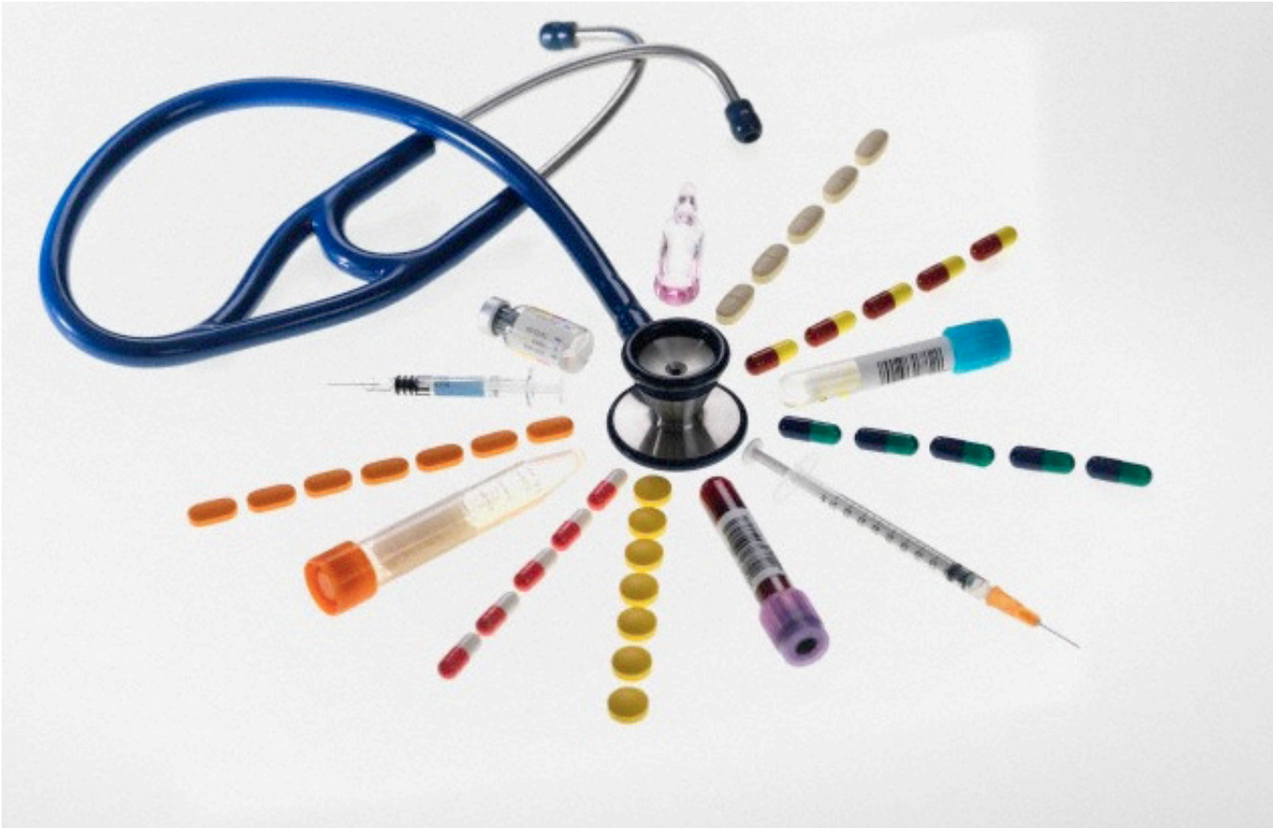

Inês Isabel da Silva Barejo

A SYSTEMATIC REVIEW OF THE TRIGGER-BASED ADE DETECTION SYSTEM

Monografia realizada no âmbito da unidade Estágio Curricular do Mestrado Integrado em Ciências Farmacêuticas, orientada pelo Professor Doutor Francisco Batel Marques e apresentada à Faculdade de Farmácia da Universidade de Coimbra

Julho 2015

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UNIVERSIDADE DE COIMBRA

Eu, Inês Isabel da Silva Barejo, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o número 2010140341, declaro assumir toda a responsabilidade pelo conteúdo da Monografia Apresentada à Faculdade de Farmácia da Universidade de Coimbra.

Mais declaro que este é um trabalho original e que toda e qualquer afirmação ou expressão, por mim utilizada, está referenciada na Bibliografia desta Monografia, segundo os critérios bibliográficos legalmente estabelecidos, salvaguardando sempre os Direitos de Autor, à exceção das minhas opiniões pessoais.

Coimbra, 8 de julho de 2015.

_____

O Orientador da Monografia

(Professor Doutor Francisco Batel Marques)

A Aluna

(Inês Isabel da Silva Barejo)

Os meus sinceros agradecimentos:

À minha família,

Aos amigos,

Aos professores,

A Coimbra.

