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

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Abstract

Purpose: Children are vulnerable to suffer negative outcomes due to medication (NOM), social media (SM) can be a non-interventional tool to gather safety data. The aim of this study is to assess paediatric Adverse Events (AE) or suspected Adverse Drug Reaction (ADR) detected in SM. Secondary objectives are the assessment of NOM, Drug Related Problems (DRP) and Medication Errors (ME).

Methods: Observational, ambispective study assessing NOM in Public Parenting Forums (PPF) using data mining software. Entries that mentioned a medicine administered to children were analyzed and, if NOMs were detected, DRP, ME and AE were categorized. ME and ADR seriousness were assessed. ADR causality according Liverpool Causality Assessment (LCAT) and prevalence compared with those reported in Summary of Product Characteristics (SmPC) of each product.

Results: Two forums (mumsnet.uk; socpetit.cat 2733 (81%)) were analyzed. Of 3375 entries, 635 contained a NOM and a DRP, 214 in English, 6 in Spanish and 217 in Catalan. 161 ADR were detected, including Serious AEs (SAEs), unknown, rare or very rare ADR. 29(16%) were not reported in SmPC. 95 ME were found, caused parents or caregivers (40; 42%) and healthcare professionals (HCP) (55; 58%). Severity ranged from no harm up to harm required intervention.

Conclusion: ADR were found in PPF, including SAEs and ADR with low or unknown prevalence and suspect ADRs not included in the SmPC. ME that reached children were also found. As consequence, despite that the overall number of entries is not high, forums are a source of valuable pharmacovigilance information.

Introduction

NOMs are situations in which the patient is at risk of suffering from a health problem, due to the existence of DRP, undesirable events experienced by the patient involving or suspecting medicines interfering with the desired outcome [1, 2]. Most relevant NOMs are ME and ADR. Both refer to an untoward medical occurrence that may present using a medicine. While ME could be preventable [3], ADR are attributable to pharmacological properties in which individual factors play a role [4].

Pharmacovigilance englobes the activities for early detection of unknown ADR, risk factors and any frequency change [5]. Traditionally, ADR were collected by “yellow cards” but are infranotified, so observational studies, have been used to gather further information. SM has been recently considered as a pharmacovigilance source by multi-stakeholders projects and by regulatory bodies [6–8].

Children’s NOM vulnerability is due to their immaturity and non-pharmacological causes [9–11]. The use of SM has been considered paediatric-specific topics such as vaccine hesitancy [12], adherence [13], ADR [14]. The aim of this study is to assess if SM could detect ADR in the paediatric population. Secondary objectives are NOM, DRP and ME detection assessment.
Methods

Observational, ambispective study on PPF. To identify PPF, an exploratory search on the first 10 pages from Google results was conducted for “Parents Forum” “Forums de padres” or “Fòrums de pares” on January 2021. PPF were considered if included child-health sections in Catalan, Spanish or English and excluded if explicit that data could not be used for research purposes. Permission was requested to users and administrators.

A data mining software was developed. Ontologies were used to export active pharmaceutical ingredients, brand names from the Spanish Medicines Agency nomenclator and AEs from the Medical Dictionary for Regulatory Activities (MedDRA). Posts were retrieved until December 2021.

Duplicates, written by professionals, referring to non-pharmacological therapies or hospitalary use, intra-uterine or adult exposure were excluded. Number of entries mentioning medicines per language, notifier kinship and gender were analyzed.

Child age, when mentioned in the post, was classified considering International Conference Harmonization (ICH) E11 categories, newborns from birth to less than 28 days, infants from 28 days to less than 24 months, children from 24 months to less than 12 years and adolescents from 12 and less than 18 years old. Socpetit.cat included 0-12 month, 12-36 month, 3-5 year and above 8 years sections; when age was not mentioned, these ranges were considered.

NOM demographics (ICH E11 age group, gender), medicines according Medicine Anatomical Therapeutic Classification (ATC) code [15] and administration route. NOMs and DRP were stratified by the Third Granada Consensus (TGC) [2], ME were detected according the definition by the American Society of Health-System Pharmacists (ASJHP) [16] and severity was assessed by National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) [3]. ADR were detected and seriousness assessed by World Health Organisation definition [17]. Organ affected and ADR classified by MedDRA [18] using Preferred term (PT)). Prevalence was extracted from SmPC and causality assessed by LCAT [19]. Off-label was considered when age was different than the SmPC, Study received ethics committee approval from the University of Barcelona Institutional Review Board (IRB00003099).

