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Abstract

Title: Factors Leading to False Positive Computerized Provider Order Entry (CPOE) Opiate Allergy Alerts

Background: Computerized provider order entry (CPOE) drug alert overrides generally exceed 80%, of which opiate allergies are significant contributors. With an increasingly complex, information dependent healthcare culture, providers do not have unlimited cognitive capacity to interpret and effectively act on high volumes of low value alerts. Strategies are needed to improve clinical value and reduce alert volume, both of which are significant factors in intentional and unintentional alert overrides.

Purpose: This study examined the frequency and characteristics of opiate allergy alerts, and the influence of patient characteristics, reaction/severity, and provider role on alert override. Findings will be used to improve future allergy alerts.

Method: This was a retrospective, quantitative analysis of all FY10 adult opiate allergy alerts, related orders and patient characteristics at a large academic medical center. Three reaction/severity groups were created: (1) Non-Allergic/Low Severity (NALS=15%), (2) Unknown reaction with Unknown severity (16%), and (3) All else (69%). Data quality limited the NALS group to gastrointestinal reactions only (nausea, constipation, etc.). Effect of age, race, gender, visit type, provider type, and reaction/severity on the likelihood of overriding the patient's first opiate alert (alert1) was analyzed using Generalized Estimating Equations (GEE).

Results: Over half of all patients had opiates ordered. Those orders alone triggered 25461 allergy alerts for 2767 patients. This represented, minimally, a 9% opiate allergy

prevalence across all inpatients (2767/30321). Opiate reaction severity was 2.5% mild, 6.5% moderate, 16.8% severe and 74.3% unknown. Codeine was rarely ordered, but accounted for 32% of the alerts due to cross reactivity algorithms. Of the factors tested, only prescriber role had a significant influence on alert1 overrides. Advanced practice nurses were generally less likely to override alert1 (80% OR) as compared with physicians (90% OR, GEE β= -.793, p=.001).

Conclusion: Drug allergy alerting was one of the earliest and supposedly simplest forms of CPOE clinical decision support, yet has failed to attain acceptable override rates. Explicit allergy definitions, staff training, allergy data entry decision support and CPOE (GI) symptom management for all medications could significantly reduce alert volume and improve patient care.

Factors Leading to False Positive Computerized Provider Order Entry (CPOE) Opiate Allergy Alerts

by
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DEDICATION

I wish to dedicate this dissertation to my husband

Rob Ariosto

in appreciation for his sacrifice, loving support and sense of humor
along this six year journey.

And in loving memory of my parents,

who believed their daughters could do anything.

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1.0 Background

1.1 Overview of Chapter

Chapter 1 discusses computerized provider order entry (CPOE) allergy alerts, the rationale, aims and clinical significance of this study.

1.2 Introduction

The Harvard Medical Practice Study reported adverse drug events as the second leading cause of patient injury nearly thirty years ago. In 1999 the Institute of Medicine released its report "To Err is Human", citing 7,000 medication error related deaths annually and potentially $2 billion in costs (Kohn et al., 1999). (Brennan et al., 2004). In 2009 President Obama signed into law the Health Information Technology Economic and Clinical Healthcare Act (HITECH), which significantly ramped up the investment in this nation's health care infrastructure by providing significant reimbursement incentives for "meaningful use" of electronic health record (EHR) technology. The National Coordinator for Healthcare IT at the time, David Blumenthal, MD, said that " By focusing on 'meaningful use,' we recognize that better healthcare does not come solely from the adoption of technology itself, but through the exchange and use of health information to best inform clinical decisions at the point of care" (Blumenthal, 2009).

HITECH "meaningful use" focuses on using the EHR to improve population health, quality of care, reducing disparities, protecting personal health information and engaging patients in their care. Of the 25 meaningful use objectives described for phase I, 9 directly relate to electronic medication decision support (HIMSS, 2010). These

include computerized provider order entry (CPOE) adoption, drug-allergy checking, coded problem lists, allergy lists, e-prescribing, medication reconciliation, demographics, and electronic access to vital signs (Dept. of HHS & Centers for Medicare and Medicaid, 2010). With increasing incentives to implement these objectives comes increasing need to mitigate adverse, unintended consequences of this evolving technology.

1.3 Problem Statement

Despite increasing technology with linkages to expanding clinical datasets, clinical decision support (CDS) is still in its early developmental stages. Timely drug alerts, a common CDS feature, warn clinicians of potentially serious adverse drug reactions (ADR's) during order entry, yet most of these types of alerts are rejected. Numerous studies cite the excessive alert volume and low clinical value as significant factors in intentional and unintentional alert overrides (van der Sijs, 2009). Two classes of drugs, antibiotics and opiates, represent the majority of CPOE alerts and alert overrides (Hsieh et al., 2004; Hunteman et al., 2009). This study focused on the latter. Increasing interest in clinical decision support by a risk adverse health care system has created an urgency to get data, often unvalidated, into the EMR for use by CPOE drug alerts without consideration of all the effects. Clinical systems now have virtually unlimited capacity to collect, store, and prompt on clinical data. With an increasingly complex, information dependent healthcare culture, we do not have unlimited cognitive capacity to interpret and effectively act on high volumes of low value data. The fatigue and distraction of high volumes of low value alerts calls for focused research to understand and mitigate these unintended consequences.

1.3.1 Hypersensitivity vs. Side Effects

Increasingly patients are listed as opiate allergic in their electronic medical record. There is no evidence that this represents a true increase in opiate allergies. It is likely the by-product of a longitudinal EMR that has moved unconnected, and often unsubstantiated, allergy records into a centralized data repository. It is facilitated by lack of staff education and reinforced by data entry screen design.

Most EMRs have an associated data input screen named "Allergy" that was designed to store allergy data, but has expanded to collect any possible adverse drug reaction. The more appropriate term purposed for CPOE is "drug hypersensitivity" which is the umbrella term that includes both allergic (immune system mediated) and non-allergic types of reproducible adverse drug reactions. The European Academy of Allergy and Clinical Immunology proposed a definition, which will be used in this study:

> *"Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects" (Johansson I, 2005).*

While both types of hypersensitivities (allergic, non-allergic) may include mild to severe reactions, the allergic type has the capacity to escalate on the next dose due to an individual's immune response.

Hypersensitivity reactions are based on the individual, and should be recorded in the patient's medical record. Mild drug side effects, based on their expected pharmacologic actions affecting the gastrointestinal tract or respiratory system (nausea, vomiting, constipation, slowed breathing) should be anticipated as a standard of care but should not be recorded in a patient's medical record as an allergy.

Another term used is drug intolerance or sensitivity. It has been loosely defined, and sits somewhere between side effect and hypersensitivity. This may reflect an adverse patient response to a drug based on the patient's current clinical conditions and treatment regimens or a higher sensitivity to the drugs known action. Clearly, moderate to severe intolerances expressed by the patient, whether reproducible or not, should be noted and available for drug alerting.

1.3.2 Cross Reactivity

Drugs such as antibiotics and opiates each belong to a class of drugs. Patient that are allergic to one drug in a particular class have a high probability of being allergic to other drugs in that same class due to chemical similarities – called class cross reactivity. Without additional testing, it is difficult to tell if the patient is allergic to the drug, or one of the ingredients that make up the drug. So cross reactivity alerts may not always hold true. Patients allergic to Percocet are automatically flagged as allergic to acetaminophen (an ingredient) as well. Patient's that are hypersensitive to one opiate such as codeine may or may not be hypersensitive to other opiates. To be on the "safe" side, CPOE alert logic generally considers a patient "allergic" to the class due to potential cross-reactivity, exponentially increasing the number of potential alerts.

Expanded use of the "allergy field", compounded with cross-reactivity safeguards, has led to a significant increase in alerts. The increased volume of non-specific alerts has affected the efficiency and effectiveness of care. False alerts which delay care or inappropriately encourage less effective or no pain control medication cause

harm. Conversely, alerts which are missed due to alert fatigue may contribute to preventable adverse drug events.

1.3.3 Alert Outcomes

There are a number of outcomes from allergy alerts under the previously stated conditions. A true positive alert warns of an unexpected adverse effect from an ordered drug. A false positive alert represents those alerts which offer no new or valid data to the provider's decision making. This includes alerts that are wrong, or those that repeated standards of care already known such anticipatory treatment of constipation from opiates.

For alerts that accepted, there are both positive and negative outcomes. If the patient was truly hypersensitive (true positive alert), an adverse drug reaction was avoided when the alert resulted in the provider cancelling the order (positive outcome). However, if the patient was not hypersensitive (false positive alert), a less effective drug may have been ordered in its place (negative outcome). In the case of opiates, less than optimal pain control may be achieved. For antibiotics, a second line drug choice may delay recovery from an infection.

For alerts that are rejected, which is most of the time, there are good, bad, and unknown outcomes. If the drug was ordered for the patient that was hypersensitive (true positive), the override may have occurred for a number of reasons: The provider (1) didn't think the patient was hypersensitive (mistake); (2) accidentally hit the override button (slip); or (3) assessed the patient and felt that the benefit of the drug outweighed the risk of reaction. Of note is that the pharmacist, nurse, and patient have opportunities

to prevent the administration of the drug – or be prepared with symptom control measures.

For overridden alerts on false hypersensitivies (false positive alert), the additional work (negative outcome) may negatively impacted patient care and provider satisfaction and trust in CPOE alerts in general. This also applies to the pharmacist and nurse evaluation who must take time to evaluate alerts and/or related data on dispense and administration. Table 1.1 summarizes some of these consequences of CPOE Allergy Alert decisions.

Table 1.1 Consequences of CPOE allergy alerts

Alert Response → ↓ Allergy Status	Accept Alert Cancel Order	Reject/Override Alert Place Order
True Hypersensitivity	Potential ADR Avoided	Benefit outweighs the risk or Alert Fatigue - Slip or Mistake
False Hypersensitivity	No med is ordered or 2nd line drug chosen	Alert burden/wasted time Incorrect/Clinically insignificant

1.4 Purpose and Aims

This study examined the frequency and characteristics of opiate allergy alerts, and the influence of patient characteristics, reaction/severity, and provider role on alert override. Findings will be used to improve future allergy alerts. Opiate alerts were selected because they represented the most common over-alerting problem in the literature and comfort management is a significant component of clinical care in most settings. Comfort management refers not only to timely and effective pain relief, but management of undesirable opiate side effects such as nausea and constipation. Patient and prescribing provider attributes were also evaluated to determine if factors other than the allergy reaction influenced response to opiate allergy alerts. The study aims were:

Aim 1: To describe the prevalence and attributes of opiate hypersensitivity alerts.

Aim 2: To analyze the influence of patient characteristics (age, sex, race), reason for admission (medical, procedural) and prescriber role (physician, advanced practice nurse) and reaction/severity group on opiate alert overrides.

