Study protocol: a mixed methods evaluation of health system responsiveness to FDA psychotropic medication warnings

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Abstract

Background: Recent United States Food and Drug Administration (FDA) warnings and medical association guidelines focus on potential health risks associated with psychotropic medications, suggesting modifications for clinical practice. The US Veterans Affairs Pharmacy Benefits Management Services (VA PBM) is responsible for initiating VA responses to FDA warnings. Despite VA PBM's use of several approaches to disseminate warnings throughout VA, much remains unknown about the multiple contextual and organizational factors influencing responsiveness to these warnings. A better understanding of VA system and provider level responsiveness could lead to developing and sharing best practices and informing future strategies to improve warning adoption, thereby improving patient care and population safety.

Objectives: Given that considerable VA facility-level variation exists in psychotropic prescribing practices, the overarching goal of this study is to examine multilevel responses to external warnings regarding psychotropic medications.

Methods: Using both qualitative and quantitative methods, we will evaluate multiple factors that could influence facility and provider responsiveness to warnings. We will detail the processes by which VA prescribing policies and guidance were developed, how dissemination was accomplished, and perceived barriers and facilitators to adoption across the system. We will employ segmented regression techniques using administrative data pre- and post-warning to identify changes in psychotropic medication prescriptions and patient health monitoring in VA by VISN and facility. We will detail processes by which facilities and providers changed practice in response to warnings and PBM dissemination efforts.

Discussion: This study's impact derives from its ability to overcome weaknesses of previous studies by bringing together unprecedented data resources, qualitative and quantitative methods, new applications of organizational theories, and diverse investigator expertise. This work could improve clinical care and patient safety, directly benefiting VA practice and patients.

Keywords: pharmacy, FDA warnings, citalopram, zolpidem

BACKGROUND

Public health policy, in the form of laws, regulations, and guidelines, has a profound effect on population health.[1] In the United States, Food and Drug Administration (FDA) warnings are common; FDA issued over 60 drug safety communications in 2011 alone.[2] It is critical to evaluate warnings to understanding their impact on community and individual level behavior and patient health outcomes. To effectively conduct policy dissemination research within an organization, it is important to understand the responses of participants at multiple levels. This study uses the Veterans Affairs health system (VA) as a case study to identify how health systems respond to external patient safety communications such as FDA warnings. Within a large integrated healthcare system, such as the VA, a timely and systemic response to an FDA warning can have a significant impact on patient health and safety.

Previous studies have assessed methods of improving medication safety through effective risk communication, assuming that appropriate communication strategies can positively influence prescribing practices. Although distribution of educational materials is a frequently used approach, it is not effective as a stand-alone intervention to achieve behavior change.[3] Audit with feedback interventions have had limited positive results.[3,4] Educational outreach visits (i.e., academic detailing) have consistently demonstrated a small but significant impact on provider behavior.[5] When choosing a strategy, it is necessary to strike a balance between needing to disseminate warnings broadly and quickly, and the need to employ an approach likely to be effective in leading to prescriber behavior change. This study will help inform best practices associated with risk communication, which could ultimately improve prescribing practices and patient outcomes.

To date, warning implementation has been mixed at best, with many such policies having minimal impact.[6,7] In a recent systematic review of 49 studies including 16 medications (more than one third of which were focused on potential suicidality associated with antidepressant use), Dusetzina et al found that most warnings modestly decreased medication use and led to short term increases in monitoring.[6] Repeated warnings had larger but delayed effects and decreased incident more than prevalent use.[6] Briesacher et al found that many studies evaluating warnings suffered from substantial methodological limitations, such as lacking evaluations of patient outcomes and use of comparison groups.[7] Dusetzina et al and Briesacher et al each highlighted the limited qualitative data incorporated in these studies,[6,7] as almost all relied only on administrative data.

Given limitations and gaps in knowledge associated with prior research, the overarching goals of this study are to identify and understand health system responses to warnings for psychotropic medications, examine factors associated with higher and lower levels of responsiveness, and to use these insights for quality improvement. We seek to understand variation in adoption of warnings, and the effect of varying levels of clinical integration between pharmacists and prescribing providers on responses to warnings. We will use two examples of recent warnings for psychotropic medications: 1) sudden cardiac events associated with

high doses of the antidepressant citalopram [Celexa];[8,9] and, 2) impaired driving associated with zolpidem [Ambien], a sedative hypnotic medication.[10,11]

This is a national and comprehensive yet exploratory study. Although definitive hypotheses may be premature, we expect that greater integration among clinical pharmacists, PCPs, and psychiatrists will be associated with greater responsiveness to warnings. We anticipate that appropriate decreased use of target medications, increased substitution, and effective monitoring will vary by facility, thereby unevenly generating potential patient safety risks. Methods developed in this novel, mixed methods, longitudinal study will be applicable to a broad range of medication use policies and pharmacosurveillance. This study will overcome major methodological limitations of prior studies by using strong quantitative methods coupled with qualitative data, which provides a unique opportunity to characterize strategies associated with successful response to warnings regarding psychotropic medication safety.

VA Pharmacy Benefits Management

The VA Pharmacy Benefits Management (PBM) is a national leader in medication safety. The central function of PBM is to maintain a national formulary, and also has a key role in managing and improving access to national directives regarding medication use and safety, which is led by the VA Center for Medication Safety (VAMedSafe)[12,13]. One initiative VAMedSafe maintains to address medication safety is the web-based application for coordinating medication-use evaluation tracker (MUET), which was created to improve VA's ability to conduct national medication-related interventions throughout its network of 147 medical centers[14]. However, the VA does not mandate use of this system. VA PBM has also demonstrated a well-developed and multifaceted process for quickly responding to warnings, including interpreting their relevance for VA prescribing and patient care, and disseminating that information to VISNs, facilities, and providers. However, internal VA PBM data has shown that responses to these initiatives vary at the VISN and facility levels. It remains unclear how information regarding warnings is received by VISN and facility leadership and prescribers, and what actions, if any, take place as a result of these communications and programs. Thus, it follows that it is not known whether sending out bulletins nationally to individual medical centers is the most efficient, and appropriate means to alert providers, and more importantly, affect change, and whether and how academic detailing programs or MUETs can and will be implemented locally.

Conceptual model

Our work extends beyond simply seeking to identify systems of pharmacosurveillance. We will examine mechanisms for action by focusing on pharmacy clinical integration. We will use two interrelated conceptual models: a) integration of pharmacy and clinical care, and b) implementing and routinizing innovations such as warnings into care practices. We argue that organizational structure within which social norms are constructed includes system integration, which is linked to capability. Following the seminal work by Gillies et

al[15], we will examine clinical process integration, with a focus on the integration between pharmacy policy setting services, such as a single central VA pharmacy benefits management (PBM) committee, regional PBM committees (located in Veteran Integrated Service Networks or VISNs), individual VA facility Pharmacy and Therapeutics (P&T) committees, and providers prescribing psychotropic medications. We define integration as a multifaceted concept that includes: 1) existence of a group that is responsible for pharmaceutical policy within the organization; 2) degree of coordination between this group and providers who prescribe pharmaceutical agents to patients; 3) mechanisms of coordination; 4) perceived ease of coordination; and 5) perceived effectiveness of coordination.[16,17]

This work is developmental because it has not previously been addressed in the literature, as policy dissemination research is still developing as a field of inquiry.[1] A key source of heterogeneity in responsiveness to warnings derives from the interaction between the individual and the context in which the warning is being disseminated and implemented, and in which individuals need to act in order to effect change based on the warnings.

