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ORIGINAL ARTICLE

Social media as a source of drug safety information in the paediatric population

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Aims: The paediatric population is vulnerable to suffering adverse drug events (ADEs) such as negative outcomes due to medication (NOMs)–drug related problems (DRPs), especially adverse drug reactions (ADRs) and medication errors (MEs). Social media (SM) is considered an interesting tool for pharmacovigilance. This study aims to assess descriptions of ADRs, NOM-DRPs and MEs in SM.

Methods: Observational, ambispective study assessing NOM-DRPs, ADRs and MEs in posts of child-rearing public parenting forums from inception until December 2021 of drugs dispensed in outpatient setting. ADEs were classified, assessing causality by Liverpool Causality Assessment Tool and seriousness by the World Health Organization criteria. Summary of product characteristics were used to determine ADR prevalence.

Results: In total, 3573 posts of 2 child-rearing public parenting forums were retrieved; 906 (25%) contained descriptions of medicine of which 823 (91%) were analysed; 425 posts (52%) described 636 NOM-DRPs (1 NOM-DRP median per child, interquartile range [IQR] 1–8), from which 161 (26%) were ADRs in 105 posts (1.5 ADR median per child, IQR 1–4) and 95 (15%) were MEs in 64 posts (1 ME median per child, IQR 1–4). From posts mined with medicines mentions, 70% included NOM-DRPs, 18% ADRs and 10% MEs. More ADRs occurred in females and infants. Most ADRs (158; 98%) were evaluated as possible and 17 ADRs (11%) were serious. Uncommon 19 (12%), (14, 9%), very rare (3, 2%) and rare (1, 1%) ADRs were also found.

Conclusion: Results suggest that information retrieved from SM may be useful to assess paediatric ADEs and provide valuable pharmacovigilance complementary data.

KEYWORDS
drug safety, paediatrics, pharmacovigilance

1 | INTRODUCTION

The paediatric population is a heterogeneous population vulnerable to ADEs due to their immaturity, lack of age-appropriate medicines and data from clinical trials.[1–4] ADEs are defined as "any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment", and it includes several terms such as drug-related

problems (DRPs), which are undesirable events experienced by the patient in which drugs are suspected or known to interfere with the desired outcome.[5,6] DRPs could be caused by several problems or negative outcomes to medication (NOMs): situations in which the patient is at risk of disease due to the existence of the DRP.

The most relevant DRPs are medication errors (MEs) and adverse drug reactions (ADRs). While an ME may be preventable,[7] ADRs may not unavoidable because in some cases individual or unknown factors may play a role in their occurrence.[8]

ADEs, although recorded on yellow cards in many countries, are underreported[4]; thus, observational studies could fill this information gap. Social media (SM) has recently gained relevance as a valuable source of pharmacovigilance data by multistakeholder projects (Web-RADR) and regulatory agencies.[9,10] Child-rearing public parenting forums (CPPFs) can be considered a niche area for pharmacovigilance in paediatrics, as parents share their child's health experiences.[11,12] This niche SM can be more efficient in extracting valuable information than other SM such as Twitter.[10]

Currently, SM is used to gather information on paediatric-specific topics such as vaccine hesitancy,[13] ADRs,[14] adherence[15] and age-specific concerns in the use of medicines.[16] However, to date, no studies with a more holistic approach have provided a realistic evaluation of SM as a pharmacovigilance tool. For this reason, this study aimed to assess whether SM could be used to detect ADRs in the paediatric population by analysing CPPF entries (CPPFEs). The secondary objective was to identify the NOMs, DRPs and MEs in these entries.

What is already known about this subject

- Information obtained from social media can provide signals for detection of adverse drug events (ADEs).
- Forums dedicated to a specific topic or population can provide pharmacovigilance data.
- It is not known if information in forums posts contain sufficient information to assess drug reactions.

What this study adds

- Social media is a source of information on ADEs in paediatrics.
- In paediatrics, ADE-related information is high in niche forums such as child-rearing public parenting forums, especially when focusing on posts that contains drug comments.
- Information in posts allows assessment of adverse drug reactions in many cases.

2 | METHODS

An observational, longitudinal, ambispective study was conducted on CPPFEs to analyse NOMs, DRPs, ADRs and MEs in children from CPPF inception to December 2021. For CPPFE analysis, a pilot data-mining software program was developed tested on a limited number of CPPFs. To our knowledge, there are no guidelines for selecting CPPFs; hence, we followed the methodology from prior similar studies in which search engines were used to identify suitable CPPF.[13,15] In similar studies, researchers used Google to search using specific keywords for specific topics[13,15] and reviewed the first 1–3 pages of search results. In this study, CPPFs were identified by employing keywords in 3 different languages *Parents' Forum* (English), *Forums de padres* (Spanish) or *Fòrums de pares* (Catalan) to search twice for each keyword via Google between 4th January 2021 to 13th January 2021. The first 10 pages of Google results were evaluated Google were chosen because it accounts for >80% of the world's searches from 2010–2022.[16]

Permission was requested by writing to administrators via private messages and, when necessary, writing an open post explaining the current study. After permission was granted by administrators or after 1 month without receiving a response to the open post, the CPPF was considered for analysis. Afterwards, existing posts from inception to December 2021 and those written in the next 11 months were examined. The CPPFs and post inclusion and exclusion criteria are summarized in Table 1. The study received ethics committee approval from the University of Barcelona Institutional Review Board (IRB00003099).