Aim 1 results provide information on the problem scope as well as informing the classification of reaction/severity groups used in Aim 2 based on attribute detail. A recent Delphi study of 69 CPOE experts identified "severity of effect" as the most important aspect of a drug alert (Riedmann et al., 2011). Aim 2 compared the influence of three reaction/severity groups, as well as patient and provider attributes on overrides.

Patient attributes were considered since they may have additional influencing effects on how allergy data is collected and how providers respond to certain populations. Elderly patients may have more allergies recorded and may be more sensitive to the effects of drugs in general. Women may be more likely to report intolerances, and providers may have biases based on patient gender regarding pain self-report and need for opiates.

The medical versus procedural reason for admission may reflect the type of pain being treated, such a cancer or a surgical repair. It may also reflect the provider, such as internist versus surgeon. Physicians and advanced practice nurses may also respond differently to alerts based on education or level of responsibility. Opportunities for improving opiate allergy alerts will be described.

1.5 Significance

There are significant dollars, workload and patient safety issues associated with in CPOE drug alerting. Federal electronic health record (EHR) incentive programs under

the Centers for Medicare and Medicaid Services (CMS) have allocated millions of dollars in incentive payments to eligible hospitals and providers to demonstrate meaningful use of certified EHR technology starting in 2011. The certification process includes topics of particular interest to this study: the medication allergy list, use of CPOE, and drug:allergy checking (https://www.cms.gov/EHRIncentivePrograms) . If the criteria is not met by 2015, there will be financial penalties. When there are federal incentives, looming mandates and millions of dollars at stake, the rush to implement complex systems without thoughtful consideration of the unintended consequences may subvert the goals of "meaningful use".

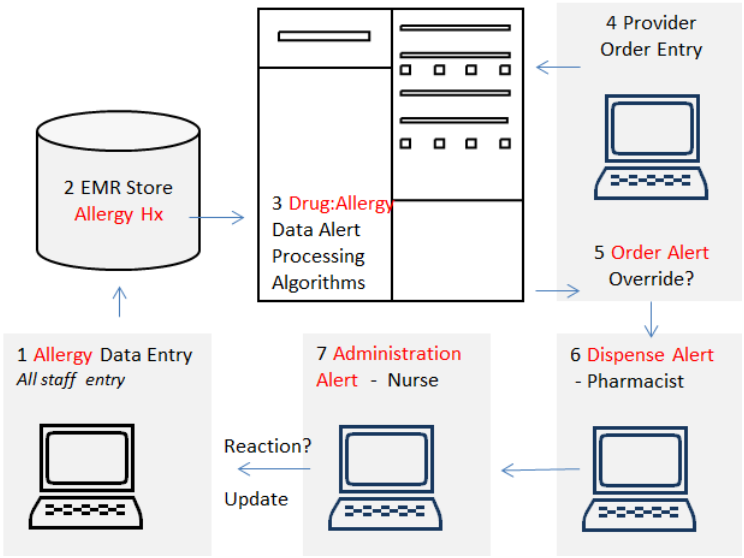
Stage I is about widespread adoption of the technology. However, the success of decision support depends heavily upon its ability to deliver trusted, clinically significant, actionable information at the point of care. The following exemplar highlights the need:

> *A patient was urgently admitted and underwent open heart surgery. In recovery, an order was placed for needed pain medication for this intubated, agitated patient. A narcotic was ordered and the CPOE system alerted the provider that the patient was allergic to the ordered class of narcotics. Review of the documented allergy history showed an adverse reaction to codeine, but the reaction and severity were not documented. Family was unavailable. Nurse, physician and pharmacist conferred, during which time patient experienced increasing distress. The decision to give morphine was made, the patient was monitored closely, and no adverse response was observed. When questioned prior to discharge, the spouse had told the admission nurse that he "felt funny" after taking cough syrup with codeine a couple of years ago. The patient was discharged, and unfortunately for next time, his electronic allergy history was not updated.*

While this patient suffered no allergic reaction, he did suffer for 20 minutes while the decision was being made whether or not to give the opiate. Valuable clinician time was spent trying to get the right information to make a decision. This type of adverse event is

not generally formally reported on, and therefore may be underestimated. There are multiple systems involved in the alert. These conceptually involve (1) allergy data entry by multiple staff types or from other systems; (2) storage of allergy data in a machine readable format for CPOE and other programs; (3) coding of allergy data according for use by pharmacologic algorithms (class, ingredients, reaction, severity etc.); (4) alert trigger when allergic drug is ordered; (5) alert response capture, and override reason storage; (6) alert to pharmacist on dispense; (7) potential alert to nurse on administration and update of reaction data post administration. Figure 1.0 depicts the multiple computer systems that reflected this clinical scenario.

Figure 1.1 Clinical Systems Supporting Allergy Alerts



This research focuses on the high volume of rejected opiate allergy alerts. These findings should contribute to the refinement of current and future CDS constructs for medications in general. These constructs include how data is collected, processed, and displayed to users. Research findings will help inform the next stage objectives for meaningful use towards the goal of safe, effective and efficient medication ordering.

2.0 Literature Review

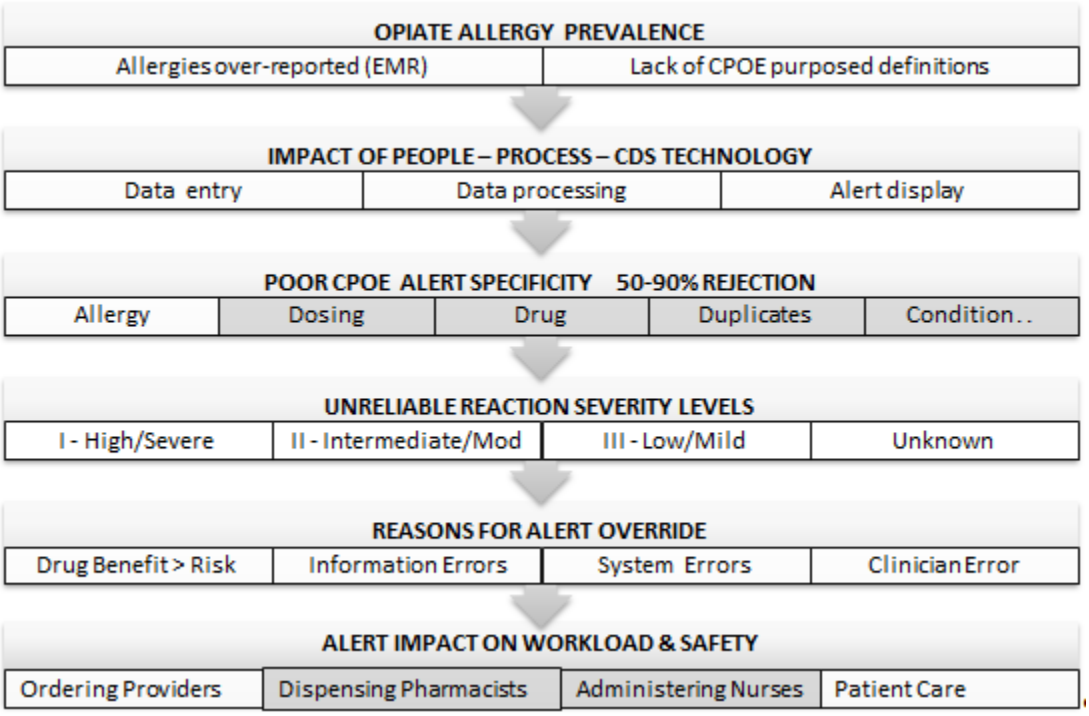
2.1 Overview

The previous chapter introduced the problem of high volumes of CPOE drug alerts with correspondingly high rates of override. The focus of this study is on opiate allergy alerts because it represents a drug class with one of the highest volumes of alerts and overrides and safe, effective pain and comfort management is a cornerstone of clinical care. This chapter reviews the literature that relates to concepts in the alert trajectory from (1) allergy data collection through (2) computerized allergy alert processing and alert presentation, to (3) clinicians response to accept or reject (override). It includes a review and discussion of what is currently known about opiate allergies, clinical decision support, CPOE allergy alerts, factors influencing alert overrides, conceptual models relating to decision support, and the secondary alerts that affect pharmacists and nurses on administration.

A review of the literature was conducted to reveal what is known about opiate allergies, allergy alerts, CPOE alert overrides and the unintended consequences of CPOE alerts. Searching strategies included identifying databases that collected peer-reviewed research about the safe ordering and administering medications in an electronic environment. Databases searched were CINHAL (1984-2011), Medline (1996–2011), EMBASE Drugs and Pharmacology (1980-2011), the AHRQ Patient Safety Network database (all 'CPOE' Classics), PsychINFO (1887-2011) and the Cochrane Collaborative (2005-2010). Key search words included alert fatigue, desensitization, alerts, pop-ups, reminders, medication errors, opiates, opioids, opiate allergies, decision

support, CPOE, bar code medication administration, and BCMA. Bibliographic references to "alert fatigue" within the articles were further explored. Reference Manager™ v.11 was used to organize relevant articles by primary author and content area. Descriptions of causes and effects of CPOE alert overrides were organized into themes. Figure 2.1 below show the logical progression for understanding the significant concepts and issues influencing opiate allergy alerts.

Figure 2.1 Opiates & Allergy Alerts Issues and Concepts



2.2 Opiate Allergies May Be Overstated

The bulk of the CPOE drug alerts are associated with opiates and antibiotics. Antibiotics are associated with a wide reaction severity range from upset stomach to life-threatening reactions like anaphylaxis which reinforce the high safety value of alerts.

However, opioid allergies are rare, and previous studies have identified that from 31-80% of the patients with opioid/narcotic allergies are labeled inappropriately (Gilbar 2004, Pilzer 1998). Non-allergy reasons may include unintended drug overdosing or attributing known drug side effects to an allergic response.

Consumer information from product inserts or reputable websites such as National Library of Medicine MedlinePlus provide guidance on how to identify reactions needing medical attention. Serious opiate side effects requiring immediate reporting include rash, itching, hives, dyspnea, difficulty swallowing, vision changes or seizures (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682065.html). Less specific instructions include "*Tell your doctor if any of these symptoms are severe or do not go away"*. It is left to the consumer to determine their personal measure of severity or how long is too long. If these references are read, they may be well beyond the health literacy levels of the general public to interpret and accurately report (http://www.health.gov/communication/literacy/quickguide/factsbasic.htm). At the point of care, patients rely on the allergy intake history form questions and prompts by the healthcare staff to accurately recall their allergy history.

The list of opioid system effects published by the American Chronic Pain Association in 2011 show a spectrum of reactions: (http://www.theacpa.org/uploads/ACPA_Consumer_Guide_2011%20final.pdf):

- "Central nervous system: A sense of well-being and euphoria; Drowsiness, sedation, and sleep disturbance; Hallucinations ; Potential for diminished psychomotor performance; Dysphoria and agitation; Dizziness and seizures; Aberrant behavior; Hyperalgesia

- Endocrine: Hormonal and sexual dysfunction

- Gastrointestinal system: Constipation, nausea and vomiting; Delayed gastric emptying
- Genitourinary : Urinary retention

- Ocular system : Constriction of the pupil of the eye

- Respiratory system: Respiratory depression is the major adverse effect and may result from toxicity; Diminution of pain or pain relief by other modalities may exacerbate respiratory depression. "

The above reflect known side effects with varying degrees of severity. They become significant in drug allergy alerting if the effects are reproducible at normal doses (hypersensitivity) and require medical intervention to resolve (moderate to high severity).