Candidate warnings

This study uses two psychotropic medication warnings to evaluate our research questions of interest and test our conceptual model: citalopram and zolpidem. We chose to focus on psychotropic medication safety for several important reasons. Medications are one of the mainstays of treatment for psychiatric disorders and are being prescribed more frequently over time.[18,19] These medications are widely and increasingly used.[20,21] There is also considerable variation in prescribing practices for psychotropic medication and dosing both geographically and by physician specialty.[22,23] Studying psychotropic medications is a particularly good opportunity to create generalizable knowledge about responses to warnings in part due to the high variation in clinical response to these medications and wide variation in side effects that patients experience[24] (compared to assessing warnings for medications with more narrow use and specified impact). These warnings are focused on potential health risks associated with psychotropic medications,[25] which are of increasing concern based on broad use and lengthening treatment periods.[26] Further, medications are ideal for studying the diffusion of changing treatment practices. Adopting new prescribing behavior does not rely on expensive technology or new resources. Thus, there are lower barriers to diffusion. PCPs and specialists often prescribe psychotropic medications, allowing study of provider and treatment setting effects. Although there may be relatively low barriers to adoption, there is still uncertainty about how systems and providers respond to recommendations. See **Appendix 1** for the two case studies: 1) cardiac risks and citalopram, and 2) zolpidem and driving.

Table 1. Candidate warnings			
Drug (class) and adverse outcome	**FDA issue date**	**PBM communication date**	**Action**
Citalopram and cardiac events	08/2011[8]	*08/2011[27]	The antidepressant Celexa (citalopram) should no longer be used at doses greater than 40 mg per day because it can cause abnormal changes in the electrical activity of the heart.
		09/2011[28]	
	03/2012[9]	04/2012[29]	The maximum recommended dose of citalopram is 20 mg per day for patients older than 60 years of age.
Zolpidem and driving	01/2013[10]	**01/2013[30]	FDA recommends that the bedtime dose be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. The recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products and from 12.5 mg to 6.25 mg for extended-release products. For men the labeling should recommend that health care professionals consider prescribing the lower doses--5mg for immediate-release products and 6.25 mg for extended-release products.
	***05/2013[11]	No new communication	The recommended initial dose of immediate-release zolpidem products is 5 mg for women and either 5 mg or 10 mg for men. The recommended initial dose of zolpidem extended-release is 6.25 mg for women and either 6.25 mg or 12.5 mg for men.
* cited in Ez Minutes 08/2011-11/2011, Medication Safety in Seconds 09/2011 and 10/2011; ** cited in Ez Minutes 11/2012-01/2013, 02/2013-04/2013, Medication Safety in Seconds 01/2013, 02/2013; ***cited in Medication Safety in Seconds 06/2013			

Research study aims

The research study design will be a mixed methods approach. We recognize that system integration can operate across entire health systems, regionally, within individual facilities, and at the individual provider level. In Aims 1 and 3 we will conduct theory-based implementation interviews [31,32] with leaders at three organizational levels: national PBM, VISN PBM, and facility level leaders to elucidate opportunities and difficulties associated with responsiveness to warnings.[31,32] The interviews will focus on warnings in general and our chosen two cases (**Table 1**). In Aim 3B, we will conduct exploratory, brief surveys of front-line pharmacists and prescribing providers to assess their awareness of and responsiveness to these warnings. The choice of facilities and sampling of providers for Aim 3 will be informed both by Aim 1 interviews and quantitative analysis findings from Aim 2.

Aim 1. The first aim is to assess and describe PBM and VISN-level responsiveness and variation in responsiveness to warnings regarding psychotropic medications.

Aim 2. The second aim is to assess prescribing patterns before and after warnings regarding psychotropic medications.

Aim 3A. This aim is to understand strategies used by facilities with high response to warnings and barriers in facilities with low response to warnings.

Aim 3B. This exploratory aim is to identify strategies used by providers in facilities with high response to warnings and barriers encountered by providers in facilities with low response to warnings.

METHODS

In this section, we describe the evaluation aims, study participants/patient populations, data collection methods, and analysis plans for each study aim. This mixed methods study includes theory-based semi-structured interviews and surveys, and interrupted time series (ITS) analyses.

Aim 1. This aim will detail processes by which VA prescribing policies and guidance were developed at the national and VISN levels for the two psychotropic warnings, how dissemination was accomplished, and perceived barriers and facilitators to adoption across the VA, based on semi-structured interviews with national VA PBM leaders and pharmacy leaders at each VISN (N=21) at the time of the warnings. This aim focuses on VISN level organizational factors and integration of pharmacy services into clinical care.

Interviews and participant selection. Aim 1 will use semi-structured interviews with national PBM leaders and VISN PBM leaders to examine factors influencing responsiveness to warnings in general and the two cases. Interviews will be semi-structured, with questions about the warnings covering key constructs from our conceptual model using Gillies et al. We will identify key informants in the national VA PBM office, to participate in interviews. Based on our preliminary discussions with PBM staff, we anticipate that we will interview five to six individuals at PBM. The interviews with PBM officials will focus on their knowledge of VISN level coordination of pharmaceutical services, and the degree to which this is focused on quality of care and patient safety. We will ask PBM staff to identify individuals in each VISN who are responsible for pharmacy policy at the VISN level. We will also ask PBM staff to send a letter to the VISN pharmacy leaders to inform them about our study and recommend participation when we contact them for interviews.

Data collection. We will ask PBM and VISN participants open-ended questions about the integration of pharmacy and prescribing focusing on the five key constructs described by Gillies et al: 1) existence of a group that is responsible for pharmaceutical policy within the organization; 2) degree of coordination between this group and providers who prescribe pharmaceutical agents to patients; 3) mechanisms of coordination; 4) perceived ease of coordination; and, 5) perceived effectiveness of coordination. Pharmacy and Therapeutics (P&T) Committees are organized throughout VA, but we expect that how they function,

the scope of their purview, and the degree to which they can support action on warnings varies across VISNs and facilities. We will conduct each of these telephone interviews with two interviewers, one who guides the interview using the semi-structured interview guide, and the other who takes comprehensive notes during the interview. Interview notes will be detailed and rich, and developed by both interviewers. See **Appendix 2** for the VISN-level interview guide.

