Trackers for Adverse Events in Child Mental Health: descriptive analysis using the global trigger tool

Sandna Larissa Freitas dos Santos[1*], Ana Paula Soares Gondim[2]

[1]Pharmaceutical Sciences at the Federal University of Ceará, Fortaleza, Ceará, Brazil,
[2]Public Health from the Federal University of Bahia, Fortaleza, Ceará, Brazil

The goal of this study is to identify the global trigger tool trackers used to place the adverse drug events presented in children that use psychotropic drugs accompanied by Child-adolescent Psychosocial Care Centers. This is a descriptive study carried out with the secondary data of 112 child care records that began in January 2017 in two Child-adolescent Psychosocial Care Centers. A median of medicine per child was 1.71 and among the most used we were to risperidone 100%, followed by valproic acid and periciazine with 16% each. A total of 42 adverse drug events were found in 36 medical records, being agitation 29.7% and agressive 16.2%, being the most frequent, and in 45.2% of infants presenting only one event. 50 were trackers detected in 83.3%, two records that identified adverse drug events. In 38.8% were found only one tracker, the most found ones were: combination of psychotropic medicines 32%, abrupt reduction of medicine dose 22% and abrupt cessation of medicine 12%. Finally, the present study showed that the global trigger tool evidenced adverse drug events by means of the detection of trackers in children and that it had to offer interventions to improve the quality of psychiatric therapy within two community services.

Keywords: Drug-related side effects and adverse reactions. Psychotropic drugs. Child.

INTRODUCTION

In 2009, World Health Organization (WHO) defined Adverse Drug Events (ADE) as any undesirable medical occurrence that may happen during a medical treatment, not necessarily having a casual relation with the treatment itself (WHO, 2009a). In the same year, supported in this concept, the Institute for Healthcare Improvement (IHI) with the goal to propose a identification measure, showed in a general way the ADE as a resulting lesion to medical intervention related to a medication and can be expressed as signals, symptoms or laboratory abnormalities (Griffin, Resar, 2009). With the understanding of these concepts, as they are important causes of iatrogenic morbidity and mortality specially in children, the warning strategies contextualize the monitoring process of ADEs, with the

goal to promote security when using medication on people (WHO, 2015).

Some descriptive studies have shown that classes of nervous system medicine most prescribed in children are the antipsychotics, psychostimulants and anti-epileptics, being respectively, risperidone, methylphenidate and valproic acid as the main representatives (Vizotto, Ferrazza, 2017; Molina-Castillo, Leonés-Gil, López-Espuela, 2021). Due to this wide use, researches have shown the relationship with ADE in children's mental health, in addition to considering that the greater the number of medicines used by a child, the greater the chances of occurring an event, especially among children up to twelve years of age (Menard *et al.*, 2019; Borges *et al.*, 2020).

Associated with these drugs, some clinical trials have revealed adverse events to psychotropics, such as the weight gain that was observed with risperidone treatment that can influence the cascade of biochemical indices associated with insulin resistance and metabolic syndrome (Scahill *et al.*, 2016; Vanwong *et al.*, 2020). Some cross-sectional studies have pointed out the use of methylphenidate associated

*Correspondence: S. L. F. dos Santos. Departamento de Farmácia. Faculdade de Farmácia, Odontologia e Enfermagem. Universidade Federal do Ceará. Rua Pastor Samuel Munguba, 1210, Rodolfo Teófilo. CEP: 60.430-372, Fortaleza, Ceará, Brasil. E-mail: sandy.lary@hotmail.com. ORCID: https://orcid.org/0000-0002-2697-2874

with decreased appetite, which are directly proportional to the dose of this medicine (Lee *et al.,* 2015) and valproic acid that was more associated with gastrointestinal symptoms compared to other antiepileptic medicines such as levetiracetam and carbamazepine (Egunsola *et al.,* 2018).

From these data, the increased interest in research that evaluates the occurrence of ADE and provides safety in the use of nervous system medicines in children, has been influenced by the increasing consumption of these drugs, characterized as an early, prolonged practice and associated with the data that showed the extrapolation of the approval of the registration of medicines for use in adults. This highlights that the production of information about the occurrence of these events has an important role in the elaboration of health surveillance politics, based on the systematization of pharmacovigilance associated with child mental health care (Bayer *et al.,* 2021).