A recent review of the allergy literature confirmed significant variations in allergy terminology and definitions and recommended standards for describing drug allergy and hypersensitivity with objective definitions for reaction severity (Ariosto, 2009). These include three levels of reaction severity: (1) Low/Mild = response disappears when the drug is discontinued; (2) Intermediate/Moderate = some medical intervention is required, and may increase LOS; and (3) High/Severe = life-threatening; disability or death if untreated. Translating the patient experience into reliable EMR data well purposed for CPOE alerting has been difficult due to lack of objective measures for allergy, reaction and severity.

2.3 Collecting and Displaying the Right Information is Difficult

The "Five Rights of Clinical Decision Support (CDS)" conceptual framework guides developers on how to achieve desired healthcare outcomes if CDS can communicate the (1) right information (drug allergy), (2) to the right person (prescriber),

(3) in the right format (alert), (4) through the right channel (CPOE), (5) at the right time (drug ordering) in the workflow (Osheroff, 2009). Osheroff describes the right information as "evidence based, suitable to guide action, and pertinent to the circumstance". The part of the framework for obtaining the "right information" is the focus of this CPOE opiate allergy alert research.

Defining a generic approach to presenting the right amount of information that is needed to respond to an alert is difficult. Accuracy has been described as "a complex quality of data and it occurs on several levels of interpretation. At its simplest level, accuracy has been described as the percentage of correctness and completeness in a data set" (Hogan and Wagner, 1997). The absence of clear definitions of alertable "allergies" at all levels, and lack of complete allergy reaction descriptions and severity level in the data suggest low levels of accuracy.

2.3.1 Guided allergy data entry screens

Early electronic decision support included the structured intake form with check boxes and/or pick lists to guide users similar to how they used paper forms. Generally, these data entry screens pre-dated allergy alerting. Developers designed allergy data entry screens to display all the fields needed to help remind the user of key questions to ask in order to ensure an accurate and complete allergy history. At a minimum these included the allergen, reaction and severity, data source (patient, spouse, medical record), date of onset and a space for free text comments for further clarification. Previously collected data was displayed and new data, once saved, was immediately available to all (people and systems) who had access to EMR data.

Computerization enhanced the use of these templates by adding features to make it easy to enter and share coded data. On-screen choices reduced the amount of typing needed. Pick lists in the form of drop-down lists or checkboxes displayed common hypersensitivities. In the past, free text based misspellings (codine) caused recorded drug hypersensitivities to be missed by alert algorithms needing coded data. Use of pick lists ensured that the allergen selected (codeine) would be coded and reliably matched to the opiate order class (opiates) to trigger an alert.

While there are many benefits to user assisted screen displays, there are disadvantages. Problems with pick lists occurs when there is no exact match, or the list reflects an extensive list of too many similar matches (especially when the entire drug formulary is displayed) resulting in the user guessing, giving up and/or entering data in a free-text comments fields. How choices are presented may also influence how a user makes their choice. Drop-down lists that default to a value such as "unknown" may inadvertently encourage the busy user to skip the item and save the default value. Slips can also occur when the user mistakenly clicks on a nearby value above or below the box. Once saved to the EMR, clinicians may be reluctant to remove questionable or even erroneous data that they did not enter.

There are numerous studies that discuss the influence of screen design on user behavior (Khajouei, etal., 2010). One anecdotal story relates to new resident physicians who felt that when a list of drugs, such as antibiotics, were presented during order entry, the first drug listed was the recommended one. But in fact, the developers had weighted the list to display the most commonly ordered drugs first (Ariosto, 2009). In the case of opiate allergy history, codeine is often listed at the top of the list when sorted

alphabetically. This could cue the interviewer to ask about, and possibly perpetuate the over-collection of codeine allergies.

2.3.2 Knowledge based vs. Non-Knowledge based alerts

There are two major categories of computerized clinical decision support (CDS) – (human) knowledge based and non-knowledge based (machine learning). Knowledge based is the type of CDS used in CPOE alerting and relies on a knowledge dataset which should be evidence based (Bates, etal 2003) and applies structured rules based on available data. Below is a discussion of how both categories of CDS may be used with alerts.

Knowledge based CDS represents attempts to replicate human logic. Decisions are made based on information known. In this study, simple rules triggered alerts based on the knowledge of opiate allergies in the EMR which are triggered by opiate order initiation. However, when allergy data is incomplete or inappropriate, generic rules result in sub-optimal results.

Non-knowledge based CDS include neural networks and genetic algorithms. Neural networks use the concept of nodes and weighted connections – much like Pavlov's classical conditioning in animals. In this type of CDS the computer must be "trained" based on past experiences. When a response type (node) is correct it increases the weight of the node, increasing the probability of it being suggested next time. An example would be the ability to correctly identify patients with specific symptoms or attributes as frequently having a specific diagnosis – especially where there is no definitive test for that diagnosis. While there was no CPOE studies found that used

neural networks, one could imagine increasing the weight of those alert types that were accepted and not firing those that fell below a specific threshold weight.

Genetic algorithms identify relevant features using an iterative approach to eliminate those features that don't significantly contribute to accurately classifying the content (Berner, 2007). In the case of allergy alerts, identifying those attributes which result in alerts that are not overridden would be valuable. We might discover that the reaction itself was not significant, and that the patient's subjective severity level had the most influence on an appropriate provider alert response.

A hybrid approach using multiple types of CDS will likely be most effective with more complex clinical decision making. Non-knowledge based and applied use of knowledge based "fuzzy logic" has been suggested for use in CPOE (Phansalkar, etal 2010). Fuzzy logic may be helpful in cases where there is clinical vagueness to suggest diagnoses, alerts and actions based on related but imprecise data. Warren, etal. applied fuzzy logic to cholesterol management recommendations that take into account primary versus secondary disease, elderly status, temporal considerations, etc. (Warren, etal 2000). Sivasankar, etal (2010) used fuzzy logic to diagnosis the severity (mild, moderate, severe) of appendicitis using the input parameters of "pain site, pain nature, nausea, previous surgery, rebound tenderness, guarding, rigidity, temperature, white blood cell count, and neutrophil count". Fuzzy logic has not yet been reported as being applied to allergy alerts. When there is availability of coded, discrete data surrounding the allergic event, research may emerge to reveal more usable allergy alerts with this approach.

2.4 CPOE Drug Alerts Have Evolved – But Specificity Remains Low

Alerts have grown increasingly complex and ubiquitous with increasing availability of coded clinical data. Adoption of common electronic EMR standards (LOINC, SNOMED, ICD9-CM, HL7) have enabled data sharing across systems. While there are naming standards for sending and receiving data, the definitions that underlie fields like allergy and reaction severity have yet to be standardized and purposed for alerting. We have increased ability to alert, but specificity remains low.

Early CDS allergy alerting and simple dosing range prompts were followed by the development of more complex CPOE drug alerts and are listed in Table 2.1 (Kuperman, 2007; Schedbauer et al, 2008). This was a natural evolution since many recorded "allergies" were likely symptoms of overdose which are better handled in the newer types of alerts. These include more complex drug:dosing alerts which evaluate patient weight and age (pediatric, elderly) along with drug:condition alerts that look a lab values and conditions (renal failure, liver cirrhosis) to evaluate a patient's ability to metabolize and excrete drugs.

Duplicate drug checking warns of ordering multiple drugs that have ingredients of similar action. In one environment that is helpful to avoid overdosing the patient. In another environment it is a nuisance such as when there are multiple p.r.n. (as needed) opiates prescribed that intentionally leave it up to the nurse to choose analgesics based on pain severity levels. Computerized alerting for ordering, dispensing, and administering systems are still not adept at handling parameter based orders (if this condition, then this drug or dose) or variable daily orders (decrease dose by this amount each day).

Table 2.1 CPOE Alert Types

Complexity	Alert Type	Definition
Basic		
	Drug – Allergy	Allergy or Hypersensitivity to drug
	Drug - Drug	When one drug adversely affects another's action
	Drug – Dosing	Suggested dosing, route, timing, out of range message
	Duplicate	Drug or a similar one is already ordered
Advanced		
	Drug – Lab	Comparison to lab values, like renal function or Missing values
	Drug – Condition	Condition (pregnancy, renal)
	Drug – Disease	Drug contraindicated in this disease
	Drug – Age	Elderly, pediatric limitations
	Dosing Guide	Individualized to patient condition (VS, lab, comorbidities
Complex		Considers all of the above

Adapted from (Gilad J.Kuperman MD, 2007; Schedlbauer et al., 2009)

The emerging field of personalized medicine and growing body of genomic knowledge about how patients individually metabolize drugs (Wilke, etal., 2011) may be the next generation of tailoring drug alerts to individual patients. While the current alerts are designed as separate pieces of advice, the integrating capacity of computerized decision support can move us towards a synthesized view that includes the patient's genetic makeup as well as past and current clinical states to better inform CPOE decision support and ensure patient safety.

Alerting environments reviewed included inpatient, outpatient, and a community pharmacy (Lapane et al., 2006). Alert research also evaluated adult, pregnant (Raebel et al., 2007a), elderly (Cresswell et al., 2007; Raebel et al., 2007b), and pediatrics (Mitchell et al., 2009) populations. Across all types of alerts, the findings were consistent - CPOE

alerting has high value for a small percent of the population. High value alerts warn of severe allergies, duplicate and/or dangerous drug combinations, excessive or non-therapeutic dosing, and contraindications related to disease or pregnancy state to name a few. With a 50-95% rejection rate overall, they don't yet reflect the clinical condition well. There is consensus that there are too many low value alerts, but there are limited innovations on how to improve and reduce them.

2.5 Alerts Should Meaningfully Reflect Severity Levels

The allergy alert has several attributes which have not been well utilized to improve allergy alert specificity or meaningfulness to the ordering provider. Basic attributes include reaction (rash, dyspnea), severity (mild, severe), extent (localized, systemic) and duration. This type of information has been poorly described, and infrequently recorded. Without reliable attribute definitions and data, CPOE CDS systems have been hampered in their ability to take alerting to the next level of clinical usefulness.

Paterno etal. (2009) studied drug:drug interaction severity which may have applicability to drug:allergy severity levels. Experts reviewed individual drug pairs to arrive at highly specific alerting. Three warning levels or tiers were developed. Level 1 required the drug order be stopped. Level 2 is less serious but requires action. Level 3 is the least serious and is presented as FYI (for your information only) requiring no user response. Analysis of alert responses showed higher acceptances of tiered drug:drug alerts (Hospital A), and that lack of tiering (Hospital B) was associated with higher override rates of more severe alerts.