INDEX

1. ABBREVIATIONS

AAED T	Automated Adverse Event Detection Tool
AE	Adverse Event
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ADE TT	Adverse Drug Event Trigger Tool
AKI TT	Acute Kidney Injury Trigger Tool
APTT	Activated Partial Thromboylastin Time
CPOE	Computer Provider Order Entry
CTCAE	Common Terminology Criteria for Adverse Events
DO	Direct Observation
FHRR	Full Health Record Review
GTT	Global Trigger Tool
ICU	Intensive Care Unit
IHI	Institute for Healthcare Improvement
INR	International Normalized Ratio
MB TT	Medication-based Trigger Tool
ME	Medication Error
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NH	Nursing Home
NPV	Negative Predictive Value
NNA	Number Needed to Alert
OS	Observational Study
OTT	Oncology Trigger Tool
pADE	Preventable Adverse Drug Event
PCR	Patient Chart Review
PICU TT	Pediatric Intensive Care Unit Trigger Tool
PPV	Positive Predictive Value
PTT	Pediatric Trigger Tool
RCT	Randomized Controlled Trial
SR	Survey Research
STT	Surgical Trigger Tool
TAT	Trigger Assessment Tool
TT	Trigger Tool
USA	United States of America
VR	Voluntary Reporting

2. ABSTRACT

Purpose: To carry out a systematic review about the use of the trigger tool method in the detection of Adverse Drug Events (ADE's), as a part in the patient's safety monitoring methods.

Methods: Databases (Pubmed and Cochrane Library) were systematically searched for ADE trigger tools (ADE TT) from April up to June 2015. Experimental and Observational studies were included when their main purpose was the application of trigger-based ADE detection tools. Studies in which that purpose wasn't the major goal were excluded.

Results: Thirty-one studies were included in this review. 29 Observational Studies and 2 Randomized Controlled Trials. ADE TT (modified or non-modified) was the most frequent trigger tool found, followed by the Institute for Healthcare Improvement Global Trigger Tool (IHI GTT). General Medicine, Pediatrics and Geriatrics were the main medical specialities found to be involved in the studies.

Conclusions: This review suggests the creation of a "guideline", in order to all researchers use the same methods and evaluate similar outcomes. However, the trigger tool should be modified and adjusted to the needs of each research aim.

Key-Words: Trigger Tool, Adverse Drug Event, Pharmacovigilance

3. RESUMO

Objetivo: Levar a cabo uma revisão sistemática sobre o uso do método 'trigger tool' na detecção de ADE's, como parte dos métodos de monitorização da segurança do doente.

Métodos: Bases de dados ('Pubmed' e a 'Cochrane Library') foram pesquisadas sistematicamente para encontrar 'ADE trigger tools' desde abril até junho de 2015. Estudos Experimentais e Observacionais foram incluídos. O principal objetivo deste estudos deveria ser a aplicação de ferramentas de detecção de ADE's baseadas em 'triggers'. Estudos onde este não era o principal objetivo foram excluídos.

Resultados: Trinta e um estudos foram incluídos nesta revisão. Destes, 29 Observacionais e 2 Ensaios Clínicos Aleatórios Controlados. A 'trigger-tool' mais frequente foi a ADE TT (modificada ou não modificada), seguida pela IHI GTT. As principais áreas médicas envolvidas foram Medicina Geral, Pediatria e Geriatria.

Conclusão: Este estudo salienta o facto de haver necessidade da criação de uma 'guideline', para que todos os investigadores possam utilizar os mesmos métodos e avaliar os mesmos resultados. Mesmo que a 'trigger tool' necessite de algumas modificações para ser ajustada às necessidades dos investigadores ou que tenha de ser criada uma nova.

Palavras-Chave: Trigger Tool, Eventos Adversos a Fármacos, Farmacovigilância

4. INTRODUCTION

An Adverse Event (AE) is considered an injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. AE's may be preventable or non-preventable.[1] Examples of AE's are Adverse Drug Events (ADE) and Medical Errors.

An Adverse Drug Event (ADE) is a noxious, unintended response to a drug,[2] It covers noxious and unintended effects resulting not only from the authorized use of a medicinal product at normal doses, but also from medication errors (ME) and use outside the terms of the marketing authorization, including the misuse and abuse of the medicinal product.[3] ADEs are the most common AE's.[4]

Since the disaster of thalidomide, in 1961, international efforts have been initiated to address drug safety issues. From these beginnings emerged the practice and science of pharmacovigilance.[5] Ensuring patient safety became a common goal for every healthcare provider, and it includes the prevention of ADEs related to the exposure to medical care provided.[4]

Multiple event detection methods, in pharmacovigilance, are needed to identify ADEs across both pre- and post-marketing phases. The four primary event-detection methods, in post-marketing phase, are voluntary event (incident) reports, direct observation, chart review, and application of trigger-tools.[6]

The concept of a "trigger" (or clue) to identify adverse events through the review of medical records was introduced by Jick in 1974. Classen refined the approach by using automated triggers. The use of triggers with manual record reviews was initially developed by the Institute for Healthcare Improvement (IHI) in 1999 to identify only adverse medication events; then ensued the adaptation of the methodology for other areas of the hospital, such as intensive care. Recent publications describe the use and development of trigger-tools.[7]

A trigger-tool (TT) is a list of sentinel words (triggers). A trigger can be defined as an occurrence, prompt, or flag (eg, laboratory values or medication orders) found on review of the medical chart that 'triggers' further investigation to determine the presence or absence of an adverse event. The TT is a relatively simple method, which permits consistently accurate identification of a broad range of adverse events that are directly linked to clinical harm.[8]

There are two standard methods of trigger-based ADE detection: manual and automated. The manual method is based on the review of randomly selected charts, for specific pre-specified triggers.[8] The automated method applies algorithms to medical charts in order to automatically identify pre-specified triggers.[9]

The aim of this study was to carry out a systematic review in order to evaluate the characteristics and applications of the trigger-based ADE detection methods.