Descriptive statistics include frequencies and percentages for categorical variables.

Results

Total posts retrieved

Catalan language socpetit.cat and English mumsnet.com forums were selected. A total of 3572 posts were retrieved by the data mining software from which 2733 (77%) were from socpetit.cat. Posts that mentioned medicines (821; 23%) were considered for analysis. In Catalan (483; 59%), English (325; 40%) and Spanish (13; 1%). Users were parents (363; 44%), caregivers (419; 51%), other relationships (8;
1%) or unassessable (31; 4%). Most cases gender was unassessable 780 (95%), 40 (4%) were females and 1(1%) male. Excluded entries (11%; 94) due to administration of hospitalary medicines (27; 3%), for adults (12;1%), non-pharmacological treatments (42; 5%), in-utero (2; 0,02%), non-original entries (9; 1%) and duplicates (2; 0,02%). Included posts (727; 20%) were analyzed, with 1165 medicines (1,4 per post).

**Negative Outcomes due to Medications**

635 (87%) posts included at least one NOM, in 430 children (1,5 per child). NOMs mostly occurred in females 222 (52%), males 181 (42%) and 27 (6%) un-assessable gender. Most occurred in infants (147, 23%) and children (116, 18%) whereas newborns (1, 0,2%) and 3-5 age (5;1%) were reported less frequently (Figure 1).

Most medicines were J01-Antibacterials for systemic use (94, 15%), N02-Analgesics (85, 14%), J07-Vaccines (79, 13%), M01-Anti-inflammatory and antirheumatic products (50, 8%) and R03-Drugs for obstructive airway diseases (46, 7%) (Figure 2). Drugs administered orally (425; 70%), parenteral (48; 8%), topical (58, 9%), not specified (28; 4%), inhaled (24; 4%), Rectal (15; 2%), Ocular (5, 1%) and others (nasal 3, Buccal 2, otological 1 and vaginal 1).

NOM referred to non-quantitative ineffectiveness (318, 51%), followed by non-quantitative safety problems (239, 38%), untreated health problems (56, 9%) and effect of unnecessary medicine (15, 2%).

**Drug Related Problems**

Most frequent DRPs were health problem insufficiently treated (273, 44%), probability of AE (161, 26%), personal characteristics (46, 6%) and contraindication (27, 4%) (Figure 3). Off-label use was found in 62 (10%) entries mostly prevalent for antihistamines for systemic use-r06 (6), cough and cold preparations-r05 (16), dermatological corticosteroids-d07 (5), drugs for constipation-a06 (5) and for functional gastrointestinal disorders-a03 (3). In 60 cases, DPR could not be classified (other DRP), including difficulties to administer medicines in children (51), non-prescribed medicines use (2), administrative issues (4), medicine stockout (2), or family members affecting medicines administration (1).

**Adverse events**

AEs 161 (26%) were experienced by females (60; 56%), 42 (39%) males and 6 (6%) unassessable gender. AE were most frequent reported by infants (44, 27%), 0-12 month (17, 16%), 12-36 month (14, 13%). No AEs were found in newborns. Children and adolescents were less reported. Most frequent ATCs were Vaccines-J07 (57, 35%), followed by Antibacterials for systemic-use J01 (34; 21%), anti-inflammatory and antirheumatic products-M01 (12; 7%); analgesics-N02 (11; 7%); drugs for acid related disorders-A02 (11;7%). Medicines were mostly administered orally (91; 57%), followed by parenteral (58; 36%), topical (4; 2%) and rectal route (1; 1%). Route could not be assessed in 2 (1%) posts. By PTs diarrhea (15; 9%), pyrexia (12; 7%), rash (9; 6%), acne (8; 5%) vomit (7; 4%) and abdominal pain (6; 4%).
21 (13%) SAES were found. In terms of causality, 158 (98%) were possible AEs (158; 98%) and 3 (2%) were unlikely. By prevalence, uncommon (14; 9%), very rare (3; 2%) or rare (2; 1%), common (24; 15%) and very common (11; 7.5%).

107 AEs has unknown prevalence (107; 66%) from which 29 (16%) were not in the SmPc. Rare, very rare cases are further explained in Table 1. Also, description of suspected ADRs not included in SmPC (Table 2).

Posts contained sufficient information to evaluate seriousness but none provided information for objective evidence (ie, laboratory investigations) or positive rechallenge which also impacted quality data for causality assessment.