Identifying which alerts should be in a Level 3 severity would require careful consideration of all clinical scenarios in which the alert will present (Berner & Moss, 2005) (Glassman et al., 2002). In general, the research does not recommend that drug alerts be turned off as they are helpful in identifying potentially serious adverse drug reactions (Bates et al., 1999; Mahoney et al., 2007; van der Sijs et al., 2008b). However, in general, unintended consequences of CPOE systems need to be addressed (Hsieh et al., 2004; Ash et al., 2007e).

2.5.1 Matching Alert Behaviors to Severity

Another challenge for CPOE developers and users is to find and apply the right visual and behavioral cues for the alert beyond the actual message text. Colors can be used to indicate severity. Alert behaviors can be (1) prohibitive and/or interruptive, (2) distracting (visual or audible), or (3) passive, non-interruptive (Lo et al., 2009).

Prohibitive and/or interruptive alerts stop the user from ordering the drug, or prohibit them from moving forward until they do something (cancel order, override alert, state rationale for override). Shah, et. al 2006) reduced the number of interruptive alerts by interrupting only on drug:drug interactions (DDI) considered to be high to critical severity.

Visually distracting alerts are a relatively newly used category of alerts (Kucher, Puck et al. 2009) that have historically been used by marketing, and whose value is questionable (Edwards et al., 2002). This group of alerts can interrupt workflow because it diverts attention from the intended task until addressed. These are characterized by

movements such as flashing, bouncing, or crawling across the screen. These have not been applied to CPOE.

Studies on passive, non-interruptive alerts suggest that they do not significantly improve compliance with desired actions (Lo et al., 2009). These are characterized by on screen warnings related to the order, but do not require the user to respond. The intent is to give additional information that may or may not be important to the decision maker. A summary of alert behaviors is compiled in Table 2.2.

Table 2.2 Summary of Alert Behaviors

Behavior	Examples
Prohibitive	Hard stop for contraindicated drugs. Clinician cannot order drug without additional authority or co-signature
Interruptive	Cannot proceed with order until the reason for giving the drug is stated and or monitoring actions will be implemented. e.g. patient has tolerated this before; benefit outweighs the risk, will closely monitor, etc.
Distracting	Movement related – flashing or crawling across the screen. Does not stop the user, but distracts from the current task until addressed.
Non-Interruptive	These alerts appear with the order. They tend to be informational such as "did you remember to order related labs"
Static, Non-discriminatory	Allergy and other precautions (swallowing, suicide, fall risk) may appear permanently on the screen header.

Audible alerts are those heard when you have selected a keystroke that does not follow the desired alert path (e.g. try to override alert without stating reason). Nurses may respond to audible alerts when they administer medications and the computer screen is not visible at the point of administration. Audible alerts are more commonly used with physiological monitors and pagers. Alarm fatigue studies (Xiao et al., 2004; Calvitti et al., 2006; St-Etienne, 2008; Blum et al., 2009) may highly correlate with alert fatigue, as

both are characterized by a desensitization to frequent low or no value warnings requiring no action by the responder. Hazards relating to alarm fatigue and other related concerns has been name as a top technology hazard for 2012 by the ECRI Institute, an independent non-profit group for improving patient care (www.ecri.org/2012_Top_10_Hazards).

Today's clinician responds to numerous electronic messages during the course of a day. In addition to alerts and reminders within clinical systems, personal cell phones, e-mail and calendaring applications reminds them to check messages and be on time for meetings. Internet browsing is fraught with pop-ups that recommend other sites and ask responses to surveys, etc. Across software developers there are different symbols, signals, colors, navigation and presentation styles which all increase cognitive burden. The combined effect of these all daily alerts on attention and fatigue has not been reported and offers opportunities for improving the fields of study related to computer assisted decision making.

2.6 Alert Fatigue

The previous discussions focused on the workflow burden of excessive low value alerts - those that were purposely rejected. However, when clinically significant alerts are overridden, there is the possibility that it was not a result of poor judgment, but a mental slip or lapse (Reason, 1990; Norman, 1998). There is increasing reports of desensitization to the high volume of low value alerts and reminders being attributed to alert fatigue. Most CPOE studies reference the definition by van der Sijs et al. who described (CPOE) alert fatigue as "the mental state that is the result of alerts consuming too much time and mental energy, which can cause relevant alerts to be unjustifiably

overridden along with clinically irrelevant ones" (van der Sijs et al., 2006) (Judge et al., 2006; Lehmann & Kim, 2006; Kuperman et al., 2007; Osheroff et al., 2007; Harrison et al., 2007; Eslami et al., 2007; Ko et al., 2007; Handler et al., 2007; Hollingworth et al., 2007; Cresswell et al., 2007; Collins et al., 2007; Raebel et al., 2007a; Eslami et al., 2008; Lapane et al., 2008; Paterno et al., 2009).

Variations on alert fatigue definitions include: Excessive alerting and repeated false positives (van der Sijs et al., 2006; Ash et al., 2007d; Ash et al., 2007e; van der Sijs et al., 2008a; van der Sijs, 2009); high rates of non-serious or irrelevant alerts (Magrabi & Coiera, 2009); multiple alerts on the same drug (Malone et al., 2005); cognitive overload from multi-tasking (Collins et al., 2007); poor signal to noise ratio (Glassman et al., 2002); and cognitive load caused by difficult screen navigation and response to prompts or "poor fit to the task" (Sheehan et al., 2009). Clinically irrelevant alerts result from alert algorithms with low specificity, duplicate alerting, poor discrimination between severity levels, and incorrect data in the clinical situation (Saleem et al., 2005; Calvitti et al., 2006).

Alerts that fire each time the drug is ordered and re-ordered are particularly problematic. Opiates belong to a class of controlled substances which must be re-ordered every few days to limit the number prescribed, and to assure attention to medications appropriate decreasing levels of pain. CPOE order sets contain multiple drugs which can be ordered as a single group that span several days. For example, a post-operative orderset may contain all the analgesics that may be needed in the days following surgery, leaving it to the discretion of the nurse to determine the most appropriate drug. As previously discussed, CPOE systems cannot determine which are true duplicate orders

from those that are parameter based (e.g. Intravenous morphine for severe pain while intubated, Oxycodone 10 mg for severe pain, Oxycodone 2 mg for moderate pain, Tylenol #3 for mild to moderate pain) and triggering the right alerts for each order in the order set.

To date, there are no published peer-reviewed studies found that empirically test and predictably reproduce "alert fatigue". That is, to identify cases where an error occurred that resulted from a clinically significant alert being unintentionally overridden (a slip) – and correlate same with high versus low volume alerts. There are, however, several qualitative studies (Ash & Coiera, 2004; Ash & Sittig, 2005; Sittig et al., 2005; Ash et al., 2007a; Ash et al., 2007b; Ash et al., 2007c; Ash et al., 2007e) and much anecdotal discussion. Pifer et al. examined override rates of high severity alerts as a function of volume to predict alert fatigue (Pifer et al., 2007). The study found that after the provider's first alert override, override rates increased significantly, suggesting alert desensitization, but not necessarily fatigue error.

Over-alerting may have similar effects as over-monitoring. Studies have shown that a higher level of monitoring of all patients may lead to lower attention to the truly acute ones (Xiao et al., 2004). Alert fatigue research was preceded and should be informed by research on audible alarm fatigue. As previously discussed, it is likely that alert fatigue will soon be a top priority for clinical watchdogs much like the recent Joint Commission (hospital accreditating body) designation of alarm fatigue as a top priorities for 2011 (April, 2011).
http://www.boston.com/news/local/massachusetts/articles/2011/04/18/groups_target_alarm_fatigue_at_hospitals.

Emergency response team research in alarm fatigue by Calvitti et al. (2006) may help better capture the nature of the desensitization phenomenon described below:

> *"Improving the effectiveness of the presentation stage [of the alert] is a subject of human-computer interface and cognitive science research. Studies of work under high cognitive load in various domains have called attention to human perceptual (e.g. change blindness, habituation) and cognitive (e.g. single focus of attention) limitations, and even social factors (e.g. group pressure to ignore alerts) that reduce the effectiveness of otherwise carefully designed alert systems. A true-positive alert disseminated to appropriate operators but masked by environmental noise or by other alerts ("alarm cacophony") is in effect a false negative. "*

Consequences of excessive, low value alerting is reduced credibility in the safety features – a classic example of "crying-wolf" too many times. Social pressures to ignore alerts as a result of low clinical significance may compound the problem. (Calvitti et al.,2006). Unintended consequences by Ash et al. (2007e) also describe social issues such as provider loss of control, and annoyance at constantly being told what to do (Ash et al., 2007e). In essence, alert models consist of the alert and the physical and social environment in which it exists (Kafeza et al., 2004; Calvitti et al., 2006)

2.6.1 Downstream alerting effect pharmacists and nurses

This focus of the research reported here is on the allergy alert at the point of ordering. However, high volume, low value downstream alerts to the pharmacist at dispensing, or the nurse on administration are also problematic. Prior to CPOE, physicians and nurses relied heavily on the safeguards provided by hospital pharmacists who reviewed the drug order against patient lab values, allergies, age, condition and disease states (Raebel et al., 2007a; Raebel et al., 2007b). The high rates of alert overrides by providers may also reflect the belief that the pharmacist or nurse will "catch" an

important alert prior to reaching the patient. However, one study of community based pharmacists showed significant alert overrides of minor/moderate severity (Indermitte et al., 2007). Cash et al. (2009) suggested that the potential for alert fatigue was predictable from the experiences with pharmacy systems.

Bar-coded medication administration (BCMA) systems, used by nurses, are designed to ensure the ordered drug gets to the intended patient (Kowiatek et al., 2006) (Mills et al., 2006). If safeguards fail within the ordering and dispensing process, a different kind of decision support may be available at the point of administration. Nurses are presented with multiple BCMA alerts designed to assure the right patient, drug, dose, route of administration and appropriate time (ISMP, 2007). However, in many facilities, the decision has been made to turn off interruptive allergy alerts for nursing due to the provider/pharmacist experience with the high volume of low/no severity alerts.

2.7 Preliminary Allergy Alert Research

In 2003, the American Medical Informatics Symposium (Kuperman et al., 2003) focused on the complexities of getting coded allergy information into a centralized electronic medical record. Confirming the value of CPOE CDS, Hsieh and colleagues (2004) reported that about 20% of allergic patients experience reactions when given the drug allergen. However, in that same study, 80% of the allergy alerts were considered justifiably overridden with the most common reasons being: *Aware/Will monitor* (55%), *Patient does not have this allergy/tolerates* (33%), and *Patient taking already* (10%). In this 3 month sample (1150 patients with 7761 alert overrides), the highest rate of override was for narcotics (39%, n=444) (Hsieh et al., 2004). The study concluded with

recommendations for increasing the specificity of drug allergy alerting which has been echoed by many subsequent studies (Kuperman et al., 2003; Swiderski et al., 2007; Varghese, 2007; Ariosto D, 2008; Hunteman et al., 2009). In the years since these studies, a significant amount of unvalidated "allergy" information has been added to EMRs contributing to an even higher volume of allergy alerts.

