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Strategies Prescribers and Pharmacists Use to Identify and Mitigate Adverse Drug Reactions: Implications for Clinical Decision Support

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Strategies Prescribers and Pharmacists Use to Identify and Mitigate Adverse Drug Reactions: Implications for Clinical Decision Support

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ABSTRACT

Background: Adverse drug reactions (ADRs) are the most common type of adverse drug events. The role of healthcare professionals (HCPs) is essential in preventing and managing ADRs. However, the processes that HCPs use to identify, treat, and monitor ADRs are not well understood. Understanding HCPs' cognitive processes and decisions are important to designing clinical decision support to prevent and address ADRs

Objective: to develop a descriptive model of the cognitive processes used to identify and resolve ADRs from the perspective of healthcare providers in order to inform future informatics efforts

Setting: inpatient and outpatient care at a tertiary care U.S. Veterans Affairs Medical Center

Participants: physicians, nurse, and pharmacists who report ADRs

Outcomes: descriptive model and emerging themes from interviews

Results: We conducted critical decision method interviews with 10 physicians and 10 pharmacists. We generated a descriptive model of ADR decision-making process and analyzed emerging themes, categorized into four stages: detection of potential ADR, investigation of the problem's cause, risk/benefit consideration, and plan, action, and follow-up. HCPs relied on several confirmatory or disconfirmatory cues to detect and investigate potential ADRs. Evaluating risks and benefits of related medications played an essential role in HCPs' pursuits of solutions

Conclusions: This study provides an illustrative model of how HCPs detect problems and make decisions regarding ADRs. The design of supporting technology for potential ADR problems

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should align with HCPs' real-world cognitive strategies, to assist fully in detecting and preventing ADRs for patients.

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STRENGTHS AND LIMITATIONS

Strengths:

- The ADR model developed can serve as valuable resources for alert system designers and educators who train future HCPs
- The finds of this study have several key implications:
  1. develop technologies to facilitate ADR communication between HCPs and patients
  2. incorporate confirmatory and disconfirmatory cues into ADR alert systems to more closely align with HCPs' cognitive strategies
  3. design alert systems that account for negative cues to facilitate decision making

Limitations:

- We only interviewed physicians and pharmacists regarding ADRs but not other HCPs such as nurse practitioners, registered nurses, or physician assistants
- Decision-making processes between physicians and pharmacists were not directly compared because of the variations in incidents.
- We only examined incidents from a single large V.A. medical center and EHR system.
- All incidents collected and analyzed were voluntarily provided which could influence our findings.

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INTRODUCTION

Adverse drug events (ADEs) harm over 1.5 million patients and cost over $500 million each year in the U.S. [1]. These concerning statistics prompted the U.S. Office of Disease Prevention and Health Promotion to develop a National Action Plan for Adverse Drug Event Prevention in 2014[2]. This plan called for actions, including developing health information technology to promote best practices in prescribing, and in detecting cases of high risk for ADEs [2]. Many factors contribute to the high incidence of ADEs in the U.S., including an increasing number of adverse drug reactions (ADR), an aging population, and a rising trend in polypharmacy [3]. ADR, defined as an unintended response to a drug that occurs at normally used doses, is the most common type of ADE [4]. Healthcare professionals (HCPs) such as physicians and pharmacists are essential in preventing and managing ADRs because they directly prescribe drugs and provide clinical care. However, the processes that individual HCPs adopt to identify, treat, and monitor ADRs are not well understood.

Healthcare systems leverage many different approaches to support HCPs in assessing and preventing ADRs, including systematic efforts to collect and review data to assess the risk of ADRs [5-7]. With advances in the development and implementation of electronic health records (EHR), alert systems that help HCPs identify and prevent ADEs have become more feasible and promising. Indeed, automated computerized order checks, frequently resulting in drug alerts, are often based on triggers such as the documentation of a patient's allergies [8].

While medication alert systems for allergies have been implemented regularly, alert systems with decision support to identify and resolve newly occurring ADRs are rarely found. In addition, many EHR alert systems have a technology-centric design that fails to take into

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account the HCPs' cognitive processes and workflow [9-11]. HCP decision-centered design, in contrast, focuses on HCPs' cognitive processes and key decisions, such as prescribing a drug, or choosing a drug regimen, as a core function of design [12, 13] With a foundational understanding of the cognitive strategies that HCPs use to prevent and respond to ADRs in clinical practice, healthcare systems and EHR vendors can develop systemic interventions and technologies to help HCPs prevent and resolve ADRs. Recent studies emphasize that cognitive studies are needed to help understand HCPs' decision making [9, 14] in order to develop more meaningful and effective clinical decision support. Therefore, the objective of this study was to develop a descriptive model of the cognitive processes used to identify and resolve ADRs from the perspective of HCPs in order to inform future informatics efforts.

METHODS

Study site and participant characteristics

This research is part of a larger study [15, 16] conducted at a tertiary care Veterans Affairs Medical Center. Eligible HCPs were physicians, nurse practitioners, and pharmacists who prescribed medications, managed medications, or verified prescriptions in an inpatient or outpatient setting. We excluded medical and pharmacy residents, trainees, pharmacy technicians, and those with a purely administrative role. We invited all remaining eligible HCPs at the study site to participate.

Patient and public involvement

No patient and public involved.

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Study design

The study procedure and data analysis are illustrated in four steps in **Figure 1.**

Potential ADR incident capture

Participants, when encountering a potential ADR, were ask to complete an incident card [15], which captured detailed information about the potential ADR incident, such as the type of ADR, suspected medication(s), and when the participant first became aware of the problem. Given that recall is often difficult for tasks and decisions that are made many times each day [17], the incident card was designed to help capture an ADR event close to the time of the incident, *before* it was forgotten or "merged" in memory with similar events. A similar approach of administering a small set of questions soon after an incident has been shown to increase accuracy of recall days later [18]. Subsequently, the incident card that HCPs submitted was used to assist with the critical decision method (CDM) interviews if the incident was selected, as described below.

Incident selection: A research team, consisting of a physician, pharmacist, and human factors expert, reviewed each incident card to determine eligibility for an interview. Incident cards were reviewed based on five criteria: incident was appropriately addressed, incident required great expertise or consideration, incident had potential to cause serious injury, incident was unique or challenging, or incident would be difficult for trainees to resolve alone.

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Critical decision method

Selected incidents led to scheduling of follow-up CDM interviews with HCPs, to collect further details [15]. The CDM interview technique, often used as part of a cognitive task analysis, is designed to capture detailed incident accounts from participants, including strategies, critical cues, and contextual elements as experienced by the interviewee [17]. Interviews were scheduled within two to four weeks of the incident date. One human factors scientist, trained in the CDM technique, conducted a 60-minute, semi-structured CDM interview with each HCP. These interviews were structured in the following three phases:

1) Capture a brief summary of the incident: The interviewer asked the participant to summarize the incident as it pertained to the ADR concern. If multiple eligible incidents were received from a participant, the interviewer asked questions at the beginning of the interview, to select the more challenging incident.
2) Construct an incident timeline: The interviewer asked participants probing questions, to reconstruct a high-level timeline of the incident. This timeline was recorded and displayed on a whiteboard, visible to both the interviewer and HCP during the interview session. The timeline helped the interviewer organize the incident in chronological order and provided a common point of reference for the rest of the interview.
3) Ask in-depth questions. The interviewer asked additional questions to investigate the HCPs' decision-making process, and to identify cognitive cues used during the course of the incident. The interviewer then asked hypothetical questions to gain further insights about the cognitive cues or strategies that the participant used to detect and respond to the ADR incident.

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The incident timeline was photographed. Interviews were audio-recorded and transcribed for analysis. The complete interview guide and a more detailed description of study methods is available elsewhere [15]. Examples of interview questions are below.

1. What caused you to be concerned about the medication for this patient?
2. In what ways did computerized alerts help you notice the right things and take action?
3. What tools/software/technology were used to help manage the medication conflict?
4. What, if any, documentation in the EHR helped you know what to do?
5. Under what circumstances, if any, would you have discontinued the medication for this patient, rather than reducing the dose?

Qualitative data analysis

Interview transcripts were independently analyzed by a human factors engineer and a clinical pharmacist, to generate decision requirement tables for each incident. The decision requirements table is a representation commonly used to examine key information within and across incidents [13]. Any discrepancies in table content were discussed by the analysts until they reached consensus [19]. These decision requirements tables summarized each incident and examined key elements. Specifically, researchers identified key decision points inductively, and for each decision point, recorded several components, including cues, strategies, potential errors, and any factors that made the decision difficult. (See online Supplemental document A for a sample decision requirements table.)

Three analysts (human factors engineer, pharmacist researcher, and cognitive psychologist) then used these tables to identify initial themes across four selected incidents. Each analyst

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independently coded the *problem detection* aspect of each incident from those decision requirements tables, then met weekly to discuss whether the data supported the initial conception of the model, and whether the proposed codes adequately captured the incident. Refinements were made to the codebook, including merging codes and adding new ones, refining the definition of codes, and adding examples to the codebook. When they completed this process for the first four incidents, they worked through the same process with the *investigate the cause* codes, followed by the codes for *plans/address/follow-up* from the decision requirements tables.

After analyzing the first four incidents, two of the analysts (pharmacist researcher and cognitive psychologist) independently analyzed the remaining data in blocks of four incidents (two pharmacist cases, and two physician cases), using the complete codebook. Each incident was discussed until consensus was reached. When a block of four random incidents had been analyzed and discussed, the two analysts summarized any new insights and potential refinements to the codebook (i.e., clarifying definitions, nesting or un-nesting codes to reflect the data more completely), in consultation with the human factors engineer. See online Supplemental document B for the final codebook. Final consensus codes were entered into NVivo software (QSR international, version 10), to assist with data management and analysis.

Descriptive model of ADR decision-making

To inform the descriptive model of ADR decision-making, we conducted a card sort of the key decision points identified in each ADR incident. Decision points from each of the decision requirement tables were placed on individual paper cards. A multidisciplinary team of five

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researchers, including two human factors professionals, two pharmacists, and one physician, individually sorted cards into meaningful groups based on their background and perspectives, then reviewed and discussed together in a group. From these collective data sources, initial models were developed by two human factors professionals, and were then reviewed and refined with input from all research team members, including practicing physicians and pharmacists. The model was intended to characterize the cognitive processes that HCPs in our study described as they were confronted with potential ADRs.

RESULTS

Participants and ADRs reported

HCPs submitted a total of 35 ADR incident cards. We completed interviews with ten physicians and ten pharmacists (**Table 1**) regarding 20 incidents. **Table 2** provides a brief description of the incidents.

Table 1: Characteristics of participants (N=20) who were interviewed regarding an ADR incident.

Characteristic	Providers (n=10)	Pharmacists (n=10)	All participants (N=20)
Gender: female, n (%)	7 (70)	6 (60)	13 (65)
Age, mean years (SD)	45 (9)	36 (5)	41 (9)
Veterans Affairs experience, mean years (SD)	11 (7)	7 (4)	9 (6)
Setting of incident			
Inpatient	0	4*	4
Outpatient	10	6	16

Abbreviations: ADR: adverse drug reaction; S.D. = standard deviation; *: one pharmacist had both inpatient/outpatient role

Table 2: Adverse drug reaction (ADR) incidents (N = 20) selected for interviews.

Case ID	Potential ADR incident	Medication(s) of concern	Action(s) taken by the participant

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A. Incidents reported by physicians			
#1	Patient complained of chest muscle spasms	duloxetine (Cymbalta)	Switched to escitalopram
#2	Patient reported skin irritation on dorsum of feet	capsaicin, gabapentin (2 separate medications)	Stopped capsaicin, increased dose of gabapentin
#3	Patient reported trouble breathing	venlafaxine (Effexor)	Stopped Effexor for 3 days Started Vistaril (take as needed)
#4	Patient reported difficulty swallowing	suboxone	Switched from suboxone sublingual to film strip
#5	Patient reported itching	dorzolamide	Switched to latanoprost
#6	Patient reported muscle aches and had “swollen eyes”	emtricitabine/rilprivirine/tenofovir (Complera)	Switched from Complera to patient's previous HIV regimen
#7	Elevated AST and ALT	HIV medications	Held HIV meds while treating Hepatitis C
#8	HCP reported that patient had a history of kidney stones	topiramate	Advised the medical resident to taper and then discontinue topiramate
#9	Patient reported swelling, angioedema	hydrochlorothiazide/ lisinopril	Discontinued lisinopril
#10	Elevated hemoglobin	testosterone	Recommended PCP decrease or stop testosterone
B. Incidents reported by pharmacists			
#1	Patient reported chest tenderness	spironolactone	Switched from spironolactone to eplerenone
#2	Patient reported nightmares	varenicline	Stopped varenicline, prescribed nicotine patch
#3	Thrombocytopenia	heparin	Stopped heparin, transitioned from bivalirudin to rivaroxaban
#4	Patient reported chest pain	montelukast	Stopped montelukast
#5	Patient had low blood pressure	doxazosin	Contacted PCP and suggested stopping doxazosin
#6	Patient reported rash	piperacillin + tazobactam	Switched to clindamycin
#7	Patient reported chest pain	abiraterone	Reaffirmed to the patient that it is not a heart attack; Continued abiraterone for cancer treatment
#8	Patient reported diarrhea	atorvastatin	Switched to simvastatin
#9	Orthostatic hypotension	tamsulosin	Recommended the rounding team stop tamsulosin
#10	Electronic health record alerted the	furosemide (new order)	Advised the nurse practitioner that furosemide can be started

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	participant about a sulfa allergy		

Abbreviations: ADR = adverse drug reaction, AST = aspartate aminotransferase, ALT = alamine aminotransferase, HIV = human immunodeficiency viruses, PCP = primary care provider

ADR decision-making model

The resulting ADR model (**Figure 2**) outlines participants' cognitive processes when they detected and responded to potential ADRs. This model consists of four medication-related stages: problem detection, investigation of the problem's cause, risk/benefit considerations, and plan, action, and follow up. Below, we organize results by the stages in this model. Emergent themes within each stage are underlined, and sample quotes from participants are presented in **Table 3.**

Table 3: **Main themes and quotes from participants.** Themes (bolded) and quotes (italicized) are organized based upon the four stages of the ADR decision making model (Figure 2). The numbers for each participant map to the incident descriptions in Table 2.

1. Detection of potential ADR
HCP detected potential ADR based upon from symptoms and signs *Patient called [the] pharmacy [and] said [that] after only 3 capsules of Cymbalta, the patient had muscle spasms and chest muscle spasms.* -Physician #1 *Patient mentioned [starting] varenicline and having crazy dreams. The patient stopped varenicline on his own.* – Pharmacist #2 **A new medication or a medication that is already known to commonly causes the ADR symptoms**

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I asked the patient if he was taking the atorvastatin. Patient [said] 'Yes, and [I] have had a lot of diarrhea since starting the medication'. Pharmacist #8

Tamsulosin [is] used for benign prostatic hypertrophy. One of its main side effects is orthostatic hypotension or orthostasis. [This patient had orthostatic symptoms] Pharmacist #9

Information from another HCP

I got a view alert [notification in my EHR inbox], so I think [the patient] called the pharmacy and then they sent me a triage note with a box checked [for] adverse reaction. Physician #1

Provider B from my clinic sent me an e-mail and came by my office to talk… [S/he] told me the patient had a reaction to Effexor. Physician #3

2. Investigate the cause of the problem

Reasons and strategies for investigating

[Participant] interviewed a patient and asked follow-up questions [including]: having trouble breathing, sweating? when did the burning sensation start? Pharmacist #7

In UpToDate, I looked up the incidence of diarrhea with atorvastatin to see how likely this med[ication] was causing the issue. [I] confirmed also with Epocrates on my phone. Pharmacist #8

Confirmatory cues

Via phone call, [the] patient reported chest pain and muscle spasms. These [symptoms] occurred within the first 15 minutes of taking [the medication] [Cymbalta]. Symptoms consistently happened within 15 minutes for each of the 3 doses. [Confirming that these symptoms were from taking Cymbalta.] Physician #1

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I think that because the patient had taken it [montelukast], had the side effects, stopped it, taken it again, had the same side effects and stopped it, maybe it put [in] everyone's mind that [these symptoms were related] to the medication. Pharmacist #4

Disconfirmatory cue

Before starting Cymbalta [the suspected medication], the patient had reported muscle spasms/muscle cramps all over as part of a general pain syndrome. Physician #1

It sounds a little unusual, did not look typical for a normal drug rash allergy related to antibiotics because it [the rash] was in the axilla [armpit] area; [it was only] a little bit on his trunk; not an erythematous [red coloration, irritated[rash that you should see with drug reactions; and d) rash cleared up pretty quickly (<24 hours). Pharmacist #4

Negative cue (i.e. information that is absent)

No other medications were concerning/identified as potential causes of high calcium. Physician#8

I rechecked [AST/ALT] on the end of October… and they were [about] the same [as before]. The AST was 204 and ALT was 434…. Since [it] was about the same, liver function issues [were] NOT due to patient drinking. "I was hoping maybe [the cause was] was drinking [which is easier to address than an ADR]." Physician #7

3. Risk and benefit considerations

Severity of side effects

There is no reason that I would not use that drug just because it upset their stomach. Pharmacist #7

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Patient [is] tolerating the pain, not doing anything to compensate. Pain [is] not effecting [sic] patient's behavior [in the context of chemotherapy, the potential benefits are very high]. Pharmacist #7

Anticipated benefits

Furosemide [if taken] will take fluid off patient's lungs [patient had sulfa allergy]. Pharmacist #10

Encouraging patient adherence

So if you try several ones [statins], eventually sometimes patients are like: 'I'm not doing this anymore.' So I didn't want to put him on something that had a decent risk and run the risk that he would have a problem and refuse statins down the line. Pharmacist #8

Which risk is greater?

