adolescents are more likely to have suicidal tendencies and to contemplate suicide [31, 42], while in the context of major depression, adolescent males have been reported to be at higher risk than females [39].

To date, little data is available on drug abuse or overdose in children under 12 years old worldwide; most reports are related to specific drugs and derive from safety communications by Medicine Agencies (i.e. dextromethorphan [41], codeine [47]), or from studies carried out in specific settings [2]. Our analysis showed that the drugs involved in both intentional and accidental overdose in children differ from those observed in the other three analysed groups: we detected antiepileptics (carbamazepine), psychoanaleptics (sertraline, mirtazapine, amitriptyline), and psycholeptics (risperidone, olanzapine). Although in young children, ingestions of carbamazepine are often unintentional [28], this antiepileptic drug was reported as a suspect drug in all cases of intentional overdose we detected. The intentional overdose potential of carbamazepine due to its euphorigenic effects has been previously reported in adults [21] and many studies have suggested that carbamazepine may have psychotropic actions; so, it is not surprising that carbamazepine is used to produce occasional emotional reactions [21]. This pattern is likely to be attributed to the exploratory behaviours and curiosity of this age group [28].

Significantly, our findings suggest that when CNS drugs are overdosed, either intentionally or accidentally, they can lead to death among children, including the youngest; an increase in the overdose was reflected in an increase in the number of deaths. The highest number of deaths was detected among adolescents and most of them were due to intentional overdose, suicide, and other serious adverse events with fatal

Table 2 Serious ADR reports in different age groups with MedDRA preferred terms: accidental overdose, intentional overdose, and overdose

PT terms	No. of serious ADR reports	Most frequent suspected drugs (percentage of no. of reports drug involved in specific age group)	Most frequent reported co-PT (percentage of no. of reports in specific age group)
Adolescent			
Accidental overdose	176	Oxycodone (10.6), paracetamol (8.5), morphine (6.5), and alprazolam (5.0)	Somnolence (3.9), vomiting (3.7), medication error (3.2) substance use disorder (2.8), and toxicity to various agents (2.7)
Intentional overdose	1.014	Paracetamol (16.9), and quetiapine (3.1)	Suicide attempt (5.2), tachycardia (3.2), vomiting (3), and somnolence (2.1)
Overdose	897	Paracetamol (14), bupropion (4.4), oxycodone (4), quetiapine (3.9), and methylphenidate (3.7)	Suicide attempt (4.4), toxicity to various agents (2.6), drug use disorder (2.3), somnolence (2.2), and vomiting (2.2)
Children			
Accidental overdose	302	Paracetamol (17.6), risperidone (4.5), olanzapine (3.9), morphine (3.9), and clonidine (3.7)	Somnolence (3.9), accidental exposure to product (3.7) vomiting (1.9) toxicity to various agents (1.5), and lethargy (1.4)
Intentional overdose	19	Carbamazepine (19), sertraline (14), paracetamol (5), mirtazapine (5), and amitriptyline (5)	Toxicity to various agents (6.1), vomiting (4.5), serotonin syndrome (4.5), dystonia (3), and confusional state (3)
Overdose	314	Paracetamol (16), clonidine (5), oxycodone (4), and methylphenidate (3)	Toxicity to various agents (4.2), somnolence (4), vomiting (3.2), seizure (2.6), and coma (1.8)
Infants and toddlers			
Accidental overdose	170	Paracetamol (21.5), lidocaine (5.4), oxycodone (4.8), and levetiracetam (3.8)	Somnolence (4.3), accidental exposure to product by child (3.3), toxicity to various agents (3.1), tachycardia (3.0), and vomiting (2.4)
Intentional overdose	14	Paracetamol (25.1), oxycodon (8.5), methadone (4.2), and fentanyl (2.3)	Toxicity to various agents (3.7), unresponsive to stimuli (2.7), off-label use (2.0), seizure (1.9), and accidental exposure to product by child (1.9)
Overdose	189	Paracetamol (26.5), oxycodone (8.5), methadone (4.2), and fentanyl (2.3)	Toxicity to various agents (3.7), unresponsive to stimuli (2.7), off-label use (2.0) seizure (1.8), and respiratory arrest (1.6)
Newborns			
Accidental overdose	40	Paracetamol (16.7), morphine (11.5), phenobarbital (6.3), methadone (4.2), and fentanyl (3.1)	Medication error (4.7), seizure (2.8), incorrect dose administered (2.8), apnoea (2.8), and no adverse event (2.8)
Intentional overdose	0	–	–
Overdose	43	Paracetamol (16.1), oxycodone (10.7), propofol (5.4), tramadol (5.4), and levetiracetam (5.4)	Medication error (4.3), seizure (3.3), incorrect dose administered (2.7), toxicity to various agents (2.7), and somnolence (2.2)

outcome (including hypoxic-ischemic encephalopathy, brain death and cardio-respiratory arrest). Similar patterns among serious ICSRs were detected also for deaths due to drug overdose among infants and children. Exposure during pregnancy and breastfeeding to methadone, morphine, and cocaine caused death due to respiratory depression, cerebral haemorrhage, and metabolic acidosis, among newborns and infants.