Three preliminary, unpublished studies in which this author participated have also informed this research. The first being a study done at a large academic medical center in the mid-atlantic region that analyzed the frequency with which serious allergy alerts (e.g. anaphylaxis, bronchospasm) were overridden (Pifer et al., 2007). The assumption was that serious alerts would not be ignored except by accident (slips or mistakes). High rates of overrides were still identified in these serious allergic reactions. Anaphylaxis, one of the highest severity alerts, was overridden in 60% of the cases – suggesting that a true history of anaphylactic reactions were unlikely. This calls into question that skill and understanding of allergic reactions by the staff member collecting and recording allergy history data. Subsequent analysis of a random sample of charts (n=70) revealed no adverse drug reactions in this population. While this suggested that overrides were predictable, it did not answer the question of data reliability versus alert fatigue as a cause of high override rates in this population.

A secondary data analysis of that same dataset examined the number of overrides across all drugs and all severity levels of reactions. This identified antibiotics and opiates as contributing to the highest number of alerts and alert overrides, which was well supported in the literature (Hsieh et al., 2004; Hunteman et al., 2009).

The third study of opiate orders at a small cardiac specialty hospital revealed minimal differences in opiate ordering for patients recorded as allergic as opposed to those who had no opiate allergy recorded (Ariosto, 2008). This supports the assumption that opiate allergies are rare, and that opiate allergy alerting has low value. Secondary analyses described the prevalence of opiate allergies in the target population, the incompleteness of the narcotic allergy history, and the lack of documented reactions of allergic patients who received a narcotic. In this study of 9,648 patient allergies, 778 were opiates "allergic"(8%). Of these, Codeine (3%), Oxycodone (2%) and Morphine (1%) were the most commonly recorded allergies.

2.8 Alert Value versus Alert Burden

Human error models describe a "cognitive 'balance sheet' where each entry on the asset side (alert on all possible ADR) carries a corresponding debit" – alert fatigue. (Reason, 1990). In allergy alerting, the asset is the capacity to capture and electronically display all possible drug sensitivities – shifting the cognitive burden from clinician memory to computer. The debit is information overload/alert de-sensitization or second line drug choices and treatment delays while acquiring additional data. In clinical terms, we are speaking of the balance of safe and effective medication ordering. Research on alert fatigue demonstrates that a "better safe than sorry" approach to over-alerting no longer holds true. If the CDS algorithms in use today were precise, there would be no question as to how to proceed. Hard decisions will need to be made to eliminate alerts, where there is no guarantee that there will never be an adverse patient outcome. The

clinical question is changing from "Is this patient sensitive to this drug?" to "What is a reasonably safe and effective drug to order?"

2.8.1 Norman's Theory of Action

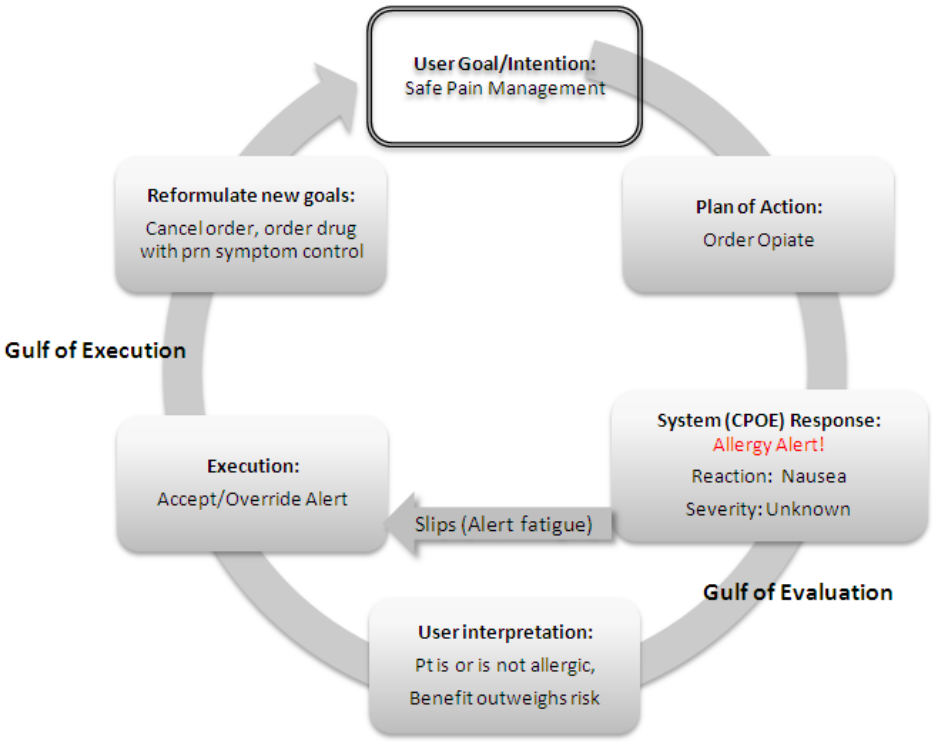
The fields of cognitive psychology, human-computer interaction (HCI), and computer-supported collaborative work (CSCW) heavily inform this work. Norman's Theory of Action (Norman, 1998) is a frequently cited model for clinical decision support research and will be used to visualize parts of this work. The model starts with a goal (patient comfort) and then cycles through stages of actions: plan of action (*order drug*), the response by the system (*warning – patient is allergic*!), user interpretation (*patient needs this drug and is probably not allergic*), evaluation (*accept/reject alert*) and re-formulation of new goals (*cancel order, order drug, order p.r.n. symptom control*).

Norman's model categorizes these stages into gulfs of execution and gulfs of evaluation. The gulf of execution refers to how easy or hard is it to get from intention to execution (safe and effective medication ordering practices) using automated affordances (CPOE). The gulf of evaluation reflects the mental processing required interpreting the system and how well expectations and intentions were met.

Norman states that there are gulfs on the system side (CPOE CDS design) and the user side (provider information needs). The goals and intentions are never perfectly matched. The psychological goal of the user, in this case, is to quickly and safely order medications. Some providers know their patients well and can mentally fill in the gaps. Others may have little or no information and depend upon their skills to acquire needed

information from other parts of the electronic medical record and/or their ability to get further information from patient and staff.

Figure 2.2 Norman's Theory of Action applied to CPOE



The goal of the system (CPOE CDS) is to process orders and alert when coded allergy matches coded drug or related drug class. These mismatches, or gulfs, can be bridged by both the system designer or system user. The system user starts off with goals expressed in psychological terms (safe medication ordering), but adapts to the system as they move through a sequence of actions, filling in the gaps with other known information or retrieved about the patient. The system designer evaluates system inputs (allergy data) and outputs (allergy alert) and tries to anticipate the psychological intent of

the users (Norman, 1986). In our highly litigious society, pharmacologic vendors who develop the embedded alert logic have no incentives to change the algorithm to reduce the numbers of alerts identified. Pharma vendors like First DataBank, Inc. are working on the system-side to give user facility-based rights (and responsibilities) to block certain types of alerts. This model highlights significant opportunities for improvement at every action stage and reducing the gulfs between design intent and user experience.

2.9 Summary

With computerization and increasing use of electronic monitoring systems comes virtually unlimited capacity to remind, alert, and alarm the clinician. Yet, complex clinical environments are not well simulated in most computer labs – although this science is starting to emerge. Shifting workflow contexts are typically not observable to the decision logic when alerts are programmed. An alert in one setting may aid decision making in one workflow context yet be disruptive in another (Saleem et al., 2005). Excluding fatigue, reasons for alert override fell into three broad categories: (1) information errors (not allergic), (2) systems errors (duplicate medication or class), and (3) clinician decision (benefit outweighs the risk) (Weingart et al., 2003; Mille et al., 2008). In each of these categories, no published strategies to implement change in practice or processing for allergy alerts have been identified. While there is evidence on how to treat allergies and hypersensitivities, there is no consensus on how to classify non critical hypersensitivities for CPOE drug alerting except by direct allergy testing. Allergy alerts differ from other types of alerts in that they often depend upon patient recall rather than those that depend on discrete lab values, diagnoses, or known

interactions with other drugs. Allergy data is collected by clerical and/or clinical staff across multiple venues (clinic, inpatient, doctor's office) and during care encounters of varied intensity (routine, urgent) from patients or their surrogates (spouse, aide, etc.). This suggests that allergy alerts, while simpler to program, may be more complex to successfully to design and implement than other types of drug alerts.

There is general consensus in the literature that CPOE drug alerts are excessive, distracting, contribute to significant clinician cognitive burden and raise patient safety and quality of care concerns. Despite these problems, by apparent agreement, these alerts should not be turned off.

3.0 Methods

3.1 Overview

This chapter describes the methods used in the study in detail. The setting describes relevant characteristics of the data collection related to allergy history and allergy alerting. Considering that this is an analysis of administrative data from multiple files, the creation of the analytic file is described in detail. Some of the descriptive data are presented in this chapter since the analytic file was created based on characteristics of the supporting files. The statistical analyses related to the aims are also described.

3.2 Study aims

The study purpose was to analyze allergy reaction and severity attributes to identify approaches that could be manipulated by future developers to reduce the volume of opiate allergy alerts. Specific study aims were to: (1) describe the prevalence and attributes of opiate hypersensitivity alerts and (2) analyze the influence of reaction/severity group, patient characteristics, reason for admission and prescriber role on opiate allergy alert overrides.

3.3 Setting

The study was conducted at a large urban, southeastern academic medical center with approximately 40,000 adult inpatient discharges and over 1.2 million clinic visits annually. IRB permission was obtained from both the study site and University of Maryland. The center has a large biomedical informatics department, and extensive clinical systems development capacity. It has a long history of electronic medical record

and inpatient computerized order entry use. The inpatient CPOE system in use was a hybrid application of internally developed (WizOrder^{tm}) and commercial product by McKesson/Horizon Expert Orders^{tm} (HEO).

Two other internally developed data input applications supplied allergy data which were used in both inpatient and outpatient settings. The first application used two screens for allergy data collection. The collection used consisted of 12 checkbox choices related to opioid allergies (No known drug allergy, Codeine, Hydrocodone, Oxycodone, Butophanol, Fentanyl, Hydromorphone, Meperidine, Morphine, Pentazocine, and Propoxyphene) as well as dozens of a non-opiate checkboxes. There was also a space for free text if the choice was not in the list. The continuation screen (page 2) displayed five reaction checkboxes (Anaphylaxis, Rash, Urticaria, Nausea/Vomiting, Intolerance) as well as a free text box for other reactions to be recorded.