**Medication errors**

ME (94; 15%) represented 3% from all posts. ME affected 64 aged 0-12 (8; 13%), 12-36 month (5; 8%), 3-5 year (2; 2%), child (13; 17%), infant (26; 43%), newborn (1; 2%) and unspecified (9; 14%); no ME were found in adolescents. ME were made by parents or caregivers (40; 42%) and HCP (55; 58%), Table 3. Describes the type of ME according their responsible. Parents made ME in administrating non-prescribed medicines (16, 17%) and non-compliance (15, 16%); HCP lack of monitoring (17, 18%) and prescription errors (36, 38%). Most MEs reached the patient but did not cause harm (C; 69), occurred but not arrived (Category B; 14), circumstances/events with the capacity to cause error (A 8), reached the patient and required monitoring and/or required intervention to preclude harm (D, 3) and occurred, may have contributed to or resulted in temporary harm and required intervention (E, 1).

**Discussion**

This was an ambispective, observational study of 3572 posts, from which 821 (23%) mentioned medicines with 635 (87%) NOM, 635 (87%) DRP, 161 (26%) ADR and 94 (15%) ME. Study sample size was similar to other forum studies, for example 4581 post [20] but below other studies using Twitter and Facebook [8]. SM has been recently considered for pharmacovigilance [7]. However, SM pharmacovigilance reporting presents issues like insufficient detail for meaningful evaluation, large volumes, poor quality and is non-informative [21]. Thus, the Web-RADR project shared recommendations such as to focus on niche populations and as a source to complement traditional like forums [6], to decrease irrelevant data. Paediatric focused searches for product or disease-specific have been studied in Facebook [22–25], Pinterest [26], Twitter [27–31] and forums [12,20,32–38]. Most authors searched for ADR mentions in SM for particular medicines [39,40] and ADR [41] but, to date, none conducted a global analysis in paediatrics. Thus, focused studies in certain medicines could not capture all relevant information in medicines. This study allowed to analyze all non-hospitalary medicines to provide an overview of the usefulness of SM in pharmacovigilance.

635 (87%) NOM were found, occurred to infants (237; 38%) and children (117; 19%) and 318 (51%), referred as non-quantitative ineffectiveness. These results could be explained by the higher
medicine use in pre-schoolers [42], lack of knowledge of medicines in those ages [43,44] off-label high prevalence use, lack of reliable safety and pharmacokinetic data from clinical trials, drug-induced growth and development disorders as delayed ADRs not findable in adults [10,45]. To overcome this, authors recommended conducting paediatric pharmacoepidemiological studies on top of spontaneous reporting [10,45]. To date, no other SM studies focused on detecting ME or NOM/DRP from SM; although is considered a valuable source of information for pharmacovigilance [46]. In Twitter, for all-age AE detection where PT Drug ineffective dominated the list, which is in line to the results found in this study [20]. Other NOM were non-quantitative safety problem (245; 39%), untreated NOM (56, 9%) or unnecessary medicines (15; 2%); the last two according to user consideration since no medical records were available for validation.

In this study, 635 (87%) DRP were found, with a similar number to a survey where 824 (21%) where detected by 4032 Finnish parents [47]. In this study, most frequent DRP was health problem insufficiently treated (273; 44%), once discarding non-compliance (23%) and incorrect medicine administration (11; 2%). No SM DRP studies were found, rather than casual findings. Lack of medicines information in children, un-licensed medicines use and difficulties to develop paediatric medicines [45,48] prevents the effective and safe use of medicines. SM articles are focused in either a specific therapeutic area or DRP such as non-compliance with vaccines schedules, found in (60%) of the posts [37] and the difficulties to administer oral formulations to young children and strategies parents use to do it [20]. Most affected ages were infants (165, 26%) and children (98,15%). Infant DRP prevalence could be high, presumably as this is the age with more medicines consumption [44,49]. Most prevalent ATC codes in this study were antibacterials, analgesics, vaccines, anti-inflammatory and antirheumatic products and drugs for obstructive airway diseases. ATC codes are similar the mostly used medicines by paediatric outpatients [43,44,49].