Posts were retrieved via ontologies. Active pharmaceutical ingredients or brand names were detected from the AEMPS nomenclator, and ADRs from the Medical Dictionary for Regulatory Activities (MedDRA) ontology.[17] To overcome the actual limitations of the process of mining ADRs from SMs (i.e., medicines or symptoms misspelled or using argot not described in ontologies), data were evaluated qualitatively by authors.[18]

Demographic data (sex and age), notifier kinship (parent, caregiver or other and sex), number of CPPFEs mentioning medicines per language, drug name, administration route and problem reported were analysed. In Mumsnet CPFFs, users use argot to simplify kinship and age (e.g., DD = dear daughter, DS = dear son, LO = little one), which was annotated, reviewed via Urbandictionary.com, circulated among the investigators and considered for analysis in the absence of quantitative data. Sex was extracted if mentioned in the post or pronouns were stated, in the absence of argot.

In socpetit.cat, demographic data can be identified. The child's age was extracted if mentioned in the post, and in the absence of such mention, the age was determined based on the subforum where the post was written (i.e., subforums for 0–12 months and 12–36 months). Moreover, notifiers and child-affected sex and kinship were identified by pronouns or words related to sex and were directly extracted when mentioned. No argot was identified regarding kinship in this forum.

Child age was classified according to the CPFF's classification, only in socpetit.cat, and according to the ICH E11(R1)-step 5-guideline on clinical investigation of medicinal products in the

TABLE 1 Inclusion and exclusion criteria of CPPF and CPPFEs.

	Inclusion	Exclusion
Child-rearing public parenting Forums	Child-health sections Catalan, Spanish or English Posted by parents, caregivers or paediatric patients *Drugs dispensed in outpatient setting** Written permission to be included in the study.	Private forums, requiring registration to read the posts, Forum user guide mentions not allowing analysing posts, including for research purposes. <10 entries discussing drugs per thread, User or forum admin denying permission to use data Disease-specific forums.
Child-rearing public parenting Forums Entries	Mention to medicines Medicine administered to children aged 0–18 years	Nonoriginal entries (e.g., links to news or from industry) Duplicates written by healthcare professionals Other languages Pregnancy or adult exposure Medicines administered during hospitalization, intravenous drugs or hospital use dispensing drugs, Nonpharmacological measures or products not considered drugs according to the Spanish Agency of Medicines and Medical Devices such as vitamin supplements, physiotherapy and homoeopathy

*According to the current Spanish legislation (*Royal Legislative Decree 1/2015, of 24 July, which approves the consolidated text of the Law on guarantees and rational use of medicines and health products*).

paediatric population categories. More than 1 notifier per post was considered if a notifier of a post also referred to someone else's comment. The total extraction percentage was calculated by dividing the number of posts with NOMs-DRPs, ADRs or MEs by the total number of posts retrieved from the 2 CPPFs. Specific percentage of extraction was obtained by dividing the number of posts of each item by the total number of posts containing data regarding medicines.

The active pharmaceutical ingredients were classified via the Anatomical Therapeutic Classification[19] code. DRPs were stratified by the Third Consensus of Granada (TCG)[6] and the Pharmaceutical Care Network Europe (PCNE) v9.1,[20] considering NOMs by TCG as DRP problems by PCNE and DRP as DRP causes by PCNE.

ADRs were determined according to the World Health Organization definition. An ADR is defined as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".[8] An ME is any preventable event that may cause or lead to inappropriate medication use or patient harm when the medication is under the control of the healthcare professional, patient or consumer.[4] Off-label use was assessed when the indication or the patient's age was different from the summary of product characteristics (SmPC) recommendations. No unlicensed medicines, defined as those for which no marketing authorization has been granted by a relevant licensing authority,[21] were considered.

For all included ADRs, organ affected, causality, seriousness and prevalence were analysed. Affected organs were classified by MedDRA[17] using the preferred term Causality was assessed by Liverpool Causality Assessment Tool (LCAT), as to our knowledge, it is the only assessment tool developed for children.[22] Seriousness was analysed according to World Health Organization criteria.[8] ADR prevalence was categorized following the SmPC, which classifies ADRs according to the *Guidelines for Preparing Core Clinical Safety information on Drugs of the CIOMS III Working Group*[23] as unknown (if it cannot be estimated from the available data), very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000) and very rare (<1/10 000).

MEs were categorized by American Society of Health-System Pharmacists classification,[24] and their seriousness was determined by the National Coordinating Council for Medication Error Reporting and Prevention National Coordinating Council for Medication Error Reporting and Prevention index[25] and according to who caused the errors.