Paracetamol and opioid analgesics, or their combinations, were the most common suspect drugs in death across all age groups. The easy access to paracetamol could be one of the first causes of drug overdose deaths, not only for the adult population but also among younger children, resulting in a public health burden [12]. Although the risk of developing toxic reactions to paracetamol appears to be lower in children

Table 3 Number of reports with mortality outcome and most frequent suspected drugs with reported ADRs in different paediatric age groups

Age groups	No. of reports of mortality	Most frequent suspected drugs reported with fatality in specific age group; n (%)	Most frequent reported ADRs SOCs: [ADRs by MedRA-PTs (n)]
Adolescents	538	Oxycodone 99 (7.7), paracetamol 79 (6.1), alprazolam 73 (5.7), methadone 59 (4.6), hydrocodone; paracetamol 54 (4.2), morphine 49 (3.8), quetiapine 36 (2.8), fentanyl 30 (2.3), and dextromethorphan 27 (2.1)	Nervous system disorders: seizure (22), unresponsive to stimuli (17), coma (12), loss of consciousness (10), and hypoxic-ischemic encephalopathy (7) Psychiatric disorders: drug abuser (8), suicide attempt (8), suicidal ideation (6), depression (3), and insomnia (2) Injury, poisoning, and procedural complications: toxicity to various agents (245), overdose (103), intentional overdose (60), accidental overdose (49), intentional product misuse (39), and brain oedema (11) Cardiac disorders: cardio-respiratory arrest (56), cardiac arrest (53), tachycardia (7), pulmonary congestion (6), and pulmonary oedema (6) General disorders and administration site conditions: completed suicide (128), death (35), brain death (11), drug interaction (6), pyrexia (5) Investigations: drug level increased (5), drug level above therapeutic (2), electrocardiogram QT prolonged (2), analgesic drug level increased (2), and drug screen positive (2)
Children	226	Paracetamol 39 (9.9), oxycodone 29 (7.4), methadone 20 (5.1), fentanyl 15 (3.8), valproic acid 13 (3.3), buprenorphine 13 (3.3), clonidine 12 (3.1), codeine 11 (2.8), morphine 11 (2.8), and quetiapine 10 (2.5)	Injury, poisoning, and procedural complications: toxicity to various agents (125), overdose (70), accidental overdose (30), accidental exposure to product by child (26), and intentional product misuse (14) General disorders and administration site conditions: death (26), drug interaction (8), pyrexia (3), malaise (3), condition aggravated (2) Nervous system disorders: unresponsive to stimuli (15) loss of consciousness (11), hypoxic-ischemic, encephalopathy (8), seizure (8), and respiratory depression (7) Respiratory, thoracic, and mediastinal disorders: respiratory arrest (15), aspiration (6), respiratory failure (4), apnoea (4), and wheezing (2) Cardiac disorders: cardio-respiratory arrest (17), cardiac arrest (10), pulmonary oedema (6), bradycardia (5), and dyspnoea (2)
Infants and toddlers	207	Oxycodone 31 (8.6), paracetamol 30 (8.4), methadone 29 (8.1), pseudoephedrine 16 (4.5), morphine 15 (4.2), alprazolam 15 (4.2), dextromethorphan 13 (3.6), fentanyl 11 (3.1), amitriptyline 9 (2.5), and clonazepam 8 (2.2)	Injury, poisoning, and procedural complications: toxicity to various agents (124), overdose (54), accidental overdose (18), wrong drug administered (16), and accidental exposure to product by child (15) Nervous system disorders: unresponsive to stimuli (19), hypoxic-ischemic encephalopathy (10), loss of consciousness (10), respiratory depression (6), and seizure (5)

Table 3 (continued)