5. METHODS

This systematic review followed the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.[10]

A systematic search was carried out up to June 1, 2015 in Pubmed and Cochrane Library in order to identify studies describing the main characteristics and applications of trigger-tools. The search strategy is listed in Table 1.

Search terms related with trigger-based ADE detection tools were combined with ADE-related terms. Only literature published in the English language was considered for inclusion.

Table 1. Search Strategy.

Strategy for literature search june 1, 2015
((trigger tool) **OR** (medication-based trigger tool) **OR** (adverse drug event trigger tool) **OR** (adverse drug reaction trigger tool) **OR** (global trigger tool)) **AND** ((adverse drug reaction) **OR** (adverse drug reactions) **OR** (adverse drug event) **OR** (adverse drug events)) Filter: English

Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion. Disagreement was resolved by discussion and consensus with a third investigator.

Studies were included according to the following criteria: experimental and observational studies of application of trigger-based ADE detection tools.

The quality of the retrieved studies was not assessed. The included studies addressed the application of a tool in clinical practice and the available quality assessment checklists aimed at evaluating clinical studies of interventions.

Information extracted from each of the studies was the following: characteristics of the TT, such as name of the TT, and respective number of triggers addressed; manual or automated application; time used to evaluate a case; type of evaluators; medical speciality of

the TT; and number of healthcare institutions, and country where TT was applied; type, and period of study; main results of the study; and other punctual interesting information.

Data were analyzed using descriptive statistics.

6. RESULTS

The search yielded a total of 266 potentially relevant references. After excluding for duplicates, 266 abstracts were reviewed and screened for eligibility. Based on above inclusion criteria, 52 references were selected for full-text further evaluation. A final sample of 31 references were eligible for inclusion: 29 observational studies (OS) and two randomized controlled trials (RCT). The selection of references is presented in Figure 1. The references of the included studies are listed in Table 2.