The second data collection screen used a simpler user interface consisting of only one screen. It was accessible from the EMR during activities such as the admission history. This style of screen display uses an extensive drop down list of drugs from the hospital formulary. A "type-ahead" feature is used, whereby each letter that the user types matches on a similar drug name, thus shortening the list. For example, typing "MOR" returned all the morphine choices in alphabetic order . Reaction worked the same way, by typing the letter "A", the system retrieved all the reactions starting with the letter "a": agitation, anaphylaxis, angioedema, anxiety, etc. The same for severity: mild, moderate, severe, unknown. There were no forcing functions to fill out any of the data.

Allergy information is generally self-reported. All allergy data, regardless of originating system is collected by a patient summary service (PSS) application that makes

this data available to CPOE and other decision support decisions. The CPOE drug alert logic, however, is commercially supplied by First DataBank, Inc. [tm]

3.4 Design

This was a retrospective, quantitative analysis of 25,461 CPOE opiate allergy alerts across 3,473 discharges (2,767 patients). Since this was a large data set, representative of the entire population of patients, power and sample size was not a concern.

Prevalence of opiate allergy alerts across all FY10 opiate orders was calculated. Descriptives of related attributes included: (1) patient (age, race, sex), (2) prescriber alert override (APN, physician), (3) reason for admission (medical, procedural), (4) reaction descriptions (i.e. nausea) and (5) severity (mild, moderate, severe).

Descriptives from opiate allergy reaction descriptions and associated severity were combined to create a new reaction/severity variable with three groups: (1) Non-allergic/Low Severity (NALS), (2) Unknown Reaction with Unknown Severity (Unk), and (3) everything else (NoNALS).

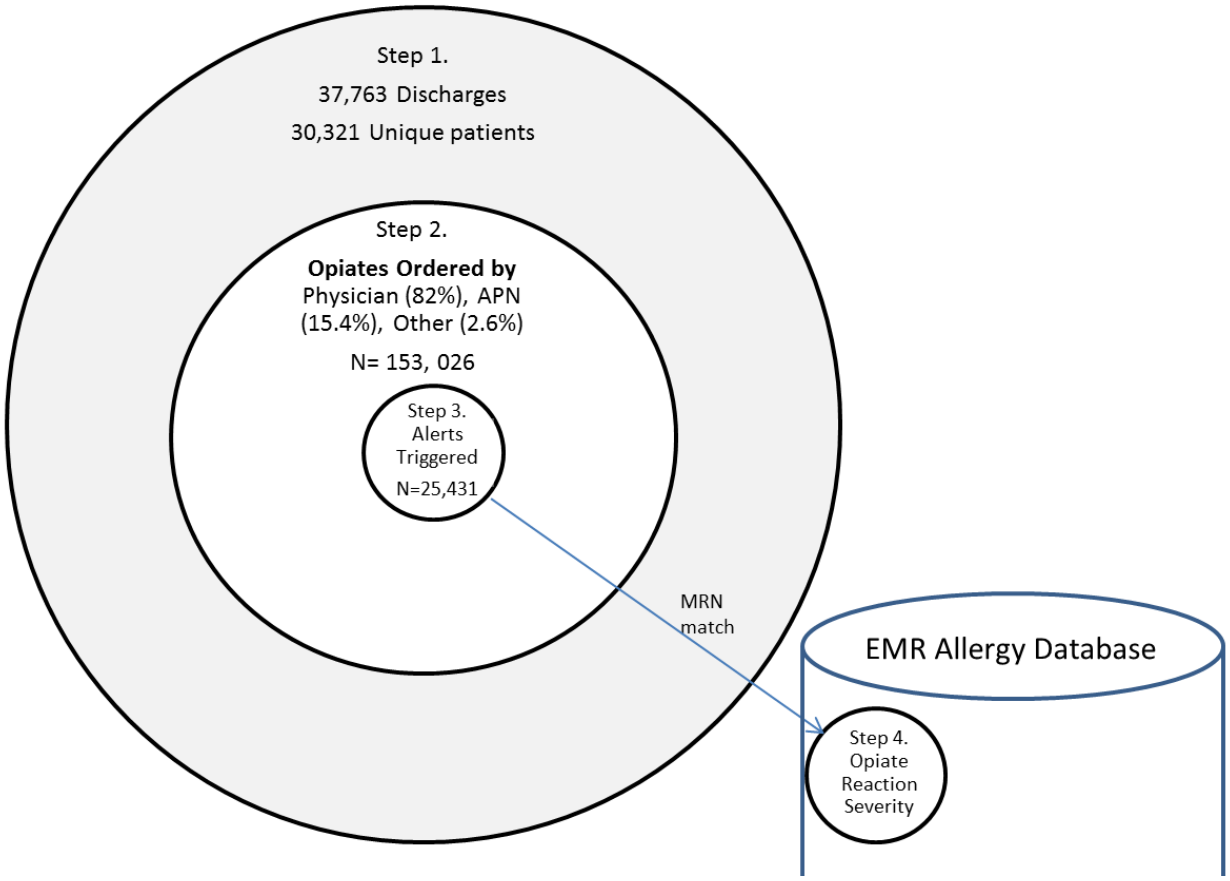
3.5 Research File Development

Four datasets were extracted from the medical center electronic data repository to develop the analytic file:

1. FY10 Patient demographics and admission type
2. FY10 Opiate orders
3. FY10 Provider opiate order alert log
4. Current patient allergy history

The files were merged on patient medical record number and de-identified to protect confidentiality of patients and providers. Figure 31 schematic below shows the relationship of the of the data files which are linked by unique medical record number.

Figure 3.1 Analytic File Development



All discharge records were selected in the first step. The most recent full fiscal year was selected to adjust for seasonal variations in diagnoses, the influence of new

residents who will gain and mature their CPOE skills over the course of the year, and to correlate with one version of the diagnosis related groups. From 10/1/2009 to 9/30/2010 (FY10) there were 37,763 discharges extracted, representing 30,321 adult patients.

The patient's unique medical record number, race, gender, discharge date, admission date and birthdate were extracted. Age was calculated based on subtracting date of birth from admission date. Patients less than 18 years old at admission were excluded. The distribution of these demographic variables across FY10 patients is shown in the table 3.1 was evaluated to evaluate missing data and identify logical groups.

Table 3.1 FY10 Demographic Discharge Characteristics of Adult Patients

	Total	Medical	Procedural
Unique Patients	30,321		
Discharges	37,763	56%	44%
Average Age	51	48	53
Gender			
Female	52.1%	30.9%	21.2%
Male	47.9%	24.9%	23.0%
Race			
White	78.7%	41.9%	36.8%
Black	15.6%	10.3%	5.3%
Unknown	2.5%	1.5%	0.9%
Hispanic	2.3%	1.5%	0.9%
Asian	0.7%	0.5%	0.2%
Indian	0.1%	0.1%	0.1%

As expected, there was no missing data since these were derived from databases that drive hospital reimbursement. Medical and procedural variables were already pre-assigned to the discharge record based on the FY10 *All Patient Diagnosis Refined Groups* (APDRGs) billing code type. These codes reflect the reason for patient

admission. The six race variables (White, Black, Other/Unknown, Hispanic, Asian, Indian) were recoded into 3 (Black, White, Other) variables based on volume. After these variables were created, date of birth and admission date were removed from the file.

The second step was to extract all opiate orders (n=153,026) from the FY10 CPOE orders database based on the American Hospital Formulary System (AHFS) opiate class code =28080800. These orders were matched to the discharges identified in step 1 to calculate the percentage of discharges with opiates ordered (53%).

In addition to opiate ordered, prescriber ID and role were captured. Prescriber roles were recoded into 5 groups: (1) Physician, (2) Advanced Practice Nurse, (3) Staff Nurse, (4) Pharmacist, (5) Physician Assistant, and (6) Other (i.e. clerical/billing, etc.). Those in clerical/billing roles enter orders for drugs retrospectively in cases where the original order may have not have been captured electronically (verbal, handwritten, or part of a protocol set). These were excluded from the analysis.

In the final research file, only the physician and APN role groups were retained, representing 97% of the FY10 opiates ordered. Those in the APN group were nurse practitioners, clinical nurse specialists with ordering privileges, midwives, and nurse anesthetists. Table 3.3 below shows the frequency distribution of roles ordering opiates based on these groupings. Physician assistants and pharmacists represented a special class of clinicians that would have been logical groups for consideration, but were not evaluated due to their low volume in this dataset. Pharmacists' responses to alerts were reflected in the medication dispensing system, but not captured as part of this study.

Table 3.2 Frequency of FY10 Opiates ordered by Provider Type

Provider type	#	%
Physician	125,491	82.0%
APN	23,535	15.4%
Other	2,028	1.3%
Staff RN	1,910	1.2%
Physician Assistant	62	0.0%
Total	153,026	

In the third step, the opiate allergy alert response log was extracted from the CPOE allergy alert dataset. This log recorded whether the provider cancelled the order or overrode the alert. The extraction criterion for the opiate alert log was any CPOE warning to the opiate class triggered during the study period.

There were 25,431 opiate related alerts triggered for 3,473 discharges during the study period. To reduce the dataset, and minimize the influence of excessive repeating alerts for some patients with long lengths of stay and re-admissions, only the patient's first opiate allergy alert (alert1) was used in the regression analysis for each patient.

The two provider CPOE alert responses were (1) Override alert (place order) or (2) Accept alert (cancel order). The reason for override field was available, but was excluded since it was 99% blank.

The drug orders and related drug allergy groupings were identified through manual assignment to groups based on string matches to data in the parsed allergy alert warning. Below is an example of an opiate alert string which was then later parsed into order = morphine, allergy = codeine:

> *! The use of MORPHINE INJECTION: may result in an allergic reaction based on a reported history of allergy to codeine.*

This was repeated for all opiates in the dataset. The allergy alert contained information about the ordered drug, and the allergen the alert was based on. Of note is that the reaction severity is not displayed in the body of the alert, but was somewhere on the ordering screen.

In the fourth and final step, patients with opiate allergies were extracted from the EMR allergy database where their MRNs matched those in the discharge dataset created in step 1. This was necessary because the allergy alert log did not contain needed information about the allergy reaction and severity to create the NALS variable. While some of these patients had multiple allergies, only opioid allergies were retained.

3.6 Creating a Combined Allergy Reaction + Severity Variable (NALS)

The second aim of this study was to identify factors that influence opiate allergy alert overrides (false positives). Study factors such as (1) patient demographics (sex, age, race), (2) medical vs. procedural admission, or (3) prescriber role have standard definitions and are well defined in the database. The fourth factor of interest, allergy reaction severity has not been well delineated into meaningful groups. To that end, 3 mutually exclusive, reaction/severity groupings were created from the allergy file developed in step 4. These allergy/reaction groups were: (1) Non-allergic reactions of low severity (NALS); (2) Unknown reaction with unknown severity (Unknown) and (3) everything else (NoNALS).

To create the NALS variable, opiate reactions were first stratified by severity levels. Severity distribution was 2.5% mild, 6.5 % moderate, 16.8 % severe and 74.3 % unknown/blank based on coding, and explicit text in the reaction field. That is, if the

reaction type was entered as “severe vomiting” and the severity was coded “unknown”, it would be assigned to the severe group. Patient with multiple opiate allergies of varying severity were assigned the most severe level that was recorded for them. All severity assignments were visually inspected for accuracy.