For each post with relevant information, a quantitative, descriptive analysis including tables of frequencies and percentages for categorical variables was conducted.

3 | RESULTS

The first 2 CPPFs that met all the inclusion criteria and none of the exclusion criteria were socpetit.cat and mumsnet.com (Table S1). Socpetit.cat includes sections grouped by ages 0–12 months, 12–36 months, 3–5 years and above 8 years, whereas mumsnet.com does not classify posts by age.

3.1 | Total number of posts retrieved

In total, 3573 CPPFEs were reviewed, of which 906 (25%) mentioned medicines, excluding 83 (9%) due to 95 references to hospital medicines (28, 29%) or use by adults (11,12%), nonpharmacological treatments (44, 46%), pregnancy (2, 2%), nonoriginal entries (9, 9%) or duplicates (1, 1%; Figure 1).

Ultimately, 823 (91%) posts were analysed. A total of 398 (48%) posts included discussions about drugs without any ADRs, NOMs-DRPs or MEs. Instead, the 425 remaining posts (52%) described

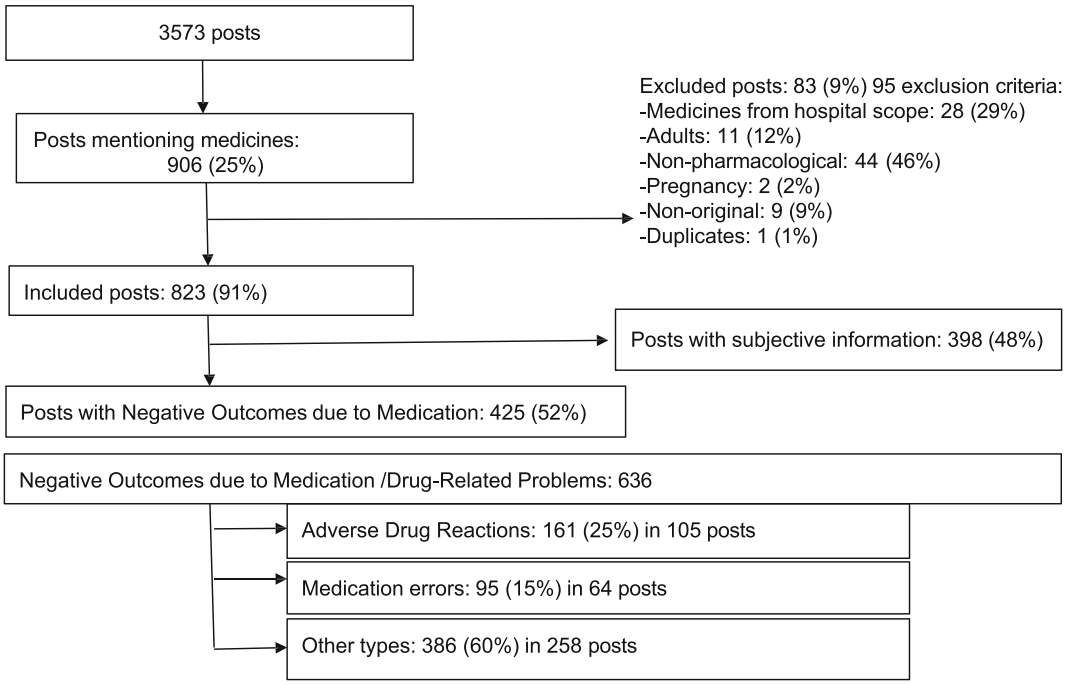

FIGURE 1 Flow diagram of posts reviewed and information extracted.

636 NOMs-DRPs (median: 1 NOM-DRP per child, interquartile range [IQR] 1–8), of which 105 posts mentioned 161 (25%) ADRs (median: 1 ADR per child, IQR 1–4) and 95 (15%) mentioned MEs (Figure 1) in 64 posts (median: 1 ME per child, IQR 1–4). The data extracted from the 3573 total posts retrieved were 18% for NOMs and DRPs, 5% for ADRs and 3% for MEs, whereas the data extracted from the 906 posts with medical information increased to 70% for NOMs and DRPs, 18% for ADRs and 10% for MEs. Reviewed posts were written in Catalan (485, 59%), English (325, 39%) and Spanish (13, 2%). More than 1 notifier per post was found, as some notifiers shared other people's experiences. Most notifiers (825) described themselves as parents (364, 44%) or caregivers (419, 51%), whereas other notifiers were not assessable (32, 4%) or had other relationships to the children (10,1%). Sex was not disclosed in most cases (784, 95%), but when this factor was identified, females were found to write more posts (40, 5%) than males did (1, 0%).