For this implementation of pharmacovigilance in health services, traditional methods to detect ADE have focused on voluntary notification, however several strategies have already been analyzed, such as the retrospective analysis of medical records, the extraction of information in package inserts or even interviews with patients (Griffin, Resar, 2009; Bayer *et al.,* 2021). Directed to the pediatric population, Coates *et al.* (2018) presented the Safety Monitoring Uniform Report Form (SMURF) as a questionnaire designed to collect data on the occurrence of possible ADRs (Adverse Drug Reaction) through interviews with children and adolescents and their parents / guardians. And in the context of mental health, Palanca-Maresca *et al.* (2014) showed an online database platform, called SENTIA (Safety of Neuroleptics in Infancy and Adolescence), which allows the recording of information on the safety of antipsychotics in children and adolescents in the short and long term, with the objective of prevent early ADE.

In this study, the tool used was the Global Trigger Tool (GTT) for Measuring ADE in a Mental Health Setting developed by IHI as a method for identifying ADE in mental health, consisting of thirty trackers, which are considered an indicative condition that is believed to be associated the occurrence of an adverse event (Institute for Healthcare Improvement, 2008). The use of the tool is initially directed to the hospital context, however, its methodology also provides a flexibility of its usefulness

in several clinical environments, from outpatient units, community services and intensive care units (Griffin, Resar, 2009; Nilsson *et al.*, 2020).

Even research showing identifying methods of ADE in pediatrics, the findings are not always consistent and there are limitations in strategies aimed at community services for child mental health that meet the specificities of this type of assistance (Ji *et al.,* 2018; Fajreldines *et al.*, 2019; Ivashchenko *et al.,* 2020). Therefore, this study aimed to describe the tracers for adverse events in children who use psychotropic drugs followed up at Centers for Psychosocial Care for Children and Adolescents using the GTT tool.

MATERIAL AND METHODS

Type of study

Descriptive study with secondary data in medical records of children who started care from January to December 2017 at Centers for Psychosocial Care for Children and Adolescents in the city of Fortaleza-CE.

Study location

The study was carried out in two CAPSi that make up the Psychosocial Care Network (Rede de Atenção Psicossocial) of the county. The services provide assistance to children and adolescents up to the age of 17, through therapeutic, social and psychiatric activities in groups and individually, in addition to dispensing medications according to individual needs. The Centers for Psychosocial Care for Children and Adolescents team consists of a psychologist, psychiatrist, social workers, occupational therapists, pharmacist, nurse, coordinator and assistants. One of the Centers for Psychosocial Care for Children and Adolescents contemplates the dispensing of Centers for Psychosocial Care for Children and Adolescents in the service itself and in the other, this service is directed to a basic health unit belonging to the same regional health unit. The dispensation of nervous system medicines is linked to the Specialized Pharmaceutical Assistance Components (SPAC) and the medicines subject to special control belong to Ordinance 322/98 (Brasil, 1998; Brasil, 2014).

The services were covered with the medical records of the children who are being monitored in the therapeutic interventions offered with the records of the professionals of each activity performed. The medical records were filed when the child was absent from consultations or from therapeutic groups over six months. In addition, the pharmacy had a record of the history of receipt of SPAC medications by each person responsible for the children each quarter, they are considered inactive when there is a shortage in this dispensation for more than six months.

Study population

All children with mental disorders who started care in 2017 and who were being followed up at the services at the time of data collection resulted in 112 medical records. The medical records of the children being monitored, the active records for receiving nervous system medicines by SPAC were included and the medical records that were not in the service and the inactive records were excluded.

Description of the variables

The study variables were: age (from six to twelve years old), attending school (yes or no), diagnostic hypothesis (present in the medical record), name of the prescribed time (categorical variable defined by the names of the drugs used), quantity of medicine prescribed for each child, description of the adverse drug event, amount of event per child, ADE trackers (present or absent) and number of trackers per child.

The age group was established according to the classification of the Health Sciences Descriptors (DeCs), in which children aged between six and twelve are adopted. The diagnostic hypotheses were categorized by the International Statistical Classification of Diseases and Health-Related Problems established by the World Health Organization (WHO, 2021). The drugs were grouped according to the Anatomical Classification Therapeutic Chemical Classification System - ATC in antiepileptics, antipsychotics, antidepressants and psychostimulants (WHO, 2009b).

The identification of ADE was based on the symptoms recorded in the medical records, described

below: agitation, aggressiveness, hallucinations, itching, constipation, visual deficiency, dyspnoea, foam in the mouth, stereotypes, weight gain, insomnia and drowsiness. The trackers collected from the GTT were: antihistamines, antiemetics, antidiarrheals, abrupt cessation of the medicine, abrupt reduction in the dose of medicines, transfer to a higher level of care, laxatives, significant weight gain and combination of nervous system medicines. The choice of these trackers because they categorize the use of medicines as described in the tool itself. (Institute for Healthcare Improvement, 2008).