Age groups	No. of reports of mortality	Most frequent suspected drugs reported with fatality in specific age group; n (%)	Most frequent reported ADRs SOCs: [ADRs by MedRA-PTs (n)]
			Respiratory, thoracic, and mediastinal disorders: respiratory arrest (19), apnoea (4), aspiration (4), respiratory failure (2), and bronchitis (1) Investigations: drug level increased (8), drug screen positive (8), pulse absent (3), analgesic drug level above therapeutic (2), and blood culture positive (2) Vascular disorders: cyanosis (7), hypotension (4), adrenal haemorrhage (3), central nervous system necrosis (2), and pallor (2)
Newborns	26	Methadone 11 (20.8), diamorphine 4 (7.5), morphine 3 (5.7), fluoxetine 3 (5.7), promethazine 2 (3.8), oxycodone 2 (3.8), clonazepam (1.9), caffeine; codeine; paracetamol (1.9)	Injury, poisoning, and procedural complications: toxicity to various agents (7), accidental overdose (6), foetal exposure during pregnancy (6), exposure during breast feeding (4), and overdose (3) Nervous system disorders: respiratory depression (2), agitation neonatal (1), cerebral haemorrhage (1), cerebral haemorrhage neonatal (1), and cerebral infarction (1) Respiratory, thoracic, and mediastinal disorders: hypoxia (2), neonatal respiratory distress syndrome (2), bronchopulmonary dysplasia (1), influenza (1), and middle lobe syndrome (1) Infections and infestations: pneumonia (2), cytomegalovirus infection (1), device related infection (1), Epstein Barr virus infection (1), and herpes simplex (1) Metabolism and nutrition disorders: metabolic acidosis (3), hyperkalaemia (2), acidosis (1), alkalosis (1), and hyperglycaemia (1)
Total	997	–	–

than in adults, such reactions occur in paediatric patients from intentional overdoses [26]. Moreover, the symptoms of paracetamol intoxication are nonspecific, thus the diagnosis and treatment of paracetamol intoxication are more likely to be delayed in unintentional cases of toxicity. Patterns of ADRs we detected suggest the occurrence of paracetamol intoxication, including serious events such as encephalopathy with fatal outcome [30]. The perceived safety of paracetamol may contribute to delays in diagnosis and treatment of paracetamol intoxication, although fatal outcomes, above all in younger children, may be avoided by using the antidote for paracetamol toxicity, N-acetylcysteine.

Our analysis shows a difference in terms of drugs involved in overdose deaths across different countries; the majority of paracetamol overdose deaths were detected in the USA (815; 81.7% of total fatalities) and the UK (73; 7.3%); paracetamol and/or its combination products were the most frequently reported suspects in ADR-related death ICSRs. Notably, we identified 23 ADR-related death ICSRs in which both paracetamol and its combination products were reported as suspects. Lack of knowledge about maximum recommended daily dosages and failure to recognise duplicate therapies can contribute to inadvertent paracetamol overdose. Therapeutic duplication involving multiple paracetamol-containing products may lead to an increase in the cumulative dose above the maximum recommended daily dosage. To prevent this issue, in 2014, the Food and Drug Administration (FDA) issued a statement urging health professionals to discontinue the prescription and dispensing of combination drug products containing more than 325 mg of paracetamol per dose [46].

Table 4 Top 10 countries by number of reports with mortality

Country	Number of ICSRs with death *n* (%)	Most frequent suspected drugs (*n*)
USA	815 (81.7)	Oxycodone (155), paracetamol (117), alprazolam (95), methadone (75), hydrocodone; paracetamol (60), morphine (51), fentanyl (44), and dextromethorphan (44)
UK	73 (7.3)	Paracetamol (23), methadone (21), tramadol (6), dosulepin (5), codeine (4), amitriptyline (4), citalopram (4), diamorphine (4), diazepam (4), and dihydrocodeine (4)
Germany	30 (3)	Methadone (6), morphine (6), codeine (4), paracetamol (4), fentanyl (3), cocaine (2), and hydromorphone (2)
Canada	17 (1.7)	Fentanyl (6), morphine (5), methadone (3), oxycodone (2), amphetamine (2), and paracetamol (1)
Austria	10 (1)	Morphine (9), flunitrazepam (2), oxazepam (2), buprenorphine (1), codeine (1), diazepam (1), and dihydrocodeine (1)
Italy	10 (1)	Methadone (9), buprenorphine (1), and naloxone (1)
Australia	10 (1)	Paracetamol (4), morphine (3), promethazine (1), quetiapine (1), tramadol (1), alprazolam (1), and oxycodone (1)
France	10 (1)	Methadone (4), codeine (2), morphine (1), paracetamol (1), and diamorphine (1)
Belgium	5 (0.5)	Alprazolam (1), methylphenidate (1), pipamperone (1), tramadol (1), and venlafaxine (1)
Croatia	4 (0.4)	Fentanyl (2), methadone (1), and antidepressants (1)
Other	13 (1.3)	–

Despite this, our analysis recorded 17 ADR-related death ICSRs from the USA between 2012 and 2017, reporting the simultaneous use of multiple paracetamol-containing products as suspects. Likewise, in 2011, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK announced that paracetamol dosing instructions for children were to be changed by the end of 2011 [3]. Despite these safety efforts, according to our findings, duplication of paracetamol-containing products continues to be a public health problem. Additional measures are needed to ensure the safe use of OTC medications.