[I need to] make sure that the risk of anticoagulating her [with heparin] was not greater than the risk of having this aortic dissection [bleeding risk]. Pharmacist #3

There's really no data for doing that [putting HIV meds on hold if they might be causing hepatic problems] and so we [a clinical pharmacist and I] both were kind of like 'What's the harm?'. [There's no data for] just stopping everything [all HIV meds] and I mean nobody, there's no, there's no one looking at [studying] that. [M.D. was evaluating the risk of holding HIV meds versus the risk of having irreversible liver injury]. Physician *#7*

4. Plan, action, and follow up

Stop/put on hold/ adjust the medication

[I] told the patient to stay off Effexor… I wanted to be on the safe side… [I] wanted to make sure it was not an activation syndrome, which I have seen before. Physician #3.

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I alerted the patient's primary care provider [PCP] and the PCP discontinued the varenicline. Pharmacist #2

Delayed start of bivalirudin until 3 days later because patient had had an ablation procedure, [so I] felt patient's risk of bleeding was higher. Pharmacist #3

Deep down, I was skeptical Effexor was causing issue, severe SOB [shortness of breath; dyspnea], because I had never seen this issue before with Effexor and not seen this issue in the literature. [I] restarted patient on Effexor… patient said she was comfortable with this as long as she could stay on Vistaril. Physician #3

[I] chose the simvastatin dose to match the equivalent potency of the [previous] atorvastatin dose. Also, this is the dose of simvastatin the patient was on before. I prescribed 40mg daily of simvastatin to get equivalent potency as 20mg atorvastatin. Pharmacist #8

Patient communication

[I] encouraged [the] patient to titrate up on gabapentin, as previously planned… I also try and address issues with diabetic socks/shoes so the patient does not perseverate. I discussed with patient and underscored the need for regular use of capsaicin, [including] how it works and why we use it. Physician #2

I told the nurse, 'Please make sure that the patient understands that if he does not eat, [he should] hold his glipizide.' Pharmacist #9

Follow-up and monitoring patients

At the patient's next routine nursing visit, [the] nurse asked me to meet with the patient again. I briefly examined the patient and he had no signs of an allergic reaction. Physician #4

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I checked to make sure the patient had been called [and knew] to stop the medication. Pharmacist #5

Documenting the ADR in the EHR

[I] entered nightmares for varenicline into the [EHR] allergy section. I was adding it to his allergies so no one would reorder it [again]. Pharmacist #2

I did not enter montelukast as a medication allergy because … [it is] hard to remove it once it's documented [and I] was uncertain whether or not the medication was the culprit. Pharmacist #4

1. Detection of potential ADR

In this first stage, HCPs relied on cues that signaled an initial concern. *Patient's symptoms* (reported) *and signs* (observed) were common cues to help HCPs recognize a potential ADR. Additionally, *abnormal lab values* reported within the EHR can also help HCPs detect the problem. Furthermore, HCPs reviewed medication characteristics to sense potential ADRs. Common characteristics of ADR detection were either *a new medication* that was recently prescribed or started by the patient, or a *medication that is commonly known to cause the ADR symptoms that the patient is experiencing.* Usual causes of ADR symptoms were often recognized by HCPs from clinical experience. Finally, HCPs sometimes detected a potential ADR based on *information (e.g., tip-off) from another healthcare professional or the patient themselves.*

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2. Investigate the cause of incident

After detecting the problem, HCPs started to investigate the potential cause. This stage involved *information that prompted HCPs to investigate,* and *their strategies for investigating*. For each specific reason to investigate, HCPs used a distinct, corresponding strategy, such as interviewing a patient who reported a certain symptom, or searching in drug references if the HCP suspected that a drug caused the sign or symptom. HCPs also *examined confirmatory and disconfirmatory cues,* to validate the connection between ADR concerns and their suspected medications.

When investigating the connection between an ADR and a possible problematic medication, HCPs searched for certain *confirmatory cues*. These were cues that helped providers to conclude that the medication was the likely cause of the ADR. Likewise, HCPs also looked for "*disconfirmatory cues*" that suggested that the suspected medication was *not* causing an ADR (see **table 3** for examples of confirmatory and disconfirmatory cues). HCPs often reviewed the disconfirmatory cues through clinical references such as provided by UpToDate, Micromedex, and Lexicomp.

HCPs not only searched for documented and available clinical information but also looked for factors that were absent, to confirm or reject the connection between the ADR concern and the suspected medication. This is known as negative cue. An example includes medications that commonly cause the problem but were not part of the patients' medication regimen.

3. Risk and benefit considerations

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When the cues indicated the occurrence of an ADR, HCPs often considered the risk and benefits associated with continuing or stopping the suspected medication. As part of this solution-seeking activity, HCPs often considered whether available alternative treatments could alleviate the ADR. They also weighed the risks and benefits associated with such alternatives. While weighing risks and benefits is an essential element of medical decision-making, our study found several components that HCPs also take into consideration. These components include:

Severity of side effects. HCPs often evaluated the severity of the current side effects, and the patient's willingness to tolerate them. The HCP chose to continue the medication, but educated the patient about potential problems, and suggested increased monitoring (e.g., follow-up by nursing staff, or more frequent patient appointments). In contrast, if the side effects were more severe, the HCP sought alternative medications or treatment.

Anticipated benefits. If the treatment benefits of the medication were expected to outweigh the risk for the patient, the HCPs tended to continue the medication.

Fostering patient adherence. When investigating options for addressing and solving an ADR, the HCPs also incorporated the patient's feedback and the likelihood that the patient will abandon treatment with the medication in question. Rather than sequentially trying a series of closely related medications (medications in the same class) in hopes that one will have the desired benefits without the adverse reaction, the HCP sometimes switched to a different class of medication therapy to help alleviate the patient's concern.

Which risk is greater? In some cases, HCPs framed the problem in terms of which risk was greater: stopping the medication, or experiencing the ADR. Conversely, at times they assessed

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which benefit was greater. This happened most often for patients with particularly challenging health conditions, such as HIV or multiple chronic comorbidities. In these cases, the patient may be taking a medication that has benefits for managing a chronic condition (e.g., treating HIV), but stopping the medication may have benefits for mitigating ADR.

4. Plan, Action, and Follow-Up

The last stage of this decision-making model includes planning, selecting actions, and follow-up with patients. Based primarily on information collected stages 2 and 3, HCPs would determine appropriate plans and actions to address the problem. The three main actions in response to incidents in our study included changes to medication management, patient counseling, and follow-up appointments and monitoring. Changes to medications included stopping the offending medication, temporarily placing the medication on hold until the ADR was alleviated, changing the drug to one that is unlikely to cause the ADR, or continuing the medication if its perceived benefits outweigh risks.

Patient communication was an important activity that HCPs used, in some cases, to initiate shared decision making with the patient about the new medication action and plan. After the new action was taken to mitigate the ADR, the HCP would *follow-up and monitor the new action and plan with patients.* HCPs used various strategies to monitor and follow up with patients, such as ordering a new lab test, or examining the patient at the next visit, to ensure that the ADR concern was resolved. Finally, if the ADR was confirmed during the investigation stage, several HCPs reported *documenting the ADR* in the EHR to help prevent recurrence. HCPs

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also followed up with other HCPs, to confirm that the ADR was correctly documented in the EHR if they did not input it directly.

It is important to recognize that the decision-making steps in stage 4, plan, action, and follow-up, are iterative steps. If a certain plan and action did not resolve the suspected ADR, HCPs described developing a new plan and action until the problem is resolved.

DISCUSSION

To our knowledge, this is the first study to examine the cognitive processes of HCPs when they detect and solve potential ADR incidents. Our study explored the iterative steps of HCPs' decision making, from detection of potential ADR incidents to plans and actions they took to resolve incidents. The study illustrates the cognitive complexity of the work conducted by HCPs when resolving ADR problems. Our findings point to four important implications, discussed below, to develop novel clinical decision support systems that more closely align with HCPs' cognitive workflow.

1. Develop technologies to facilitate communication between HCPs and patients regarding ADRs. Detecting potential ADRs requires *identifying* patients' signs or symptoms that may be related to a drug [20]. For ADR alerts to work more efficiently, EHR systems could collect reliable information about patients' signs and symptoms, and then display and communicate that information. Therefore, patient-generated data, which is not a typical element of many current alerting systems, may play an important role in future decision support for ADRs [21]. Additionally, communication between HCPs and patients also plays an important role in resolving ADRs that are already occurring. In some cases, HCPs may help the patient set realistic

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expectations about the type and severity of symptoms. Throughout the course of ADR investigation and treatment, HCPs need to communicate closely with the patient, to share potential risks and benefits and engage patients in a shared decision-making process [22]. Topaz *et al.* study demonstrated that HCPs were more likely to override an alert for medications that patients are currently tolerating or have previously tolerated [23]. Indeed, communicating with patients about symptoms, medical history, etc. is an important element in HCPs' decision making. Such communication may occur not only through direct patient interactions but also indirectly through patient portals, secure messaging, and other telehealth technologies [24]. These modalities may also increase patients' access to care, facilitating patient-HCP communication to resolve ADRs.

2. Incorporate confirmatory and disconfirmatory ADR cues into alerting systems. Rapid, accurate, and complete information is important to help detect and resolve ADR problems. Our study found that additional information ADR detection, such as the confirmatory cues and disconfirmatory cues, were important to assist HCPs with the ADR investigation process. HCPs used these cues to organize and assemble a constellation of information in a form that is meaningful for sensemaking. This concept is known as knowledge-base cognitive mode [25]. Subsequently, EHR alerts systems for ADRs should align with a knowledge-base cognitive mode by including important cues while filtering distracting information to optimally help HCPs with clinical decision making. Since ADR alerts detect potential ADRs from symptoms and abnormal lab results, confirmatory and disconfirmatory cues provided by the alerts could allow HCPs to confirm the alerts' trustworthiness and avoid overlooking alerts. In fact, a study on drug allergy

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alert-overrides showed that providers were more likely to override alerts derived from non-important cues [23]. Our findings, in combination with those results, highlight the importance of providing cognitive cues to assist HCPs with decision making.

3. Design alert systems that account for negative cues: The absence of certain cues, known as negative cues, is another important factor for decision making. HCPs are aware of this absence of information based on familiar perceptual patterns. For example, one experienced provider in our study described how s/he confirmed that a patient did not have a myocardial infarction (Table 2, case B7). Although the patient reported a burning chest sensation, the patient did not have other symptoms such as numb fingers, arm pain, or diaphoresis. The absence of the companion symptoms was reassuring, allowing the provider to focus on other potential causes of the symptoms, such as a potential ADR with abiraterone. This type of negative cue is often overlooked in technology-centric design but is a critical component of decision making, especially during the evaluation of potential ADRs. Complex algorithm development that includes negative cues could advance decision support and help HCPs better detect and investigate potential ADRs.

4. Advance alert information to better support HCPs' risk-benefit evaluation: Our ADR decision-making model (**Figure 2**) underscores that even when an ADR is confirmed, HCPs still need to evaluate the medication's risks and benefits. Existing medication alert systems identify potential problems but the information they provide is often insufficient to help HCPs weigh risks and benefits of the problematic medication. As a result, HCPs seek information from drug references, colleagues, and other sources. Indeed, ADR alert design without consideration of risks vs. benefits is likely to "fail" (be overridden) in many instances. For complex risk-benefit

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evaluation, ADR alerts should provide quick access to a comprehensive list of risks and benefits, or corresponding sections of drug information resources, to help HCPs make a sound clinical decision [13].

This study has several limitations. First, we interviewed only physicians and pharmacists regarding ADRs, since incident submissions from nurse practitioners were low. Nurse practitioners, registered nurses, and physician assistants, also interact with patients and play important roles in ADR decision making, warranting further research. Second, we were not able to directly compare the decision-making processes of physicians and pharmacists, because the variation in incidents precluded direct comparisons (e.g., involved different medications or patients with varying medical conditions). Third, we examined incidents from a single large V.A. medical center and EHR system. Our findings might not always apply to other settings. Fourth, all incidents collected and analyzed were voluntarily provided by HCPs. This could influence our findings, because HCPs might be more inclined to submit incidents for which they felt most confident in their handling of the ADR; thus, incidents that created even greater challenges or uncertainty for HCPs as they resolved ADRs may have not have been captured. Fifth, most incidents we studied, especially those from physicians, were obtained from outpatient care. Thus, our results might not always apply to inpatient settings. Finally, we were not able to fully incorporate two incidents (Table 3. Physician #8 and Pharmacist #10) into our decision making model. Unlike other incidents, these two incidents focused on prevention of an ADR instead of resolving suspected ADRs. Further research is needed on HCPs' decision-making with respect to ADR prevention.

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Our study findings have several practical applications. The ADR decision-making model we developed through this research has important implications for the design of clinical decision support. This model could be used as the foundation for a novel ADR alert system to support HCPs in recognizing and resolving ADRs. Evolving alert systems by applying this model is anticipated to increase the cognitive support of alerts for HCPs, which subsequently can improve medication safety outcomes for patients. In addition, the ADR decision-making model is expected to be valuable for teaching medical and pharmacy trainees about the decision-making process for ADR mitigation.

CONCLUSION

This is likely the first study to identify the decision-making processes of HCPs when they detect and resolve potential ADR incidents. The ADR decision-making model developed from this study consists of four important stages: problem detection, investigating the cause of the problem, consideration of risks and benefits, and plan, action, follow-up. This model is expected to be valuable for alert system designers as well as educators who are training future physicians and pharmacists about ADR decision-making. Our findings have four key implications for clinical decision support systems: develop technologies to facilitate communication between HCPs and patients to better detect and address ADRs; incorporate confirmatory and disconfirmatory cues into ADR alerting systems to more closely align with cognitive strategies from HCPs; design alert systems that account for negative cues to further facilitate decision making; and enhance alert system displays to better support HCPs' risk-benefit evaluation process for ADRs. The

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design of supporting technologies for potential ADR problems should align with the real-world cognitive strategies of HCPs in order to achieve the best health outcomes for patients.

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Conflicts of interest: L.M. is co-owner of Applied Decision Science, LLC, a company that studies decision making in complex environments and utilizes the critical decision method. She aided in the design of the cognitive task analysis approach used in this study and trained the interviewer. M.W. has stock in Allscripts and Express Scripts Holding Company. All other authors report they have no conflicts of interest.

Authors' contributions: ARJ wrote the funded grant proposal (VA HSR&D CDA 11-214), with input from P.G., L.M. and M.W. All authors, except A.I. and K.N., participated in study planning meetings and contributed to the design of the larger study. L.M. trained ARJ on cognitive task analysis and the critical incident technique. ARJ conducted all cognitive task analysis interviews. ARJ and A.I. analyzed interview transcripts to develop a decision requirements table for each incident. K.N. and L.M. analyzed decision requirements tables to identify emergent themes across incidents, under the mentorship of ARJ. K.N. drafted the journal manuscript. All

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Figure legends:

Figure 1: Overview of the study procedure.

Figure 2: Adverse drug reaction decision-making model.

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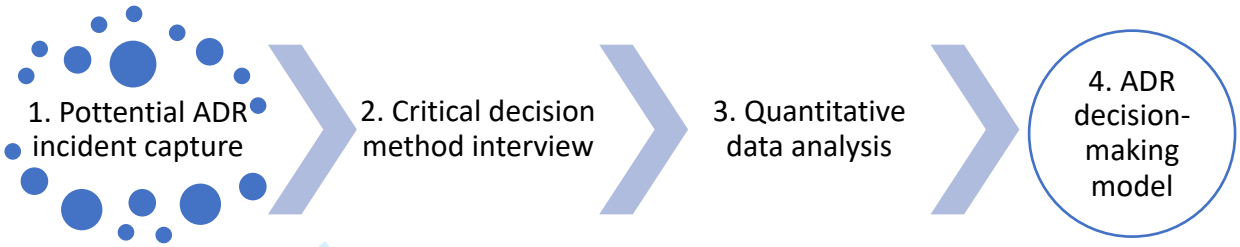
Figure 1. Overview of the study procedure. Four main steps are shown in the illustration.



