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Utility of an Adverse Drug Event Trigger Tool in Veterans Affairs Nursing Homes

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Abstract

Objective—To determine the utility (i.e., positive predictive value [PPV] and time requirement) of an adverse drug event (ADE) trigger tool in Veterans Affairs (VA) nursing homes (NHs); and to describe the most common types of potential ADEs detected with the trigger tool.

Design—Retrospective chart review.

Setting/Patients—Veterans residing in three VA NHs between 09/29/2010 and 10/29/2010.

Measurement—We used the Institute for Healthcare Improvement (IHI)-endorsed NH ADE trigger tool, modified to enhance its clinical relevance to detect potential ADEs. Electronic medical records were screened to identify residents with 1 abnormal laboratory value specified in the trigger tool.

Main Outcome Measures—A potential ADE was defined as the concurrent administration of medication that could cause the abnormal laboratory value. An overall PPV, or proportion of

residents with an abnormal laboratory value who had a potential ADE, and average time required to complete each trigger tool assessment were calculated.

Results—Among 321 Veterans, 50.5% (n=162) had at least one abnormal laboratory value contained in the trigger tool. Ninety-nine potential ADEs involving 146 medications were detected in 65 Veterans. The overall PPV of the ADE trigger tool was 40.1% (65/162), and the average time to complete resident assessments was 8.8 (sd ± 5.7) minutes. The most common potential ADEs were acute kidney injury (n=30 residents), hypokalemia (n=18), hypoglycemia (n=13), and hyperkalemia (n=10).

Conclusions—The modified NH trigger tool was shown to be an effective and efficient method for detecting potential ADEs.

Keywords

Adverse drug events; Trigger tool; Nursing home; Elderly

Introduction

Adverse drug events (ADEs) are defined by the Institute of Medicine (IOM) as “injuries resulting from a medical intervention related to a drug and can manifest as signs, symptoms or laboratory abnormalities.”¹ ADEs are common in elderly nursing home (NH) residents and are often a result of polypharmacy, multiple co-morbid illnesses, and difficulty with monitoring prescribed medications.^{2–4} ADEs are the most clinically significant and costly medication-related problems in NHs and are associated with an estimated 93,000 deaths a year and as much as \$4 billion in excess health care expenditures.^{4–7} Despite the consequences and costs associated with ADEs in the NH, the vast majority of these events go undetected using traditional methods, including mandatory monthly consultant pharmacist medication regimen reviews and spontaneous medication error or ADE incident reports. Therefore, alternative surveillance strategies are needed in NHs to supplement existing detection strategies and minimize the potential consequences of ADEs.

One alternative is to use trigger tool methodology that simplifies the detection process by allowing rapid and systematic examination of patient charts to extract relevant data for detection of adverse events, including potential ADEs.⁸ Strengths of the trigger tool method are that it requires minimal training, and it is versatile to use because it can be tailored to specific clinical settings.

Recently, a study was completed to develop a consensus list of laboratory triggers that was endorsed by Institute for Healthcare Improvement (IHI) entitled the “Nursing Home Adverse Drug Event Trigger Tool.”^{9,10} However, to the best of our knowledge, there has been no formal utility evaluation or application of the tool in the NH setting. Thus, the main objective of this study was to determine the utility (i.e., positive predictive value, PPV [proportion of residents with an abnormal laboratory value who had a potential ADE] and average time requirement) of an ADE trigger tool in Veterans Affairs (VA) NHs. Secondarily, we describe the types of potential ADEs detected with the trigger tool.

Methods

Development and Modification of the Nursing Home ADE Trigger Tool

Development of the NH ADE trigger tool has been previously detailed.¹⁰ Briefly, the authors conducted a comprehensive literature search for potential ADE triggers, followed by an Internet-based, two-round modified Delphi survey of physician, pharmacist, and advanced practitioner experts in geriatrics.¹⁰ Panelists reached consensus on 40 triggers,

including laboratory/medication combinations, medication concentrations, antidotes, and Resident Assessment Protocols (RAPs; conditions that are triggered by certain responses to items in the federally-mandated Minimum Data Set [MDS]). The IHI formally adopted this set of 40 triggers as the NH ADE trigger tool.^{9,11}