Figure 1. Flow Diagram of Literature Search

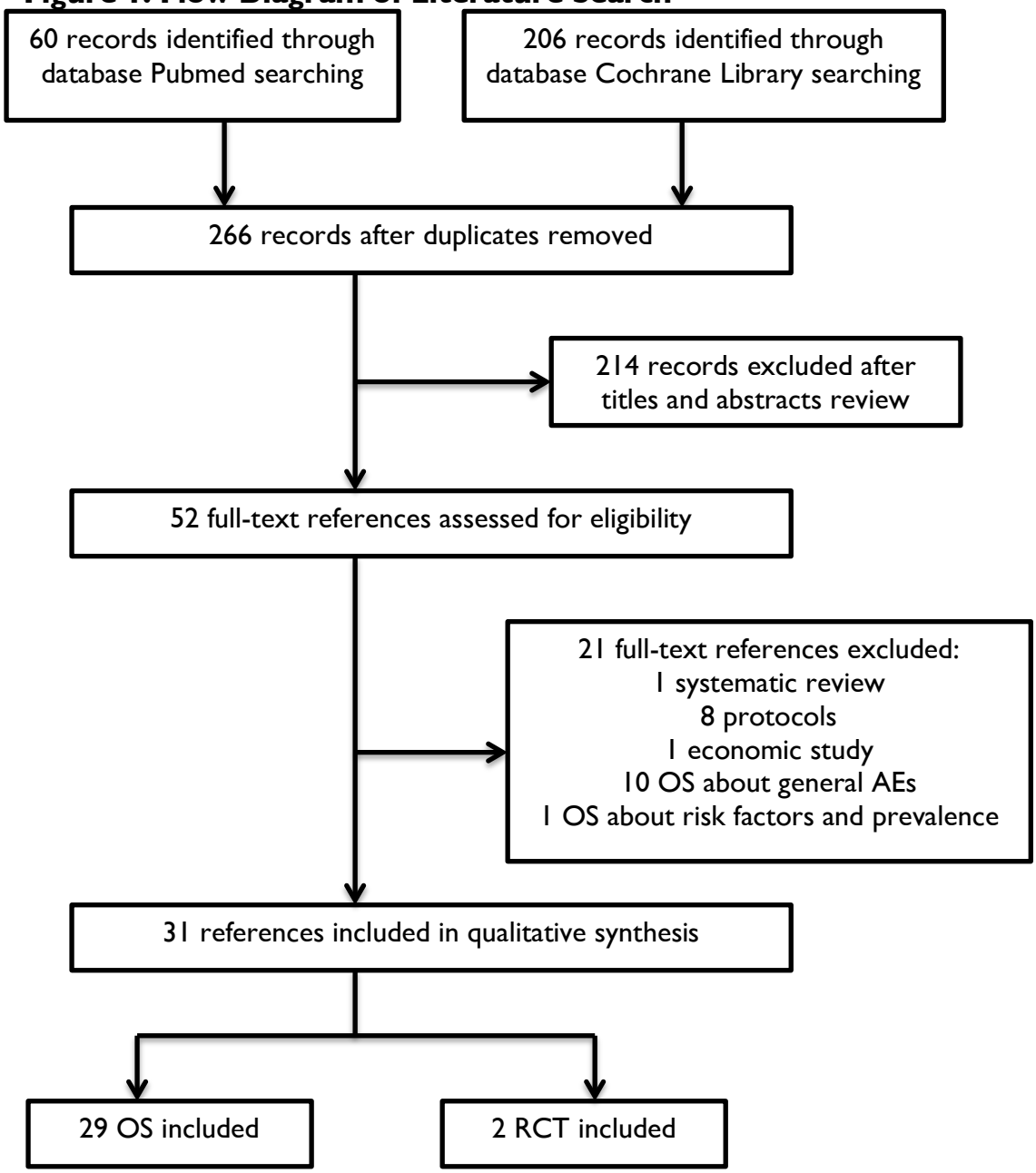

Table 2. Overview of the Main Characteristics and Results of the Included Studies

Main characteristics								Main Results		
Author, Date	**Trigger Tool (Number of Triggers)**	**Medical Specialty/ N° of institutions/ Country**	**Type of Study / Period of study**	**N**	**Manual or Auto-mated**	**Compa-risons**	**Time*/ Evalua-tor/ Others**	**Results of Main Outcomes Evaluated**	**Main Triggers (max. 5)****	**Main Drugs (max. 5)****
Staines A, 2015[11]	IHI ADE TT (21)	General Medicine (10 hospitals) Switzerland	Retrospective (Oct 2010-March 2012, March 2013)	3876 charts	Manual (Electronic records)		20 minutes Physician, Pharmacist and Nurse	ADE/1000 doses (different measures, across time) Severity (Harm)		
Sam AT, 2015[12]	IHI GTT (ADE triggers) (24)	General Medicine (1 hospital) Malaysia	Retrospective (Sept 2013 - Aug 2014)	100 patient case sheets	Manual		Pharmacists	45 triggers 153 AE (60 ADR, 71 ME) 29 ADE/100 patients 2,03 ADE/1000 doses Severity (Harm) Causality	Rashes Nausea Vomiting	Furosemide
Hébert G, 2015[13]	OTT (22)	Oncology (1 institute) France	Retrospective (Oct 2010 - Sept 2011)	288 admis-sions	Manual		21,8 minutes Pharmacists	884 triggers 42,4 ADE/100 admissions 46 ADE/1000 patient days PPV (20,7 %) Incidence Severity (Harm) Inter-rater reproducibility (IRR = 0,965 trigger)	Hyperglycae-mia Unplanned drug-related admission within 30 days Opiate-induced constipation	Anticancer drugs
Lau I, 2014[14]	IHI ADE TT (21)	General Medicine (1 hospital) Canada	Retrospective (Jan 2011 - Dec 2011)	204 encoun-ters	Manual		Pharmacists ADEs before admission excluded	15 ADE 7% ADE (Incidence) Severity (Harm) Causality	C. Difficile-associated diarrhea Rash Vomiting Neutropenia	Vancomycin Ciprofloxacin Ceftriaxone Piperacilin - tazobactam Mixofloxacin

Table 2. Overview of the Main Characteristics and Results of the Included Studies (continuation)

Main characteristics								Main Results		
Author, Date	**Trigger Tool (Number of Triggers)**	**Medical Specialty/ N° of institutions/ Country**	**Type of Study / Period of study**	**N**	**Manual or Auto-mated**	**Compa-risons**	**Time*/ Evalua-tor/ Others**	**Results of Main Outcomes Evaluated**	**Main Triggers (max. 5)****	**Main Drugs (max. 5)****
Härkänen M, 2015[15]	IHI GTT (modified) (22)	General Medicine (1 hospital) Finland	Retrospective (Jan 2011 - Dec 2011)	463 records	Manual (Electronic records)		Physicians and Pharmacists	180 ADE 61,3 ADE/1000 patient days 27% ADE (Prevalence) Severity (Harm) Preventability (41,1%)	Abnormal level in potassium in the blood Nausea Hypotension, dizziness or fall	
McClead RE Jr, 2014[16]	TT	Pediatrics (1 hospital) USA	Retrospective (Jul 2009 - June 2013)	20 charts per month	Manual (Electronic records)	with VR, PCR, pharmacy interv.		ADE/1000 doses (different measures, across time) Severity (Harm)		
Kirkendall ES, 2014[17]	AKI TT	Pediatrics (1 hospital) USA	Prospective (Sept 2011 - Sept 2013)		1° Manual, than Automated		Pharmacists	Sensitivity (SN = 0,98) Specificity (SO = 0,99) PPV (0,92) NPV (0,99)		Nephrotoxic medications (NTMx)
Call RJ, 2014[18]	MB TT (6)	Pediatrics (oncology and hematology) (1 hospital) USA	Prospective (Feb 2009 - Jan 2013)	390 patients	Automated	with VR	3 minutes Physician and Pharmacist	706 triggers 33 ADE Severity (Harm) Preventability PPV (16%)	Hyperkalemia grade 2	Naloxone Sodium polystyrene sulfonate