In the months prior to this study, the entire historical allergy database at the study site was analyzed to identify logical groupings of allergy reactions. This database is populated by a patient summary service (PSS) the pulls allergy data from different systems. This turned out be an extremely labor intensive endeavor as there were no standardized approach enforced to coding allergy reactions. Appendix B shows the raw data from the top 75% most frequently recorded reactions across all allergies and all patients. From this dataset, strategies were applied to pull out reactions by category using string matches (nausea), partial wildcard matches (*GI*), abbreviations (N/V) and misspellings (nausa), followed by visual review to remove inaccurate matches match (not **gi**ven). The data also identified implied high severity (projectile vomiting, anaphylaxis) that was not reflected in the coded severity field. This extensive, preliminary review of the entire dataset was done to ensure that findings from this study could be applicable across all allergy reactions, not just opiates.

The study reaction data was then organized under the following groups: Skin, Gastrointestinal, Nervous/Mood changes, Unknown and Other. These will be more fully discussed in chapter 4. Of note was that 74.3% had no severity described. For severe reactions like anaphylaxis or difficulty breathing, the severity is implied in the reaction description itself. Table 3.3 show reaction and severity frequency distributions.

Table 3.3 Characteristics of FY10 Opiate Reactions by severity and by group

Patients		Reaction	Severity			
#	%		Mild	Moderate	Severe	Unknown
1323	28%	Other	1%	2%	7%	91%
1142	24%	Skin	4%	7%	15%	73%
1046	22%	Gastrointestinal	2%	9%	15%	74%
504	11%	Nervous/Mood	2%	9%	22%	68%
781	16%	Unknown/Blank	0%	0%	0%	99%
4796	100%	All	2.5%	6.5%	16.8%	74.3%

Note. Some patients had more than one reaction

The next step was to assign allergy status: allergic vs. non-allergic. Each reaction within each group was evaluated. This was difficult due to the paucity of descriptive reaction detail. The following is an explanation of how reactions were assigned to or excluded from the non-allergic/low severity (NALS) category.

Skin (24%) - The predominant reaction within the skin category was itching and rash. While there were mild reactions recorded, this group as a class was excluded from the NALS category, since it is difficult to tell if these skin reactions were histamine responses of a pseudo-allergy (NALS), or a true, immune mediated allergic reaction (NoNALS).

Nervous/Mood (11%) - Those in this category ranged from nervousness, insomnia, confusion, hallucinations, to suicidal ideation. In this group, there were very few coded as mild severity. There were only 2 coded mild reaction types that could have been included in the NALS group (sleepy, headache) – but these were excluded due to low volume compared to the class.

Other Reactions (28%) – The information in this group was difficult to classify by body systems. It was highly variable, and had low volumes in any one category. It also included non-allergy type data such as:

- Patient received Narcan in the past (respiratory rescue)
- Patient has history of opiate abuse
- Patient has liver failure, dose appropriately
- Patient allergic to IV morphine, but can tolerate oral
- Patient has stomach ulcers, may bleed from NSAIDS

Gastrointestinal (22%) - The predominant reaction in the GI category was nausea and vomiting. Those coded or described within the free text as moderate or severe reactions were assigned to NoNALS category. Those GI Reactions with mild, unknown, or blank severity were assigned to the NALS group if the descriptions were nausea, vomiting, upset stomach, constipation, diarrhea, or GI upset. The assumption being that if it were more than a mild reaction, it would likely been have recorded. This is an acknowledged limitation and will be discussed later as an area for future analysis. More severe reactions such as bleeding or ulcer (exacerbation) were excluded from NALS.

After review of the data, the decision was made to limit the NALS category to GI reactions that were not severe or moderate severity. The other non-GI groups had a too wide a range of ambiguous descriptors without clear severity levels that made it difficult to assign to the NALS group. The GI category descriptors were homogenous, simple, and reflected a high volume of known side effects listed as allergic reactions.

Limiting NALS to GI only is a conservative approach that will underestimate the size of NALS, since there were many other reactions that could have been considered individually but not as a class (i.e. “jittery vs. suicidal”). In fact, one could argue that

"jittery" could be a precursor to the most severe reactions such as dyspnea, suicidal ideation, or anaphylaxis.

Each patient was assigned to one of the study categories (NALS, NoNALS, Unknown) using the coded severity and opiate reaction data in the patient allergy file. The following algorithm was used, followed by visual confirmation and assignment to one of the three following groups:

= Unknown
Where both reaction and severity are blank or stated unknown

= (GI) NALS
Where reaction = nausea, vomiting, constipation, diarrhea, or gi upset
Severity = low or unknown

= NoNALS
Assign everything else to NoNALS
Patients with multiple opiate allergies would be assigned to NoNALS at the patient level if both NALS and NoNALS were present.

3.7 Statistical Analysis

The Generalized Estimating Equation (GEE) was selected as the statistical approach to model the effect that patient, provider, and reaction severity factors had on opiate allergy alert overrides. A number of strategies were considered to reduce the size of the large dataset and to mitigate the patient and provider nesting effects. Nesting examples include:

- Nesting within patient: A patient with a long length of stay with opiates re-ordered every few days by the same provider would increase the influence of those alert responses on the sample; and
- Nesting within provider: A provider may have a particular population type, such as oncology, that may reflect a particularly high utilization of opiates and therefore opiate alerts and thus be overestimated in the sample.

Removing the nesting effect by patient was achieved by keeping only the patient's first FY10 opiate allergy alert, eliminating subsequent alerts. This reduced the dataset to 2,767 alerts for 2,767 unique patients. Conceptually, GEE adjusted for provider influence by "averaging" the individual provider's overall alert response rate. The final analytic file analytic file used for descriptives and GEE analyses is shown in Table 3.4.below.

Table 3.4 Variables included in final analytic file

Source File	Field	Values	Description
All	MRN	Number	Unique patient medical record number
Disch	MedProc	M,P	Visit type = medical or procedural visit based on APR-DRG code
Disch	Age*	Number	Calculated age at admission
Disch	Race*	W,B,O	White, Black, Other (combined all others)
Disch	Sex	F,M	Female, Male
Alert	Order	Percocet	The opiate order that triggered an allergy alert
Alert	Allergy	Codeine	The allergy that triggered the alert.
Alert	Response	0, 1	0=No, Cancel Order, 1 = Yes, Override alert, place order
Alert	Alert1*	0	First patient alert triggered based on earliest order date/time
Alert	Role*	Phys, APN	Role type (physician or APN) responding to the alert
Alert	Role_ID	Number	Physician or APN unique identifier
Allergy	NALS*	0,1,2	Patient opiate allergy reaction type and severity variable: 0-Unknown 1=NALS (non-allergic/low severity), 2= Not NALS

Note. * Computed or Transformed variables

4.0 Study Results

4.1 Chapter Overview

The chapter presents the results of the data analyses. Since some descriptive characteristics are summarized in Chapter 3, only a brief summary is presented of the sample characteristics. The focus of the chapter is the analyses of the aims.

4.2 Summary of Descriptive Findings – All Discharges

For inpatients of all ages, 53% had opiates ordered representing 153,026 orders. The opiate order alert sub-sample included 37,763 adult inpatient discharges for 30,321 patients, since some patients had multiple admissions (Table 3.1). These triggered 25,461 opiate allergy alerts across 3,473 discharges for 2,767 patients. Physicians responded to 82% of these alerts and Advanced Practice Nurses (APN) to 15.4%, with other responses attributed to other clinical and non-clinical roles.

When multiple admissions by patient were counted, medical discharges were higher (56%) than those for procedural (44%) discharges. This is expected as chronic medical conditions are more likely to have readmissions. The admission type variable reflects not only the patient clinical condition, but the provider subtype (medical, surgical). The average age of medical admission (48 yrs.) was younger than those having procedures done (53 yrs.), with an average age of 51 years.

For race equal to *White* (78.7%) there were a similar proportion of medical (41.9%) to procedural discharges (36.8%). For race equal to *Black* (15.6%), there were twice as many medical (10.0%) to procedural (5.2%) based discharges. *Hispanic* (2.3%), *Asian* (0.7%), *Indian* (0.1%) and *Unknown* (2.5%) comprised the *Other* race category.

4.3 Prevalence and attributes of opiate hypersensitivity alerts (Aim 1)

The preceding descriptives reflected all discharges, including patients who might have been readmitted and have more than one discharge during FY10. This was important because it reflects the true alert burden. The second analysis counted patients only once using only the patient's first FY10 admission that triggered an opiate allergy alert (alert1). The opiate allergy override rate was 89% for the first patient alert only (n=2,767), and 93% overall for all alerts (n=25,461) during all admissions.

This study found, at a minimum, a reported 9.1 % (2,767/30,321) opiate allergic patient prevalence .This is understated since it only captured those patients with opiates orders. Patients who may have been recorded as having an opiate allergy may never have needed pain control during their stay.

4.3.1 Patient Level Characteristics

When the database was reduced from all discharges to include only first patient opiate allergy alert admission, the distribution of patient characteristics changed significantly. The summary of sample characteristics are represented in Table 4.1. Surprisingly, females outnumbered males 2:1. Unfortunately, gender data was not available in the initial opiate order set to determine if women had more opiates ordered. Future research to determine if opiates are ordered more frequently for women than for men might explain some of this dramatic shift. There is some research that women report use and abuse of opiates more often than men (Greene et al, 2009). The increase may have also reflected the effect of a large obstetric population that generally are not re-

admitted and would be underrepresented in the all admissions sample. Obstetric patients receive epidural opiate administration during delivery as well as other opiates for post-operative pain management. The complete list of drugs, including epidural medications, ordered in FY10 is listed in Appendix B.

Table 4.1 Summary of Sample Characteristics by First Opiate Allergy Alert Response

	Patients		Override = No n=304)	(11%)	Override = Yes (n=2463)	(89%)
	N	%	N	(%)	N	(%)
Gender						
Female	1,900	(68.7)	222	(73.0)	1678	(68.1)
Male	867	(31.3)	82	(27.0)	785	(31.9)
Race						
Black	302	(10.9)	30	(9.9)	272	(11.0)
Other	80	(28.9)	11	(3.6)	69	(2.8)
White	2,385	(81.2)	263	(86.5)	2122	(86.2)
Reason for Admission						
Medical	1,112	(40.2)	111	(36.5)	1001	(40.6)
Procedural	1,655	(59.8)	193	(63.5)	1462	(59.4)
Allergy Reaction/Severity						
Unknown	699	(25.3)	78	(25.7)	621	(25.2)
NALS	425	(15.4)	36	(11.80)	389	(15.8)
Not NALS	1643	(59.4)	190	(62.50)	1453	(59.0)
Prescriber Role						
APN	246	(8.9)	49	(16.10)	197	(8.0)
Physician	2521	(91.1)	255	(83.90)	2266	(92.0)
			Mean	(SD)	Mean	(SD)
Age in Years			54.7	(16.7)	54.5	(16.4)

The percentage of race being White increased from 78.7% to 86%, while Black decreased from 15.6% to 11%. This may reflect that Caucasians are more likely to use

hospital services and be re-admitted. The average age of the sample increased from 51 to 54 years, which may reflect the influence of the increase in Caucasian and female populations who may have higher longevity and subsequent utilization of hospital services.