Abbreviation: ADR: adverse drug reaction

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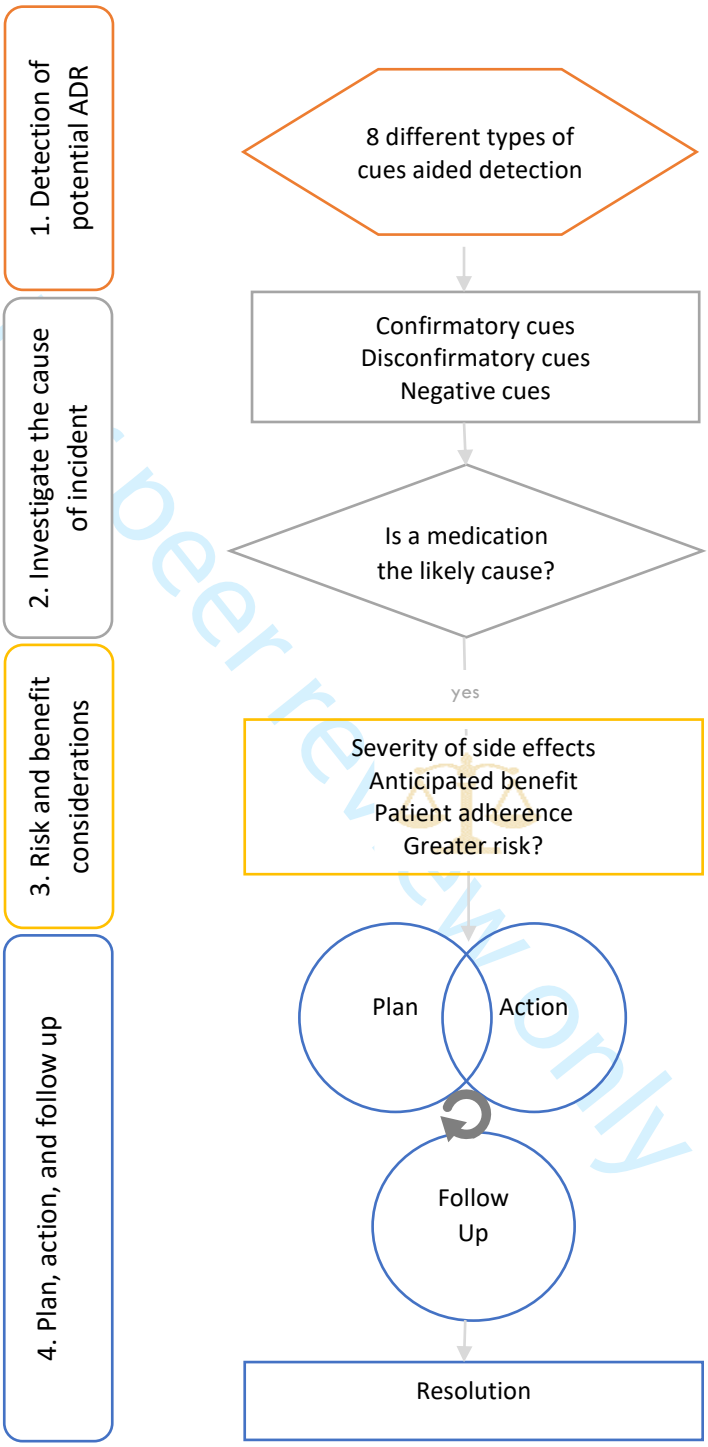
Figure 2: Adverse drug reaction decision-making model. The model has four stages. ADR = adverse drug reaction.



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Supplemental documents

A. Sample of decision requirements table					
Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that nonexperts may tend to make*	**IT Design Seeds**
1. Assessing the pt	I had only seen pt one other time. 66	Pt was referred to me for cholesterol follow-up; pt appointment with me. 52 B/c of pt's risk factors, pt needs to be on moderate to high intensity statin, which is why Dr put pt on atorvastatin. 38 Pt taking atorvastatin 20 mg daily. 120	BEFORE the visit: a. I have an excel spreadsheet that I created from the guidelines that calculates the ASCVD score. [treasure map!] Calculated ASCVD risk score to determine what intensity of statin med pt needs. it aggregates like the risk like their age, their sex, their race, what their baseline cholesterol levels are, if they have high blood pressure, what their blood pressure was, like it just calculates smoking and whether or not they have diabetes and "spits out a number at you". I calculate this before the pt walks in the room. 433 [AI: This is used by many pharms and was created in-house. They can use if internet goes down.] b. I went back [in CPRS] and looked at all his cholesterol results in the past to see	[AI: Home grown ASCVD calculator/treasure med may not hold up in a court of law. Could be programming glitch. Also, is code editable? Will not get auto-updated like the internet version should if something changes with the calculation.]	Integrate ASCVD calculator into EHR and/or decision support/med selection process in CPOE.

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A. Sample of decision requirements table					
Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that non-experts may tend to make*	**IT Design Seeds**
			how high his cholesterol been. c. I look for:pt's response to meds, to see if dose increase is needed. Was there a 50% reduction in cholesterol – aim from the guidelines. 714		
2. Recognizing a potential medication issue	"I was surprised" [that it actually turned out to be atorvastatin] b/c: 272 a. "I hadn't had anybody complain of diarrhea with atorvastatin before, so it was a new side effect for somebody to complain about." b. simvastatin also is for cholesterol, is related to atorvastatin – mechanism of action is the same- but simvastatin causes more constipation, so diarrhea was a surprise [opposite of what would expect with atorvastatin] 278 Sometimes meds in general can 'go either	I asked pt if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med/since last visit. 84, 29			

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A. Sample of decision requirements table					
Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that non-experts may tend to make*	**IT Design Seeds**
	way" – cause diarrhea OR constipation. 510. sometimes people are just prone to one side effect versus another. 533				

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B. Adverse drug reaction codebook		
CODE	**DEFINITION**	**Example of Coded Item (Cue)**
I. Problem Detection Related Decision Points:** - Assessing the pt - Deciding what drug to prescribe for treatment - Recognizing an abnormal lab value. - Recognizing a potential medication issue - Assessing the appropriateness of the medication order or regimen - Receiving the handoff about a potential medication issue - Reviewing the handoff [consult]	**Cues** that 'flagged' an initial concern and helped the participant notice a potential safety issue. These can be external information and sources; internal cues (feelings), others pointing something out to the participant, etc.	**Do NOT code at this level**
Lab values	**Cue definition**	**Example**
1.a Abnormal lab	lab value outside of normal range	"…her platelets you know were 66 and that is not normal."
Medication Characteristics	**Cue Definition**	**Example**
1.b New Med	medication that was recently prescribed or the patient recently started taking	I asked patient if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med. 84_29
1.c Common cause of ADR	medication is suspected as a potential problem b/c participant knows the ADR is often due to this med	Heparin is [the] most common med to cause thrombocytopenia
Patient information	**Cue Definition**	**Example**
1.d Symptoms	symptoms, directly or indirectly related to the ADR	I asked patient if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med.
OTHER	**Cue definition**	**Example**
1.e Tipped off to potential ADR	another healthcare professional or the patient already suspected an ADR and notified the participant	PACT RN [asked me] "what do you want to do with this patient? It looks like he had this adverse reaction to this medicine"
1.f Unknown Problem Detection	cues that helped the provider initially detect the problem could not be clearly discerned from the case	

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1.g Computerized alerts	Any kind of alerts related to ADR; also known as "order check"	
2. Investigating the cause of the problem **[Investigate]** Related decision points: - Determining the symptoms were NOT medication-related. - Is there a medication-related problem? - Investigating the cause of the problem (non-med causes, lit, colleagues) - Determining the cause of the medication-related problem Determining this is a medication-related problem	Additional information gathering, assessment, hypothesis testing	**NO coding at this level**
2.a Reasons and strategies for investigating	reasons the participant spent time investigating and what specific type of information they were seeking; (excludes reasons why they think there is an ADR – that goes under 'problem detection') Types of strategies used, labs ordered, resources used, etc to look into the problem	To make sure diarrhea wasn't due to another medication, I verified that nothing else had changed for pt since last visit [in terms of meds] 190 (3d) [MD Residents] Ordered confirmatory tests. 78: a. heparin antibody b. Serotonin release assay (SRA) 101, 557 (18c)
2.b Confirmatory cues	Information and other cues that suggested the specific med may be causing the ADR (med-ADR relationship)	I concluded diarrhea due to atorvastatin, not non-med issue b/c pt had more problems when taking the medication more often…190, 209 (3d)
- 2.b.1 Negative confirmatory cue	The absence of something is a cue for the participant that points to the suspect medication.	Pt not on many meds [or many others that could cause HIT, except heparin]. (18c)
2.c Disconfirmatory cues	Information and other cues that suggested the specific med may NOT be causing the ADR (Different than a 'negative' cue that means a lack of something is a cue.)	"It's [thrombocytopenia] usually something else, not the Heparin, but we always stop the Heparin until we know for sure." 551 (18c)

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- 2.c.1 Negative cue that is disconfirmatory	Noticing the absence of something is a cue for the participant and points AWAY from the suspect medication. (Excludes looking up something intentionally and finding the answer is no)	[no examples yet…?]
2.d Ambiguous/ Dual meaning cue	Cue that not clearly confirmatory or disconfirmatory Participant unclear if cue point toward or away from ADR	My initial concern was that maybe this was just her normal muscle cramps (pt Hx) (112-113)
3.Plan/Action/Follow-up [PAF] [all other decision points]	DEFINITION (propose your own, below) actions taken to address and/or follow up on the safety concern	NO coding at this level
3.a Stop Med	Cues, strategies, actions, related to a decision that the suspect ADR-related medication needs to be discontinued.	Check in CPRS to see if Lisinopril was discontinued. 499 (7b) Told RN: • Have pt throw Lisinopril away so doesn't accidentally take. 373 • stop Lisinopril, tell pt not to ever take again. 325 (7b)
- 3.a.1 Negative Cue related to stopping med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586
3.b Hold Med	Cues, strategies, actions, related to a decision that the suspect, ADR-related medication needs to be put on hold or the start of a new medication treatment needs to be delayed.	"Normally, if pt has HIT, we would initiate meds for direct thrombin inhibitors to anticoagulate the pt b/c HIT increases risk of clots. 121. Decided NOT to do that [immediately] for this pt. Instead, delayed start of bivalirudin until 3 days…" (18c)
- 3.b.1 Negative Cue related to holding med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586

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3.c. Change to new med	Reasons, cues, strategies, actions, related to a decision that the medication needs to be changed. This does NOT include the dose of the new med: that goes in the sub-code below This includes aspects that helped them make the choice of the alternate medication or treatment (surgery), as well as other options they considered for now or in the future. This also includes reviewing the patient's ADR/medication history to inform a decision about the new medication. (EXCLUDES renewals of the exact same prescription)	We switched pt back to simvastatin and stopped atorvastatin. 46 (3d) If the pt's cholesterol would have been higher [around 120] I would have: a. Rxed Crestor (rosuvastatin) has high intensity at higher doses. [switched pt to higher intensity med that the pt hadn't tried yet], but Crestor is non-formulary med and requires special consult/approval. 723 (3d)
- 3.c.1 Negative cue related to change to a new med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586
- 3.c.2 Dose Selection	Cues and strategies that helped the participant determine what medication dose to use, how to change the dose, etc	I Rxed 40mg daily of simvastatin to get equivalent potency as 20mg atorvastatin. 132
- 3.c.3 Risk/Benefit	Consideration of the risk and benefits (or pros and cons) of one or more treatment options	PharmD (participant) recognizes limitations of ASCVD calculator and is able to recognize when other risk factors may need to be considered like family history (633):
3.d ADR documentation	Cues, reason, and strategies related to documenting or not document the ADR, including information documented, double-checking/confirming it was documented, reasons for documenting etc.	Check in CPRS to see if ADR entered. 512 (7d)

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3.e Pt counseling	Counsel, inform patient regarding new action/plan Includes direct communication with patient, checking to see that key information has been communicated to patient, or instructing someone else to communicate with patient.	made sure patient's discharge instructions included verbiage related to patient stopping lisinopril Told RN: • Have pt throw Lisinopril away so doesn't accidentally take 373 • stop Lisinopril, tell pt not to ever take again. 325 • we will replace Lisinopril with something else. 81 • give pt a list of all other meds in same [drug] class [as Lisinopril] and tell pt not to ever take any of these. 228, 325 • have pt check BP at home/ keep log. 385 have pt come in 2 weeks for BP check 331
3.F Follow –up/Monitor	Follow up after certain change Ex: BP, lipid panel, cholesterol Includes follow up by interviewee or by other member of the healthcare team Reassess pt on certain measurements Includes cues, strategies, reasons, and actions related to follow up	Check pt's BP 2 weeks after D/C b/c: • allows pt to recover after hospitalization • let's BP stabilize on altered BP med regimen (now HCTZ only; and get rid of Lisinopril in system which can lower BP). 754, 962 • -gets steroids out of pt's system before checking BP again, since they elevate BP. 754 • 2-4 weeks is acceptable range in my assessment. 766 If pt had NOT been given steroids, see back sooner, around 1 week. 962
3.G Continue the med	Reason, cue, strategy for continue current med. This includes aspects that helped them make the choice of the alternate medication or treatment (surgery), as well as other options they considered for now or in the future. This also includes reviewing the patient's ADR/medication history to inform a decision about the continue the medication	
3.g.1 Dose selection	Cue and strategy for choosing a new dose (increase or decrease the dose) to improve tolerance	Decided to have pt try low potency capsaicin again at 3x/day

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Strategies Prescribers and Pharmacists Use to Identify and Mitigate Adverse Drug Reactions in Inpatient and Outpatient Care: A Cognitive Task Analysis at a U.S. Veterans Affairs Medical Center

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Strategies Prescribers and Pharmacists Use to Identify and Mitigate Adverse Drug Reactions in Inpatient and Outpatient Care: A Cognitive Task Analysis at a U.S. Veterans Affairs Medical Center

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ABSTRACT

Objective: to develop a descriptive model of the cognitive processes used to identify and resolve ADRs from the perspective of healthcare providers in order to inform future informatics efforts

Setting: inpatient and outpatient care at a tertiary care U.S. Veterans Affairs Medical Center

Participants: physicians, nurse practitioners, and pharmacists who report ADRs

Outcomes: descriptive model and emerging themes from interviews

Results: We conducted critical decision method interviews with 10 physicians and 10 pharmacists. No nurse practitioners submitted ADR incidents. We generated a descriptive model of ADR decision-making process and analyzed emerging themes, categorized into four stages: detection of potential ADR, investigation of the problem's cause, risk/benefit consideration, and plan, action, and follow-up. HCPs relied on several confirmatory or disconfirmatory cues to detect and investigate potential ADRs. Evaluating risks and benefits of related medications played an essential role in HCPs' pursuits of solutions

Conclusions: This study provides an illustrative model of how HCPs detect problems and make decisions regarding ADRs. The design of supporting technology for potential ADR problems should align with HCPs' real-world cognitive strategies, to assist fully in detecting and preventing ADRs for patients.

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STRENGTHS AND LIMITATIONS

Strengths:

- The finds of this study have several key implications:
    1. develop technologies to facilitate ADR communication between HCPs and patients
    2. incorporate confirmatory and disconfirmatory cues into ADR alert systems to more closely align with HCPs' cognitive strategies
    3. design alert systems that account for negative cues to facilitate decision making

Limitations:

- We only interviewed physicians and pharmacists regarding ADRs but not other HCPs such as nurse practitioners, registered nurses, or physician assistants
- We only examined incidents from a single large V.A. medical center and EHR system.

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INTRODUCTION

Adverse drug events (ADEs) harm over 1.5 million patients and cost over $500 million each year in the U.S. [1]. These concerning statistics prompted the U.S. Office of Disease Prevention and Health Promotion to develop a National Action Plan for Adverse Drug Event Prevention in 2014[2]. This plan called for actions, including developing health information technology to promote best practices in prescribing, and in detecting cases of high risk for ADEs [2]. Many factors contribute to the high incidence of ADEs in the U.S., including an increasing number of adverse drug reactions (ADR), an aging population, and a rising trend in polypharmacy [3]. ADR, defined as an unintended response to a drug that occurs at normally used doses, is the most common type of ADE [4]. Healthcare professionals (HCPs) such as physicians and pharmacists are essential in preventing and managing ADRs because they directly prescribe drugs and provide clinical care. However, the processes that individual HCPs adopt to identify, treat, and monitor ADRs are not well understood.

Healthcare systems leverage many different approaches to support HCPs in assessing and preventing ADRs, including systematic efforts to collect and review data to assess the risk of ADRs [5-7]. With advances in the development and implementation of electronic health records (EHR), alert systems that help HCPs identify and prevent ADEs have become more feasible and promising. Indeed, automated computerized order checks, frequently resulting in drug alerts, are often based on triggers such as the documentation of a patient's allergies [8].

While medication alert systems for allergies have been implemented regularly, alert systems with decision support to identify and resolve newly occurring ADRs are rarely found. In addition, many EHR alert systems have a technology-centric design that fails to take into

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account the HCPs' cognitive processes and workflow [9-11]. HCP decision-centered design, in contrast, focuses on HCPs' cognitive processes and key decisions, such as prescribing a drug, or choosing a drug regimen, as a core function of design [12, 13] With a foundational understanding of the cognitive strategies that HCPs use to prevent and respond to ADRs in clinical practice, healthcare systems and EHR vendors can develop systemic interventions and technologies to help HCPs prevent and resolve ADRs. Recent studies emphasize that cognitive studies are needed to help understand HCPs' decision making [9, 14] in order to develop more meaningful and effective clinical decision support. Therefore, the objective of this study was to develop a descriptive model of the cognitive processes used to identify and resolve ADRs from the perspective of HCPs in order to inform future informatics efforts.