For the purposes of this study, we modified the original IHI-endorsed instrument and assessed 27 abnormal laboratory/medication combinations and select supratherapeutic medication concentrations.[Appendix 1] Among the 27 total trigger labs, 14 were abnormal laboratory/medication combinations, and 13 were supratherapeutic medication concentrations. We did not assess antidote triggers as part of this study because previous research by our investigative team showed that these triggers were associated with poor PPVs.^{9,12} Antidote triggers often yield low PPVs because “antidotes” (e.g., sodium polystyrene or epinephrine) can be used to treat multiple medical conditions, only a fraction of which are related to an ADE. Resident Assessment Protocols (RAPs) were also not included in this study because these data were no longer reported as part of the new MDS 3.0 assessments, which became effective October 2010.

Additional modifications were made to the original trigger tool in order to broaden and enhance the clinical relevance of the NH ADE trigger tool. These modifications included removing the *Clostridium difficile* toxin trigger in an individual taking a medication that may cause pseudomembranous colitis (due to its lack of specificity) and adding one additional supratherapeutic medication concentration signal for vancomycin. With the aid of a survey of clinicians at a national meeting, clinically relevant cut-points for the laboratory abnormalities were established for each of the 27 triggers.¹² For the purposes of this study, we further modified the trigger tool to improve its clinical relevance by: increasing the total bilirubin concentration cut-point to $2 \times \text{ULN}$; decreasing the platelet concentration cut point to $<75,000/\text{mm}^3$; and decreasing the sodium concentration cut point to $<130 \text{ mmol/L}$. In addition, recently published guidelines for determining acute kidney injury and drug-induced hepatotoxicity were used to further refine the cut points for kidney and liver function tests (Appendix 1).^{13,14}

To operationally define drugs that could be associated with the 14 abnormal laboratory signals and be considered potential ADEs, several strategies were employed. First, a clinical pharmacist (ZM) conducted a computerized search of the American Hospital Formulary System (AHFS) Drug Information to establish specific drug classes or individual drugs that could be linked to the 14 laboratory abnormalities.¹⁵ This was supplemented with information derived from an updated text book devoted to drug-induced diseases¹⁶ and a comprehensive medical online reference.¹⁷ Using a previously published and validated approach, this list of potentially causative agents was reviewed, edited, and agreed upon by our expert panel consisting of two clinical pharmacist/pharmacoepidemiology researchers (SA, JH), two geriatric clinical pharmacists (SJ, SF), and a geriatrician (SH).¹⁸

Study Design, Setting, and Sample

For the current cross-sectional study, the trigger tool (Appendix 1) was applied to Veterans residing in three VA NHs (Durham, North Carolina; Pittsburgh, Pennsylvania; and West Haven, Connecticut) over one-month (09/29/2010–10/29/2010). The study was approved by the VA Institutional Review Boards at each site.

Source of Patient Data and Screening for Potential ADEs

We obtained data for all residents included in the study using VA electronic health records through VistA/Computerized Patient Record System (CPRS). Data retrieved included pharmacy data, laboratory test results, and other key demographic and clinical

characteristics described below. To screen for potential ADEs, each trained clinical pharmacist reviewed electronic health records from their respective sites to evaluate abnormal laboratory values as listed in the modified NH trigger tool and regularly scheduled medications (excluding topicals, vitamins and laxatives) that were active within 30 days prior to the date of the laboratory trigger.

Primary Outcomes

In order to calculate the PPV, we determined the occurrence of potential ADEs during the study period. Similar to previous studies, we operationally defined a potential ADE as the concurrent administration of medication that could cause the abnormal laboratory value listed in the NH ADE trigger tool.¹⁹ In order to prevent multiple repeated abnormal laboratory values in one patient counted as separate potential ADEs, we required that the abnormal laboratory values must have returned to baseline before being considered for a new potential ADE. For one of the NH sites (Durham), the total time required to complete each trigger tool assessment (i.e., time to complete review for one resident) was recorded.