Table 2. Overview of the Main Characteristics and Results of the Included Studies (continuation)

Main characteristics								Main Results		
Author, Date	**Trigger Tool (Number of Triggers)**	**Medical Specialty/ N° of institutions/ Country**	**Type of Study / Period of study**	**N**	**Manual or Auto-mated**	**Compa-risons**	**Time*/ Evalua-tor/ Others**	**Results of Main Outcomes Evaluated**	**Main Triggers (max. 5)****	**Main Drugs (max. 5)****
Carnevali L, 2013[19]	IHI ADE TT (modified) (20)	General Medicine (1 hospital) Belgium	Retrospective (Feb 2010 - Jan 2011)	240 admissions	Manual	with MM GTT (medic module) (11)	Physicians, Pharmacists and Nurses	200 triggers 62 ADE 26 ADE/100 admissions 23 ADE/1000 patient days PPV Severity (Harm)	C. difficile + Sodium polystyrene INR >6 Abrupt medic stop / Rash	
Klopotow sko JE, 2013[20]	IHI ADE TT	Geriatrics (3 Hospitals) Netherlands	Retrospective (Apr 2007 - Nov 2007)	250 patients (from the study WINGS)	Manual	with PCR	Physician and Pharmacist	118 ADE's (43 ADE TT) 42,7 ADE/100 hospital Preventability (70,3%) Intra-rater (k= 0,74) Inter-rater (k= 0,24) Severity (Harm) Causality		
Khoo AL, 2013[21]	IHI GTT (modified) (19)	General Medicine (6 institutions) Singapore	Retrospective (9 months)	1020 records			Physicians, Pharmacists and Nurses	ADE occurrence Severity (Harm) Preventability		
de Boer M, 2013[22]	STT (51)	Surgical (1 health center) Netherlands	Prospective (Mar 2009 - Jun 2009)	262 patients	Manual	with ADE TT	Physicians and Pharmacists	538 triggers 91 ADE Preventability (7,7%) Causality Severity (Harm) Intra-rater (k=0,83) Inter-rater (k=0,81) (Reproducibility)		

Table 2. Overview of the Main Characteristics and Results of the Included Studies (continuation)

Main characteristics								Main Results		
Author, Date	**Trigger Tool (Number of Triggers)**	**Medical Specialty/ N° of institutions/ Country**	**Type of Study / Period of study**	**N**	**Manual or Auto-mated**	**Compa-risons**	**Time*/ Evalua-tor/ Others**	**Results of Main Outcomes Evaluated**	**Main Triggers (max. 5)****	**Main Drugs (max. 5)****
Marcum Za, 2013[23]	IHI NH ADE TT (modified) (27)	Geriatrics (3 Veteran Affairs Nursing Homes) USA	Retrospective (Sept 2010 - Nov 2010)	321 veterans	Manual (Electronic records)		8,8 minutes Physician and Pharmacist	99 ADE's PPV (40,1%) NNA (2,5)	Acute Kidney Injury Hypokalemia Hypoglycemia Hyperkalemia	Cardiovas-cular Medications
Seddon ME, 2012[24]	IHI ADE TT (19)	General Medicine (3 health boards) New Zealand	Retrospective (Mar 2010 - Feb 2011)	1210 charts	Manual (Electronic records)		1 Assessor	353 ADE 28,9 ADE/100 admissions 38 ADE/1000 bed days Severity (Harm)	Abrupt cessation of medications Antiemeticcs Falls, Hipotens. Raised creatinine	Morphine Warfarin Tramadol Aspirin Furosemide
Lemon V, 2012[25]	AAED T	Pediatrics (1 medical center) USA	Prospective (Sept 2007 - Jan 2012)		Automated (24 hours later)	with VR	1 Physician	3222 triggers 2441 AE's (drug related) PPV (37,2 %) Severity (Harm)		
Brenner S, 2012[26]	IHI ADE TT (modified) (6)	General Medicine (1 clinic) USA	Retrospective (Nov 2008 - Nov 2009)	583 patients	Manual (Electronic records)		2 Physicians	1342 triggers 91 ADE's Preventability Severity (Harm)	INR >5	

Table 2. Overview of the Main Characteristics and Results of the Included Studies (continuation)