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METHODS

Study site and participant characteristics

This research is part of a larger study [15, 16] conducted at a tertiary care Veterans Affairs Medical Center. The study was approved by the Indiana University IRB (protocol 1301010433.) Eligible HCPs were physicians, nurse practitioners, and pharmacists who prescribed medications, managed medications, or verified prescriptions in an inpatient or outpatient setting. We excluded medical and pharmacy residents, trainees, pharmacy technicians, and those with a purely administrative role. We invited all remaining eligible HCPs at the study site to participate. Eligible HCPs were invited to participate via emails, flyers, and follow-up via phone calls. All participants were consented in written prior to the critical decision method interviews. An extended version of the recruitment can be found from the method paper. [15]

Study design

The study procedure and data analysis are illustrated in four steps in **Figure 1.**

Potential ADR incident capture

Participants, when encountering a potential ADR, were ask to complete an incident card [15], which captured detailed information about the potential ADR incident, such as the type of ADR, suspected medication(s), and when the participant first became aware of the problem. Given that recall is often difficult for tasks and decisions that are made many times each day [17], the incident card was designed to help capture an ADR event close to the time of the incident, *before* it was forgotten or "merged" in memory with similar events. A similar approach of administering a small set of questions soon after an incident has been shown to increase

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accuracy of recall days later [18]. Subsequently, the incident card that HCPs submitted was used to assist with the critical decision method (CDM) interviews if the incident was selected, as described below.

Incident selection: A research team, consisting of a physician, pharmacist, and human factors expert, reviewed each incident card to determine eligibility for an interview. Incident cards were reviewed based on five criteria: incident was appropriately addressed, incident required great expertise or consideration, incident had potential to cause serious injury, incident was unique or challenging, or incident would be difficult for trainees to resolve alone.

Critical decision method

Selected incidents led to scheduling of follow-up CDM interviews with HCPs, to collect further details [15]. The CDM interview technique, often used as part of a cognitive task analysis, is designed to capture detailed incident accounts from participants, including strategies, critical cues, and contextual elements as experienced by the interviewee [17]. A human factors expert conducted pilot testing of the interview guide with three HCPs (2 physicians, 1 pharmacist) to further refine interview questions prior to data collection [15]. Interviews were scheduled within two to four weeks of the incident date. One human factors scientist, trained in the CDM technique, conducted a 60-minute, semi-structured CDM interview with each HCP. These interviews were structured in the following three phases:

1) Capture a brief summary of the incident: The interviewer asked the participant to summarize the incident as it pertained to the ADR concern. If multiple eligible incidents

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were received from a participant, the interviewer asked questions at the beginning of the interview, to select the more challenging incident.

2) Construct an incident timeline: The interviewer asked participants probing questions, to reconstruct a high-level timeline of the incident. This timeline was recorded and displayed on a whiteboard, visible to both the interviewer and HCP during the interview session. The timeline helped the interviewer organize the incident in chronological order and provided a common point of reference for the rest of the interview.
3) Ask in-depth questions. The interviewer asked additional questions to investigate the HCPs' decision-making process, and to identify cognitive cues used during the course of the incident. The interviewer then asked hypothetical questions to gain further insights about the cognitive cues or strategies that the participant used to detect and respond to the ADR incident.

The incident timeline was photographed. Interviews were audio-recorded and transcribed for analysis. The complete interview guide and a more detailed description of study methods is available elsewhere [15]. Examples of interview questions are below.

1. What caused you to be concerned about the medication for this patient?
2. In what ways did computerized alerts help you notice the right things and take action?
3. What tools/software/technology were used to help manage the medication conflict?
4. What, if any, documentation in the EHR helped you know what to do?
5. Under what circumstances, if any, would you have discontinued the medication for this patient, rather than reducing the dose?

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Qualitative data analysis

Interview transcripts were independently analyzed by a human factors engineer and a clinical pharmacist, to generate decision requirement tables for each incident. The decision requirements table is a representation commonly used to examine key information within and across incidents [13]. Any discrepancies in table content were discussed by the analysts until they reached consensus [19]. These decision requirements tables summarized each incident and examined key elements. Specifically, researchers identified key decision points inductively, and for each decision point, recorded several components, including cues, strategies, potential errors, and any factors that made the decision difficult. (See online Appendix A for a sample decision requirements table.)

Three analysts (human factors engineer, pharmacist researcher, and cognitive psychologist) then used these tables to identify initial themes across four selected incidents. Each analyst independently coded the *problem detection* aspect of each incident from those decision requirements tables, then met weekly to discuss whether the data supported the initial conception of the model, and whether the proposed codes adequately captured the incident. Refinements were made to the codebook, including merging codes and adding new ones, refining the definition of codes, and adding examples to the codebook. When they completed this process for the first four incidents, they worked through the same process with the *investigate the cause* codes, followed by the codes for *plans/address/follow-up* from the decision requirements tables.

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After analyzing the first four incidents, two of the analysts (pharmacist researcher and cognitive psychologist) independently analyzed the remaining data in blocks of four incidents (two pharmacist cases, and two physician cases), using the complete codebook. Each incident was discussed until consensus was reached. When a block of four random incidents had been analyzed and discussed, the two analysts summarized any new insights and potential refinements to the codebook (i.e., clarifying definitions, nesting or un-nesting codes to reflect the data more completely), in consultation with the human factors engineer. See online Appendix B for the final codebook. Final consensus codes were entered into NVivo software (QSR international, version 10), to assist with data management and analysis.

Initial model development of ADR decision-making

Data from all sources were collected and analyzed to develop the initial model of ADR decision-making. To develop the initial model of ADR decision-making, we conducted a card sort of clinicians' key decision points identified in each ADR incident. Decision points from each of the decision requirement tables, such as "investigate the cause of the problem," were written on individual paper index cards. A multidisciplinary team of five researchers, including two human factors professionals, two pharmacists, and one physician, individually sorted cards into meaningful groups based on their background and perspectives to collapse similar decision points across incidents into one decision point, then reviewed and discussed the terminology for each decision point until reaching consensus.

From these card sort results, two human factors professionals developed the initial model, and then reviewed and refined the model monthly with input from all research team members,

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including practicing physicians and pharmacists. The model was intended to characterize the cognitive processes that HCPs in our study described as they were confronted with potential ADRs.

Patient and Public Involvement

No patient involved. This study focused on HCPs. However, the results of this study on ADR were important to improve patient safety in medication use.

RESULTS

Participants and ADRs reported

HCPs submitted a total of 35 ADR incident cards. We completed interviews with ten physicians and ten pharmacists (**Table 1**) regarding 20 incidents. No nurse practitioners submitted ADR incident cards. Reasons for exclusion of the remaining 15 ADR incident cards include: no action needed for clinical care (1), low ratings from incident cards from reviewers (2), illegible handwriting (1), participant submitted multiple cases (11). **Table 2** provides a brief description of the incidents.

Table 1: Characteristics of participants (N=20) who were interviewed regarding an ADR incident.

Characteristic	Physicians (n=10)	Pharmacists (n=10)	All participants (N=20)
Gender: female, n (%)	7 (70)	6 (60)	13 (65)
Age, median, (range)	42 (34-60)	36 (29-45)	38.5 (29-60)
Veterans Affairs experience, median, (range)	10 (3.5-26)	7.5 (2-13.5)	9 (2-26)
Setting of incident			
Inpatient	0	4*	4
Outpatient	10	6	16

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Abbreviations: ADR: adverse drug reaction; S.D. = standard deviation; *: one pharmacist had both inpatient/outpatient role

Table 2: Adverse drug reaction (ADR) incidents (N = 20) selected for interviews.

Case ID	Potential ADR incident	Medication(s) of concern	Action(s) taken by the participant
A. Incidents reported by physicians			
#1	Patient complained of chest muscle spasms	duloxetine (Cymbalta)	Switched to escitalopram
#2	Patient reported skin irritation on dorsum of feet	capsaicin, gabapentin (2 separate medications)	Stopped capsaicin, increased dose of gabapentin
#3	Patient reported trouble breathing	venlafaxine (Effexor)	Stopped Effexor for 3 days Started Vistaril (take as needed)
#4	Patient reported difficulty swallowing	suboxone	Switched from suboxone sublingual to film strip
#5	Patient reported itching	dorzolamide	Switched to latanoprost
#6	Patient reported muscle aches and had “swollen eyes”	emtricitabine/rilprivirine/tenofovir (Complera)	Switched from Complera to patient's previous HIV regimen
#7	Elevated AST and ALT	HIV medications	Held HIV meds while treating Hepatitis C
#8	HCP reported that patient had a history of kidney stones	topiramate	Advised the medical resident to taper and then discontinue topiramate
#9	Patient reported swelling, angioedema	hydrochlorothiazide/ lisinopril	Discontinued lisinopril
#10	Elevated hemoglobin	testosterone	Recommended PCP decrease or stop testosterone
B. Incidents reported by pharmacists			
#1	Patient reported chest tenderness	spironolactone	Switched from spironolactone to eplerenone
#2	Patient reported nightmares	varenicline	Stopped varenicline, prescribed nicotine patch
#3	Thrombocytopenia	heparin	Stopped heparin, transitioned from bivalirudin to rivaroxaban
#4	Patient reported chest pain	montelukast	Stopped montelukast
#5	Patient had low blood pressure	doxazosin	Contacted PCP and suggested stopping doxazosin
#6	Patient reported rash	piperacillin + tazobactam	Switched to clindamycin
#7	Patient reported chest pain	abiraterone	Reaffirmed to the patient that it is not a heart attack; Continued abiraterone for cancer treatment

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#8	Patient reported diarrhea	atorvastatin	Switched to simvastatin
#9	Orthostatic hypotension	tamsulosin	Recommended the rounding team stop tamsulosin
#10	Electronic health record alerted the participant about a sulfa allergy	furosemide (new order)	Advised the nurse practitioner that furosemide can be started

Abbreviations: ADR = adverse drug reaction, AST = aspartate aminotransferase, ALT = alamine aminotransferase, HIV = human immunodeficiency viruses, PCP = primary care provider

ADR decision-making model

The resulting ADR model (**Figure 2**) outlines participants' cognitive processes when they detected and responded to potential ADRs. This model consists of four medication-related stages: problem detection, investigation of the problem's cause, risk/benefit considerations, and plan, action, and follow up. Below, we organize results by the stages in this model. Emergent themes within each stage are underlined, and sample quotes from participants are presented in **Table 3.** Additionally, we describe each of the 4 stages in the results sections below.

Table 3: **Main themes and quotes from participants.** Themes (bolded) and quotes (italicized) are organized based upon the four stages of the ADR decision making model (**Figure 2**). The numbers for each participant map to the incident descriptions in **Table 2**.

1. Detection of potential ADR
HCP detected potential ADR based upon from symptoms and signs *Patient called [the] pharmacy [and] said [that] after only 3 capsules of Cymbalta, the patient had muscle spasms and chest muscle spasms.* -Physician #1 **A new medication or a medication that is already known to commonly causes the ADR symptoms** *I asked the patient if he was taking the atorvastatin. Patient [said] 'Yes, and [I] have had a lot of diarrhea since starting the medication'.* Pharmacist #8 **Information from another HCP** *I got a view alert [notification in my EHR inbox], so I think [the patient] called the pharmacy and then they sent me a triage note with a box checked [for] adverse reaction.* Physician #1

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2. Investigate the cause of the problem
Reasons and strategies for investigating *[Participant] interviewed a patient and asked follow-up questions [including]: having trouble breathing, sweating? when did the burning sensation start?* Pharmacist #7
Confirmatory cues *Via phone call, [the] patient reported chest pain and muscle spasms. These [symptoms] occurred within the first 15 minutes of taking [the medication] [Cymbalta]. Symptoms consistently happened within 15 minutes for each of the 3 doses. [Confirming that these symptoms were from taking Cymbalta.]* Physician #1
Disconfirmatory cue *Before starting Cymbalta [the suspected medication], the patient had reported muscle spasms/muscle cramps all over as part of a general pain syndrome.* Physician #1
Negative cue (i.e. information that is absent) *I rechecked [AST/ALT] on the end of October… and they were [about] the same [as before]. The AST was 204 and ALT was 434…. Since [it] was about the same, liver function issues [were] NOT due to patient drinking. "I was hoping maybe [the cause was] was drinking [which is easier to address than an ADR]."* Physician #7
3. Risk and benefit considerations
Severity of side effects *Patient [is] tolerating the pain, not doing anything to compensate. Pain [is] not effecting [sic] patient's behavior [in the context of chemotherapy, the potential benefits are very high].* Pharmacist #7
Anticipated benefits *Furosemide [if taken] will take fluid off patient's lungs [patient had sulfa allergy].* Pharmacist #10
Encouraging patient adherence *So if you try several ones [statins], eventually sometimes patients are like: 'I'm not doing this anymore.' So I didn't want to put him on something that had a decent risk and run the risk that he would have a problem and refuse statins down the line.* Pharmacist #8
Which risk is greater? *[I need to] make sure that the risk of anticoagulating her [with heparin] was not greater than the risk of having this aortic dissection [bleeding risk].* Pharmacist #3
4. Plan, action, and follow up
Stop/put on hold/ adjust the medication *[I] told the patient to stay off Effexor… I wanted to be on the safe side… [I] wanted to make sure it was not an activation syndrome, which I have seen before.* Physician #3. *I alerted the patient's primary care provider [PCP] and the PCP discontinued the varenicline.* Pharmacist #2 *Delayed start of bivalirudin until 3 days later because patient had had an ablation procedure, [so I] felt patient's risk of bleeding was higher.* Pharmacist #3
Patient communication *[I] encouraged [the] patient to titrate up on gabapentin, as previously planned… I also try and address issues with diabetic socks/shoes so the patient does not perseverate. I discussed with patient and underscored the need for regular use of capsaicin, [including] how it works and why we use it.* Physician #2
Follow-up and monitoring patients *At the patient's next routine nursing visit, [the] nurse asked me to meet with the patient again. I briefly examined the patient and he had no signs of an allergic reaction.* Physician #4
Documenting the ADR in the EHR

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> *[I] entered nightmares for varenicline into the [EHR] allergy section. I was adding it to his allergies so no one would reorder it [again].* Pharmacist #2

Stage 1. Detection of potential ADR

In this first stage, HCPs relied on cues that signaled an initial concern. *Patient's symptoms* (reported) *and signs* (observed) were common cues to help HCPs recognize a potential ADR. Additionally, *abnormal lab values* reported within the EHR can also help HCPs detect the problem. Furthermore, HCPs reviewed medication characteristics to sense potential ADRs. Common characteristics of ADR detection were either *a new medication* that was recently prescribed or started by the patient, or a *medication that is commonly known to cause the ADR symptoms that the patient is experiencing.* Usual causes of ADR symptoms were often recognized by HCPs from clinical experience. Finally, HCPs sometimes detected a potential ADR based on *information (e.g., tip-off) from another healthcare professional or the patient themselves.*

Stage 2. Investigate the cause of incident

After detecting the problem, HCPs started to investigate the potential cause. This stage involved *information that prompted HCPs to investigate,* and *their strategies for investigating*. For each specific reason to investigate, HCPs used a distinct, corresponding strategy, such as interviewing a patient who reported a certain symptom, or searching in drug references if the HCP suspected that a drug caused the sign or symptom. HCPs also *examined confirmatory and disconfirmatory cues,* to validate the connection between ADR concerns and their suspected medications.

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When investigating the connection between an ADR and a possible problematic medication, HCPs searched for certain *confirmatory cues*. These were cues that helped providers to conclude that the medication was the likely cause of the ADR. Likewise, HCPs also looked for "*disconfirmatory cues*" that suggested that the suspected medication was *not* causing an ADR (see **table 3** for examples of confirmatory and disconfirmatory cues). HCPs often reviewed the disconfirmatory cues through clinical references such as provided by UpToDate, Micromedex, and Lexicomp.

HCPs not only searched for documented and available clinical information but also looked for factors that were absent, to confirm or reject the connection between the ADR concern and the suspected medication. This is known as negative cue. An example includes medications that commonly cause the problem but were not part of the patients' medication regimen.

Stage 3. Risk and benefit considerations

When the cues indicated the occurrence of an ADR, HCPs often considered the risk and benefits associated with continuing or stopping the suspected medication. As part of this solution-seeking activity, HCPs often considered whether available alternative treatments could alleviate the ADR. They also weighed the risks and benefits associated with such alternatives. While weighing risks and benefits is an essential element of medical decision-making, our study found several components that HCPs also take into consideration. These components include:

Severity of side effects. HCPs often evaluated the severity of the current side effects, and the patient's willingness to tolerate them. The HCP chose to continue the medication, but educated the patient about potential problems, and suggested increased monitoring (e.g., follow-up by

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nursing staff, or more frequent patient appointments). In contrast, if the side effects were more severe, the HCP sought alternative medications or treatment.

Anticipated benefits. If the treatment benefits of the medication were expected to outweigh the risk for the patient, the HCPs tended to continue the medication.

Fostering patient adherence. When investigating options for addressing and solving an ADR, the HCPs also incorporated the patient's feedback and the likelihood that the patient will abandon treatment with the medication in question. Rather than sequentially trying a series of closely related medications (medications in the same class) in hopes that one will have the desired benefits without the adverse reaction, the HCP sometimes switched to a different class of medication therapy to help alleviate the patient's concern.