Analysis

All information derived from each site was entered into a Microsoft® Access database developed to minimize data entry errors. Descriptive statistics (means, frequencies) were used to summarize all variables for the sample, including the most common types of ADEs. Additionally, for descriptive purposes, the number-needed-to-alert (NNA; 1/PPV), defined as the number of alerts that need to be reviewed to detect one potential ADE, was calculated. [19] For the primary outcome (PPV) and similar to previous research¹⁹, our unit of analysis was the patient – i.e., the PPV was calculated by dividing the number of residents for whom a potential ADE was detected by the total number of patients who had one (or more) abnormal laboratory values. To calculate the other primary outcome of average time to apply the trigger tool, the time required for each resident was recorded, summed and the average was calculated. All analyses were conducted using SAS® version 9.2 (SAS® Institute, Inc., Cary, NC).

Results

Among all Veterans residing in a VA NH during the one-month study period (n=321), 50.5% (162/321) had at least one abnormal laboratory value contained in the trigger tool. The mean age of Veterans with 1 abnormal laboratory value was 70.6 years, most were male, and about one-fourth of the residents were black (Table 1). On average, the number of regularly scheduled medications was 13.3 per resident, and the number of chronic comorbid conditions was 9.7 per resident.

Ninety-nine potential ADEs involving 146 medications were detected in 65 residents. The overall PPV of the ADE trigger tool was 40.1% (65/162), and the number-needed-to-alert (NNA= 1/PPV) was 2.5 (i.e., 2.5 patients' charts have to be reviewed before a potential ADE was detected using the modified NH ADE trigger tool). The average time to complete an individual assessment was 8.8 (sd ± 5.7) minutes.

The most common potential ADE was acute kidney injury (AKI; n=30 residents) (Table 2). Other common potential ADEs included hypokalemia (n=18), hypoglycemia (n=13), and hyperkalemia (n=10). The most common medication classes associated with potential ADEs are listed in Table 2, with cardiovascular medications (e.g., ACE-inhibitors, ARBs, loop diuretics) being most frequently implicated.

Discussion

To the best of our knowledge, this is the first study to report on the PPV, NNA, and average time requirement using the modified IHI-endorsed ADE NH trigger tool. This research is important because improved surveillance of ADEs is particularly needed in the NH setting. The PPV reported in our study (40.1%) compares well to other screening tests used in clinical practice, such as the fecal occult blood test (PPVs ranging from 2% to 18%) which is recommended for all adults > 50 years of age by the United States Preventative Services Task Force.²⁰ Furthermore, the NNA found in the current study (n=2.5) is less than that reported by previous work in which the NNA ranged from 4 to 25 charts reviewed across four types of ADE triggers among patients at a university-based teaching hospital.¹⁹ This may be a direct result of the comprehensive literature review and modified Delphi consensus process that was used to develop the triggers.¹⁰ However, we did not assess ADE causality in this study, which may have led to a lower NNA compared to previous work. Finally, the average time to complete resident screens seems reasonable and is consistent with recommendations from the IHI to spend no longer than 20 minutes reviewing each chart as this does not usually yield additional events.²¹

It is interesting to note the most common ADEs detected using the trigger tool in Veterans residing in NHs. We found that 5 triggers (i.e., AKI, hypokalemia, hypoglycemia, hyperkalemia, and hyponatremia) out of 27 were associated with almost 80% of the total potential ADEs detected. This is similar to a previous study by Singh et al (2009) who found that 9/39 triggers accounted for 94% of ADEs detected in an ambulatory care setting.²² This suggests that abbreviated versions of the trigger tool could potentially be used and still detect the majority of potential ADEs.

There are several potential implications of these findings. First, NH residents should have their medication regimens systematically reviewed in order to prevent and/or minimize ADEs. One suggestion could be that this modified ADE trigger tool be incorporated into the consultant pharmacist federally mandated medication regimen review (MRR) process, which is required to occur on a monthly basis for every U.S. NH resident. The U.S. State Operations Manual provides a definition for MRR (i.e., F428) as a thorough evaluation of the medication regimen of a resident, with the goal of promoting positive outcomes and minimizing adverse consequences.²³ Incorporating the NH-specific ADE trigger tool into current practice could improve the quality of patient care in the NH setting without adding a substantial amount of time to complete MRRs. In addition to using trigger tool methods, the IHI and the Institute of Medicine recommend that NHs assess the safety of medication use through active monitoring systems.^{21,24} The use of active medication monitoring systems will undoubtedly become more feasible over time despite most NHs lagging behind the implementation and use of health information technology.²⁵ Future research is needed to assess the impact of well-developed automated ADE detection systems on patient safety and healthcare spending in the NH setting.