3.2 | Adverse drug reactions

A total of 161 (25%) ADRs in 105 children (median = 1, IQR 1–4) were reported. ADRs were more commonly reported in females (58, 55%) than in males (42, 40%), although the sex could not be identified in 5 (5%) cases. ADRs mostly occurred in infants (44, 42%), 0–12-month-old infants (17, 17%) and 12–36-month-old toddlers (14, 13%). No ADRs were reported in newborns (0/4), and few were reported in children (12, 11%) or adolescents (7/30, 7%). A total of 134 medicines were reportedly associated to 161 ADRs, with the 5 most common being unspecified vaccines (39, 29%), antibiotics (29, 22%), ibuprofen (10, 7%), paracetamol (10, 7%) and proton-pump inhibitors (4, 3%). The medicines were mostly administered via the oral (91, 57%), parenteral (58, 36%), topical (4, 2%) and rectal (1, 1%) routes. In 2 (1%) posts, the route of administration could not be assessed.

The most reported ADRs were diarrhoea (15, 9%), pyrexia (12, 7%), rash (9, 6%), acne (8, 5%), vomiting (7, 4%) and abdominal pain (6, 4%). Causality evaluation suggested that most ADR causalities were possible (158, 98%), and few were unlikely (3, 2%). A total of 64 (40%) entries did not mention any specific drug; thus, the frequency of ADRs could not be determined. The ADRs with identifiable drugs were mostly common (24, 15%) or very common (11, 7,5%). A non-negligible number of 18 ADRs (12%) were either uncommon (14, 9%), very rare (3, 2%) or rare (1, 1%). Among the ADRs described in the SmPC, 40 (25%) were not described, and the prevalence of 4 (2%) ADRs was unknown (Table 2).

Seventeen ADRs (11%) were considered serious adverse events (SAEs), and the remaining ADRs (144, 89%) were considered nonserious (Table 2). Information from the entries allowed the determination of severity, including information about visits to hospital or emergency room and life-threatening symptoms. Causality could be assessed despite the lack of objective evidence such as laboratory investigations or positive rechallenge (Table 3).

3.3 | Negative outcomes due to medications and drug-related problems

A total of 636 NOMs or DRP problems by PCNE, were identified in 428 children (median: 1, IQR 1–8). NOMs were more prevalent in females (220, 51%), 181 males (42%), 27 (6%) inaccessible sex,

TABLE 2 Analysis of adverse drug reactions (ADRs) with low prevalence (very rare, rare, not known prevalence) or without described prevalence according to Summary of Product Characteristics (SmPC).

Active ingredient (keyword mentioned in post) causing ADRs	Number of ADRs/number of patients	Route	MedDRA PT	Prevalence	Probability by LCAT
Paracetamol	9/8	Oral	Abdominal pain upper	No prevalence in SmPC	Possible
			Somnolence	No prevalence in SmPC	Possible
			Heart rate increased	No prevalence in SmPC	Possible
			Loss of consciousness	No prevalence in SmPC	Possible
			Rash	Very rare	Possible
			Cough (×2)	No prevalence in SmPC	Possible
			Vomit	No prevalence in SmPC	Possible
Ibuprofen	4/3	Oral	Cough	No prevalence in SmPC	Possible
			Transaminases increased	No prevalence in SmPC	Possible
			Blood alkaline phosphatase increased	No prevalence in SmPC	Possible
			Heart rate increased	No prevalence in SmPC	Possible
			Rash	**Uncommon**	**Unlikely**
Amoxicillin	5/3	Oral	Decreased appetite	No prevalence in SmPC	Possible
			Pain	No prevalence in SmPC	Possible
			Acne	No prevalence in SmPC	Possible
			Flatulence	No prevalence in SmPC	Possible
			Gastroenteritis	No prevalence in SmPC	Possible
Prednisolone Steaglate	2/1	Oral	Somnolence	No prevalence in SmPC	Possible
Dimenhydrinate	1/1	Oral	Lethargy	No prevalence in SmPC	Possible
Lactulose	1/1	Oral	Anal fissure	No prevalence in SmPC	Unlikely
Salbutamol	1/1	Unknown	Cough	No prevalence in SmPC	Possible
Acetylcysteine	1/1	Oral	Cough	No prevalence in SmPC	Possible
Chlorphenamine maleate	1/1	Oral	Sting	No prevalence in SmPC	Possible
			Crying	No prevalence in SmPC	Possible
			Urticaria	Unknown	Possible
Meveberine	2/1	Oral	Nausea	No prevalence in SmPC	Possible
			Pain	No prevalence in SmPC	Possible
Domperidone	1/1	Oral	Pain	No prevalence in SmPC	Possible
Miconazole nitrate, hydrocortisone	1/1	Topical	Pain of skin	No	Possible
Lansoprazole	1/1	Oral	Sleep disorder	No prevalence in SmPC	Possible
Magnesium alginate, sodium alginate	1/1	Oral	Nausea	Not in SmPC	Possible
	1/1	Oral	Constipation	Very rare	Possible
	1/1	Oral	Abdominal pain	Not in SmPC	Possible
Varicella-zoster vaccine (varicella vaccine)	1/1	Parenteral	Mouth ulcer	Rare	Possible
Rotavirus Vaccine	1/1	Oral	Flatulence	Not in SmPC	Possible
Metronidazol	1/1	Oral	Diarrhoea	Unknown	Possible
Penicillin	1/1	Oral	Crying	Not in SmPC	Possible