Qualitative analysis. We will code the interview notes into a coding framework based on Gillies et al.'s integration framework. We will code comments that do not fit into the existing framework into new categories. Two coders will code each transcript independently, and we will discuss all discrepancies in regular study team meetings. We will conduct concurrent analysis as interviews are conducted to ensure that we are current with themes emerging from the analysis, and to assess degree of saturation, which we define as no new substantive themes detected in additional interviews.

A primary initial goal of our qualitative analysis will be to derive a quantitative variable measuring clinical process integration related to pharmaceutical policy and prescribing practices for each VISN. To accomplish this, we will assess the five key constructs from Gillies et al. Our full research team will rate each VISN using a scale of 0=absent, 1=limited, 2=adequate, 3=outstanding for each category, then sum ratings across categories to derive a final score for each VISN. We will use the final summative rating for each VISN as the clinical integration variable covariate in the ITS analysis in Aim 2. Beyond creating this summative rating, this information can be used to identify specific areas that are essential for VISN responsiveness to warnings or are particularly vulnerable to breakdown.

Use of Aim 1 findings. In addition to important and policy relevant findings gleaned from national VA PBM and VISN interviews (**Aim 1**), findings will be used to inform the selection of facilities for interviews (**Aim 3A**) and providers for surveys (**Aim 3B**). **Aim 1** data will also be used as a key covariate in **Aim 2** analyses.

Aim 2. This aim will use segmented regression techniques using administrative data pre- and post-warning to identify changes in psychotropic medication prescriptions and patient health service use in VA by VISN and facility. Aim 2 will assess the impact of the two warnings on prescribing practices and clinical outcomes and monitoring. The warnings created conditions of natural experiments including comparison groups (individual agents or groups of agents not subject to the warnings). We will use VA patient pharmacy and health service use data. We will use interrupted time series (ITS) analyses to assess facility level variation in responsiveness to warnings. Those findings, in combination with findings from **Aim 1** interviews will inform the selection of VISNs within which we will conduct facility level interviews (**Aim 3A**) and provider surveys (**Aim 3B**).

We expect decreases in the medication use post-warning and either no changes or increases in use of comparison medications (**Table 2**). We also anticipate that in VISNs with greater clinical pharmacist integration defined by the integration scale score from **Aim 1**, there will be more systematic responses to external clinical recommendations, more effective implementation, more monitoring, and more changes in delivery than in VISNs that are less well integrated, derived based on the scoring system used to code interview responses. Our primary outcomes (first-order effects) will be rates of initiation and continuation of each medication of interest, pre and post warning. Secondary outcomes (second-order effects) will be rates of physician visits and other relevant clinical monitoring, pre and post warning. The key explanatory variable will be the interaction between time and warning, and secondarily an indicator of integration.

Table 2. Target and comparison medication groups‡	
Citalopram	**SSRIs**: fluoxetine**, paroxetine**, sertraline**
	Other antidepressants: bupropion, venlafaxine***, mirtazapine***, nortriptyline
Zolpidem	**Sedating antidepressants**: doxepin, trazodone, amitriptyline, nortriptyline, mirtazapine
	Antipsychotics: quetiapine
	Benzodiazepines: alprazolam, clonazepam, diazepam, lorazepam, temazepam
	Eszopicone
* indicates medications with risk of QT prolongation (which will also be assessed in a separate analysis compared to citalopram)[33] ** conditional risk; *** possible risk; ǂ we will include another comparison group for both citalopram and zolpidem	

Patient population. We will examine use, and changes in use, of two target psychotropic medications in patient samples that meet criteria for observation periods, cohort identification, and will also conduct sensitivity analyses. Multiple samples across primary, sensitivity, and subanalyses will be used, drawn from an overall VA patient population of roughly five million patients per year, with 91% male, 43% age 65+, 4% Hispanic, and 21% non-white patients. Based on preliminary data, we anticipate that there will be >340,000 patients per year taking citalopram (>300,000 with high dose use) and >250,000 per year taking zolpidem (>25,000 with high dose use), with variation in the number of patients using each medication over time.

Table 3. Observation periods					
Warning	**Cohort definition**	**Pre-period starts**	**1st warning**	**2nd warning**	**Post-period ends**
Citalopram	Citalopram use	08/2010	08/2011	03/2012	03/2013
Zolpidem*	Zolpidem use	01/2012	01/2013	05/2013	05/2014
* we will add an early warning period in sensitivity analyses for zolpidem given that VA PBM implemented its own program to decrease zolpidem doses in 06/2007, therefore, an early warning period will start in one year prior in 06/2006					

Observation periods. Study periods will include 12 months prior to the first of two warnings for each medication and conclude 12 months after the second of the two warnings per medication (**Table 3**), using monthly prescription rates. Continuous VA users, defined as at least one VA encounter per year during the

relevant study periods, with fewer than 30 days in an institutional setting (e.g. nursing home) during the study period will comprise the inclusion criteria. The observation period will begin when patients first meet criteria for cohort identification and for new, established, or comparison group medication use and will end either on: 1) the date of death, 2) two years following the last date of VA service use, or 3) the end of the observation period, whichever comes first.

Cohort assembly and analysis of drug use patterns. User cohorts will initially be defined based on use among all patients with an outpatient prescription for the medications of interest. We will conduct analyses with any medication use and with high dose use (**Table 4**). Sensitivity analyses will include analyses restricted to patients with relevant diagnoses (depression for citalopram and sleep disorders for zolpidem[34]). For each analysis, we will broadly stratify patients according to primary diagnoses: mental illness (ICD-9 codes: 290-316), or no mental illness (excluding ICD-9 codes: 290-316). New users will be monthly rolling cohorts of individuals who had no prescription claims for a study drug in the 180 days prior to the index dispensing. Established (or prevalent) users will be monthly rolling cohorts of individuals who had filled at least one prescription for a study drug during the previous 180 days.

Comparison groups. Although we could examine changes in study medication use before and after warnings, our findings can be strengthened by using comparison groups, e.g. patients that were not subject to the warnings. For each warning, we will identify changes in use of other classes of medications typically used for the same clinical condition. Target and comparison medications are presented in **Table 2**.

Dependent variables. We will assess outcomes (Table 5) to examine drug use patterns before and after the warnings. We will use pharmacy data to construct indicators of drug availability using the days' supply field, as this information is often complete and highly stable.[35,36] We will include information on all prescriptions filled, including doses, medication changes, and refill gaps. The study team has extensive experience using pharmacy claims for policy evaluations.[37-40] Unless otherwise noted, each outcome measure will be assessed monthly for each warning. Days supplied of study medication dispensed will be documented before and after the warning. Medication initiation will be estimated as the proportion of the denominator population who initiated a study drug (once an individual initiates treatment, s/he will be removed from the denominator for the subsequent months). Medication continuation will be assessed to see if individuals continue the drug therapy for three, six, or twelve months. Use of non-medication services will be assessed using inpatient and outpatient claims data as both indicators of monitoring activity (physician visits) and potential unintended negative outcomes associated with medication changes (ER and inpatient use).