Which risk is greater? In some cases, HCPs framed the problem in terms of which risk was greater: stopping the medication, or experiencing the ADR. Conversely, at times they assessed which benefit was greater. This happened most often for patients with particularly challenging health conditions, such as HIV or multiple chronic comorbidities. In these cases, the patient may be taking a medication that has benefits for managing a chronic condition (e.g., treating HIV), but stopping the medication may have benefits for mitigating ADR.

Stage 4. Plan, Action, and Follow-Up

The last stage of this decision-making model includes planning, selecting actions, and follow-up with patients. Based primarily on information collected stages 2 and 3, HCPs would determine appropriate plans and actions to address the problem. The three main actions in response to incidents in our study included changes to medication management, patient counseling, and

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follow-up appointments and monitoring. Changes to medications included stopping the offending medication, temporarily placing the medication on hold until the ADR was alleviated, changing the drug to one that is unlikely to cause the ADR, or continuing the medication if its perceived benefits outweigh risks.

Patient communication was an important activity that HCPs used, in some cases, to initiate shared decision making with the patient about the new medication action and plan. After the new action was taken to mitigate the ADR, the HCP would *follow-up and monitor the new action and plan with patients.* HCPs used various strategies to monitor and follow up with patients, such as ordering a new lab test, or examining the patient at the next visit, to ensure that the ADR concern was resolved. Finally, if the ADR was confirmed during the investigation stage, several HCPs reported *documenting the ADR* in the EHR to help prevent recurrence. HCPs also followed up with other HCPs, to confirm that the ADR was correctly documented in the EHR if they did not input it directly.

It is important to recognize that the decision-making steps in stage 4, plan, action, and follow-up, are iterative steps. If a certain plan and action did not resolve the suspected ADR, HCPs described developing a new plan and action until the problem is resolved.

DISCUSSION

To our knowledge, this is the first study to examine the cognitive processes of HCPs when they detect and solve potential ADR incidents. Our study explored the iterative steps of HCPs' decision making, from detection of potential ADR incidents to plans and actions they took to resolve incidents. The study illustrates the cognitive complexity of the work conducted by HCPs

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when resolving ADR problems. Our findings point to four important implications, discussed below, to develop novel clinical decision support systems that more closely align with HCPs' cognitive workflow.

1. Develop technologies to facilitate communication between HCPs and patients regarding ADRs. Detecting potential ADRs requires *identifying* patients' signs or symptoms that may be related to a drug [20]. For ADR alerts to work more efficiently, EHR systems could collect reliable information about patients' signs and symptoms, and then display and communicate that information. Therefore, patient-generated data, which is not a typical element of many current alerting systems, may play an important role in future decision support for ADRs [21]. Additionally, communication between HCPs and patients also plays an important role in resolving ADRs that are already occurring. In some cases, HCPs may help the patient set realistic expectations about the type and severity of symptoms. Throughout the course of ADR investigation and treatment, HCPs need to communicate closely with the patient, to share potential risks and benefits and engage patients in a shared decision-making process [22]. Topaz *et al.* study demonstrated that HCPs were more likely to override an alert for medications that patients are currently tolerating or have previously tolerated [23]. Indeed, communicating with patients about symptoms, medical history, etc. is an important element in HCPs' decision making. Such communication may occur not only through direct patient interactions but also indirectly through patient portals, secure messaging, and other telehealth technologies [24]. These modalities may also increase patients' access to care, facilitating patient-HCP communication to resolve ADRs.

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2. Incorporate confirmatory and disconfirmatory ADR cues into alerting systems. Rapid, accurate, and complete information is important to help detect and resolve ADR problems. Our study found that additional information ADR detection, such as the confirmatory cues and disconfirmatory cues, were important to assist HCPs with the ADR investigation process. HCPs used these cues to organize and assemble a constellation of information in a form that is meaningful for sensemaking. This concept is known as knowledge-base cognitive mode [25]. Subsequently, EHR alerts systems for ADRs should align with a knowledge-base cognitive mode by including important cues while filtering distracting information to optimally help HCPs with clinical decision making. Since ADR alerts detect potential ADRs from symptoms and abnormal lab results, confirmatory and disconfirmatory cues provided by the alerts could allow HCPs to confirm the alerts' trustworthiness and avoid overlooking alerts. In fact, a study on drug allergy alert-overrides showed that providers were more likely to override alerts derived from non-important cues [23]. Our findings, in combination with those results, highlight the importance of providing cognitive cues to assist HCPs with decision making.

3. Design alert systems that account for negative cues: The absence of certain cues, known as negative cues, is another important factor for decision making. HCPs are aware of this absence of information based on familiar perceptual patterns. For example, one experienced provider in our study described how s/he confirmed that a patient did not have a myocardial infarction (Table 2, case B7). Although the patient reported a burning chest sensation, the patient did not have other symptoms such as numb fingers, arm pain, or diaphoresis. The absence of the companion symptoms was reassuring, allowing the provider to focus on other potential causes of the symptoms, such as a potential ADR with abiraterone. This type of negative cue is often

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overlooked in technology-centric design but is a critical component of decision making, especially during the evaluation of potential ADRs. Complex algorithm development that includes negative cues could advance decision support and help HCPs better detect and investigate potential ADRs.

4. Advance alert information to better support HCPs' risk-benefit evaluation: Our ADR decision-making model (**Figure 2**) underscores that even when an ADR is confirmed, HCPs still need to evaluate the medication's risks and benefits. Existing medication alert systems identify potential problems but the information they provide is often insufficient to help HCPs weigh risks and benefits of the problematic medication. As a result, HCPs seek information from drug references, colleagues, and other sources. Indeed, ADR alert design without consideration of risks vs. benefits is likely to "fail" (be overridden) in many instances. For complex risk-benefit evaluation, ADR alerts should provide quick access to a comprehensive list of risks and benefits, or corresponding sections of drug information resources, to help HCPs make a sound clinical decision [13].

This study has several limitations. First, we interviewed only physicians and pharmacists regarding ADRs, since incident submissions from nurse practitioners were low. Nurse practitioners, registered nurses, and physician assistants, also interact with patients and play important roles in ADR decision making, warranting further research. Second, we were not able to directly compare the decision-making processes of physicians and pharmacists, because the variation in incidents precluded direct comparisons (e.g., involved different medications or patients with varying medical conditions). Third, we examined incidents from a single large V.A.

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medical center and EHR system. Our findings might not always apply to other settings. Fourth, all incidents collected and analyzed were voluntarily provided by HCPs. This could influence our findings, because HCPs might be more inclined to submit incidents for which they felt most confident in their handling of the ADR; thus, incidents that created even greater challenges or uncertainty for HCPs as they resolved ADRs may have not have been captured. Fifth, most incidents we studied, especially those from physicians, were obtained from outpatient care. Thus, our results might not always apply to inpatient settings. Finally, we were not able to fully incorporate two incidents (Table 3. Physician #8 and Pharmacist #10) into our decision making model. Unlike other incidents, these two incidents focused on prevention of an ADR instead of resolving suspected ADRs. Further research is needed on HCPs' decision-making with respect to ADR prevention.

Our study findings have several practical applications. The ADR decision-making model we developed through this research has important implications for the design of clinical decision support. This model could be used as the foundation for a novel ADR alert system to support HCPs in recognizing and resolving ADRs. Evolving alert systems by applying this model is anticipated to increase the cognitive support of alerts for HCPs, which subsequently can improve medication safety outcomes for patients. In addition, the ADR decision-making model is expected to be valuable for teaching medical and pharmacy trainees about the decision-making process for ADR mitigation.

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CONCLUSION

This is likely the first study to identify the decision-making processes of HCPs when they detect and resolve potential ADR incidents. The ADR decision-making model developed from this study consists of four important stages: problem detection, investigating the cause of the problem, consideration of risks and benefits, and plan, action, follow-up. This model is expected to be valuable for alert system designers as well as educators who are training future physicians and pharmacists about ADR decision-making. Our findings have four key implications for clinical decision support systems: develop technologies to facilitate communication between HCPs and patients to better detect and address ADRs; incorporate confirmatory and disconfirmatory cues into ADR alerting systems to more closely align with cognitive strategies from HCPs; design alert systems that account for negative cues to further facilitate decision making; and enhance alert system displays to better support HCPs' risk-benefit evaluation process for ADRs. The design of supporting technologies for potential ADR problems should align with the real-world cognitive strategies of HCPs in order to achieve the best health outcomes for patients.

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Conflicts of interest: L.M. is co-owner of Applied Decision Science, LLC, a company that studies decision making in complex environments and utilizes the critical decision method. She aided in the design of the cognitive task analysis approach used in this study and trained the interviewer. M.W. has stock in Allscripts and Express Scripts Holding Company. All other authors report they have no conflicts of interest.

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drafted the journal manuscript. All authors reviewed and made important scientific edits to the manuscript and approved it for submission.

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Figures and legends

Figure 1. Overview of the study procedure. Four main steps are shown in the illustration.
Abbreviation: ADR: adverse drug reaction

Figure 2. Adverse drug reaction decision-making model. The model has four stages.
ADR: adverse drug reaction.

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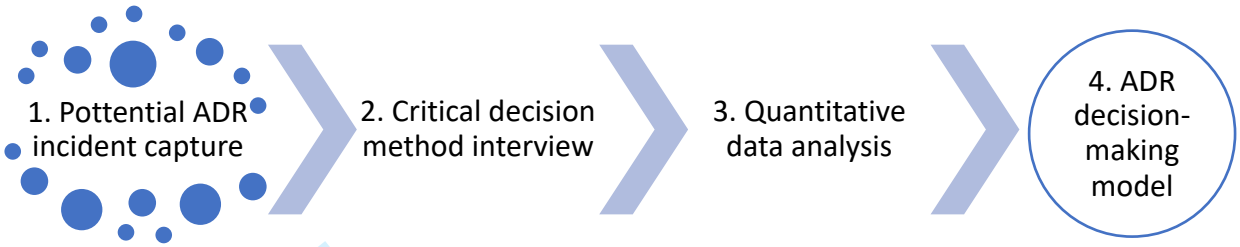
Figure 1. Overview of the study procedure. Four main steps are shown in the illustration.



Abbreviation: ADR: adverse drug reaction

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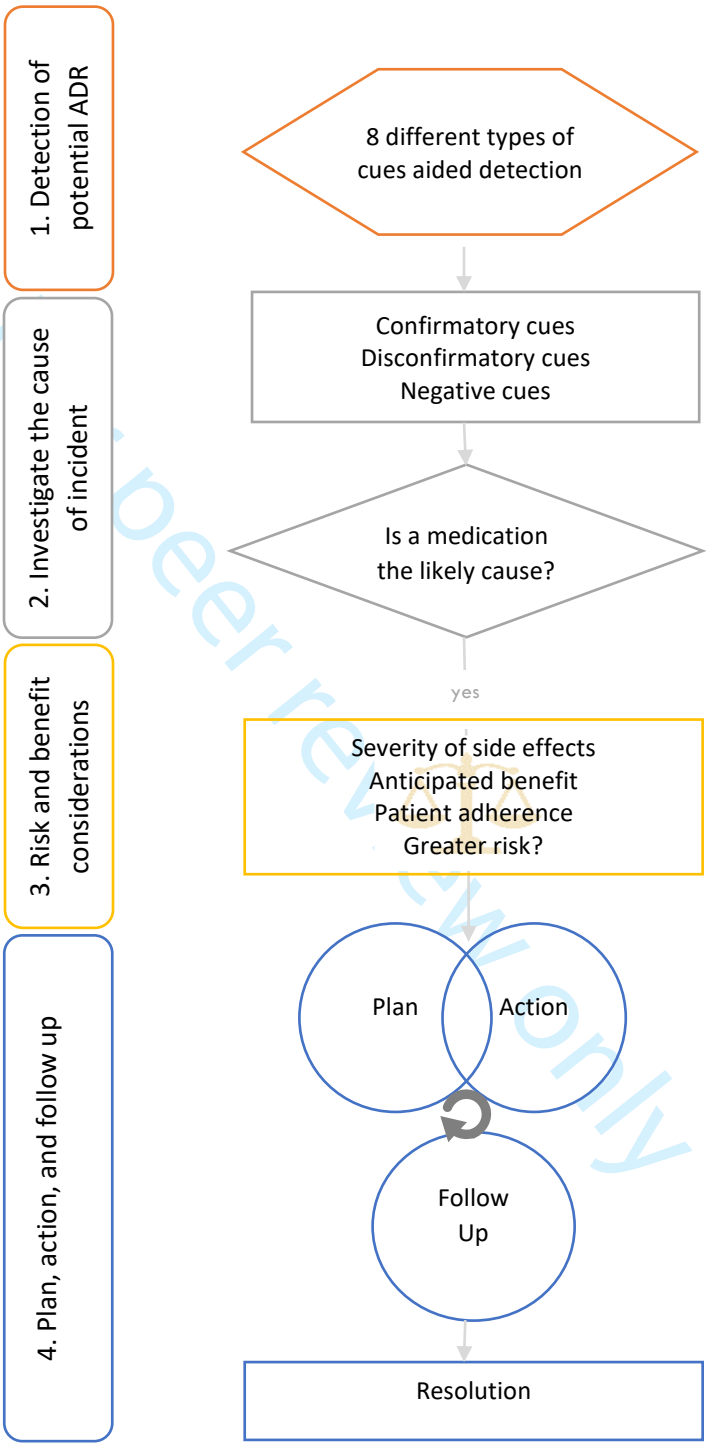
Figure 2: Adverse drug reaction decision-making model. The model has four stages. ADR = adverse drug reaction.



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Supplemental documents

Appendix A. Sample of decision requirements table					
Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that nonexperts may tend to make*	**IT Design Seeds**
1. Assessing the pt	I had only seen pt one other time. 66	Pt was referred to me for cholesterol follow-up; pt appointment with me. 52 B/c of pt's risk factors, pt needs to be on moderate to high intensity statin, which is why Dr put pt on atorvastatin. 38 Pt taking atorvastatin 20 mg daily. 120	BEFORE the visit: a. I have an excel spreadsheet that I created from the guidelines that calculates the ASCVD score. [treasure map!] Calculated ASCVD risk score to determine what intensity of statin med pt needs. it aggregates like the risk like their age, their sex, their race, what their baseline cholesterol levels are, if they have high blood pressure, what their blood pressure was, like it just calculates smoking and whether or not they have diabetes and "spits out a number at you". I calculate this before the pt walks in the room. 433 [AI: This is used by many pharms and was created in-house. They can use if internet goes down.] b. I went back [in CPRS] and looked at all his cholesterol results in the past to see	[AI: Home grown ASCVD calculator/treasure med may not hold up in a court of law. Could be programming glitch. Also, is code editable? Will not get auto-updated like the internet version should if something changes with the calculation.]	Integrate ASCVD calculator into EHR and/or decision support/med selection process in CPOE.