Abbreviations: LCAT, Liverpool Causality Assessment Tool; PT, preferred term; SmPC, summary of product characteristics.

infants (148, 35%) and children (116, 27%). The drugs most frequently involved in NOMs were antibacterials (94, 15%), analgesics (86, 14%), vaccines (79, 12%), anti-inflammatory/antirheumatic products (50, 8%) and drugs for treating obstructive airway diseases (46, 7%), which were administered mainly via the oral (426, 67%), parenteral (74, 11%) or topical (58, 9%) routes. Regardless of the classification used, NOMs/DRPs problems nonquantitative ineffectiveness (319, 50%), safety problems (245, 39%) and, less frequently, untreated health problems (56, 9%) and unnecessary medicines or treatment (16, 3%). Likewise, the identified DRPs comprised

TABLE 3 Description of serious adverse events (SAEs).

Age	Sex	Drug	AE causality	AE probability	SAE description (MedDRA PT)	SAE categorization
Infant	F	Vaccine	Possible	---	Unresponsive to stimuli	Hospitalization
Infant	F	Antibiotic	Possible	---	Hypothermia	Life-threatening symptom
0–12 months	M	Amoxicillin/clavulanic acid[a]	Possible	Uncommon	Acne	Symptoms are related to an allergic reaction, mentions a visit to the ER. A potential life-threatening symptom
		Ibuprofen[a]	Possible	Uncommon	Acne	
		Paracetamol[a]	Possible	Prevalence not in SmPC	Acne	
		Amoxicillin[a]	Possible	Common	Acne	
Infant	M	Paracetamol	Possible	Prevalence not in SmPC	Loss of consciousness	Hospitalization
Child	M	Dimenhydrinate	Possible	Prevalence not in SmPC	Lethargy	Life-threatening symptom
12–36 months	M	Paracetamol[a]	Possible	Prevalence not in SmPC	Cough	Symptom described appears as cough but it can be a bronchospasm, visit to the ER A potential life-threatening symptom
		Ibuprofen[a]	Possible	Prevalence not in SmPC	Cough	
		Paracetamol[a]	Possible	Prevalence not in SmPC	Cough	
12–36 months	F	MMR vaccine	Possible	Prevalence not in SmPC	Hypothermia	Hospitalization
		MMR vaccine	Possible	Prevalence not in SmPC	Pallor	
Child	M	Unknown medication	Possible	----	Musculoskeletal stiffness	Symptom described is musculoskeletal stiffness but it can be a convulsion, thus, a potential life-threatening. An electroencephalogram was done to confirm.
Infant	F	Antibiotic	Possible	----	Rash	Hospitalization
Unknown	F	Penicillin[a]	Possible	Prevalence not in SmPC	Inconsolable crying.	Multiple visits to ER, other cause likely but only refers to inconsolable crying. A potential life-threatening.
		Antibiotic[a]	Possible	----	Abdominal pain	Hospitalization

[a]Adverse drug event attributable to more than one drug.
Abbreviations: ER, emergency room; PT, preferred term.

insufficiently treated health problems (273, 43%) and probable AEs (161, 25%), personal characteristics (such as child reluctance to use the medicine or the belief that the child was susceptible to a certain condition; 46, 7%) and contraindications (27, 4%; Table 4). In 61 cases, DRPs were classified under the *Other* category, which mainly included difficulties in administering medicines to children (51, 84%) but also included nonprescribed medicine use (3,5%), administrative issues such as reimbursement of medicines (4, 7%), medicine stockouts (2, 3%), or family members influencing the treatment decision (1, 1%).

Off-label use was found in 62 (10%) entries, and such use mostly involved cough and cold preparations (16, 26%) and antihistamines (6, 10%). Dermatological corticosteroids (5, 8%) and drugs for constipation (5, 8%) or for functional gastrointestinal disorders (3, 5%) were also used off-label.

3.4 | Medication errors

A total of 95 (15%) MEs affecting 64 children (median: 1, IQR 1–4) were found. MEs were more common in infants (26, 41%), 0–12-month-old infants (8, 13%) and 12–36-month-old toddlers (5, 8%), followed by children (13, 20%), 3–5-year-old children (1, 2%) and newborns (1, 2%). No MEs were found in adolescents, but age and sex could not be specified in 10 (16%) cases. Among those known cases, MEs affected males (27, 42%) and females (27, 42%) equally. MEs were caused by parents or caregivers (40, 42%) and healthcare providers (HCPs; 55, 58%), the types of which also depended on who caused the errors. While parents were mostly noncompliant with treatments (32, 80%) and caused dosing errors (4, 10%), HCP errors were due to a lack of monitoring (17, 31%) and prescription MEs (34, 62%; Table 5). Most of the MEs reached the patient but did not cause harm (69, 73%), occurred but did not reach the patient (14, 15%) or were circumstances or events with the capacity to cause error (8, 8%). Only a few MEs reached the patient and required monitoring and/or intervention to preclude harm (3, 3%) or occurred and may have contributed to or resulted in temporary harm and required intervention (1, 1%).