In our analysis of ADR-related death ICSRs, oxycodone was recorded as the most frequent suspect drug in almost all top reporting countries, with a sharp increase in the number of death reports that involved oxycodone as a suspect drug between the year 2014 and 2015, suggesting the need to implement strategies of risk-minimisation worldwide. We identified 26 death reports in the USA in our analysis, which involved codeine as a suspect drug; this may be due to the fact that many low-dose codeine-containing OTC medicines are available in some states of the USA. A 2012 review of paediatric deaths linked to codeine use resulted in an FDA boxed warning,

Table 5 Count of paracetamol and/or oxycodone deaths by country, year, age groups, and ADRs

Drug/drug combination	No. of death reports	Country of death reports (*n*)	Year of report (*n*)	Age group (*n*)	Adverse drug reactions reported
Paracetamol	154	USA (212), UK (25), Australia (4), Germany (4), and Canada (2)	2007 (1), 2008 (32), 2009 (27), 2010 (31), 2011 (27), 2012 (37), 2013 (3), 2014 (35), 2015 (37), and 2016 (17)	Adolescents (160), children (53), infants and toddlers (33), and newborns (1)	Cardio-respiratory arrest (22), cardiac arrest (15), acute hepatic failure (13), hepatic failure (12), liver injury (11), hepatic necrosis (11), seizure (10), hypotension (7), coagulopathy (7), hypoxic-ischaemic encephalopathy (7), brain death (6), renal failure (6), hepatic encephalopathy (5), encephalopathy (4), hepatotoxicity (3), and ischemic hepatitis (2)
Hydrocodone; paracetamol	62				
Diphenhydramine; paracetamol	17				
Oxycodone; paracetamol	16				
Chlorphenamine; dextromethorphan; paracetamol	8				
Oxycodone	161	USA (169), UK (2), Canada (2), Australia (1), and Denmark (1)	2008 (17), 2009 (18), 2010 (23), 2011 (11), 2012 (15), 2013 (6) , 2014 (35) ,2015 (27), 2016 (18), and 2017 (5)	Adolescents (110), children (32), infants and toddlers (31), and newborns (2)	Respiratory arrest (18), cardio-respiratory arrest (12), cardiac arrest (10), substance use disorder (9), brain death (2), somnolence (2), and respiratory depression (2)

restricting its use below 18 years of age. Despite this warning, some children continue to be prescribed codeine, and other opioid prescriptions for children have continued to increase since then. Consequently, in early 2018, the FDA further restricted the use of codeine below 12 years of age [47], while Australia's Therapeutic Goods Agency re-categorised codeine-containing analgesics to "prescription only" medicines [13].

The strength of this study is that the source data consisted of all paediatric ADR reports connected with drug abuse and overdose entered in VigiBase over a 10-year period. VigiBase collects ADR ICSRs from most countries worldwide, reflecting real-life prescriptions and adverse events, even those not studied in clinical trials. The most prominent limitation is to know the exact causal relationship between drug use and ADRs, typical of pharmacovigilance database studies. However, ADRs we detected are in line with the toxicity profile of CNS drug abuse/overdose. Secondly, VigiBase reports are heterogeneous with respect to ethnicity, national reporting behaviour, available drug substances, and prescription regulations may vary both between countries and over time.

Conclusion

The number of paediatric ADR reports associated with drug abuse and overdose (above all for opioid and paracetamol-containing products) is increasing worldwide and a considerable number of ADRs are serious. Data on the patterns of use of such medicines from each country can help to implement strategies of risk-minimisation and renew healthcare recommendations worldwide, including specific programmes of education and rehabilitation. Increased clinical awareness is essential to help reduce prescription drug abuse and overdose, while continuing to provide effective treatments.

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Authors' Contributions Dr. C. Carnovale conceptualised and designed the study, interpreted the data drafted the manuscript, and revised and approved the final manuscript as submitted.

Dr. F. Mahzar participated in the conceptualisation and design of the study, carried out the initial analyses, revised the manuscript, and approved the final manuscript as submitted.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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