Table 4. Cohort identification diagnoses, outcomes monitoring, and sensitivity analyses (excluding pre-existing diseases)		
Warning	**Purpose**	**ICD-9 or CPT codes**
Citalopram	Cohort	any outpatient citalopram use; any high dose outpatient citalopram use
	Monitoring	cardiac (e.g. EKG): 9300, 93005, 93010, 93040, 93041, and 93042
	Sensitivity analyses	Restricting to patients with depression diagnosis: 293.83, 296.2, 296.3, 296.90, 296.99, 298.0, 300.4, 301.12, 309.0, 309.1, 311; further restriction to major depression diagnosis: 296.2, 296.3; excluding patients with pre-existing: myocardial infarction 410, 411.0, 411.1, 411.81, 412, 414.2, 414.8, 429.7, 429.71, 429.79; congestive heart failure: 428.9, 429.1, 402, 402.0, 402.00, 402.02, 402.1, 402.10, 402.11, 402.9, 402.90, 402.91, 404, 414.19, 425.4, 428, 428.0, 428.1, 4282, 428.20, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40, 428.41, 428.42, 428.43, 428.9, 424, 997.1; arrhythmia: 427, 427.0, 427.1, 427.2, 427.3, 427.31, 427.32, 427.4, 427.41, 427.42, 427.5, 427.8, 42781, 427.89, 427.9, 4294, 997.1, V125.3; angina: 411.1, 413, 413.0, 413.1, 413.9
Zolpidem	Cohort	any outpatient zolpidem use; any high dose outpatient zolpidem use
	Monitoring	motor vehicle collision injuries: E810-E819.9
	Sensitivity analyses	Restricting to patients with sleep disorder diagnosis: 307.41, 307.42, 780.49, 780.51, 780.52

Stratification / independent variables. This study will include facility level demographic and clinical covariates, including age, sex, race, ethnicity, provider type, psychiatric service use, prior psychiatric hospitalization, and clinical integration as shown in **Table 5**. Although facility level characteristics will be available for all analyses, variable(s) indicating clinical integration within a facility and survey-based provider-related variables will only be available for VISNs included in Aim 3 analyses.

Descriptive and preliminary statistics. We will examine demographic and clinical characteristics of the study cohorts overall, by VISN, and by facility. We will use comparisons of means (t-statistics) and multidimensional contingency tables (χ^2) to examine cohort differences by VISN and facility with respect to independent variables (**Table 5**). We will examine unadjusted outcome differences by independent variables.

Table 5. Dependent and independent variables and data sources			
Type	**Variable**	**Description**	**Source**
	Days supplied†‡	Number of days for which the drug was supplied	VA Administrative Data
	Medication initiation†	Medication release data	
	Medication continuation‡	Medication continuation for 90, 180 days	
	Use of non-medication services†‡	Mean # of physician visits	
		% with ER visit	
		% with inpatient stay	
		% with psychotherapy visit	
		Cardiac monitoring ♦	
		Motor vehicle collision injuries Δ	
Stratification / independent variables	Sex	Male, female	
	Race	White, Black, Other, Unknown	
	Ethnicity	Hispanic, non-Hispanic	
	Age	18-60, 61+	
	Provider type	PCP, SMH, other specialty ▫	
	Psychiatric service use (e.g. consult)	Any, none	
	Prior psychiatric hospitalization	Inpatient stay in prior 12 months (Y, N)	
	VISN and facility characteristics	Rural/urban, region, academic affiliation	
	Clinical integration at VISN level	Ordinal variable constructed from qualitative analysis measuring degree of process integration between pharmacy and prescribing providers in a VISN	VISN interviews **(Aim 1)**
	Clinical integration at facility level ◊	Ordinal variable constructed from qualitative analysis measuring degree of process integration between pharmacy and prescribing providers in a VISN	Facility interviews **(Aim 3A)**
	Provider responsiveness ◊	Variable(s) constructed from provider surveys	Provider surveys **(Aim 3B)**
† assessed for new users; ‡ assessed for established users; ♦ citalopram only sensitivity analysis; Δ zolpidem only sensitivity analysis; ▫ based on VA clinic stop, for first prescription; ◊ variables available for secondary adjusted analyses only			

Primary adjusted analyses. We will conduct ITS analysis for citalopram and zolpidem (**Tables 2 and 4**), and each outcome (**Table 5**) separately. Outcomes[41] will be measured at 12 time points before the first warning (pre-warning period) and 12 time points after the second warning (post-warning period) as well as

the period between the two warnings. The pre-warning period data series will allow controlling for unmeasured facility-level differences. The assumption is that extrapolating the pre-warning level and trend correctly reflects the (counterfactual) outcome that would have occurred had the warning not happened. We will use segmented regression models[42] implemented using mixed effects model to estimate changes in outcome measures after selected warnings. The basic ITS model includes a constant term; an integer variable indicating time in months (t) from the start of the observation period; an indicator representing the time period after the 1st warning; an indicator representing the time period after the 2nd warning; and interaction terms between each post-warning period indicator and time. Each of the two cases includes two warnings. As shown in **Table 6**, β_1 controls for most internal threats to validity (e.g., history and maturation) by estimating the 12-month pre-policy trend in study outcomes.[43] Together, β_2 and β_3 provide an estimate of the policy effect of the first warning, controlling for baseline trends in the study cohort. Similarly, β_4 and β_5 provide an estimate of the policy effect of the second warning, controlling for baseline trends and trends following the first warning.

The model will include VISNs and facilities as random intercepts, with facilities nested within VISNs. Outcome measures will be modeled with autoregressive (AR) correlation of monthly data within facilities. Mixed effects regression models allow within-group errors to have an AR structure of order ≥ 1, and do not require first differencing. We will test whether first or higher order AR is more appropriate using likelihood ratio tests rather than the Durbin Watson statistic, which tests whether adjacent residuals are correlated.[44,45] To estimate a warning effect for each facility, we will fit a model with interactions of facility intercepts by the indicator for 2nd warning announcement, which will estimate facility specific differences between pre- vs. post-warning means. We will conduct analyses using each stratification variable (**Table 5**).

Secondary adjusted analyses. Secondary analyses will differ from primary analyses in the following ways: a) secondary analyses will be conducted in the subset of VISNs (N=3) that are selected for inclusion in **Aim 3A and 3B** for facility level interviews and provider surveys; b) secondary analyses will include additional variables (**Table 5**) based on findings from **Aim 3A and 3B**.