For the study, the term adverse drug event was used, due to the lack of proof of records by professionals in the medical records of the direct relation with the medicine.

Data collect

Data collection was performed by applying a form with the analysis of medical records. The form was divided into four parts: identification of the child, use of medicine, identification of the ADE and presence of trackers.

Initially, were collected from the medical records of the services, in physical documents, data related to the identification of children on the admission form at the services. The information regarding the use of medicines was collected in medical prescriptions attached to the medical records, described by the professionals of the service itself. The identification of the ADE was collected by the professionals' evolution records and, finally, the GTT was applied to detect the trackers. The collection was carried out by a trained professional during the period from October 2019 to November 2020.

Statistical analysis

The data were stored using the Epi Info statistical program, version 3.5.2, and analyzed with the aid of the STATA program, 12 version. The analysis of the results started with a simple descriptive statistics of the variables, using relative and absolute frequency, measure of central tendency (average) and measures of dispersion (standard deviation) and were presented in tables.

Ethical aspects

The study is part of one of the goals of the broad research project constituted by the Research for Brazil's Unified Health System: shared management in Health (PPSUS) entitled "Adverse events of psychotropics in children in Primary Health Care and Psychosocial Care: signs, meanings and management practices for promoting health related to safety", developed by the Federal University of Ceará (Universidade Federal do Ceará [UFC]) in which it was approved by the Research Ethics Committee according to opinion 1,684,517 in the referred institution.

RESULTS

From the total of 112 children, 57.2% (64) were between 9 and 12 years old, with a minimum age of five years and a maximum of 12 years, with an average age of 9 years, with a standard deviation of 2.6 years and 67.8% (76) attended school. A total of 123 mental disorders were identified, highlighting that in 57 medical records they presented more than one diagnostic hypothesis. The main ones were: Psychological development disorders 91.3% (84), Mental Retardation 17.4% (16) and Behavioral and emotional disorders with onset generally occurring in childhood and youth 14,1% (13) (Table I).

TABLE I – Distribution of the number of children attended at Centers for Psychosocial Care for Children and Adolescents according to the variables (age, attending school and diagnostic hypothesis) Fortaleza. Ceará. Brazil. 2019-2020

Variables	Average (StandardDeviation)	N	%
Age (years) (N=112)	9.0 (2.6)		
5-8		48	42.8
9-12		64	57.2
Attend to School (N=112)			
Yes		76	67.8
No		36	32.2
CID-10: Diagnostic hypothesis (N=123)*			
F00 - F09 Organic, including symptomatic mental disorders		1	1.1
F20 – F29 Schizophrenia, schizotypical and delusional disorders		6	6.5
F30 – F39 Mood disorders [affective]		2	3.1
F40 – F48 Neurotic disorder, stress-related and somatoform		1	1.1
F70 – F79 Mental Retardation		16	17.4
F80 – F89 Psychological development disorders		84	91.3
F90 – 99 Behavioral and emotional disorders usually beginning in childhood and youth		13	14.1

*one or more hypotheses.

A total of 192 nervous system medicines used by the 112 children analyzed were found, with an average of 1.71 medicines per child and a standard deviation of 0.85. As for the amount of medicine per child, 41% (46) used only one, 39.2% (44) used two medicines, 14.2% (16) used three and only 0.8% (1) used five medicines.

Risperidone was identified in the prescription of all children analyzed 100% (112), followed by valproic acid

16% (18), periciazine 16% (18), fluoxetine 7.1% (8) and carbamazepine 7.1% (8). In the therapeutic classification of the 192 medicines found, antipsychotics were used, with 72.3% (139) being the most prevalent, represented by risperidone, pericizine, haloperidol, quetiapine and levomepromazine, followed by antiepileptics 15.6% (30) represented by valproic acid, carbamazepine and phenobarbital, the 8.3% antidepressants (16) such as fluoxetine, amitriptyline, citalopram and imipramine, and finally the psychostimulants 3.6% (7) among the methylphenidate and lithic carbonate (Table II).