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Appendix A. Sample of decision requirements table					
Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that non-experts may tend to make*	**IT Design Seeds**
			how high his cholesterol been. c. I look for:pt's response to meds, to see if dose increase is needed. Was there a 50% reduction in cholesterol – aim from the guidelines. 714		
2. Recognizing a potential medication issue	"I was surprised" [that it actually turned out to be atorvastatin] b/c: 272 a. "I hadn't had anybody complain of diarrhea with atorvastatin before, so it was a new side effect for somebody to complain about." b. simvastatin also is for cholesterol, is related to atorvastatin – mechanism of action is the same- but simvastatin causes more constipation, so diarrhea was a surprise [opposite of what would expect with atorvastatin] 278 Sometimes meds in general can 'go either	I asked pt if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med/since last visit. 84, 29			

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Appendix A. Sample of decision requirements table					
Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that non-experts may tend to make*	**IT Design Seeds**
	way" – cause diarrhea OR constipation. 510. sometimes people are just prone to one side effect versus another. 533				

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Appendix B. Adverse drug reaction codebook		
CODE	**DEFINITION**	**Example of Coded Item (Cue)**
I. Problem Detection Related Decision Points:** - Assessing the pt - Deciding what drug to prescribe for treatment - Recognizing an abnormal lab value. - Recognizing a potential medication issue - Assessing the appropriateness of the medication order or regimen - Receiving the handoff about a potential medication issue - Reviewing the handoff [consult]	**Cues** that 'flagged' an initial concern and helped the participant notice a potential safety issue. These can be external information and sources; internal cues (feelings), others pointing something out to the participant, etc.	**Do NOT code at this level**
Lab values	**Cue definition**	**Example**
1.a Abnormal lab	lab value outside of normal range	"…her platelets you know were 66 and that is not normal."
Medication Characteristics	**Cue Definition**	**Example**
1.b New Med	medication that was recently prescribed or the patient recently started taking	I asked patient if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med. 84_29
1.c Common cause of ADR	medication is suspected as a potential problem b/c participant knows the ADR is often due to this med	Heparin is [the] most common med to cause thrombocytopenia
Patient information	**Cue Definition**	**Example**
1.d Symptoms	symptoms, directly or indirectly related to the ADR	I asked patient if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med.
OTHER	**Cue definition**	**Example**
1.e Tipped off to potential ADR	another healthcare professional or the patient already suspected an ADR and notified the participant	PACT RN [asked me] "what do you want to do with this patient? It looks like he had this adverse reaction to this medicine"
1.f Unknown Problem Detection	cues that helped the provider initially detect the problem could not be clearly discerned from the case	

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1.g Computerized alerts	Any kind of alerts related to ADR; also known as "order check"	
2. Investigating the cause of the problem **[Investigate]** Related decision points: - Determining the symptoms were NOT medication-related. - Is there a medication-related problem? - Investigating the cause of the problem (non-med causes, lit, colleagues) - Determining the cause of the medication-related problem Determining this is a medication-related problem	Additional information gathering, assessment, hypothesis testing	**NO coding at this level**
2.a Reasons and strategies for investigating	reasons the participant spent time investigating and what specific type of information they were seeking; (excludes reasons why they think there is an ADR – that goes under 'problem detection') Types of strategies used, labs ordered, resources used, etc to look into the problem	To make sure diarrhea wasn't due to another medication, I verified that nothing else had changed for pt since last visit [in terms of meds] 190 (3d) [MD Residents] Ordered confirmatory tests. 78: a. heparin antibody b. Serotonin release assay (SRA) 101, 557 (18c)
2.b Confirmatory cues	Information and other cues that suggested the specific med may be causing the ADR (med-ADR relationship)	I concluded diarrhea due to atorvastatin, not non-med issue b/c pt had more problems when taking the medication more often…190, 209 (3d)
- 2.b.1 Negative confirmatory cue	The absence of something is a cue for the participant that points to the suspect medication.	Pt not on many meds [or many others that could cause HIT, except heparin]. (18c)
2.c Disconfirmatory cues	Information and other cues that suggested the specific med may NOT be causing the ADR (Different than a 'negative' cue that means a lack of something is a cue.)	"It's [thrombocytopenia] usually something else, not the Heparin, but we always stop the Heparin until we know for sure." 551 (18c)

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- 2.c.1 Negative cue that is disconfirmatory	Noticing the absence of something is a cue for the participant and points AWAY from the suspect medication. (Excludes looking up something intentionally and finding the answer is no)	[no examples yet…?]
2.d Ambiguous/ Dual meaning cue	Cue that not clearly confirmatory or disconfirmatory Participant unclear if cue point toward or away from ADR	My initial concern was that maybe this was just her normal muscle cramps (pt Hx) (112-113)
3.Plan/Action/Follow-up [PAF] [all other decision points]	DEFINITION (propose your own, below) actions taken to address and/or follow up on the safety concern	NO coding at this level
3.a Stop Med	Cues, strategies, actions, related to a decision that the suspect ADR-related medication needs to be discontinued.	Check in CPRS to see if Lisinopril was discontinued. 499 (7b) Told RN: • Have pt throw Lisinopril away so doesn't accidentally take. 373 • stop Lisinopril, tell pt not to ever take again. 325 (7b)
- 3.a.1 Negative Cue related to stopping med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586
3.b Hold Med	Cues, strategies, actions, related to a decision that the suspect, ADR-related medication needs to be put on hold or the start of a new medication treatment needs to be delayed.	"Normally, if pt has HIT, we would initiate meds for direct thrombin inhibitors to anticoagulate the pt b/c HIT increases risk of clots. 121. Decided NOT to do that [immediately] for this pt. Instead, delayed start of bivalirudin until 3 days…" (18c)
- 3.b.1 Negative Cue related to holding med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586

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3.c. Change to new med	Reasons, cues, strategies, actions, related to a decision that the medication needs to be changed. This does NOT include the dose of the new med: that goes in the sub-code below This includes aspects that helped them make the choice of the alternate medication or treatment (surgery), as well as other options they considered for now or in the future. This also includes reviewing the patient's ADR/medication history to inform a decision about the new medication. (EXCLUDES renewals of the exact same prescription)	We switched pt back to simvastatin and stopped atorvastatin. 46 (3d) If the pt's cholesterol would have been higher [around 120] I would have: a. Rxed Crestor (rosuvastatin) has high intensity at higher doses. [switched pt to higher intensity med that the pt hadn't tried yet], but Crestor is non-formulary med and requires special consult/approval. 723 (3d)
- 3.c.1 Negative cue related to change to a new med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586
- 3.c.2 Dose Selection	Cues and strategies that helped the participant determine what medication dose to use, how to change the dose, etc	I Rxed 40mg daily of simvastatin to get equivalent potency as 20mg atorvastatin. 132
- 3.c.3 Risk/Benefit	Consideration of the risk and benefits (or pros and cons) of one or more treatment options	PharmD (participant) recognizes limitations of ASCVD calculator and is able to recognize when other risk factors may need to be considered like family history (633):
3.d ADR documentation	Cues, reason, and strategies related to documenting or not document the ADR, including information documented, double-checking/confirming it was documented, reasons for documenting etc.	Check in CPRS to see if ADR entered. 512 (7d)

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3.e Pt counseling	Counsel, inform patient regarding new action/plan Includes direct communication with patient, checking to see that key information has been communicated to patient, or instructing someone else to communicate with patient.	made sure patient's discharge instructions included verbiage related to patient stopping lisinopril Told RN: • Have pt throw Lisinopril away so doesn't accidentally take 373 • stop Lisinopril, tell pt not to ever take again. 325 • we will replace Lisinopril with something else. 81 • give pt a list of all other meds in same [drug] class [as Lisinopril] and tell pt not to ever take any of these. 228, 325 • have pt check BP at home/ keep log. 385 have pt come in 2 weeks for BP check 331
3.F Follow –up/Monitor	Follow up after certain change Ex: BP, lipid panel, cholesterol Includes follow up by interviewee or by other member of the healthcare team Reassess pt on certain measurements Includes cues, strategies, reasons, and actions related to follow up	Check pt's BP 2 weeks after D/C b/c: • allows pt to recover after hospitalization • let's BP stabilize on altered BP med regimen (now HCTZ only; and get rid of Lisinopril in system which can lower BP). 754, 962 • -gets steroids out of pt's system before checking BP again, since they elevate BP. 754 • 2-4 weeks is acceptable range in my assessment. 766 If pt had NOT been given steroids, see back sooner, around 1 week. 962
3.G Continue the med	Reason, cue, strategy for continue current med. This includes aspects that helped them make the choice of the alternate medication or treatment (surgery), as well as other options they considered for now or in the future. This also includes reviewing the patient's ADR/medication history to inform a decision about the continue the medication	
3.g.1 Dose selection	Cue and strategy for choosing a new dose (increase or decrease the dose) to improve tolerance	Decided to have pt try low potency capsaicin again at 3x/day

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Strategies Prescribers and Pharmacists Use to Identify and Mitigate Adverse Drug Reactions in Inpatient and Outpatient Care: A Cognitive Task Analysis at a U.S. Veterans Affairs Medical Center

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Strategies Prescribers and Pharmacists Use to Identify and Mitigate Adverse Drug Reactions in Inpatient and Outpatient Care: A Cognitive Task Analysis at a U.S. Veterans Affairs Medical Center

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ABSTRACT

Objective: to develop a descriptive model of the cognitive processes used to identify and resolve ADRs from the perspective of healthcare providers in order to inform future informatics efforts

Setting: inpatient and outpatient care at a tertiary care U.S. Veterans Affairs Medical Center

Participants: physicians, nurse practitioners, and pharmacists who report ADRs

Outcomes: descriptive model and emerging themes from interviews

Results: We conducted critical decision method interviews with 10 physicians and 10 pharmacists. No nurse practitioners submitted ADR incidents. We generated a descriptive model of ADR decision-making process and analyzed emerging themes, categorized into four stages: detection of potential ADR, investigation of the problem's cause, risk/benefit consideration, and plan, action, and follow-up. HCPs relied on several confirmatory or disconfirmatory cues to detect and investigate potential ADRs. Evaluating risks and benefits of related medications played an essential role in HCPs' pursuits of solutions

Conclusions: This study provides an illustrative model of how HCPs detect problems and make decisions regarding ADRs. The design of supporting technology for potential ADR problems should align with HCPs' real-world cognitive strategies, to assist fully in detecting and preventing ADRs for patients.

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STRENGTHS AND LIMITATIONS

Strengths:

- First study that to examine the cognitive process that HCPs use to detect and investigate ADRs
- Utilized critical decision method to construct a descriptive model

Limitations:

- We only interviewed physicians and pharmacists regarding ADRs but not other HCPs such as nurse practitioners, registered nurses, or physician assistants.
- We only examined incidents from a single large V.A. medical center and EHR system.

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INTRODUCTION

Adverse drug events (ADEs) harm over 1.5 million patients and cost over $500 million each year in the U.S. [1]. These concerning statistics prompted the U.S. Office of Disease Prevention and Health Promotion to develop a National Action Plan for Adverse Drug Event Prevention in 2014[2]. This plan called for actions, including developing health information technology to promote best practices in prescribing, and in detecting cases of high risk for ADEs [2]. Many factors contribute to the high incidence of ADEs in the U.S., including an increasing number of adverse drug reactions (ADR), an aging population, and a rising trend in polypharmacy [3]. ADR, defined as an unintended response to a drug that occurs at normally used doses, is the most common type of ADE [4]. Healthcare professionals (HCPs) such as physicians and pharmacists are essential in preventing and managing ADRs because they directly prescribe drugs and provide clinical care. However, the processes that individual HCPs adopt to identify, treat, and monitor ADRs are not well understood.

Healthcare systems leverage many different approaches to support HCPs in assessing and preventing ADRs, including systematic efforts to collect and review data to assess the risk of ADRs [5-7]. With advances in the development and implementation of electronic health records (EHR), alert systems that help HCPs identify and prevent ADEs have become more feasible and promising. Indeed, automated computerized order checks, frequently resulting in drug alerts, are often based on triggers such as the documentation of a patient's allergies [8].

While medication alert systems for allergies have been implemented regularly, alert systems with decision support to identify and resolve newly occurring ADRs are rarely found. In addition, many EHR alert systems have a technology-centric design that fails to take into

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account the HCPs' cognitive processes and workflow [9-11]. HCP decision-centered design, in contrast, focuses on HCPs' cognitive processes and key decisions, such as prescribing a drug, or choosing a drug regimen, as a core function of design [12, 13] With a foundational understanding of the cognitive strategies that HCPs use to prevent and respond to ADRs in clinical practice, healthcare systems and EHR vendors can develop systemic interventions and technologies to help HCPs prevent and resolve ADRs. Recent studies emphasize that cognitive studies are needed to help understand HCPs' decision making [9, 14] in order to develop more meaningful and effective clinical decision support. Therefore, the objective of this study was to develop a descriptive model of the cognitive processes used to identify and resolve ADRs from the perspective of HCPs in order to inform future informatics efforts.

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METHODS

Study site and participant characteristics

This research is part of a larger study [15, 16] conducted at a tertiary care Veterans Affairs Medical Center. The study was approved by the Indiana University IRB (protocol 1301010433.) Eligible HCPs were physicians, nurse practitioners, and pharmacists who prescribed medications, managed medications, or verified prescriptions in an inpatient or outpatient setting. We excluded medical and pharmacy residents, trainees, pharmacy technicians, and those with a purely administrative role. We invited all remaining eligible HCPs at the study site to participate. Eligible HCPs were invited to participate via emails, flyers, and follow-up via phone calls. All participants were consented in written prior to the critical decision method interviews. An extended version of the recruitment can be found from the method paper. [15]

Study design

The study procedure and data analysis are illustrated in four steps in **Figure 1.**

Potential ADR incident capture

Participants, when encountering a potential ADR, were ask to complete an incident card [15], which captured detailed information about the potential ADR incident, such as the type of ADR, suspected medication(s), and when the participant first became aware of the problem. Given that recall is often difficult for tasks and decisions that are made many times each day [17], the incident card was designed to help capture an ADR event close to the time of the incident, *before* it was forgotten or "merged" in memory with similar events. A similar approach of administering a small set of questions soon after an incident has been shown to increase

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accuracy of recall days later [18]. Subsequently, the incident card that HCPs submitted was used to assist with the critical decision method (CDM) interviews if the incident was selected, as described below.

Incident selection: A research team, consisting of a physician, pharmacist, and human factors expert, reviewed each incident card to determine eligibility for an interview. Incident cards were reviewed based on five criteria: incident was appropriately addressed, incident required great expertise or consideration, incident had potential to cause serious injury, incident was unique or challenging, or incident would be difficult for trainees to resolve alone.

Critical decision method

Selected incidents led to scheduling of follow-up CDM interviews with HCPs, to collect further details [15]. The CDM interview technique, often used as part of a cognitive task analysis, is designed to capture detailed incident accounts from participants, including strategies, critical cues, and contextual elements as experienced by the interviewee [17]. A human factors expert conducted pilot testing of the interview guide with three HCPs (2 physicians, 1 pharmacist) to further refine interview questions prior to data collection [15]. Interviews were scheduled within two to four weeks of the incident date. One human factors scientist, trained in the CDM technique, conducted a 60-minute, semi-structured CDM interview with each HCP. These interviews were structured in the following three phases:

1) Capture a brief summary of the incident: The interviewer asked the participant to summarize the incident as it pertained to the ADR concern. If multiple eligible incidents

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were received from a participant, the interviewer asked questions at the beginning of the interview, to select the more challenging incident.

2) Construct an incident timeline: The interviewer asked participants probing questions, to reconstruct a high-level timeline of the incident. This timeline was recorded and displayed on a whiteboard, visible to both the interviewer and HCP during the interview session. The timeline helped the interviewer organize the incident in chronological order and provided a common point of reference for the rest of the interview.
3) Ask in-depth questions. The interviewer asked additional questions to investigate the HCPs' decision-making process, and to identify cognitive cues used during the course of the incident. The interviewer then asked hypothetical questions to gain further insights about the cognitive cues or strategies that the participant used to detect and respond to the ADR incident.

The incident timeline was photographed. Interviews were audio-recorded and transcribed for analysis. The complete interview guide and a more detailed description of study methods is available elsewhere [15]. Examples of interview questions are below.

1. What caused you to be concerned about the medication for this patient?
2. In what ways did computerized alerts help you notice the right things and take action?
3. What tools/software/technology were used to help manage the medication conflict?
4. What, if any, documentation in the EHR helped you know what to do?
5. Under what circumstances, if any, would you have discontinued the medication for this patient, rather than reducing the dose?

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Qualitative data analysis

Interview transcripts were independently analyzed by a human factors engineer and a clinical pharmacist, to generate decision requirement tables for each incident. The decision requirements table is a representation commonly used to examine key information within and across incidents [13]. Any discrepancies in table content were discussed by the analysts until they reached consensus [19]. These decision requirements tables summarized each incident and examined key elements. Specifically, researchers identified key decision points inductively, and for each decision point, recorded several components, including cues, strategies, potential errors, and any factors that made the decision difficult. (See online Appendix A for a sample decision requirements table.)

Three analysts (human factors engineer, pharmacist researcher, and cognitive psychologist) then used these tables to identify initial themes across four selected incidents. Each analyst independently coded the *problem detection* aspect of each incident from those decision requirements tables, then met weekly to discuss whether the data supported the initial conception of the model, and whether the proposed codes adequately captured the incident. Refinements were made to the codebook, including merging codes and adding new ones, refining the definition of codes, and adding examples to the codebook. When they completed this process for the first four incidents, they worked through the same process with the *investigate the cause* codes, followed by the codes for *plans/address/follow-up* from the decision requirements tables.

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After analyzing the first four incidents, two of the analysts (pharmacist researcher and cognitive psychologist) independently analyzed the remaining data in blocks of four incidents (two pharmacist cases, and two physician cases), using the complete codebook. Each incident was discussed until consensus was reached. When a block of four random incidents had been analyzed and discussed, the two analysts summarized any new insights and potential refinements to the codebook (i.e., clarifying definitions, nesting or un-nesting codes to reflect the data more completely), in consultation with the human factors engineer. See online Appendix B for the final codebook. Final consensus codes were entered into NVivo software (QSR international, version 10), to assist with data management and analysis.

Initial model development of ADR decision-making

Data from all sources were collected and analyzed to develop the initial model of ADR decision-making. To develop the initial model of ADR decision-making, we conducted a card sort of clinicians' key decision points identified in each ADR incident. Decision points from each of the decision requirement tables, such as "investigate the cause of the problem," were written on individual paper index cards. A multidisciplinary team of five researchers, including two human factors professionals, two pharmacists, and one physician, individually sorted cards into meaningful groups based on their background and perspectives to collapse similar decision points across incidents into one decision point, then reviewed and discussed the terminology for each decision point until reaching consensus.

From these card sort results, two human factors professionals developed the initial model, and then reviewed and refined the model monthly with input from all research team members,

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including practicing physicians and pharmacists. The model was intended to characterize the cognitive processes that HCPs in our study described as they were confronted with potential ADRs.

Patient and Public Involvement

No patient involved. This study focused on HCPs. However, the results of this study on ADR were important to improve patient safety in medication use.