94 (3%) ME were found, occurring mostly in infants. Most ME arrived to patients without causing harm or occurred but did not reach the patient without consequences. In general, children have higher ME prevalence than adults with more severe consequences and occurring during prescription and administration [50]. In pediatric outsetting, the prevalence of ME is probably underestimated due to the failure to communicate the event, especially if no harm occurred [51], thus, SM could be a potential source of ME. In a multicentric study of children admitted to the emergency room, ME incidence were higher in 1-5 years old, like in this study [42]. So far, no paediatric ME have been studied in SM. In this study, were caused by HCP due to the potential lack of monitoring causing off-label use whereas the use of non-prescribed medicines or non-compliance were done by parents. Parents/caregivers self-medicating their children is reported in literature as a prevalent issue [52,53]. Parents or caregivers, caused ME by accidental administration of medicines, treatment discontinuation, preparation or reconstitution ME ranging from 30% to 80% [54]. A French database reported ME caused by HCP (514; 34.1%) [55]. In this study, a higher prevalence of ME in HCP could be done due attributed to the identification of off-label use. Considering that the actual prevalence of ME at home is not routinely reported, SM could be a source of ME as parents [51] broadly use SM to seek information and support about children's health [56]. Despite that HCP already have tools to self-report ME [3], SM could also be a source for ME in HCP.
In our study we found 161 AEs (26%). In paediatrics, the risk of potential AE was higher (115 (1.1%) compared to 35 (0.35 in adults) p.001) [57]. In a systematic review the percentage of ADR from all posts ranged from 0.2%-8%, with higher percentage from YouTube videos in disease specific forums than general health forums [21]. Noteworthy, this study could retrieve more ADR than the systematic review and with higher percentage than in paediatric out settings (0.2%-8%) and EudraVigilance (11%). The prevalence and range of ADR greatly varies depending on the methodology used, this could be due the niche forum population [6] due to the ADR infranotification of traditional pharmacovigilance systems and, as observed in ME [51], parents may not communicate ADR if they do not perceive harm.

In this study, reported information could be analyzed quantitatively as percentage and number. Although LCAT algorithm could be used in the study, items that required further information on the patient such as history of the same event, positive rechallenge, due to an underlying disease; unless otherwise stated in the post, were considered unassessable. The lack of information impacts data quality from SM which is still immature to use it as an alternative to traditional reporting systems [6,21]. Moreover, this study analyzes ADR prevalences found, detecting 21 SAEs (13%), 2 (1%) rare, 3(2%) very rare included in SmPC and 106 (66%) unknown prevalence, from which 29 (18%) were not found in SmPC. Such prevalence require post-marketing experience for detection [58], thus SM is a tool to gather it. A study comparing ADR in the French database and forums posts, found the later contained scarce information and were focused in non-SAEs but presented unexpected ADRs [59]. In this study only posts mentioning hospital admission were considered SAE. SM has been considered by authors as a source of emerging AE [60], unexpected [59,61] and rare [41]. Pharmacovigilance data from SM value is that is a tool for information not easily obtainable from other means such as the potential to detect ADR in populations usually excluded from clinical trials, access to ME, off-label use and lack of efficacy have been found of value by regulators. As well as being patient-generated and unsolicited [46]. However, this does not replace yellow-card since no follow-up or the lack of access to healthcare reasons to confirm causality to discard other/prior pathologies [62]. Considering that infranotification via traditional reporting is an issue [5], SM could be a potential tool to complement this [6].

This study presents limitations, as only two forums were analyzed, no other languages nor other type of SM were considered. The study did not compare to other reference set for positive or negative drug-event associations. ADR were heterogeneous compared to the ones in SmPC. However, this study detected very rare, rare or unknown prevalences which are in line to a French study [59] and, also detecting SAEs. SM for drug safety presents still presents caveats such as, SM information heterogenicity, veracity, unaccess to medical data for confirmation, difficulties to follow-up [21,62]. SM quality data found is in line with findings [6,21]. This study is also the first study on DRP and NOM in pediatrics using the TGC and categorizing ME by severity.

In conclusion, despite forums contain few medicines mentions they are useful to retrieve NOM, DRP, ADR and ME, including SAEs and ME causing harm. Since ADR not specified in SmPC have been found, SM could be a valuable source of undetected ADR. Consequently, PPF but could be use as complementary reporting.
Further studies are required to validate the usefulness of SM on LCAT, TGC and ME classification.

**Abbreviations**

Adverse Drug Reaction (ADR)

Adverse Events (AE)

Anatomical Therapeutic Classification (ATC)

American Society of Health-System Pharmacists (ASJHP)

Drug Related Problems (DRP)

healthcare professionals (HCP)

International Conference Harmonization (ICH)

Liverpool Causality Assessment (LCAT)

Medical Dictionary for Regulatory Activities (MedDRA).

Medication Errors (ME).

National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP)

negative outcomes due to medication (NOM)

Public Parenting Forums (PPF)

Preferred term (PT)).