4 | DISCUSSION

This study mined SM posts from 2 CPPFs and detected 161 ADRs, 95 MEs, 636 NOMs-DRPs and 62 off-label uses. These findings are

TABLE 4 Number and percentage of drug-related problems (DRPs) as described by the Third Consensus of Granada (TGC).

TCG DRP type	*n* (%)	PCNE 9.1 cause	*n*
Health problem insufficiently treated	273 (43)	1.1 Inappropriate drug according to guidelines/formulary	7
		1.5 No or incomplete drug treatment in spite of existing indication	5
		4.1 Duration of treatment too short	2
		7.1 Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason	1
		7.9 Patient physically unable to use drug/form as directed	3
		8.1 No or inappropriate outcome monitoring (incl. therapeutic drug monitoring)	8
		9.1 No or inappropriate outcome monitoring	2
		9.2 Other (e.g., allergies, noncompliance to hygienic or sanitary measures)	9
		9.3 No obvious cause	238
Probability of adverse effects	161 (25)	9.3 no obvious cause	157
		9.1 No or inappropriate monitoring	3
		1.2 Dose timing instructions wrong, unclear or missing	1
		1.1 Inappropriate drug according to guidelines/formulary	2
Personal characteristics	46 (7)	1.1 Inappropriate drug according to guidelines/formulary	18
		7.1 Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason	3
		7.10 Health problem insufficiently treated	1
		7,4 Patient decides to use unnecessary drug reason	4
		7,8 Patient unintentionally administers/uses the drug in the wrong way	1
		7.9 Patient physically unable to use drug/form as directed	1
		8.1 Medication reconciliation problem	2
		9.1 No or inappropriate monitoring	1
		9.2 Other causes	8
		9.3 No obvious cause	7
Contraindication	27 (4)	1.1 Inappropriate drug according to guidelines/formulary	12
		1.3 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	15
Non-compliance	(4)	7.1 Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason	17
		7.4 Patient decides to use unnecessary drug reason	3
		7.7 inappropriate timing or dosing intervals	1
		8.1 Medication reconciliation problem	1
		9.1 No or inappropriate outcome monitoring	1
Inappropriate dose, dosage schedule and/or duration	12 (2)	C1.4 Inappropriate duplication of therapeutic group or active ingredient	1
		3.1 Dose too low	1
		3.2 Dose too high	2
		3.5 Dose timing instructions wrong, unclear or missing	2
		4.1 Duration of treatment too short	1
		4.2 Duration of treatment too long	1
		6.3 Drug over-administered by a health professional	1
		7.5 Patient takes food that interacts	1
		8.1 Medication recognition problem	2
Wrongly administered drug	11 (2)	2.1 Dose timing instructions wrong, unclear or missing	1
		7.9 Patient physically unable to use drug/form as directed	9
		8.1 No or inappropriate outcome monitoring	1

TABLE 4 (Continued)

TCG DRP type	*n* (%)	PCNE 9.1 cause	*n*
Prescription error	7 (1)	1.1 Inappropriate drug according to guidelines/formulary	3
		1.2 No indication for drug	2
		3.5 Dose timing instructions wrong, unclear or missing	2
Other health problems that affect the treatment	51 (1)	7.9 Patient physically unable to use drug/form as directed	51
Interactions	4 (1)	1.3 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	4
Unsuitable storage	4 (1)	7.6 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	4
Dispensing errors	2 (0)	5.4 Wrong drug or strength dispensed	2
Other			60 (9)
Medicine Not prescribed	2 (3)	*7.4 Patient decides to use unnecessary drug*	2
Medicine stockout	2 (3)	*5.1 Prescribed drug not available*	2
Family member influencing decision	1(2)	9.2 Other cause (family member influencing decision)	1
Medicine administration issues	51 (85)	7,9 Patient physically unable to use drug/form as directed	51
Administrative issues	4 (7)	*8.1 Medication reconciliation problem = 3*	3

Note: DRPs by TGC falling under *Other* category were grouped and categorized by investigators.

TABLE 5 Analysis of medication errors (MEs) by American Society of Health-System Pharmacists (ASHP) classification according to who caused the error.