Main characteristics								Main Results		
Author, Date	**Trigger Tool (Number of Triggers)**	**Medical Specialty/ N° of institutions/ Country**	**Type of Study / Period of study**	**N**	**Manual or Auto-mated**	**Compa-risons**	**Time*/ Evalua-tor/ Others**	**Results of Main Outcomes Evaluated**	**Main Triggers (max. 5)****	**Main Drugs (max. 5)****
Singh R, 2012[27]	IHI ADE TT (modified)	Geriatrics (12 practices) USA	Cluster Randomized Trial (prospective) (1 year)	1125 charts	Manual			Preventability Severity (Harm) pADE's		
Burch KJ, 2011[28]	PTT (14)	Pediatrics (1 rehabilitation hospital) USA	Retrospective (oct-dec 2005; oct-dec 2006; jun-jul 2008)	60 charts	Manual		40 min Pediatric pharmacist	76 triggers 17 ADE ADE/patient ADE/100 medication ADE/100 patient days Severity (Harm) Preventability	Abrupt medication stop Use of laxatives or stool softeners	Ciprofloxacin Amixicilin/ Clavulanic Acid Desnopressin
Menedez MD, 2012[29]	IHI GTT with CPOE	Geriatrics (1 hospital) Spain	Retrospective (2004 - 2009)	1553 patients	1° Manual (3 years) 2° Automated (3 years)		1887 ME 29,3% AEs	8,5 AE/100 admissions Prescription errors (27,6%) 0,7 Errors/ patient month Severity (Harm)	Falls	Antihista-minics Antibiotics Hypolipide-mics
Singh R, 2012[30]	ADE TT (modified) (39)	Geriatrics (8 practices) USA	Randomized controlled trial (12 months pre-intervention and 12 months post-intervention)	1600 charts	Manual (Electronic records)		Physician and Pharmacist	ADE/ 100 patient years Severity (Harm) Preventability		

Table 2. Overview of the Main Characteristics and Results of the Included Studies (continuation)

Main characteristics								Main Results		
Author, Date	**Trigger Tool (Number of Triggers)**	**Medical Specialty/ N° of institutions/ Country**	**Type of Study / Period of study**	**N**	**Manual or Auto-mated**	**Compa-risons**	**Time*/ Evalua-tor/ Others**	**Results of Main Outcomes Evaluated**	**Main Triggers (max. 5)****	**Main Drugs (max. 5)****
Franklin BD, 2010[31]	IHI ADE TT (modified) (23)	Surgery (1 hospital) UK	Retrospective (Apr 2003 and Nov/Dec 2003)	207 patients health records	Manual	with FHRR (44 minutes)	4 minutes Pharmacists Without ADE detected in admission	168 triggers 0,7 ADE/100 patient days 0,2 pADE/100 patient days PPV (0,04) Sensitivity (k=0,4) Preventability	Calcium reso. Unexpected medic. stop APTT (>3,0) INR (>6) C.difficile diarrhea	
Muething SE, 2010[32]	IHI ADE TT (modified) (2)	Pediatrics (1 hospital) USA	Retrospective (Jul 2006 - Mar 2008)		Automated			109 triggers 64 AE's - ADE's PPV	Hypoglycaemia (Bolus) Opiate-related oversedation	Insulin Naloxone
Agarwal S, 2010[33]	PICU TT (22)	Pediatrics ICU (15 hospitals) USA	Retrospective (Sept 2005 - Dec 205)	734 patients records	Manual		24,7 minutes Physicians, Pharmacists and Nurses	2816 triggers 256 ADE 28,6 AE/100 patient days 4,9 ADE/100 patient days 0,3 ADE/patient 13,0 pADE/patient days PPV (0,44) Severity (Harm) Preventability		
Louie K, 2010[34]	TT	ICU (31 hospitals) Canada	Survey			with DO, VR, PCR, Comp Syst, Pharma Inter, Safety Huddles	Physicians and Pharmacists			

Table 2. Overview of the Main Characteristics and Results of the Included Studies (continuation)

Main characteristics								Main Results		
Author, Date	**Trigger Tool (Number of Triggers)**	**Medical Specialty/ N° of institutions/ Country**	**Type of Study / Period of study**	**N**	**Manual or Auto-mated**	**Compa-risons**	**Time*/ Evalua-tor/ Others**	**Results of Main Outcomes Evaluated**	**Main Triggers (max. 5)****	**Main Drugs (max. 5)****
Sikdar KC, 2010[35]	TAT (38)	Pediatrics (Emergency Department) (1 hospital) Canada	Retrospective (Apr 2006 - Apr 2007)	2575 patients	Manual		Physicians, Pharmacists and Nurses	68 ADE Severity (Harm) Preventability (20%) 2,1% ADE (Prevalence)		Antimicrobial (macrolide antibiotics, amoxicilin)
Singh R, 2009[36]	ADE TT (39)	Geriatrics (ambulatory) (6 practices) USA	Retrospective (1 year)	1289 chart reviews	Manual		20 minutes Physician and Pharmacist	908 triggers 232 ADE Preventability PPV Severity (Harm)	Medication stop Hospitalization Emergency room	
Takata GS, 2008[37]	PTT (11)	Pediatrics (5 hospitals) USA	Retrospective (Nov 2003 - Apr 2004)		Manual (Electronic Records)	With VR	Physicians and Pharmacists	1669 triggers 79 ADE 11,2 ADE/100 discharges 22,3 ADE/1000 patient days 5,4 ADE/100 medication orders PPV (4,7%) Severity (Harm) / Causality		Analgesics and antipiretics Antineoplasic agents Antibiotics Hormones G.anesthesics
Takata GS, 2008[38]	PTT (15)	Pediatrics (12 hospitals) USA	Retrospective (Mar 2002 - May 2002)	960 patients	Manual	with VR	Physician, Pharmacist and Nurse	2388 triggers 107 ADE 11,1 ADE/100 patients 15,7 ADE/1000 patient days 1,23 ADE/100 medication doses / PPV / Severity Preventability (22%)	Pruritus Nausea	Opioid analgesics Antibiotics