Sensitivity analyses. We will conduct sensitivity analyses among users of both medications to assess use of target medications that meet specific diagnostic criteria as outlined in **Table 4** and assess changes in medication use and monitoring among those with and without indications for use. For the citalopram warnings, we will construct a cohort excluding individuals with history of cardiovascular disease (CVD), using a monthly rolling cohort of individuals who had a CVD diagnosis during the observation period; the first observed diagnosis will be the index diagnosis. We will examine cardiac monitoring among new and established users including use of electrocardiograms. For the zolpidem warnings, we will examine whether patients had motor vehicle collision injuries. We will also conduct an analysis with a longer pre-period (e.g., an

early warning period, as in our prior research[46]), which was in response to VA PBM recommendations but before the FDA warning (**Table 3**). We will aim to assess whether the new eszopiclone warning influenced zolpidem prescribing. We will also assess use of non-medication services among dual coverage VA and Medicare patients.

Table 6. Model for Aim 3 analyses

$y_t = \beta_0 + \beta_1(time)_t + \beta_2(intervention_1)_t + \beta_3(time\ after\ intervention_1)_t + \beta_4(intervention_2)_t + \beta_5(time\ after\ intervention_2)_t + \beta 6(covariates)t + e\ t$

y_t	outcome variable at time t (see **Table 5** for all outcome variables)
time	number of months between pre-period and month t
intervention$_1$	0 for months up to 1st warning; 1 for 1st warning month and subsequent months
time after intervention$_1$	0 for months up to 1st warning, counts from 1 to X with 1st warning month through subsequent months
intervention$_2$	0 for months up to 2nd warning; 1 for 2nd warning month and subsequent months
time after intervention$_2$	counts from 1 to X with the 2nd warning month through all subsequent months
β_0	mean baseline estimate of outcome variable
β_1	estimate of slope prior to 1st warning (baseline trend during the first 12 months of observation)
β_2	estimate of level change immediately after 1st warning (policy indicator)
β_3	estimate change in slope (trend) following the 1st warning
β_4	estimate of level change immediately after 2nd warning (policy indicator)
β_5	estimate change in slope (trend) following the 2nd warning

Use of Aim 2 findings. In addition to the rich, detailed, informative national data provided in **Aim 2**, its quantitative data will be combined with interview data (**Aim 1**) as discussed above to select facilities and providers for **Aims 3A and 3B** respectively for further study. We will use **Aim 2** findings to categorize responsiveness by defining facilities with potentially actionable outcomes (> 1 standard deviation [SD] worse than national average), and strong practices (>1 SD better than national average) based on other VA reporting processes.

Aim 3A. This aim will detail facility processes for warning response. Interviews will be conducted with facility leaders (pharmacy, primary care, and mental health) who will be intentionally sampled based on Aim 1

and 2 findings. Degree of pharmacy integration into clinical care, and integration of psychiatrists and primary care providers (PCPs) in pharmacy policy, will be explored as facilitators.

Semi-structured interviews. We will conduct qualitative interviews with facility level leaders including the Chief Pharmacist, Chief of Primary Care Services, and Chief of Mental Health Services. These facility leaders should have the most knowledge of how structures and processes in their facilities have been designed and deployed to respond to warnings and new information about drugs and other therapies. As with the PBM and VISN level leaders interviewed in **Aim 1**, we will focus on critical features of integration affecting responsiveness to warnings, emphasizing key issues in clinical integration.

Table 7. VISN selection matrix for Aim 3*

	Low integration	**High integration**
Low responsiveness	1 VISN selected	0-1 VISN selected
High responsiveness	0-1 VISN selected	1 VISN selected

* Integration data come from Aim 1 (interviews), responsiveness data come from Aim 2 (time series)

Selecting VISNs for assessing processes and procedures within VISNs and facilities (Aim 3A). We will use data from VISN level interviews (**Aim 1**) and the ITS analysis (**Aim 2**) to select three VISNs for further study representing low, medium, and high degrees of integration as perceived by PBM staff and validated by VISN level pharmacy leadership, and by findings from VISN level quantitative analyses in **Aim 2**.

Using the score derived in **Aim 1**, and the degree of responsiveness to one of the two warnings in **Aim 2**, we will dichotomize at the median point of the distribution across VISNs for both factors. We will select one of the two warnings by assessing the amount of variation identified in **Aim 2** across VISNs and selecting the warning with more variation. We will classify all 21 VISNs into the 2x2 matrix in **Table 7**, and select one VISN from each of the low integration/low responsiveness and high integration/high responsiveness cells. We will then select one VISN from either the low integration/high responsiveness or the high integration/low responsiveness cells. Our rationale for selecting from both the low/low and the high/high cells is that these represent the ends of the joint continuum of integration and responsiveness to the warnings across VISNs. Choosing one from the two off-diagonal cells will allow us to understand issues faced by VISNs that are intermediary between these ends of the continuum. To keep the workload manageable, we will only select one VISN in the intermediate range.

Data collection. Similar to the semi-structured interviews with VISN level leaders, facility level leaders will be asked to describe structures for integration, such as committees or other groups focusing on pharmaceutical policy and practice, the degree of inclusion of prescribing clinicians, mechanisms or activities

in which the committee engages, ease and effectiveness of coordination, and specific actions related to these two warnings. We anticipate interviewing 50 to 60 individuals for this aim, assuming that there will be 6 facilities in each of the 3 selected VISNs, and we will attempt to interview 2-3 individuals at each facility.

Qualitative analysis. We will analyze the interview data using processes similar to those described for **Aim 1**. Our principal goal in this analysis is to understand structures and processes at the facility level that contribute to responsiveness to warnings.

Aim 3B (exploratory aim). This exploratory aim will identify strategies used by providers in facilities with high response to warnings and barriers encountered by providers in facilities with low response to warnings. Surveys will be completed by pharmacists, PCPs, and psychiatrists, who will be intentionally sampled based on findings from Aims 1 and 2. Provider factors that could influence responsiveness such as perceived degree of integration and ease of coordinating prescribing with pharmacy will be explored.

Provider surveys. The primary purpose of the exploratory survey is to understand, from a frontline perspective, barriers and facilitators to responding to the warnings. Barriers may range from lack of awareness of the warnings to lack of any supportive structures in the facility to help providers make informed decisions or contact affected patients. Facilitators may include structures like Pharmacy and Therapeutics (P&T) committees, facility level use of MUET or similar processes for alerting providers, and use of registries or other data-driven approaches to identifying affected patients and supporting providers in making optimal decisions.

Surveys will be brief, yet contain two parts. Part 1 will focus on the participant's personal experience with the target medications. Part 2 will focus on the participant's response to the patient information portion of the warning. Our primary focus will be on perceptions of system integration based on the Gillies et al framework, current prescribing practices, and real time reactions to warnings generally. We will pilot test the surveys and expect that they may be substantially revised based on findings from the multilevel interviews (**Aim 1** and **3A**).

Selection of providers to survey. We will randomly sample providers with each of the three selected VISNs, stratified by the three provider types. We anticipate surveying between 180 and 216 individuals for this Aim, assuming that there will be six facilities in each of the three selected VISNs. We seek to survey 1-2 practicing pharmacists, and at least 8-10 prescribing providers in both primary care and mental health. Surveys will be administered by email initial contact and a web link for survey completion.