Serious AEs (SAEs)

social media (SM)

Summary of Product Characteristics (SmPC)

Third Granada Consensus (TGC)

**Statements And Declarations**

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Conflicts of interest/Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions: Conceived and designed the analysis: APR, JCJ, JMSN Collected the data: IVP, APR Contributed data or analysis tools: AC, IVP Performed the analysis: IVP Wrote the paper: IVP, APR, JCJ

Ethics approval: Study received ethics committee approval from the University of Barcelona Institutional Review Board (IRB00003099).

Consent to participate: Informed consent was not requested as it is a retrospective 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.

Consent for publication: Not Applicable.

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

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Tables

Table 1. Analysis of very rare, rare and unknown prevalences
<table>
<thead>
<tr>
<th>Prevalence</th>
<th>ATC</th>
<th>N/Patient</th>
<th>Route</th>
<th>Preferred term (MedDRA)</th>
<th>SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>R06</td>
<td>3/3</td>
<td>Oral</td>
<td>-Sting</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Lethargy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Crying</td>
<td></td>
</tr>
<tr>
<td>A03</td>
<td>2/1</td>
<td>Oral</td>
<td></td>
<td>-Nausea, pain</td>
<td>No</td>
</tr>
<tr>
<td>A06</td>
<td>1/1</td>
<td>Oral</td>
<td></td>
<td>-Anal fissure</td>
<td>No</td>
</tr>
<tr>
<td>R03</td>
<td>4/2</td>
<td>Unknown (1); inhaled (1)</td>
<td>-Cough</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Sleep disorder, lethargy, anxiety</td>
<td></td>
</tr>
<tr>
<td>R05</td>
<td>1/1</td>
<td>Oral</td>
<td></td>
<td>-Cough</td>
<td>No</td>
</tr>
<tr>
<td>J01</td>
<td>5/3</td>
<td>Oral</td>
<td></td>
<td>-Decreased appetite, pain, flatulence</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Gastroenteritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Diarrhea</td>
<td></td>
</tr>
<tr>
<td>N02</td>
<td>8/7</td>
<td>Oral</td>
<td></td>
<td>-Acne</td>
<td>Serious (cough)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Loss of consciousness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Vomit</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Cough (2; rechallenge)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Somnolence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Heart rate increased</td>
<td></td>
</tr>
<tr>
<td>M01</td>
<td>4/3</td>
<td>Oral</td>
<td></td>
<td>-Cough</td>
<td>Serious (cough)</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>-Transaminases increased; Blood alkaline phosphatase increased</td>
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<td></td>
<td>-Heart rate increased</td>
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<td>1/1</td>
<td>Topical</td>
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<td>-Pain of skin</td>
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<tr>
<td>A02</td>
<td>4/2</td>
<td>Oral</td>
<td></td>
<td>-Sleep disorder</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Abdominal pain, Abdominal distension, nausea</td>
<td></td>
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<tr>
<td>Rare (1/10,000 to &lt;1/1,000)</td>
<td>H02</td>
<td>1</td>
<td>Oral</td>
<td>Unresponsive to stimuli</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>J07</td>
<td>1</td>
<td>Parenteral</td>
<td>Stomatitis</td>
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</tr>
<tr>
<td>Very rare (&lt;1/10,000)</td>
<td>N02</td>
<td>1</td>
<td>Oral</td>
<td>Rash</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Oral</td>
<td>Rash</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>A02</td>
<td>1</td>
<td>Oral</td>
<td>Rash</td>
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Table 2. ADR not found in SmPC
<table>
<thead>
<tr>
<th>ATC</th>
<th>Categoria MedDRA PT</th>
<th>Can be found in SmPC? Y/N/Not possible*</th>
<th>Serious Adverse Event?</th>
</tr>
</thead>
<tbody>
<tr>
<td>R06AB02</td>
<td>sting</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>A03AA04</td>
<td>nausea</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>A03AA04</td>
<td>pain</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>A06A D11</td>
<td>Anal fissure</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>H02AB06</td>
<td>Somnolence</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>R03</td>
<td>Cough</td>
<td>No</td>
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</tr>
<tr>
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Table 3. Description of type of medication error classified by American Society of Health-System Pharmacy according their responsible

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**Figures**
Figure 1

Distribution by age of reported cases of NOM, PRM ADR and ME.
Figure 2

Classification of most involved drugs in Negative Outcomes due to Medication
Figure 3

Most reported Drug Related Problems