Table 2. Overview of the Main Characteristics and Results of the Included Studies (continuation)

Main characteristics								Main Results		
Author, Date	**Trigger Tool (Number of Triggers)**	**Medical Specialty/ Nº of institutions/ Country**	**Type of Study / Period of study**	**N**	**Manual or Auto-mated**	**Compa-risons**	**Time*/ Evalua-tor/ Others**	**Results of Main Outcomes Evaluated**	**Main Triggers (max. 5)****	**Main Drugs (max. 5)****
Kapane KL, 2004[39]	ADE TT (modified) (10)	Geriatrics (3 nursing homes) USA	Retrospective			Pharmacis ts pADE's				
Cohen MM, 2005[40]	IHI ADE TT (24)	General Medicine (1 hospital) USA	Retrospective (Jan 2001 - Dec 2003)	20 charts monthly	Manual	Medicatio safety program		2,04 ADE/1000 doses Severity (Harm)		
Rozich JD, 2003[41]	IHI ADE TT (24)	General Medicine (86 hospitals) USA	Retrospective (June 1999)	1704 charts	Manual			720 ADE's 2,68 ADE/1000 doses		

* Time used to evaluate a case

** At maximum, there are only presented five of the main triggers and five of the main drugs.

Type of Trigger Tool. Ten different types of TT were observed. Adverse Drug Event Trigger Tool (ADE TT) (n=15; 48.4%) was the most common applied tool, followed by the Institute of Healthcare Improvement Global Trigger Tool (IHI GTT) (n=4; 12.9%). In two studies, the TT was not specified (n=2, 6,5%).

Number of triggers addressed in each TT. The number of triggers varied between the identified TT. The average of triggers per tool was 26 [minimum 2 - maximum 51][32,22].

Medical Speciality. Trigger-tools were used in six different areas. The three most common were General Medicine (n=10, 32,3%), Pediatrics (n=10, 32,3%) and Geriatrics (n=7, 22,6%), which together fulfilled 87,2% (n=27).

Number of institutions and Countries. In general, the TT was applied in one (n=17; 54,8%) institution. The average of institutions per tool was 7 [minimum 1 - maximum 86]. The Country where the TT was more frequently applied was the USA (n=17, 54,8%), followed by Canada (n=3, 9,7%).

Type of Study. From the 31 included studies, two (6,5%) were experimental studies and twenty-nine (93,5%) were observational studies. Twenty-four studies were retrospective (n=24, 77,4%).

Period of study and Number of cases evaluated. The period of study varied between the included TT, as did the number of cases evaluated.

Manual or Automated TT. The manual way was the most used (n=24, 77,4%). Three studies do not refer how they worked with the TT.

Comparisons. Some of the included studies referred and did some kind of comparison with other ADE-detection method (n=10, 32,3%).

Time used to evaluate a case. Only a few studies talked about it (n=8, 25,8%). The average of time per tool was 20 [minimum 3 - maximum 40].

Evaluators. The most common evaluators were pharmacists and physicians (n=9, 29,0%) followed by pharmacists alone (n=7, 22,6%) and the combination of the pharmacists, physicians and nurses (n=6, 19,4%). Seven studies don't mention what kind of evaluator was used (n=22,6%).

Results of Main Outcomes Evaluated. The majority of the studies provided the outcome evaluated (n=29, 93,4%).

The most common rates directly related with ADEs were ADE/1000 doses (n=5, 16,1%) and ADE/1000 patient days (n=4, 12,9%).

Positive Predictive Value (PPV) was calculated in 12 (38,7%) studies.

Preventability was referred in 13 (43,4%) studies, but only in 5 (16.1%) studies it was calculated.

Severity of the ADEs is the most frequent outcome reported (n=25, 80,6%). There are several scales to measure it. The most used was the Scale by National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) (n=13, 43,4%).[11,14-16,18,19]. Seven studies do not refer how the severity was calculated. Other Scales used were the Hartwig's Scale[12,22], the Common Terminology Criteria for Adverse Events (CTCAE) grading scale[18,20] and the National Cancer institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale[13].

Causality is the second most reported outcome (n=5, 16,1%). It was calculated in half of the studies by the Assignment of Naranjo Scores[14,22,37] and in the other half by the World Health Organization (WHO) Probability Scale[12,20,22]. One study used both scales.[22]

Main triggers and drugs. Both were appointed in almost half of the studies (n=14, 4,2%). The most common trigger described was Rash (n=3, 9,7%). The most common drug mentioned were Antibiotics (n=6, 19,4%).