RESULTS

Participants and ADRs reported

HCPs submitted a total of 35 ADR incident cards. We completed interviews with ten physicians and ten pharmacists (**Table 1**) regarding 20 incidents. No nurse practitioners submitted ADR incident cards. Reasons for exclusion of the remaining 15 ADR incident cards include: no action needed for clinical care (1), low ratings from incident cards from reviewers (2), illegible handwriting (1), participant submitted multiple cases (11). **Table 2** provides a brief description of the incidents.

Table 1: Characteristics of participants (N=20) who were interviewed regarding an ADR incident.

Characteristic	Physicians (n=10)	Pharmacists (n=10)	All participants (N=20)
Gender: female, n (%)	7 (70)	6 (60)	13 (65)
Age, median, (range)	42 (34-60)	36 (29-45)	38.5 (29-60)
Veterans Affairs experience, median, (range)	10 (3.5-26)	7.5 (2-13.5)	9 (2-26)
Setting of incident			
Inpatient	0	4*	4
Outpatient	10	6	16

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Abbreviations: ADR: adverse drug reaction; S.D. = standard deviation; *: one pharmacist had both inpatient/outpatient role

Table 2: Adverse drug reaction (ADR) incidents (N = 20) selected for interviews.

Case ID	Potential ADR incident	Medication(s) of concern	Action(s) taken by the participant
A. Incidents reported by physicians			
#1	Patient complained of chest muscle spasms	duloxetine (Cymbalta)	Switched to escitalopram
#2	Patient reported skin irritation on dorsum of feet	capsaicin, gabapentin (2 separate medications)	Stopped capsaicin, increased dose of gabapentin
#3	Patient reported trouble breathing	venlafaxine (Effexor)	Stopped Effexor for 3 days Started Vistaril (take as needed)
#4	Patient reported difficulty swallowing	suboxone	Switched from suboxone sublingual to film strip
#5	Patient reported itching	dorzolamide	Switched to latanoprost
#6	Patient reported muscle aches and had “swollen eyes”	emtricitabine/rilprivirine/tenofovir (Complera)	Switched from Complera to patient's previous HIV regimen
#7	Elevated AST and ALT	HIV medications	Held HIV meds while treating Hepatitis C
#8	HCP reported that patient had a history of kidney stones	topiramate	Advised the medical resident to taper and then discontinue topiramate
#9	Patient reported swelling, angioedema	hydrochlorothiazide/ lisinopril	Discontinued lisinopril
#10	Elevated hemoglobin	testosterone	Recommended PCP decrease or stop testosterone
B. Incidents reported by pharmacists			
#1	Patient reported chest tenderness	spironolactone	Switched from spironolactone to eplerenone
#2	Patient reported nightmares	varenicline	Stopped varenicline, prescribed nicotine patch
#3	Thrombocytopenia	heparin	Stopped heparin, transitioned from bivalirudin to rivaroxaban
#4	Patient reported chest pain	montelukast	Stopped montelukast
#5	Patient had low blood pressure	doxazosin	Contacted PCP and suggested stopping doxazosin
#6	Patient reported rash	piperacillin + tazobactam	Switched to clindamycin
#7	Patient reported chest pain	abiraterone	Reaffirmed to the patient that it is not a heart attack; Continued abiraterone for cancer treatment

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#8	Patient reported diarrhea	atorvastatin	Switched to simvastatin
#9	Orthostatic hypotension	tamsulosin	Recommended the rounding team stop tamsulosin
#10	Electronic health record alerted the participant about a sulfa allergy	furosemide (new order)	Advised the nurse practitioner that furosemide can be started

Abbreviations: ADR = adverse drug reaction, AST = aspartate aminotransferase, ALT = alamine aminotransferase, HIV = human immunodeficiency viruses, PCP = primary care provider

ADR decision-making model

The resulting ADR model (**Figure 2**) outlines participants' cognitive processes when they detected and responded to potential ADRs. This model consists of four medication-related stages: problem detection, investigation of the problem's cause, risk/benefit considerations, and plan, action, and follow up. Below, we organize results by the stages in this model. Emergent themes within each stage are underlined, and sample quotes from participants are presented in **Table 3.** Additionally, we describe each of the 4 stages in the results sections below.

Table 3: **Main themes and quotes from participants.** Themes (bolded) and quotes (italicized) are organized based upon the four stages of the ADR decision making model (**Figure 2**). The numbers for each participant map to the incident descriptions in **Table 2**.

1. Detection of potential ADR
HCP detected potential ADR based upon from symptoms and signs *Patient called [the] pharmacy [and] said [that] after only 3 capsules of Cymbalta, the patient had muscle spasms and chest muscle spasms.* -Physician #1 **A new medication or a medication that is already known to commonly causes the ADR symptoms** *I asked the patient if he was taking the atorvastatin. Patient [said] 'Yes, and [I] have had a lot of diarrhea since starting the medication'.* Pharmacist #8 **Information from another HCP** *I got a view alert [notification in my EHR inbox], so I think [the patient] called the pharmacy and then they sent me a triage note with a box checked [for] adverse reaction.* Physician #1

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2. Investigate the cause of the problem
Reasons and strategies for investigating *[Participant] interviewed a patient and asked follow-up questions [including]: having trouble breathing, sweating? when did the burning sensation start?* Pharmacist #7
Confirmatory cues *Via phone call, [the] patient reported chest pain and muscle spasms. These [symptoms] occurred within the first 15 minutes of taking [the medication] [Cymbalta]. Symptoms consistently happened within 15 minutes for each of the 3 doses. [Confirming that these symptoms were from taking Cymbalta.]* Physician #1
Disconfirmatory cue *Before starting Cymbalta [the suspected medication], the patient had reported muscle spasms/muscle cramps all over as part of a general pain syndrome.* Physician #1
Negative cue (i.e. information that is absent) *I rechecked [AST/ALT] on the end of October… and they were [about] the same [as before]. The AST was 204 and ALT was 434…. Since [it] was about the same, liver function issues [were] NOT due to patient drinking. "I was hoping maybe [the cause was] was drinking [which is easier to address than an ADR]."* Physician #7
3. Risk and benefit considerations
Severity of side effects *Patient [is] tolerating the pain, not doing anything to compensate. Pain [is] not effecting [sic] patient's behavior [in the context of chemotherapy, the potential benefits are very high].* Pharmacist #7
Anticipated benefits *Furosemide [if taken] will take fluid off patient's lungs [patient had sulfa allergy].* Pharmacist #10
Encouraging patient adherence *So if you try several ones [statins], eventually sometimes patients are like: 'I'm not doing this anymore.' So I didn't want to put him on something that had a decent risk and run the risk that he would have a problem and refuse statins down the line.* Pharmacist #8
Which risk is greater? *[I need to] make sure that the risk of anticoagulating her [with heparin] was not greater than the risk of having this aortic dissection [bleeding risk].* Pharmacist #3
4. Plan, action, and follow up
Stop/put on hold/ adjust the medication *[I] told the patient to stay off Effexor… I wanted to be on the safe side… [I] wanted to make sure it was not an activation syndrome, which I have seen before.* Physician #3. *I alerted the patient's primary care provider [PCP] and the PCP discontinued the varenicline.* Pharmacist #2 *Delayed start of bivalirudin until 3 days later because patient had had an ablation procedure, [so I] felt patient's risk of bleeding was higher.* Pharmacist #3
Patient communication *[I] encouraged [the] patient to titrate up on gabapentin, as previously planned… I also try and address issues with diabetic socks/shoes so the patient does not perseverate. I discussed with patient and underscored the need for regular use of capsaicin, [including] how it works and why we use it.* Physician #2
Follow-up and monitoring patients *At the patient's next routine nursing visit, [the] nurse asked me to meet with the patient again. I briefly examined the patient and he had no signs of an allergic reaction.* Physician #4
Documenting the ADR in the EHR

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> *[I] entered nightmares for varenicline into the [EHR] allergy section. I was adding it to his allergies so no one would reorder it [again].* Pharmacist #2

Stage 1. Detection of potential ADR

In this first stage, HCPs relied on cues that signaled an initial concern. *Patient's symptoms* (reported) *and signs* (observed) were common cues to help HCPs recognize a potential ADR. Additionally, *abnormal lab values* reported within the EHR can also help HCPs detect the problem. Furthermore, HCPs reviewed medication characteristics to sense potential ADRs. Common characteristics of ADR detection were either *a new medication* that was recently prescribed or started by the patient, or a *medication that is commonly known to cause the ADR symptoms that the patient is experiencing.* Usual causes of ADR symptoms were often recognized by HCPs from clinical experience. Finally, HCPs sometimes detected a potential ADR based on *information (e.g., tip-off) from another healthcare professional or the patient themselves.*

Stage 2. Investigate the cause of incident

After detecting the problem, HCPs started to investigate the potential cause. This stage involved *information that prompted HCPs to investigate,* and *their strategies for investigating*. For each specific reason to investigate, HCPs used a distinct, corresponding strategy, such as interviewing a patient who reported a certain symptom, or searching in drug references if the HCP suspected that a drug caused the sign or symptom. HCPs also *examined confirmatory and disconfirmatory cues,* to validate the connection between ADR concerns and their suspected medications.

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When investigating the connection between an ADR and a possible problematic medication, HCPs searched for certain *confirmatory cues*. These were cues that helped providers to conclude that the medication was the likely cause of the ADR. Likewise, HCPs also looked for "*disconfirmatory cues*" that suggested that the suspected medication was *not* causing an ADR (see **table 3** for examples of confirmatory and disconfirmatory cues). HCPs often reviewed the disconfirmatory cues through clinical references such as provided by UpToDate, Micromedex, and Lexicomp.

HCPs not only searched for documented and available clinical information but also looked for factors that were absent, to confirm or reject the connection between the ADR concern and the suspected medication. This is known as negative cue. An example includes medications that commonly cause the problem but were not part of the patients' medication regimen.

Stage 3. Risk and benefit considerations

When the cues indicated the occurrence of an ADR, HCPs often considered the risk and benefits associated with continuing or stopping the suspected medication. As part of this solution-seeking activity, HCPs often considered whether available alternative treatments could alleviate the ADR. They also weighed the risks and benefits associated with such alternatives. While weighing risks and benefits is an essential element of medical decision-making, our study found several components that HCPs also take into consideration. These components include:

Severity of side effects. HCPs often evaluated the severity of the current side effects, and the patient's willingness to tolerate them. The HCP chose to continue the medication, but educated the patient about potential problems, and suggested increased monitoring (e.g., follow-up by

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nursing staff, or more frequent patient appointments). In contrast, if the side effects were more severe, the HCP sought alternative medications or treatment.

Anticipated benefits. If the treatment benefits of the medication were expected to outweigh the risk for the patient, the HCPs tended to continue the medication.

Fostering patient adherence. When investigating options for addressing and solving an ADR, the HCPs also incorporated the patient's feedback and the likelihood that the patient will abandon treatment with the medication in question. Rather than sequentially trying a series of closely related medications (medications in the same class) in hopes that one will have the desired benefits without the adverse reaction, the HCP sometimes switched to a different class of medication therapy to help alleviate the patient's concern.

Which risk is greater? In some cases, HCPs framed the problem in terms of which risk was greater: stopping the medication, or experiencing the ADR. Conversely, at times they assessed which benefit was greater. This happened most often for patients with particularly challenging health conditions, such as HIV or multiple chronic comorbidities. In these cases, the patient may be taking a medication that has benefits for managing a chronic condition (e.g., treating HIV), but stopping the medication may have benefits for mitigating ADR.

Stage 4. Plan, Action, and Follow-Up

The last stage of this decision-making model includes planning, selecting actions, and follow-up with patients. Based primarily on information collected stages 2 and 3, HCPs would determine appropriate plans and actions to address the problem. The three main actions in response to incidents in our study included changes to medication management, patient counseling, and

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follow-up appointments and monitoring. Changes to medications included stopping the offending medication, temporarily placing the medication on hold until the ADR was alleviated, changing the drug to one that is unlikely to cause the ADR, or continuing the medication if its perceived benefits outweigh risks.

Patient communication was an important activity that HCPs used, in some cases, to initiate shared decision making with the patient about the new medication action and plan. After the new action was taken to mitigate the ADR, the HCP would *follow-up and monitor the new action and plan with patients.* HCPs used various strategies to monitor and follow up with patients, such as ordering a new lab test, or examining the patient at the next visit, to ensure that the ADR concern was resolved. Finally, if the ADR was confirmed during the investigation stage, several HCPs reported *documenting the ADR* in the EHR to help prevent recurrence. HCPs also followed up with other HCPs, to confirm that the ADR was correctly documented in the EHR if they did not input it directly.

It is important to recognize that the decision-making steps in stage 4, plan, action, and follow-up, are iterative steps. If a certain plan and action did not resolve the suspected ADR, HCPs described developing a new plan and action until the problem is resolved.

DISCUSSION

To our knowledge, this is the first study to examine the cognitive processes of HCPs when they detect and solve potential ADR incidents. Our study explored the iterative steps of HCPs' decision making, from detection of potential ADR incidents to plans and actions they took to resolve incidents. The study illustrates the cognitive complexity of the work conducted by HCPs

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when resolving ADR problems. Our findings point to four important implications, discussed below, to develop novel clinical decision support systems that more closely align with HCPs' cognitive workflow.

1. Develop technologies to facilitate communication between HCPs and patients regarding ADRs. Detecting potential ADRs requires *identifying* patients' signs or symptoms that may be related to a drug [20]. For ADR alerts to work more efficiently, EHR systems could collect reliable information about patients' signs and symptoms, and then display and communicate that information. Therefore, patient-generated data, which is not a typical element of many current alerting systems, may play an important role in future decision support for ADRs [21]. Additionally, communication between HCPs and patients also plays an important role in resolving ADRs that are already occurring. In some cases, HCPs may help the patient set realistic expectations about the type and severity of symptoms. Throughout the course of ADR investigation and treatment, HCPs need to communicate closely with the patient, to share potential risks and benefits and engage patients in a shared decision-making process [22]. Topaz *et al.* study demonstrated that HCPs were more likely to override an alert for medications that patients are currently tolerating or have previously tolerated [23]. Indeed, communicating with patients about symptoms, medical history, etc. is an important element in HCPs' decision making. Such communication may occur not only through direct patient interactions but also indirectly through patient portals, secure messaging, and other telehealth technologies [24]. These modalities may also increase patients' access to care, facilitating patient-HCP communication to resolve ADRs.

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2. Incorporate confirmatory and disconfirmatory ADR cues into alerting systems. Rapid, accurate, and complete information is important to help detect and resolve ADR problems. Our study found that additional information ADR detection, such as the confirmatory cues and disconfirmatory cues, were important to assist HCPs with the ADR investigation process. HCPs used these cues to organize and assemble a constellation of information in a form that is meaningful for sensemaking. This concept is known as knowledge-base cognitive mode [25]. Subsequently, EHR alerts systems for ADRs should align with a knowledge-base cognitive mode by including important cues while filtering distracting information to optimally help HCPs with clinical decision making. Since ADR alerts detect potential ADRs from symptoms and abnormal lab results, confirmatory and disconfirmatory cues provided by the alerts could allow HCPs to confirm the alerts' trustworthiness and avoid overlooking alerts. In fact, a study on drug allergy alert-overrides showed that providers were more likely to override alerts derived from non-important cues [23]. Our findings, in combination with those results, highlight the importance of providing cognitive cues to assist HCPs with decision making.

3. Design alert systems that account for negative cues: The absence of certain cues, known as negative cues, is another important factor for decision making. HCPs are aware of this absence of information based on familiar perceptual patterns. For example, one experienced provider in our study described how s/he confirmed that a patient did not have a myocardial infarction (Table 2, case B7). Although the patient reported a burning chest sensation, the patient did not have other symptoms such as numb fingers, arm pain, or diaphoresis. The absence of the companion symptoms was reassuring, allowing the provider to focus on other potential causes of the symptoms, such as a potential ADR with abiraterone. This type of negative cue is often

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overlooked in technology-centric design but is a critical component of decision making, especially during the evaluation of potential ADRs. Complex algorithm development that includes negative cues could advance decision support and help HCPs better detect and investigate potential ADRs.

4. Advance alert information to better support HCPs' risk-benefit evaluation: Our ADR decision-making model (**Figure 2**) underscores that even when an ADR is confirmed, HCPs still need to evaluate the medication's risks and benefits. Existing medication alert systems identify potential problems but the information they provide is often insufficient to help HCPs weigh risks and benefits of the problematic medication. As a result, HCPs seek information from drug references, colleagues, and other sources. Indeed, ADR alert design without consideration of risks vs. benefits is likely to "fail" (be overridden) in many instances. For complex risk-benefit evaluation, ADR alerts should provide quick access to a comprehensive list of risks and benefits, or corresponding sections of drug information resources, to help HCPs make a sound clinical decision [13].

This study has several limitations. First, we interviewed only physicians and pharmacists regarding ADRs, since incident submissions from nurse practitioners were low. Nurse practitioners, registered nurses, and physician assistants, also interact with patients and play important roles in ADR decision making, warranting further research. Second, we were not able to directly compare the decision-making processes of physicians and pharmacists, because the variation in incidents precluded direct comparisons (e.g., involved different medications or patients with varying medical conditions). Third, we examined incidents from a single large V.A.