ASHP ME type	Parents/caregivers *n* (%) 40 (42%)	Healthcare professionals *n* (%) 55 (58%)	Total ME *n* (%) 95 (100%)
Deteriorated medicine	1 (3%)	0 (0%)	1 (1%)
Dosing error	4 (10%)	0 (0%)	4 (4%)
Administration technique error	1 (3%)	0 (0%)	1 (1%)
Medicine not prescribed	0 (0%)	2 (4%)	2 (2%)
Monitoring error	0 (0%)	17 (31%)	17 (18%)
Omission error	0(0%)	2 (4%)	2 (2%)
Patient noncompliance—as per ASHP definition	32 (80%)	0 (0%)	32 (34%)
Erroneous preparation of medicines	2 (5%)	0 (0%)	2 (2%)
Prescription errors	0 (0%)	34 (62%)	34 (36%)

examples of the high potential of SM to detect health data, which cannot be ignored.[26] In recent years, the size and growth of data on SM have been unparalleled,[18] and the number of actively involved patients, including parents[11,12] who share and post health information, has been continuously growing.[18] In fact, 11% of caregivers and 6% of patients share experiences and post questions online.[18] In this context, SM is considered a valuable resource for pharmacovigilance,[10,27] providing clinical insights beyond traditional communication methods.[18]

ADRs are a major public health problem that requires postmarket surveillance. This surveillance allows sufficient time and population heterogeneity to identify rare and very rare ADRs that cannot be identified during clinical trials.[28] Consequently, some stakeholders reported that SM could be a valuable tool for gathering ADRs,[8,26] either to obtain early signals or to validate or reject signals that have arisen in other reporting systems.[18] First, SM can collect drug safety information that is not easily obtained by other means, including populations excluded from clinical trials, or those with high rates of off-label use such as in paediatrics.[18,26] Second, SM collects patient-generated unsolicited data,[28,29] providing a realistic setting for drug use. Third, the quantity and near-instantaneous nature of SM posts provides opportunities for real-time monitoring of ADRs.[18,26] Furthermore, SM can detect rare, very rare and emerging ADRs,[10,30,31] including unexpected nonserious ADRs,[27,30] which are missed by traditional systems.[18] For example, in this study, 18 ADRs (12%) were either uncommon (14.9%), very rare (3.2%) or rare (1.1%). Moreover, the prevalence of 40 ADRs (25%) was not described in SmPC, 4 (2%) were unknown and 17 ADRs (11%) were SAEs. This could be explained by the fact that patients and caregivers can identify more ADRs and MEs than HCPs.[32]

However, some authors argue that SM is still too premature to replace traditional reporting systems.[10,26,27] First, the process of extracting relevant ADRs from SM is challenging.[18,26] Currently, the extraction of data from SM is guided by lexicons. However, SM users may misspell medicines or ADRs, use abbreviations or creative phrases, write sentences with grammatical errors, informal symptom descriptions or idiomatic expressions that limit the performance of lexicon-based approaches,[18] although ways to correct these issues are being actively researched.[26] Moreover, some studies have focused on strategies to filter and analyse extracted drug–ADR pairs to identify potentially harmful signals.[18]

Second, the data from SM posts are poor in quality and have insufficient detail for a deep evaluation,[26] which complicates the assessment of the exact nature and causality of an ADR.[26] However, in our study, all entries had enough information to classify and detect NOM-DRPs, ADRs and MEs and to clearly distinguish them from other types of drugs discussions. Moreover, ADR severity and causality were identified, and the LCAT algorithm was used in all cases. In contrast, the prevalence of 40% of the ADRs could not be properly assessed, as users did not mention a specific drug, and some items would require further patient information, which cannot be obtained unless stated in the post. Nevertheless, this is an inherent limitation of spontaneous reporting by patients or HCPs, where incomplete data, duplicated reporting and unspecified causal links are recurrent problems.[18] Recently, the Food and Drug Administration stated that ADR reports from SM are reviewed like "any other spontaneous reporting systems while acknowledging variability in the quality of the reports submitted". The incorporation of data into pharmacovigilance records of the Food and Drug Administration and European Medicines Agency requires a minimum set of data, which is available in SM: an identifiable patient, a suspect drug, an adverse event and an identifiable reporter (including email or screen name).[18,33]

Third, a high volume of data is needed to obtain a significant amount of relevant information because of the high prevalence of noninformative posts.[27] In this study, 3573 CPPFEs were reviewed, with data extraction percentages of 18, 5 and 3% for NOM-DRPs, ADRs and MEs, respectively, which increases to 70, 18 and 10%, if only posts with medical data were considered. Several paediatric studies have reported reviewing over 3 million posts[14,29] with different levels of data extraction success. For example, the percentage of ADRs from all posts ranged from 0.2 to 8% on SM platforms such as Facebook, Twitter, and YouTube,[29] whereas in forums, this percentage ranged from 0.2 to 1.42% ($n = 4$), and when the forums were disease-specific, the prevalence increased to 12–62% ($n = 4$).[30] Moreover, some authors suggest that ADR extraction is up to 20–25% greater when focusing on health-related networks.[18] Therefore, the specificity of data extraction depends on the SM network chosen[10] and the purpose of the search; the data extraction profitability is different from a holistic study approach (such as ours) to a specific disease or drug study. In this study, 398 (48%) posts included discussions about drugs without any ADEs. Following this holistic approach, cases of interest can be extracted in future studies via AI technology that detect ADRs in SM or platforms focused on specific populations, which are currently used for ADRs[10,14] and MEs or interest.[34] However, these posts could also contain interesting information to identify the unmet needs of parents, caregivers or patients in paediatrics.