There are several potential limitations that deserve mention. First, the cross-sectional design limits our ability to assess ADEs that may more commonly occur during other times of the year in the NH setting. Moreover, this was a retrospective study, which was a necessary first step to test the utility of the trigger tool. We also did not determine the causality of these potential ADEs, and we did not conduct inter-rater reliability statistics. However, the assessments conducted in this study were objective in nature and all reviewers were equally trained on how to conduct the chart reviews. As with any study conducted in the VA system, there are limitations to generalizability as the residents in this study were predominantly male and white. However, the population was elderly with multiple comorbidities, which is similar to NH residents within and outside of the VA. In addition, the trigger tool does not

include all possible ADEs that can occur in the NH setting. For example, we included anemia (as indicated by a low or decreasing hemoglobin concentration) found in an individual taking a drug that may cause or worsen anemia (eg, nonsteroidal anti-inflammatory agents) in the initial set of laboratory/medication combination signals to determine a consensus list of signals that could be used to detect adverse drug events.¹⁰ However, this particular signal did not reach consensus agreement by a multidisciplinary panel of pharmacists, physicians, and advanced practitioners and was consequently not included in this study. Furthermore, we recognize that our trigger tool that is solely based on laboratory data will likely miss a significant number of ADEs. However, the current study was guided by the results of a previous study which was used to explicitly develop the triggers included in this and other studies. We intend on expanding the ADE trigger tool to include additional sources of data such as signs, symptoms, and incident/fall reports that could be used to detect such events.

It is important to keep in mind that reducing the number of false-positive triggers that need to be reviewed is particularly important to reduce trigger burden and more efficiently use the scarce resources available for ADE detection and management in the NH setting. One way to improve the efficiency of trigger tools recommended by the IHI is to modify or add/delete triggers based on the trigger-specific PPVs or on the needs of the facility, thus allowing for flexibility in the utility of trigger tools.²¹ In this study, we applied modifications deemed to enhance the clinical relevance of the laboratory cut-points for some of the triggers. In addition, the IHI recommends using the results of the trigger tool to measure the number of ADEs in a NH over time and to determine whether or not the changes a facility implements result in a reduction of ADEs.²¹ It is also important to recognize that the trigger tool methodology has been used in other clinical settings as well as in other countries for various other adverse events beyond medications.²¹ We recommend that a Delphi survey would need to be conducted prior to using the NH Trigger Tool in other countries due to differences in medication ascertainment and practices.

In conclusion, we found that the modified NH Trigger Tool was shown to be an effective and efficient method for detecting potential ADEs in the VA NH setting. Current ADE detection and management remain inadequate in the NH setting, and improved surveillance and novel approaches such as the ADE trigger tool are greatly needed. Future studies should be conducted (in both Veteran and non-Veteran populations) to assess the clinical impact of incorporating the trigger tool method for ADE detection by consultant pharmacists as part of monthly MRRs and through the use of computer decision support systems and active medication monitoring.

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Abbreviations

ACE	angiotensin converting enzyme
ADE	adverse drug event
AKI	acute kidney injury

ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
CPK	creatine phosphokinase
CPRS	computerized patient record system
F	free
Hgb	hemoglobin
IHI	Institute for Healthcare Improvement
INR	international normalized ratio
IOM	Institute of Medicine
MDS	Minimum Data Set
MRR	medication regimen review
NAPA	N-acetylprocainamide
NH	nursing home
NNA	number needed to alert
P	peak
PPV	positive predictive value
R	random
RAP	Resident Assessment Protocol
RIFLE	Risk, Injury, and Failure, and Loss, and End-stage kidney disease
sd	standard deviation
SSRI	selective serotonin reuptake inhibitor
T bili	total bilirubin
T	total
Tr	trough
T4	thyroxine
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VA	Veterans Affairs