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medical center and EHR system. Our findings might not always apply to other settings. Fourth, all incidents collected and analyzed were voluntarily provided by HCPs. This could influence our findings, because HCPs might be more inclined to submit incidents for which they felt most confident in their handling of the ADR; thus, incidents that created even greater challenges or uncertainty for HCPs as they resolved ADRs may have not have been captured. Fifth, most incidents we studied, especially those from physicians, were obtained from outpatient care. Thus, our results might not always apply to inpatient settings. Finally, we were not able to fully incorporate two incidents (Table 3. Physician #8 and Pharmacist #10) into our decision making model. Unlike other incidents, these two incidents focused on prevention of an ADR instead of resolving suspected ADRs. Further research is needed on HCPs' decision-making with respect to ADR prevention.

Our study findings have several practical applications. The ADR decision-making model we developed through this research has important implications for the design of clinical decision support. This model could be used as the foundation for a novel ADR alert system to support HCPs in recognizing and resolving ADRs. Evolving alert systems by applying this model is anticipated to increase the cognitive support of alerts for HCPs, which subsequently can improve medication safety outcomes for patients. In addition, the ADR decision-making model is expected to be valuable for teaching medical and pharmacy trainees about the decision-making process for ADR mitigation.

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CONCLUSION

This is likely the first study to identify the decision-making processes of HCPs when they detect and resolve potential ADR incidents. The ADR decision-making model developed from this study consists of four important stages: problem detection, investigating the cause of the problem, consideration of risks and benefits, and plan, action, follow-up. This model is expected to be valuable for alert system designers as well as educators who are training future physicians and pharmacists about ADR decision-making. Our findings have four key implications for clinical decision support systems: develop technologies to facilitate communication between HCPs and patients to better detect and address ADRs; incorporate confirmatory and disconfirmatory cues into ADR alerting systems to more closely align with cognitive strategies from HCPs; design alert systems that account for negative cues to further facilitate decision making; and enhance alert system displays to better support HCPs' risk-benefit evaluation process for ADRs. The design of supporting technologies for potential ADR problems should align with the real-world cognitive strategies of HCPs in order to achieve the best health outcomes for patients.

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Figures and legends

Figure 1. Overview of the study procedure. Four main steps are shown in the illustration.
Abbreviation: ADR: adverse drug reaction

Figure 2. Adverse drug reaction decision-making model. The model has four stages.
ADR: adverse drug reaction.

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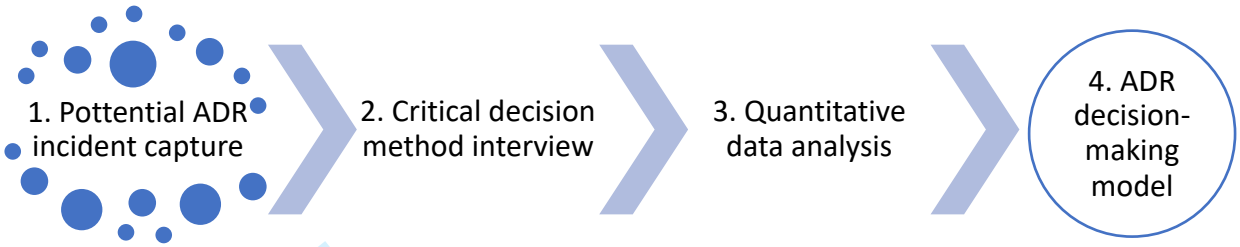

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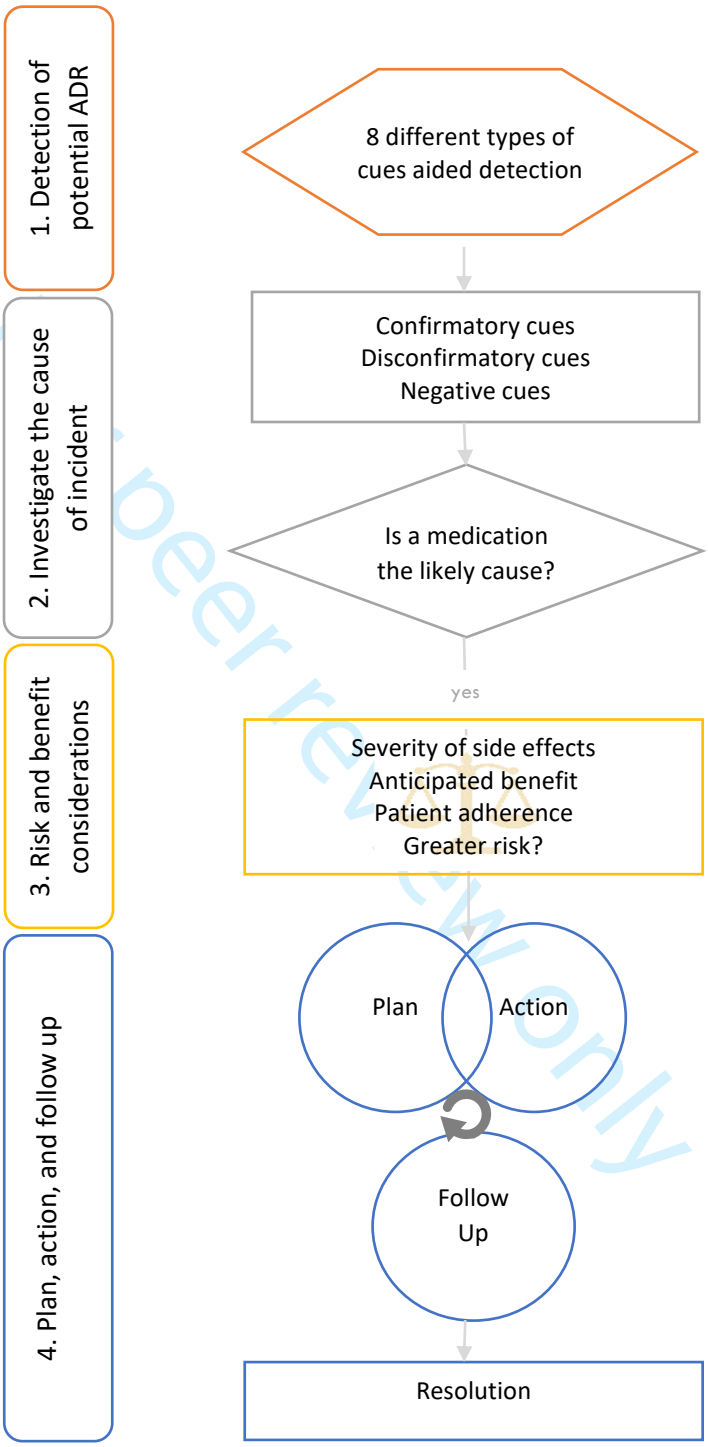
Figure 2: Adverse drug reaction decision-making model. The model has four stages. ADR = adverse drug reaction.



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Supplemental documents

Appendix A. Sample of decision requirements table					
Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that nonexperts may tend to make*	**IT Design Seeds**
1. Assessing the pt	I had only seen pt one other time. 66	Pt was referred to me for cholesterol follow-up; pt appointment with me. 52 B/c of pt's risk factors, pt needs to be on moderate to high intensity statin, which is why Dr put pt on atorvastatin. 38 Pt taking atorvastatin 20 mg daily. 120	BEFORE the visit: a. I have an excel spreadsheet that I created from the guidelines that calculates the ASCVD score. [treasure map!] Calculated ASCVD risk score to determine what intensity of statin med pt needs. it aggregates like the risk like their age, their sex, their race, what their baseline cholesterol levels are, if they have high blood pressure, what their blood pressure was, like it just calculates smoking and whether or not they have diabetes and "spits out a number at you". I calculate this before the pt walks in the room. 433 [AI: This is used by many pharms and was created in-house. They can use if internet goes down.] b. I went back [in CPRS] and looked at all his cholesterol results in the past to see	[AI: Home grown ASCVD calculator/treasure med may not hold up in a court of law. Could be programming glitch. Also, is code editable? Will not get auto-updated like the internet version should if something changes with the calculation.]	Integrate ASCVD calculator into EHR and/or decision support/med selection process in CPOE.

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Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that non-experts may tend to make*	**IT Design Seeds**
			how high his cholesterol been. c. I look for:pt's response to meds, to see if dose increase is needed. Was there a 50% reduction in cholesterol – aim from the guidelines. 714		
2. Recognizing a potential medication issue	"I was surprised" [that it actually turned out to be atorvastatin] b/c: 272 a. "I hadn't had anybody complain of diarrhea with atorvastatin before, so it was a new side effect for somebody to complain about." b. simvastatin also is for cholesterol, is related to atorvastatin – mechanism of action is the same- but simvastatin causes more constipation, so diarrhea was a surprise [opposite of what would expect with atorvastatin] 278 Sometimes meds in general can 'go either	I asked pt if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med/since last visit. 84, 29			

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Appendix A. Sample of decision requirements table					
Decision or Judgment *made by the expert; often end in 'ing'*	**Why Difficult?** *Reasons difficult for the expert or could be difficult for those with less experience*	**Cue (Source)** *Cue: salient info/signals applied when making a decision (Source: where information came from that was used to make the decision)*	**Strategies** *Used to make the decision and the actions that were taken to address the decision*	**Potential Errors** *Errors that could occur or that non-experts may tend to make*	**IT Design Seeds**
	way" – cause diarrhea OR constipation. 510. sometimes people are just prone to one side effect versus another. 533				

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Appendix B. Adverse drug reaction codebook		
CODE	**DEFINITION**	**Example of Coded Item (Cue)**
I. Problem Detection Related Decision Points:** - Assessing the pt - Deciding what drug to prescribe for treatment - Recognizing an abnormal lab value. - Recognizing a potential medication issue - Assessing the appropriateness of the medication order or regimen - Receiving the handoff about a potential medication issue - Reviewing the handoff [consult]	**Cues** that 'flagged' an initial concern and helped the participant notice a potential safety issue. These can be external information and sources; internal cues (feelings), others pointing something out to the participant, etc.	**Do NOT code at this level**
Lab values	**Cue definition**	**Example**
1.a Abnormal lab	lab value outside of normal range	"…her platelets you know were 66 and that is not normal."
Medication Characteristics	**Cue Definition**	**Example**
1.b New Med	medication that was recently prescribed or the patient recently started taking	I asked patient if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med. 84_29
1.c Common cause of ADR	medication is suspected as a potential problem b/c participant knows the ADR is often due to this med	Heparin is [the] most common med to cause thrombocytopenia
Patient information	**Cue Definition**	**Example**
1.d Symptoms	symptoms, directly or indirectly related to the ADR	I asked patient if he was taking the atorvastatin. Pt: yes, and have had a lot of diarrhea since starting the med.
OTHER	**Cue definition**	**Example**
1.e Tipped off to potential ADR	another healthcare professional or the patient already suspected an ADR and notified the participant	PACT RN [asked me] "what do you want to do with this patient? It looks like he had this adverse reaction to this medicine"
1.f Unknown Problem Detection	cues that helped the provider initially detect the problem could not be clearly discerned from the case	

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1.g Computerized alerts	Any kind of alerts related to ADR; also known as "order check"	
2. Investigating the cause of the problem **[Investigate]** Related decision points: - Determining the symptoms were NOT medication-related. - Is there a medication-related problem? - Investigating the cause of the problem (non-med causes, lit, colleagues) - Determining the cause of the medication-related problem Determining this is a medication-related problem	Additional information gathering, assessment, hypothesis testing	**NO coding at this level**
2.a Reasons and strategies for investigating	reasons the participant spent time investigating and what specific type of information they were seeking; (excludes reasons why they think there is an ADR – that goes under 'problem detection') Types of strategies used, labs ordered, resources used, etc to look into the problem	To make sure diarrhea wasn't due to another medication, I verified that nothing else had changed for pt since last visit [in terms of meds] 190 (3d) [MD Residents] Ordered confirmatory tests. 78: a. heparin antibody b. Serotonin release assay (SRA) 101, 557 (18c)
2.b Confirmatory cues	Information and other cues that suggested the specific med may be causing the ADR (med-ADR relationship)	I concluded diarrhea due to atorvastatin, not non-med issue b/c pt had more problems when taking the medication more often…190, 209 (3d)
- 2.b.1 Negative confirmatory cue	The absence of something is a cue for the participant that points to the suspect medication.	Pt not on many meds [or many others that could cause HIT, except heparin]. (18c)
2.c Disconfirmatory cues	Information and other cues that suggested the specific med may NOT be causing the ADR (Different than a 'negative' cue that means a lack of something is a cue.)	"It's [thrombocytopenia] usually something else, not the Heparin, but we always stop the Heparin until we know for sure." 551 (18c)

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- 2.c.1 Negative cue that is disconfirmatory	Noticing the absence of something is a cue for the participant and points AWAY from the suspect medication. (Excludes looking up something intentionally and finding the answer is no)	[no examples yet…?]
2.d Ambiguous/ Dual meaning cue	Cue that not clearly confirmatory or disconfirmatory Participant unclear if cue point toward or away from ADR	My initial concern was that maybe this was just her normal muscle cramps (pt Hx) (112-113)
3.Plan/Action/Follow-up [PAF] [all other decision points]	DEFINITION (propose your own, below) actions taken to address and/or follow up on the safety concern	NO coding at this level
3.a Stop Med	Cues, strategies, actions, related to a decision that the suspect ADR-related medication needs to be discontinued.	Check in CPRS to see if Lisinopril was discontinued. 499 (7b) Told RN: • Have pt throw Lisinopril away so doesn't accidentally take. 373 • stop Lisinopril, tell pt not to ever take again. 325 (7b)
- 3.a.1 Negative Cue related to stopping med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586
3.b Hold Med	Cues, strategies, actions, related to a decision that the suspect, ADR-related medication needs to be put on hold or the start of a new medication treatment needs to be delayed.	"Normally, if pt has HIT, we would initiate meds for direct thrombin inhibitors to anticoagulate the pt b/c HIT increases risk of clots. 121. Decided NOT to do that [immediately] for this pt. Instead, delayed start of bivalirudin until 3 days…" (18c)
- 3.b.1 Negative Cue related to holding med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586

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3.c. Change to new med	Reasons, cues, strategies, actions, related to a decision that the medication needs to be changed. This does NOT include the dose of the new med: that goes in the sub-code below This includes aspects that helped them make the choice of the alternate medication or treatment (surgery), as well as other options they considered for now or in the future. This also includes reviewing the patient's ADR/medication history to inform a decision about the new medication. (EXCLUDES renewals of the exact same prescription)	We switched pt back to simvastatin and stopped atorvastatin. 46 (3d) If the pt's cholesterol would have been higher [around 120] I would have: a. Rxed Crestor (rosuvastatin) has high intensity at higher doses. [switched pt to higher intensity med that the pt hadn't tried yet], but Crestor is non-formulary med and requires special consult/approval. 723 (3d)
- 3.c.1 Negative cue related to change to a new med	Noticing the absence of something is a cue for the participant	Pt doesn't have diabetes. (CPRS review). 586
- 3.c.2 Dose Selection	Cues and strategies that helped the participant determine what medication dose to use, how to change the dose, etc	I Rxed 40mg daily of simvastatin to get equivalent potency as 20mg atorvastatin. 132
- 3.c.3 Risk/Benefit	Consideration of the risk and benefits (or pros and cons) of one or more treatment options	PharmD (participant) recognizes limitations of ASCVD calculator and is able to recognize when other risk factors may need to be considered like family history (633):
3.d ADR documentation	Cues, reason, and strategies related to documenting or not document the ADR, including information documented, double-checking/confirming it was documented, reasons for documenting etc.	Check in CPRS to see if ADR entered. 512 (7d)

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3.e Pt counseling	Counsel, inform patient regarding new action/plan Includes direct communication with patient, checking to see that key information has been communicated to patient, or instructing someone else to communicate with patient.	made sure patient's discharge instructions included verbiage related to patient stopping lisinopril Told RN: • Have pt throw Lisinopril away so doesn't accidentally take 373 • stop Lisinopril, tell pt not to ever take again. 325 • we will replace Lisinopril with something else. 81 • give pt a list of all other meds in same [drug] class [as Lisinopril] and tell pt not to ever take any of these. 228, 325 • have pt check BP at home/ keep log. 385 have pt come in 2 weeks for BP check 331
3.F Follow –up/Monitor	Follow up after certain change Ex: BP, lipid panel, cholesterol Includes follow up by interviewee or by other member of the healthcare team Reassess pt on certain measurements Includes cues, strategies, reasons, and actions related to follow up	Check pt's BP 2 weeks after D/C b/c: • allows pt to recover after hospitalization • let's BP stabilize on altered BP med regimen (now HCTZ only; and get rid of Lisinopril in system which can lower BP). 754, 962 • -gets steroids out of pt's system before checking BP again, since they elevate BP. 754 • 2-4 weeks is acceptable range in my assessment. 766 If pt had NOT been given steroids, see back sooner, around 1 week. 962
3.G Continue the med	Reason, cue, strategy for continue current med. This includes aspects that helped them make the choice of the alternate medication or treatment (surgery), as well as other options they considered for now or in the future. This also includes reviewing the patient's ADR/medication history to inform a decision about the continue the medication	
3.g.1 Dose selection	Cue and strategy for choosing a new dose (increase or decrease the dose) to improve tolerance	Decided to have pt try low potency capsaicin again at 3x/day

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