7. DISCUSSION

Since the creation of the IHI ADE TT[41], several countries and institutions adopted this tool to detect ADEs. There where a lot of findings in common between studies presented in this discussion.

The ADE TT is applicable to several medical specialities.[41] However, there was a need to adjust this tool. The reasons to support this decision were: First, the country in cause[31,35], which used other types of medicines or outcomes for those medicines[20,21]. Second, specific specialities like Pediatrics[16-18], Geriatrics[15,20,23] and Oncology.[13] Other examples of specialities are the Intensive Care Unit (ICU)[33,34] and Surgery[31]. Third, some of the included studies pointed some risk factors to modify the TT.[15,20,22] Thus, there were created new tools[13,17,22] or the existing ones were modified[15,18,]. Some studies pointed that that modification was benefic and the new tool was more efficient.[13,14,17]

Certain triggers never lead to the identification of an ADE. These need to be removed or evaluated. While there are other triggers that need to be added.[14,19-23] In the application of the TT, the trigger wasn't present in the TT, but it lead to a lot of ADEs discovered.[14,15]

The number of triggers addressed in each TT went around 19 and 22. Mostly because of the IHI ADE TT that is used as 'the' standard model.

The most common type of study of TT's application was observational study.

Both period of study and number of cases evaluated were directly proportional on to the other. If we increase the time of study, proportionally, we increase the number of case sheets taken to evaluation. However, this is not a rule, because it depends also on the team of work and the number of institutions.[11,21,30,38,41]

Some of the included studies referred and did some comparisons of the TT method with other post-marketing detection methods. Those pointed the TT to be more efficient than the other ADE detection methods, especially than the Voluntary Reporting (VR).[15,16,18]

Time used to assess the TT usually goes around twenty minutes. Some researchers say that is little. For others it was enough.

Pharmacists are gaining a major role, when it comes to use the TT. The last studies refer only pharmacists as evaluators.[12,14,17]

The most important outcome evaluated was the association of the number of ADE with the number of admissions, the number of doses/medications, or the number of patients. These rates vary a lot between studies.

PPV was a good outcome to evaluate the performance of the TT. Preventability is also important for the iatrogenic evaluation of the ADEs.

The studies done so far are not concise when it comes to calculate outcomes. That is a point of bias. It should and can be removed if the authors begin to standardize methods.

Main triggers and the main drugs, if referred in future studies, are an important turnover point. It can be found if there are some medicines that need to be monitored more carefully and some triggers that should be added or maintained in the TT.

Not all studies give detailed data, and Table 2 couldn't be rightfully fulfilled. A lot of them that didn't have the inclusion criteria, talked about AEs in general[42-46]. That wasn't the main aim of this systematic review. The IHI GTT was excluded in some cases and included in others, when it referred other modules than the medication module.[7,45,46]

In this search it was found that some studies were already using the trigger tool, as a validated method to measure outcomes. With this TT, they measured the ADE's over time.[16,21,27]

ADE's that lead to admission of patients are very important. In some of the identified studies those were removed from the evaluation.[14,31] Those same studies referred the importance of adding ADE's during admission.[14,15] There where some TT concerned about distinguishing the ADE's Preventable from the Non-Preventable.[15,31]

There were referred some strengths of the TT method (in some cases specific to only some tools): requires minimal training[23]; little time needed[23]; versatile to use (it can be tailored to specific clinical settings) [23]; automated[17,18,25,32].

There were also pointed some limitations about the TT: triggers can only identify harm detected through a data point captured by health records[18,32]; low PPV[31]; low inter-rater reliability[11]; only one in-house reviewer[11,28,35]; low sensitivity[19,31]; little time (20 minutes)[14]; a lot of information bias (manual TT)[22,23,38]; triggers are difficult to detect through manual review[14]; a lack of a gold standard.[16,22,25]

Ambiguity is yet in the researchers minds. While some say that the TT is efficient[12,13,17] , others tell the opposite[23,26]. Most of them about the manual way.[14,31] Some referred that putting together all the detection methods improves the efficacy in the detection of ADE's.[18,28]

8. CONCLUSION

Medicine and Patient's Safety should evolve side by side. Managing it nowadays is a challenge. In addition to the tools included in the study, there are others TT's being developed, with new improvements.[47,48] There was also a need expressed by the included studies to do more studies with the following concerns: in different countries; prospectives[12]; with automated TT[17,18,24,31,35] and with a larger number of patients.[16,27,31,35]

The methodological quality of the studies included in this systematic review was not assessed because those weren't clinical trials. That is a probable bias for the present study.

This systematic review provides a comparative review and useful information for researchers that are looking to apply this method in a healthcare facility. A summary of all the TT used to detect ADEs since the creation of the IHI ADE TT is important. It can show how the guidance line in this method, for the different areas of medicine, is going.

This review suggests the creation of a "guideline", in order to all researchers use the same methods and evaluate similar outcomes. However, the trigger tool should be modified and adjusted to the needs of each research aim. Thus we can compare and evaluate those studies more accurately.

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