Data collection. We will request names and email lists of all pharmacists, primary care providers, and psychiatrists in all facilities (both parent station and divisions, including CBOCs) in the three selected VISNs.

We will develop web-based surveys using Qualtrics or other web-based survey technology approved by VA at the time of study initiation. Assuming a 70% response rate, we will randomly select 150% of the number of responses needed from the three provider categories at each facility from the beginning of the randomly ordered list. We will send email invitations to all sampled providers, with a link to the survey web site, and requesting that they complete the online survey. We will send follow up emails two weeks after the initial email to all non-responders, and a final email two weeks after that. If the response rate is less than 70% two weeks after the initial email, we will send invitations to additional providers from the randomly ordered list for the provider type, where the number of additional invitations will depend on the response rate at that time.

Survey data analysis. We will analyze survey data descriptively to assess existence and frequency of barriers and facilitators, and we will use items from the survey as covariates in sub-analyses of the data used in **Aim 2** for the three selected VISNs, to assess the degree to which barriers and facilitators are significantly associated with provider responsiveness to the warnings.

DISCUSSION

This study brings together multiple unique data resources with an experienced, interdisciplinary research team poised to generate novel findings. The team has conducted several high impact, national, longitudinal studies of psychotropic medication use and warnings. Information gleaned from this study will be instrumental to policy makers and health systems seeking to understand the key ingredients of effective dissemination and implementation of pharmaceutical safety policies, which could assist in potentially preventing serious adverse events. This study provides an opportunity to conduct timely, policy and public health relevant research, providing new insights into the impact of warnings on patient care and outcomes. We are not aware of any other study that fuses the depth and breadth of data with the analytic techniques and study team proposed here.

Although this study has multiple strengths, there are some limitations. Regarding the qualitative methods, our approach uses rapid analysis approaches to coding the data, and follows an existing framework rather than deriving the framework from the data. However, we are using qualitative methods to explore a previously unexplored dimension of clinical integration, using existing frameworks. Regarding the quantitative methods, the proposed study is not an RCT, as it addresses a topic not amenable to that study design. Even though we capitalize on natural experiments and use comparison groups, patients prescribed medications targeted by the warnings may have pre-existing differences from patients using comparison medications in ways not captured by the independent variables. However, ITS models with comparison groups do not require identical baseline outcome rates because of the use of pre-policy observations to control for baseline trends. ITS allows for a greater degree of control for such factors than simple pre-post studies that do not

control for pre-warning trends or that omit comparison medication groups. Finally, although the VA has strong incentives to encourage within system health service use, particularly for medications, patients could have out-of-system utilization that we will be unable to capture. Based on our prior research,[47] we anticipate minimal out of system use for psychotropic medications, and we have added sensitivity analyses using linked VA and Medicare data to assess non-medication outcomes. However, we will not be able to capture other out of system outcomes (e.g., private insurance) or any out of system medication use. Finally, although we will conduct multiple sensitivity analyses, we cannot guarantee accuracy of sleep disorder or depression diagnoses or appropriateness of monitoring using administrative data, and sensitivity analyses may not fully address this limitation.

Conclusion

This project will generate qualitative and quantitative data on multilevel responsiveness to two warnings for psychotropic medications, and provide generalizable information regarding important factors influencing facilitators and barriers of responsiveness to warnings. It will lead directly to potential future work examining patient experiences with regard to learning about and responding to warnings, both among those currently using target medications as well as patients who may be considering treatment initiation. It could inform future planning for VA PBM, VISNs, and facilities for more widespread or mandated use of MUETs, academic detailing, greater pharmacist integration, modifications to electronic medical record and prescribing options, or other means of improving responsiveness to warnings.

DECLARATIONS

Ethics approval and consent to participate: This study was reviewed and approved by the VA Ann Arbor IRB. Our team received a waiver for written informed consent. Interview participants give informed consent by responding to the recruitment email.

Competing interests: The authors declare that they have no competing interests.

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Author's Contribution: AS and KZ conceived the design of the study, including the statistical analysis plans. AS, CS, and JH developed the interview guides and coding manuals.

REFERENCES

1. Dodson EA, Brownson RC, Weiss SJ. Policy Dissemination Research. In: Brownson RC, Colditz GA, Proctor EK, eds. *Dissemination and Implementation Research in Health: Translating Science to Practice*. USA: Oxford University Press; 2012:427-458.
2. Martin CM, Borgelt L. Black box warnings: what do they mean to pharmacists and patients. *The Consultant Pharmacist*. 2012;27(7):482-492.
3. Lu CY, Ross-Degnan D, Soumerai SB, Pearson SA. Interventions designed to improve the quality and efficiency of medication use in managed care: a critical review of the literature - 2001-2007. *BMC Health Services Research*. 2008;8:75.
4. Jamtvedt G, Young JM, Kristoffersen DT, O'Brien MA, Oxman AD. Audit and feedback: effects on professional practice and health care outcomes (Review). *Cochrane Database of Systematic Reviews*. 2006(3).
5. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Systemic Reviews*. 2007(4):CD000409.
6. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Medical Care*. 2012;50(6):466-478.
7. Briesacher BA, Soumerai SB, Zhang F, et al. A critical review of methods to evaluate the impact of FDA regulatory actions. *Pharmacoepidemiology and Drug Safety*. 2013;22(9).
8. FDA. FDA Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). 2011. http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm.
9. FDA. FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. 2012. http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm.
10. FDA. FDA Drug Safety Communication: Risk of next morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). 2013. http://www.fda.gov/drugs/drugsafety/ucm334033.htm.
11. FDA. FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR. 2013. http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm.
12. Department of Veterans Affairs. *National PBM Drug Safety Alert Distribution*. 2014.
13. Sales MM, Cunningham FE, Glassman PA, Valentino MA, Good CB. Pharmacy benefits management in the Veterans Health Administration: 1995 to 2003. *American Journal of Managed Care*. 2005;11(2):104-112.
14. Burk M, Moore V, Glassman P, et al. Medication-use evaluation with a Web application. *American Journal of Health-System Pharmacy*. 2013;70(24):2226-2234.