In addition to ADRs, NOMs, DRPs and MEs could also be analysed from SM to establish a more realistic approach to drug use in the clinical setting. In this study, 636 NOM-DRP samples were extracted. To date, few SM studies have focused on detecting NOMs, DRPs or MEs in children from SM posts, despite being considered a valuable source of information for pharmacovigilance.[26] We are not aware of any lexicon used to classify or semiautomatically detect NOMs and DRPs. However, these could be further classified in the TCG by detecting ADEs. Several factors increase the prevalence of NOMs and DRPs in paediatrics, such as higher medicine use in preschoolers,[35,36] drug-induced growth and development disorders such as delayed ADRs not identifiable in adults[2–4] and the well-known lack of knowledge of medicines,[2–4] high unlicensed use prevalence, lack of reliable safety and pharmacokinetic data from clinical trials in paediatrics[2,4] and difficulties in developing commercially manufactured drug forms adapted to paediatrics.[2–4,37–39] In the majority of studies, the detection of DRPs in SM posts is a casual finding or is focused on the detection of specific DRPs as noncompliance with vaccine schedules.[40] Only Lindell *et al*. systematically evaluated DRPs in a cohort of 4032 Finnish parents. In that study, 824 responders reported at least 1 DRP, and, similar to our findings, the most frequent DRPs involved health problems that were insufficiently treated in 5.3% of the reported DRPs (273, 43%).[41]

Furthermore, in our study, 95 MEs were found (1.5 MEs/child), especially in children (13, 20%). MEs occurring at home are not routinely reported, although the prevalence is estimated to be 30–80%,[42] with a high incidence in children aged 1–5 years.[35] In the paediatric outpatient setting, the prevalence of MEs is likely to be underestimated because of underreporting, especially if no harm occurs.[36] Our results revealed that most MEs did not cause harm, and could explain why, to our knowledge, few studies have investigated MEs reported by SM. However, it would be interesting to analyse MEs in the clinical setting, as paediatric patients have higher ME prevalences with more severe consequences than adults do.[2,35] In this study, HCPs generated more MEs than parents (58 *vs*. 42%), but these data could be biased from the parents' and caregivers' perspectives, as in the MEs reported in the French database,[42] HCPs are found to be the cause of ME by only 34.1%.

This study has several limitations. First, only 2 CPPFs were analysed, but sufficient data were reported to detect ADEs and evaluate the potential of SM to be used for pharmacovigilance via a holistic approach in paediatrics. Additionally, only openly public CPPFs without registration were included, which could make users reluctant to share information. Second, this study used 2 lexicons, 1 in Spanish, for drugs in forums with different languages (Catalan, Spanish and English). It would be interesting to use lexicons in each language to maximize the results, although drug name lexicons are unavailable for all languages. Third, several limitations such as reporting and notoriety bias[26] are inherent to SM. Likewise, the use of some

specific SM networks is correlated to some demography and trends over the years.[10] Finally, some limitations of ADR analysis must be considered. For example, we cannot ignore that multiple posts may refer to the same child, as no cross-reference between user nicknames was conducted. However, it was not analysed if the same reported described the same ADR in multiple places. In addition, we did not compare the present results to those of other reference sets for positive or negative drug–event associations, but drug–ADR linkages were evaluated with the LCAT algorithm. Moreover, possible concomitant drugs or comorbidities that could interfere with the drug–ADR association were not considered, although paediatric patients are not expected to have many comorbidities or to be treated with multiple drugs. Nonetheless, our study has a data quality similar to other studies.[10,26]

In conclusion, data from CPPFEs are useful for retrieving data on ADEs in paediatric cases. In addition, unknown ADRs, SAEs and MEs, which cause harm to children, can be detected. Consequently, CPPFs are a good source of complementary pharmacovigilance reporting via a holistic approach for paediatrics. Following this holistic approach, ADRs and MEs of interest can be further researched via AI tools. However, limitations exist, and further studies are needed to validate and improve SM use in paediatric medicine.

AUTHOR CONTRIBUTIONS

Conceived and designed the analysis: A.P.R., J.C.J., J.M.S.N. Collected the data: I.V.P., A.P.R. Contributed data or analysis tools: A.C., I.V.P. Performed the analysis: I.V.P. Wrote the paper: I.V.P., A.P.R., J.C.J., M.B.P.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or nonfinancial interests to disclose.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on request.

CONSENT TO PARTICIPATE

Ethics committee allowed not request an informed consent as it is a observational study from SM and interviewing patients was not feasible as users may be inactive or no longer have that user account. Consent to use SM data was requested to the forum administrators and users will be informed in the forum itself.

The authors confirm that the PI for this observational study is Ingrid Vilimelis-Piulats (pharmacist), coauthors (A.P.R., J.C.J., M.B.P.) that they had direct clinical responsibility for patients.

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