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Appendix 1

Modified Trigger Tool for Measuring Potential Adverse Drug Events in the Nursing Home

Trigger #	<i>Laboratory/Medication Combination Signals & Abnormal Laboratory Cut-Points</i>	
1	Hypoglycemia is found in an individual taking a drug that may cause or worsen hypoglycemia.	Glucose < 70 mg/dL
2	Supratherapeutic international normalized ratio (INR) is found in an individual taking warfarin.	INR > 4.5
3	Hyperkalemia is found in an individual taking a drug that may cause or worsen hyperkalemia.	K ⁺ 5.5 mmol/L
4	Hypokalemia is found in an individual taking a drug that may cause or worsen hypokalemia.	K ⁺ 3.5 mmol/L
5	Thrombocytopenia is found in an individual taking a drug that may cause or worsen thrombocytopenia.	Platelets < 75,000/mm ³
6	Supratherapeutic activated partial thromboplastin time (aPTT) is found in an individual taking heparin.	aPTT > 100
7	Hyponatremia is found in an individual taking a drug that may cause or worsen hyponatremia.	Na ⁺ < 130 mmol/L
8	Subtherapeutic concentration of thyroid-stimulating hormone (TSH) or elevated concentration of thyroxine (T4) is found in an individual taking a drug that may cause hyperthyroidism.	TSH < 0.34 µIU/L T4 > 12 µg/dL
9	Supratherapeutic concentration of TSH or decreased concentration of T4 is found in an individual taking a drug that may cause hypothyroidism.	TSH > 5.6 µIU/L T4 < 6 µg/dL
10A	<i>Hepatotoxicity:</i> Elevated alanine aminotransferase (ALT) AND aspartate aminotransferase (AST) concentrations are found in an individual taking a drug that may cause liver toxicity (<i>Note:</i> ULN values: ALT 60 IU/L; AST 42 IU/L).	ALT/AST 3x ULN
10B	<i>Hepatotoxicity:</i> Elevated alkaline phosphatase (ALP) AND total bilirubin (T. bili) concentration is found in an individual taking a drug that may cause liver toxicity (<i>Note:</i> ULN value: T. bili 1 IU/L).	ALP > 121 IU/L T. bili 2x ULN
11	<i>Acute kidney injury (AKI):</i> Per RIFLE criteria: AKI is found in an individual taking a drug that may cause AKI.	<i>Risk:</i> 1.5-fold increase in serum creatinine value from baseline <i>Injury:</i> 2-fold increase in serum creatinine value from baseline <i>Failure:</i> 3-fold (or greater) increase in serum creatinine value from baseline
12	Neutropenia (as indicated by a low granulocyte/neutrophil count) is found in an individual taking a drug that may cause or worsen neutropenia.	Granulocyte count < 1400/mm ³
13	Elevated creatine phosphokinase (CPK) concentration is found in an individual taking a drug that may increase CPK.	CPK > 269 u/L
14	Elevated hemoglobin (Hgb) is found in an individual taking an erythropoiesis stimulating agent that may increase hemoglobin.	Hgb > 12.0 g/dL
Trigger #	<i>Medication Concentration Signals & Abnormal Laboratory Cut-Points</i>	
1	Aminoglycoside peak (P), trough (Tr), or random (R) concentration is supratherapeutic in an individual taking an aminoglycoside antibiotic (i.e., amikacin, gentamicin, tobramycin).	Amikacin: P > 30 mcg/mL; Tr > 8 mcg/mL; R > 30 mcg/mL Gentamicin: P > 10 mcg/mL (for gram negative organisms) and > 5 mcg/mL (for