15. Gillies RR, Shortell SM, Anderson DA, Mitchell JB, Morgan KL. Conceptualizing and measuring integration - findings from the Health-Systems-Integration-Study. *Hospital and Health Services Administration.* 1993;38(4):467-489.
16. Strandberg-Larsen M, Krasnik A. Measurement of integrated healthcare delivery: a systematic review of methods and future research directions. *International Journal of Integrated Care.* 2009;9:e01.
17. Ye CL, Browne G, Grdisa VS, Beyene J, Thabane L. Measuring the degree of integration for an integrated service network. *International Journal of Integrated Care.* 2012;12.
18. Mojtabai R, Olfson M. Proportion of antidepressants prescribed without A psychiatric diagnosis is growing. *Health Affairs.* 2011;30(8):1434-1442.
19. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Archives of General Psychiatry.* 2009;66(8):848-856.
20. Blow FC, Valenstein M, McCarthy JF, Visnic S, Miller E, Terlecki S. *Specialty care for Veterans with depression in the VHA 2009 National Registry for Depression (NARDEP) Report.* Ann Arbor, MI: VA National Serious Mental Illness Treatment Research & Evaluation Center (SMITREC), VHA Health Services Research and Development; 2011.
21. Bernardy NC, Lund BC, Alexander B, Friedman MJ. Prescribing trends in Veterans with posttraumatic stress disorder. *Journal of Clinical Psychiatry.* 2012;73(3):297-303.
22. Mojtabai R, Olfson M. National patterns in antidepressant treatment by psychiatrists and general medical providers: Results from the National Comorbidity Survey Replication. *Journal of Clinical Psychiatry.* 2008;69(7):1064-1074.
23. Rawal PH, Lyons JS, MacIntyre JC, 2nd, Hunter JC. Regional variation and clinical indicators of antipsychotic use in residential treatment: a four-state comparison. *Journal of Behavioral Health Services and Research.* 2004;31(2):178-188.
24. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Annals of Internal Medicine.* 2011;155(11):772-U112.
25. Bhuvaneswar CG, Baldessarini RJ, Harsh VL, Alpert JE. Adverse endocrine and metabolic effects of psychotropic drugs: selective clinical review. *CNS Drugs.* 2009;23(12):1003-1021.
26. Pratt LA, Brody DJ, Gu Q. *Antidepressant use in persons aged 12 and over: United States, 2005–2008*. Hyattsville, MD: US Department of Health and Human Services; 2011.
27. Department of Veterans Affairs. *Citalopram hydrobromide (Celexa) and dose-dependent QT interval prolongation.* 2011.
28. Department of Veterans Affairs. *Updated guidance: citalopram hydrobromide (Celexa) and dose-dependent QT Interval Prolongation.* Department of Veterans Affairs; September 29 2011.

29. Department of Veterans Affairs. *Updated guidance: citalopram hydrobromide (Celexa) and dose-dependent QT interval prolongation.* Department of Veterans Affairs; April 17 2012.
30. Department of Veterans Affairs. *Zolpidem and FDA-proposed lower doses due to impaired mental alertness.* January 16 2013.
31. Michie S, Pilling S, Garety P, et al. Difficulties implementing a mental health guideline: an exploratory investigation using psychological theory. *Implementation Science.* 2007;2:8.
32. Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Quality and Safety in Health Care.* 2005;14(1):26-33.
33. Funk KA, Bostwick JR. A Comparison of the risk of QT prolongation among SSRIs. *Annals of Pharmacotherapy.* 2013;47(10):1330-1341.
34. Morlock RJ, Tan M, Mitchell DY. Patient characteristics and patterns of drug use for sleep complaints in the United States: analysis of National Ambulatory Medical Survey data, 1997-2002. *Clinical Therapeutics.* 2006;28(7):1044-1053.
35. Roy-Byrne P, Craske MG, Sullivan G, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *JAMA.* 2010;303(19):1921-1928.
36. Adams AS, Zhang F, LeCates RF, et al. Prior authorization for antidepressants in Medicaid: effects among disabled dual enrollees. *Archives of internal medicine.* 2009;169(8):750-756.
37. Zivin K, Ganoczy D, Pfeiffer PN, Miller EM, Valenstein M. Antidepressant adherence after psychiatric hospitalization among VA patients with depression. *Administration and Policy in Mental Health and Mental Health Services Research.* 2009;36(6):406-415.
38. Zivin K, Madden JM, Graves AJ, Zhang F, Soumerai SB. Cost-related medication nonadherence among beneficiaries with depression following Medicare Part D. *American Journal of Geriatric Psychiatry.* 2009;17(12):1068-1076.
39. Pfeiffer PN, Kim HM, Ganoczy D, Zivin K, Valenstein M. Treatment-resistant depression and risk of suicide. *Suicide and Life-Threatening Behavior.* 2013;43(4):456-465.
40. Valenstein M, Kim HM, Ganoczy D, et al. Antidepressant agents and suicide death among US Department of Veterans Affairs patients in depression treatment. *Journal of Clinical Psychopharmacology.* 2012;32(3):346-353.
41. Shadish WR, Cook TD, Campbell DT. *Experimental and quasi-experimental designs for generalized causal inference.* Boston, MA: Houghton Mifflin; 2002.
42. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *Journal of Clinical Pharmacy and Therapeutics.* 2002;27(4):299-309.
43. Cook TD, Campbell DT. *Quasi-experimentation: design and analysis issues for field settings.* Boston, MA: Houghton Mifflin Company; 1979.

44. Durbin J, Watson GS. Testing for serial correlation in least squares regression .1. *Biometrika*. 1950;37(3-4):409-428.
45. Durbin J, Watson GS. Testing for serial correlation in least Squares regression .2. *Biometrika*. 1951;38(1-2):159-178.
46. Kales HC, Zivin K, Kim HM, et al. Trends in antipsychotic use in dementia 1999-2007. *Archives of General Psychiatry*. 2011;68(2):190-197.
47. McCarthy J, Zivin K, Austin K, Kales H, Valenstein M. Does consideration of Medicare use affect VA Evaluations of treatment for new episodes of depression? *Administration and Policy in Mental Health*. 2008;35(6):468-476.
48. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry*. 2006;163(1):28-40.
49. Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ*. 2013;346:f288.
50. Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA*. 2014;311(7):682-691.
51. Kuehn BM. FDA warning: Driving may be impaired the morning following sleeping pill use. *JAMA*. 2013;309(7):645-646.
52. Farkas RH, Unger EF, Temple R. Zolpidem and Driving Impairment - Identifying Persons at Risk. *New England Journal of Medicine*. 2013;269(8):689-691.
53. Leufkens TR, Lund JS, Vermeeren A. Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *Journal of Sleep Research*. 2009;18(4):387-396.
54. Verster JC, Volkerts ER, Olivier B, Johnson W, Liddicoat L. Zolpidem and traffic safety - the importance of treatment compliance. *Current Drug Safety*. 2007;2(3):220-226.
55. Dailey J. *Review of Various Trials using zolpidem at Higher Doses*. VACO Pharmacy Benefits Management; 2007.
56. Department of Veterans Affairs. *High-dose Zolpidem IR Usage and Tapering Recommendations*. June 2009.
57. Department of Veterans Affairs. *Department of Veterans Affairs Pharmacy Benefits Management Service and Medical Advisory Panel Guidance for Treatment of Insomnia in Veterans in the Primary Care Setting November 2007*. Department of Veterans Affairs; 2007.
58. FDA. FDA Drug Safety Communication: FDA warns of next-day impairment with sleep aid Lunesta (eszopiclone) and lowers recommended dose. 2014. http://www.fda.gov/Drugs/DrugSafety/ucm397260.htm.