TABLE II – Distribution of the number of children seen at Centers for Psychosocial Care for Children and Adolescents according to the variables (number of medicine used per child, name of the medicine and therapeutic class). Fortaleza. Ceará. Brazil. 2019-2020

Variables	Average (Standard Deviation)	N	%
Number of medicines per child (N=112)	1.71 (0.85)		
1		46	41.0
2		44	39.2
3		16	14.2
4		5	4.4
5		1	0.8
Medicines (N=112)			
Risperidone		112	100
Periciazina		18	16
Valproic acid		18	16
Fluoxetine		8	7.1
Carbamazepine		8	7.1
Methylphenidate		6	5.3
Haloperidol		5	4.4
Phenobarbital		4	3.5
Amitriptyline		3	2.6
Citalopram		3	2.6
Imipramine		2	1.7
Levomepromazine		2	1.7
Quetiapine		2	1.7
Lithium carbonate		1	0.8
Therapeutic classes (N=192)			
Antipsychotics		139	72.3
Antiepileptics		30	15.6
Antidepressants		16	8.3
Psychostimulants		7	3.6

In this survey, of the 112 medical records, a total of 42 ADEs were identified in 32.1% (36) of the medical records, with 29.7% (11) to agitation, in 16.2% aggressiveness, constipation and drowsiness both with 10.8% (4). The average ADE per child was 1.1 with a standard deviation of 0.3, in which 45.2% (19) one event per child was found, 16.6% (7) two events were identified and in 21, 4% (3) three events (Table III).

TABLE III – Distribution of the AME found in the medical records of children monitored by Centers for Psychosocial Care for Children and Adolescents. Fortaleza. Ceará. Brazil. 2019-2020

Variables	Average (Standard Deviation)	N	%
Number of AME per child (N=42)	1.1 (0.3)		
1		19	45.2
2		7	16.6
3		3	21.4
AME (N=42)			
Agitation		11	29.7
Aggressiveness		8	16.2
Constipation		4	2.7
Somnolence		4	10.8
Itch		3	8.1
Insomnia		3	8.1
Weight gain		3	8.1
Dyspnea		2	5.4
Visual Deficiency		1	2.7
Hallucinations		1	2.7
Stereotypes		1	2.7
Foam in the mouth		1	2.7

Regarding the identification of trackers using the GTT, it was found that out of the 36 records that were identified as ADE, 83.3% (30) records were detected with a total of 50 trackers. It was observed that in 38.8% (14) only one tracker was found, 33.4% (12) two trackers and in only 11.1% (4) just one, the average was 1.38 tracker per medical record. The combination of psychotropic drugs was the most found with 27.9% (17), followed by the abrupt reduction in the dose of the drug with 20.3% (12) and the use of antihistamines 11.1% (7) (Table IV).

TABLE IV – Distribution of trackers according to the GT tool found in medical records of children in Centers for Psychosocial Care for Children and Adolescents. Fortaleza. Ceará. Brazil. 2019-2020

Variable	Average (Standard Deviation)	N	%
Number of trackers per child (N=36)	1.38 (0.76)		
0		6	16.7
1		14	38.8
2		12	33.4
3		4	11.1
Trackers (N=50)			
Combination of psychotropic drugs		16	32
Abrupt reduction in medication dose		11	22
Abrupt drug cessation		6	12
Antihistamines		5	10
Transfer to a higher level of care		4	8
Laxatives		3	6
Significant weight gain		3	6
Antiemetics		1	2
Antidiarrheal		1	2

DISCUSSION

The survey carried out by analyzing the medical records of the two Centers for Psychosocial Care for Children and Adolescents in the city of Fortaleza-Ceará revealed a greater predominance of children aged between 9 and 12 years old, who attend school and with psychological development disorders, corroborating with data presented in other descriptive studies carried out in Brazil (Serafim *et al.*, 2019; Leitao *et al.,* 2020).

The use of nervous system medicines in children, which is evidenced in this study by all the medical records analyzed, is consistent with the results presented in the literature (Silva, Silveira, 2019; Borges *et al.,* 2020). However, evidence shows that antipsychotics should be considered a short-term strategy, while psychosocial and behavioral therapies must be continuously applied, meeting the follow-up profile applied in Centers for Psychosocial Care for Children and Adolescents, where

there is a need to establish a support point for family, with the offer of these non-drug therapies (Silva, Lima, Ruas, 2020).

In this context, the average of 1.7 medicines per child affects of the medicines process and polypharmacy rates in childhood. In this regard, a retrospective study conducted with a database between the years 2013 to 2015 with a total of 24,147 children and youth using psychotropics showed that the prevalence of polypharmacy was 20.09% and that children followed by only a medical professional was 5.3 times more likely to have polypharmacy than those who were attended by more than three health professionals, including nurses, psychologists and occupational therapists, highlighting the importance of the performance of the multiprofessional team (Medhekar *et al.,* 2019).