Trigger #	<i>Laboratory/Medication Combination Signals & Abnormal Laboratory Cut-Points</i>	
		gram positive organisms); Tr > 2 mcg/mL (for gram negative organisms) and Tr > 1 mcg/mL; R > 10 mcg/mL Tobramycin: P > 10 mcg/mL; Tr > 2 mcg/mL; R > 10 mcg/mL
2	Phenytoin free (F) or total (T) concentration is supratherapeutic in an individual taking phenytoin.	Phenytoin F > 2 mcg/mL; Phenytoin T > 20 mcg/mL
3	Lithium trough concentration is supratherapeutic in an individual taking lithium.	Lithium > 1.5 mmol/L
4	Theophylline trough concentration is supratherapeutic in an individual taking lithium.	Theophylline > 20 mcg/mL
5	Digoxin trough concentration is supratherapeutic in an individual taking digoxin.	Digoxin > 2.1 ng/mL
6	Procainamide trough concentration or N-acetylprocainamide (NAPA) concentration is supratherapeutic in an individual taking procainamide.	Procainamide > 4 mcg/mL or Procainamide + NAPA > 30 mcg/mL
7	Primidone trough concentration is supratherapeutic in an individual taking primidone.	Primidone > 10 mcg/dL
8	Quinidine trough concentration is supratherapeutic in an individual taking quinidine.	Quinidine > 5 mcg/mL
9	Valproic acid free (F) or total (T) concentration is supratherapeutic in an individual taking valproic acid.	Valproic acid F > 12 mcg/mL; Valproic acid T > 100 mcg/mL
10	Phenobarbital trough concentration is supratherapeutic in an individual taking phenobarbital.	Phenobarbital > 40 mcg/mL
11	Carbamazepine trough concentration is supratherapeutic in an individual taking carbamazepine.	Carbamazepine > 4.2 mcg/mL
12	Disopyramide trough concentration is supratherapeutic in an individual taking disopyramide.	Disopyramide > 5.1 mcg/mL
13	Vancomycin peak (P), trough (Tr), or random (R) concentration is supratherapeutic in an individual taking vancomycin.	Vancomycin: P > 40 mcg/mL; Tr > 20 mcg/mL; R > 40 mcg/mL

Abbreviations: F: free; K⁺: potassium; Na⁺: sodium; P: peak; RIFLE: Risk, Injury, and Failure, and Loss, and End-stage kidney disease; T: total; Tr: trough; ULN: upper limit of normal

Table 1

Characteristics of Residents in Three Veterans Affairs Nursing Homes (n=162)

Variable	
Age, mean (sd)	70.6 (12.2)
Male gender, n (%)	158 (97.5)
White, n (%)	119 (73.5)
Non Hispanic/Latino, n (%)	155 (95.7)
Hospice/Respite, n (%)	32 (19.8)
Number of regularly scheduled medications, mean (sd)	13.3 (5.7)
Number of active medical conditions, mean (sd)	9.7 (4.7)
Number of patients with prior history of allergy or adverse reaction, mean (sd)	115 (71.0)

Table 2

Most Common Potential Adverse Drug Events (ADEs) by Type among Those With a Trigger Alert (n=162)

Potential Adverse Drug Event (ADE)*	Residents with an ADE, n (%)	Most Common Medication Classes Associated with Potential ADEs
Laboratory Abnormality		
Acute kidney injury	30 (18.5)	ACE inhibitors/ARBs (n=18)
Hypokalemia	18 (11.1)	Loop diuretics (n=8)
Hypoglycemia	13 (8.0)	Insulin (n=14)
Hyperkalemia	10 (6.2)	ACE inhibitors/ARBs (n=6)
Hyponatremia	6 (3.7)	Loop diuretics (n=2); SSRIs (n=2)
Thrombocytopenia	4 (2.5)	Heparins (n=2)
Elevated INR	3 (1.9)	Warfarin (n=3)
Hepatotoxicity	2 (1.2)	Antilipemic Agents (n=2)
Medication concentrations	--	--
Elevated Vancomycin, trough	3 (1.9)	N/A
Elevated Phenytoin, total/free	2 (1.2)	N/A
Elevated Valproic Acid, free	2 (1.2)	N/A

* Adding up this column may result in a value >100% since some Veterans may have had abnormal laboratory results for more than one laboratory value; those Veterans who had >1 abnormal value of the same laboratory test were only counted once in this table.

Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; INR: international normalized ratio; N/A: not applicable; SSRI: selective serotonin reuptake inhibitor