59. Department of Veterans Affairs. *Eszopiclone (Lunesta): lowered dose recommendations due to next-day impairment*. 2014.

Appendix 1

Case study 1: Cardiac risks and citalopram. In 2011-2012, the FDA issued drug safety warnings regarding abnormal heart rhythms, recommending that providers no longer prescribe citalopram at doses above 40 mg (or >20 mg for older adults) because of potential abnormal changes in electrical activity of the heart, including Torsades de Pointes (TdP).[8,9] As citalopram was widely regarded as a first-line agent for depression treatment due to its minimal drug interactions, demonstrated safety in older and medically ill patients, low cost, and relative effectiveness,[48] these warnings were surprising. In our prior research, we examined health outcomes by dose for nearly one million patients and found no dose-dependent risks of ventricular arrhythmia nor mortality associated with citalopram.[39] Yet recent studies have reiterated findings of increased risks of QT prolongation with citalopram use.[49,50] This mixed evidence regarding cardiac risk could have had an important influence on how VISNs, facilities, and providers responded to the citalopram warnings. Despite this ambiguity, given that over 300,000 VA patients were taking high dose citalopram, a systemic response to the FDA warnings was warranted. VA PBM produced three National PBM Bulletins and an optional MUET for high dose citalopram.[14] Preliminary qualitative interviews revealed that VISNs and facilities expended substantial time and resources responding to this unanticipated warning. We will explore responsiveness to the citalopram warnings in the qualitative components of our study, and assess VISN and facility level variation in response using quantitative analyses.

Case study 2: Zolpidem and driving. In 2013, the FDA released two warnings regarding zolpidem, a widely used sleep medication, noting its potential to have a negative impact on next-day alertness and driving acuity.[10,11] The FDA had commissioned studies including driving simulation studies following media reports and a subsequent increase in documented adverse events associated with zolpidem use.[51] An unusual feature of this warning was that it recommended different daily doses for men (<10 mg) and women (<5 mg), noting that women eliminate zolpidem from their bodies more slowly than men.[10] Given the different brands (Ambien, Ambien CR, Edluar, and Zolpimist) and formulations of zolpidem (extended-release, immediate release, sublingual) and different recommendations by gender,[52] it is likely that there was confusion regarding zolpidem prescribing. Further, because insomnia, like depression, is addressed by a variety of providers including PCPs, it may be unclear who should be responsible for implementing the latest warnings for zolpidem.

VA PBM had a different approach regarding the zolpidem warnings compared to the citalopram warnings in light of growing evidence of substantial risk of patient harm associated with zolpidem use.[52-54] Though the total number of patients taking high dose zolpidem (N~25,000 in FY2012) was substantially lower than those taking high dose citalopram, risks associated with high dose zolpidem use may be significantly greater. VA PBM recommended in 2007, well before the FDA warning, that doses <10mg of zolpidem be used.[55-57] When the warning for zolpidem was released in 2013, VA issued a National PBM Communication recommending lowering the dose to <5mg for women. Internal VA PBM data found that

zolpidem doses decreased after prior VA PBM communications, while use of other or multiple low dose sedative hypnotic agents increased, prior to the FDA warnings. Variation in responsiveness, however, is not yet understood. Concerns about the potential negative impact of sedative hypnotic medications remain, as the FDA released a new warning regarding eszopiclone [Lunesta],[58] and the VA subsequently released a National PBM Bulletin, both in May 2014.[59] Our qualitative analyses will assess differences in responsiveness to the warnings in light of prior VA guidance, and quantitative analyses will capture potential dose and substitution effects and variation across facilities.

Appendix 2

FDA PBM Interview Guide: VISN-Level Leaders

These interviews will be with pharmacy leaders from all 21 VISNs. PBM will recommend people to consult.

Introduction

Read the following script to interviewees prior to turning on the audio recorder:

Thank you for agreeing to speak with us about your experiences with medication safety alerts, we want to remind you that is this a research study and that all research studies are completely voluntary. You can stop participating at any time, or you can decline to answer any question. Your responses will be confidential and any account of the interview, including notes or transcripts will be de-identified. The sound files will be kept on a secure VA server and will be deleted off of the recorder. Do we have your permission to audio record this interview?

After the subject agrees, turn on the recorder:

Thank you for agreeing to speak with us about your experiences with medication safety alerts. As we just spoke about this is research study is completely voluntary. You can stop participating at any time, or you can decline to answer any question. Your responses will be confidential and any account of the interview, including notes or transcripts will be de-identified. The sound files will be kept on a secure VA server and will be deleted off of the recorder. Do we have your permission to audio record this interview?

Please remember: When talking about specific VISNs, make sure to focus on the time of the FDA warnings for citalopram and zolpidem (August 2011-May 2013).

Interviewee Background:

What is your position at the VA? How long have you held that position?
How long have you been working in pharmacy?
Which VA in your VISN are you located in?

Does your VISN have a committee or established group that is responsible for setting pharmaceutical policy and practice across the VISN?

- Are you a member of such a committee?
- Please describe your role related to pharmaceutical policy and practice in your VISN.

How much does the pharmaceutical policy committee interact with clinicians?

- Are there prescribing providers involved in setting pharmaceutical policy in your VISN?
- If yes, how so?

Please describe the mechanisms or activities that you are aware of which individuals in your VISN are involved in to promote awareness of pharmaceutical safety issues.

- Involvement in Academic Detailing (targeted and individualized educational services, clinical consultation, and addressing barriers to safe medication.)
- Does your VISN use Medication Use Evaluation Tracker (MUET)? (MUET initiatives are centrally coordinated by VAMedSAFE. VAMedSAFE identifies "trigger groups" of at-risk Veterans and uploads patient lists to the secure MUET application, where locally designated personnel (typically pharmacists) can access and use data to target risk reduction efforts.)
- What other activities, if any, are in place for disseminating/acting on FDA alerts/warnings?

Has your VISN addressed either or both the citalopram warning (2011) and zolpidem warning (2013)?

- If so, what kinds of activities have been conducted related to these alerts?
- If not, have there been facility level activities focused on these two alerts?

How effectively does your VISN manage pharmaceutical safety, changes in prescribing patterns, or changes in prescribing policies?

- What are some examples of effective actions your VISN has taken to manage safety and/or changes in prescribing patterns or policy?
- Can you describe some responses individuals in your VISN have had to new evidence?
- What, if any safety issues have come up for your VISN, and how did they handle them?
- How easy is it to coordinate activities across the VISN with respect to awareness of pharmaceutical safety, prescribing policies, changes in prescribing patterns when there is new evidence about safety, efficacy, or other attributes (e.g. cost) related to pharmaceuticals and therapeutic agents?

Are there other issues that you would like to mention related to your VISN, such as managing formulary, cost of pharmaceutical and therapeutic agents, or other safety or coordination issues?

Thank you for your participation today.