The predominance of the use of risperidone in this study is consistent with other findings in studies also carried out in CAPSi, mentioning that this drug

is among the most prescribed atypical antipsychotics for pharmacological treatment in irritability and aggressiveness associated with mental disorders in children (Dinnissen, 2015; Borges *et al.,* 2020). However, the conditions of agitation and aggression were the adverse event (AE) most found in this study, being manifestations that are considered common in children's mental health environments and that can interfere in the assessment of the causality of ADE, since they can be symptoms triggered by the mental disorders themselves (Rosso *et al.,* 2020).

Bringing an approach to ADE with the use of antipsychotics in general by children, a prospective multicenter naturalistic study conducted between April 2013 and May 2016 with a sample of two hundred children with an average age of 12 years on the incidence of AE in this population, showed that 15.4% of the events were neuromotor, 14.8% gastroenterological, 12.2% metabolic and 11.8% general symptoms, in addition to that weight and body mass index increased significantly (Menard *et al.*, 2019).

Although the literature shows that risperidone is widely associated with a significant and sustained increase in the values of body mass index and abdominal perimeter, mainly in uses over a year (Abrantes, 2015; Vanwong *et al.*, 2020), the present study showed weight gain in only 8.1% of children. Regarding gastrointestinal manifestations such as constipation, nausea, vomiting, diarrhea also evidenced in this study, they are widely associated with antiepileptics such as valproic acid (Egunsola *et al.,* 2018) and neurological symptoms including delirium, hallucination, drowsiness and insomnia are associated with psychostimulants, such as methylphenidate (Hollis *et al.,* 2019).

Regarding the occurrence of ADE to nervous system medicines, it is noteworthy that the use of combinations of medicines, which has become a common practice, has stimulated the incidence of drug interactions that are capable of intensifying the effects or even preventing the action of some medicines in the organism (Spina; Leon, 2014). As, for example, risperidone concentrations can be reduced in concomitant use with carbamazepine and the use of lithium carbonate with risperidone can result in extrapyramidal symptoms, muscle weakness,

dyskinesias and brain damage, by unknown mechanisms (Micromedex, 2021). Thus, based on pharmacotherapeutic follow-up, possible drug interactions and the occurrence of ADE should be checked and the risks and benefits of psychotropic therapy should be considered.

From this, studies have shown that the tools for detecting trackers have facilitated the identification of these ADE in children, especially for those who use two or more medicines and the damage they can cause (Solevåg, Nakstad, 2014; Ji *et al.,* 2018). The high rates of ADE in children correspond to the high frequencies of trackers discovered from the analysis of medical records, matching the results of descriptive research with the application of the GTT, carried out in psychiatric environments, such as hospitals and outpatient services (Rozenfeld, Giordani, Coelho, 2013; Nilsson *et al.,* 2020).

The combination of nervous system medicines as the most commonly found tracker in this research, can be justified by the monitoring provided by the community service offered at Center for Psychosocial Care for Children and Adolescents, in children with chronic and stable conditions. Since the results of research carried out retrospectively in this population in hospital environments also with the application of the GTT showed the abrupt stop of the medicine (Ivashchenko *et al.,* 2020) and transfer of level of care (Fajreldines *et al.,* 2019) as the most found.

In general, it was observed that the trackers verified in research, vary in location, profile of care and patient attended. In the study by Ji *et al.* (2018) found in their research with the application of the GTT performed in hospitalized children diagnosed with cancer that the presence of rash and the abrupt stop of the use of the drug were the most identified trackers. And Solevåg and Nakstad, (2014) showed in a study conducted with a convenience sample of 761 children of clinical and surgical origin, using different classes of drugs, that readmission to the service and hypoxia were the most commonly found trackers. It should be noted that there is a limitation of research that evaluated the use of the GTT directed to the context of pediatric mental health associated with community services.

Retrospective analysis of the medical records was considered as limitations of the study, with risk of

information bias, since only what was documented in the records could be evaluated, as well as the scarce information recorded by health professionals in the medical records that made it difficult to verify the ADE. However, the study demonstrated the feasibility of the GTT applied in the context of mental health in a community service, highlighting the detection of trackers that can contribute to the adoption of preventive measures and reducing the damage that ADEs can cause in the pediatric population.

CONCLUSION

Finally, the present study showed that the GTT evidenced the occurrence of ADE and allowed the detection of trackers in children monitored in Center for Psychosocial Care for Children and Adolescents. This broad recognition defines the need to offer systematic interventions to improve the quality of psychiatric care within community services, integrating the finding of ADEs that are considered preventable and enhancing the safety of the use of nervous system medicines in children. With that, it was noticed the need for more in-depth studies with the child audience to evaluate strategies that facilitate the identification of psychiatric ADEs and consider the safety and effectiveness of the application of this tool in community services.

CONFLICTS OF INTEREST

None.

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