The type of admission changed as well when capturing only the first admission. Procedural representation increased from 44% to 60% and medical decreased from 60% to 40%. This is understandable since those with chronic medical conditions, like cancer, are more likely to be re-admitted multiple times. Surgical follow-up will likely occur in outpatient arenas.

4.3.2 Reported Drug Allergies Triggering Opiate Alerts

To look at the actual alert burden, all alerts across all discharges are described. There were four opiate allergies responsible for the majority of the alerts. Allergies to Codeine (32%), Morphine (28%), Hydrocodone (11%), and Oxycodone (11%) triggered 82% of the opiate allergy alerts. Table 4.2 displays the list of allergies by number of alerts triggered, and by number of discharges by opiate allergen.

Table 4.2 Patient Allergies Triggering Alerts for All Discharges in FY10

Allergy	#Alerts	%Alerts	# Disch	%Disch
Codeine	8,163	32%	1600	36%
Morphine	7,152	28%	1079	24%
Hydrocodone	2,783	11%	483	11%
Oxycodone	2,773	11%	427	10%
Hydromorphon	1,190	5%	211	5%
Tramadol	971	4%	147	3%
Nubain	595	2%	61	1%
NSAID/OTC	541	2%	148	3%
Butorphanol	536	2%	70	2%
Meperidine	306	1%	104	2%
Propoxyphene	239	1%	105	2%
Opioid	88	0%	10	0%
Fentanyl	60	0%	19	0%
Dihydrocodein	23	0%	2	0%
Oxymorphone	21	0%	2	0%
Other	20	0%	11	0%
	25,461	100%	4479	100%

Note. Some patients may have more than one reported allergy

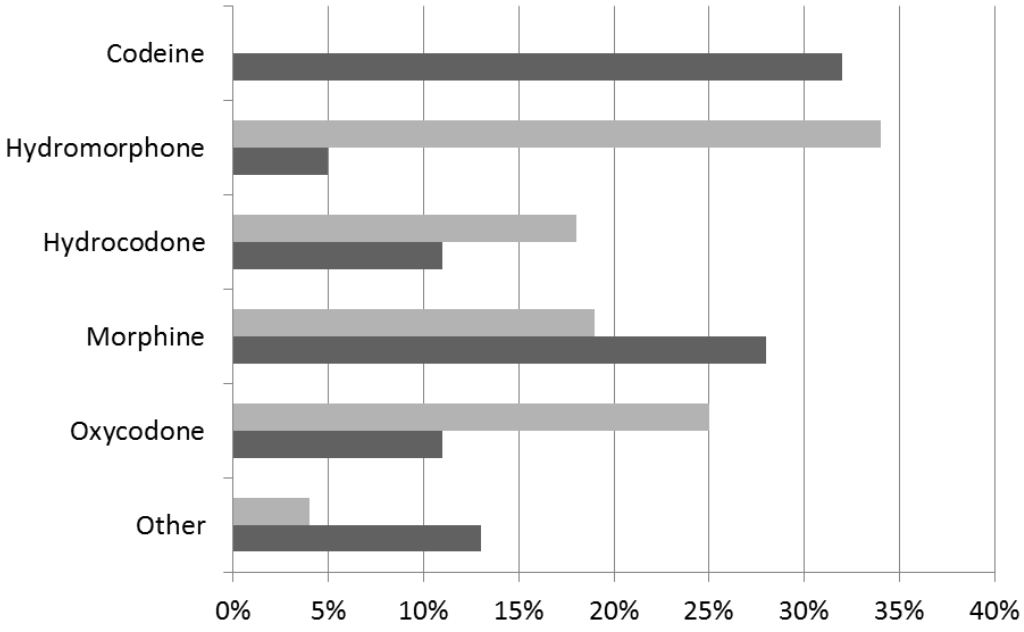
4.3.3 Drugs Triggering Alerts

The most frequently ordered drugs triggering opiate allergy alerts were: Hydromorphone (34%), Oxycodone (25%), Morphine (19%), and Hydrocodone (18%). These four drugs triggered 96% of opiate alerts. Table 4.3 lists the frequency of opiate allergy alerts by triggering drug order. Of note is that codeine is near the bottom. Although Codeine triggered the highest number of allergy alerts in the previous table, and represented the highest reported allergy (36%) it was rarely ordered. That is because opiate class alerts were triggered due to cross reactivity algorithms. That is, other opiates in the same class as codeine triggered an alert based on the patient having a codeine allergy. Figure 4.1 shows the effect of both the drug and the allergy in triggering alerts.

Table 4.3 FY10 Drug Orders Triggering Alerts (all ages)

Drug Order Group (sample trade name)	#	%
Hydromorphone (Dilaudid)	8,599	34%
Oxycodone (Percodan)	6,395	25%
Morphine	4,916	19%
Hydrocodone (Lortab,Vicodin)	4,590	18%
Tramadol (Ultram)	435	2%
Fentanyl (Duragesic patch)	354	1%
Belladonna-opium suppository	82	0%
Acetaminophen w Codeine	34	0%
Meperidine (Demerol)	20	0%
Codeine	16	0%
Propoxyphene (Darvon)	10	0%
Methadone (Dolophine)	10	0%
Total	25,461	100%

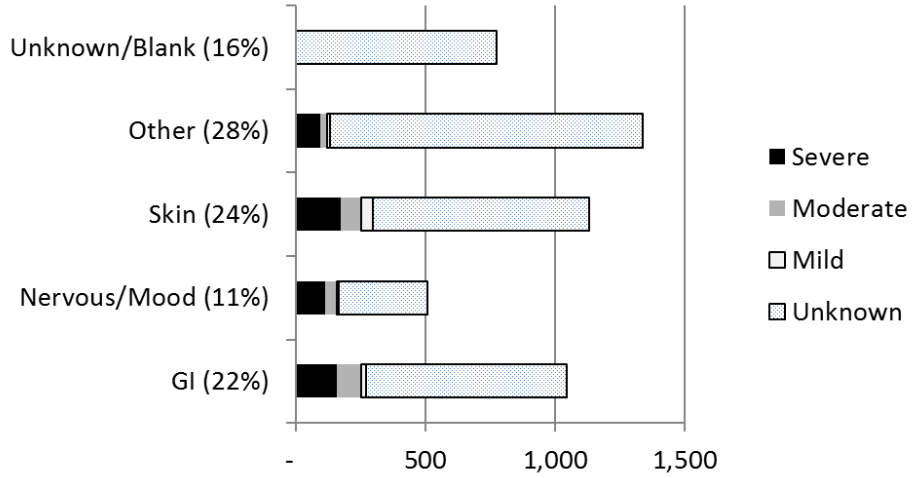
Figure 4.1 Opiate Alert Triggers



4.3.4 Reaction and Severity

The previous chapter noted that of the reactions recorded, 74.3% had no severity (mild, moderate or severe) recorded. Of those with no severity, 16% had no reaction recorded (e.g. itch, nausea, rash, anaphylaxis). To the provider, this says the patient is allergic to morphine, but we don't know what the reaction is or how bad it was. Overall, alerts with severity coded or described are 2.5% mild, 6.5% moderate, and 16.8% severe. While skin had the greatest number of mild reactions coded (itch, rash), these might be true allergic responses that could escalate on next dose. Therefore the NALS category was restricted to GI reactions only. Figure 4.2 graphically depicts the distribution of severity levels across alerts, by body system, of the data that was described in Table 3.3

Figure 4.2 Alert Severity Levels for All Discharges



The last attribute evaluated was the reaction/severity variable (NALS) previously created. First alerts were stratified into 3 allergy reaction/severity classes as previously described. Non-allergic/low severity (NALS) GI reactions accounted for 15.4% of the

first alerts. The override rate for the patient's first alert for all opiate alerts was 89%. Removing the GI NALS alerts reduced the first alert volume for opiates by 15% (425/2767) but did not significantly change the 89% overall alert override rate. Removing GI NALS alerts from all alerts would have resulted in a 9.1% reduction (2342/25461) of opiate allergy alerts fired for the discharge dataset.

4.4 Influence of patient, prescriber and reaction/severity factors on override (Aim 2)

Aim 2 analyzed the influence of patient characteristics, reason for admission, prescriber role and reaction/severity group on opiate alert overrides. The primary intent of this aim was to determine if a subset of reaction/severity types (GI NALS) had a higher override rate than other alert types. Logical factors such as patient age, race, sex, and whether they were admitted for a medical or procedural condition were also considered as potential influencing factors on the provider's opiate allergy alert response decision to accept or reject the alert.

The Generalized Estimating Equations (GEE) procedure (SPSS v20) was used to extend the generalized linear model to allow for analysis of clustering and repeated measurements. Clustering can happen when a physician may treat primarily a specialty population like orthopedics or cancer that may unduly influence outcomes based on opiate use. Repeated measurements over time may reflect the fatigue that occurs when a provider has a lot of alerts over a short period of time. The dependent variable of interest was the override response (yes, no), so a binary logistic model was selected, with "no override" as the reference category. Clinician ID was the subject variable, and Patient ID was the within subject variable. The repeated measurements were assumed to be

uncorrelated as they represented different patients, so an independent correlation matrix was selected. There were 697 providers (89% Physicians, 11% APN) who had from 1-28 first opiate allergy alerts (mode=1, median= 3). Table 4.4 shows the first alert response rates by provider.

Table 4.4 Provider First Alert Response Frequencies

Responses by Role	Alerts		Override	
	N	%	N	%
APN (n=77)	246	9	197	80
Physician (n=620)	2,521	91	2,266	90

To further visualize the value of GEE, and the problem it solves, Figure 4.3 shows the undue influence that high volume providers could have had on the model if all of their alert responses were counted. The graph below depicts the frequency of accepted alerts (override=no) in the black foreground, and the alert overrides (override = yes) in the gray background for all providers.

Conceptually, GEE adjusts by applying an advanced type of "averaging" alert responses by provider. A conceptual representation of this averaging, calculated as the average override rate by provider, is shown in the Figure 4.4 bar chart. For example, the high volume provider #1 had 28 alerts, 25 of which were overridden had a calculated override rate of 0.9 (25/28). In both the frequency and rate graphs, overrides (in gray), dominate the landscape.

This dataset was limited to only one alert per patient to reduce the volume of alerts for patients with long lengths of stay. If the dataset had not been limited to the first

alert, the model would have also had to be re-modeled to adjust for a patient having multiple alerts and multiple providers.

Figure 4.3 Patient's First Opiate Alert Response Frequency by Provider ID

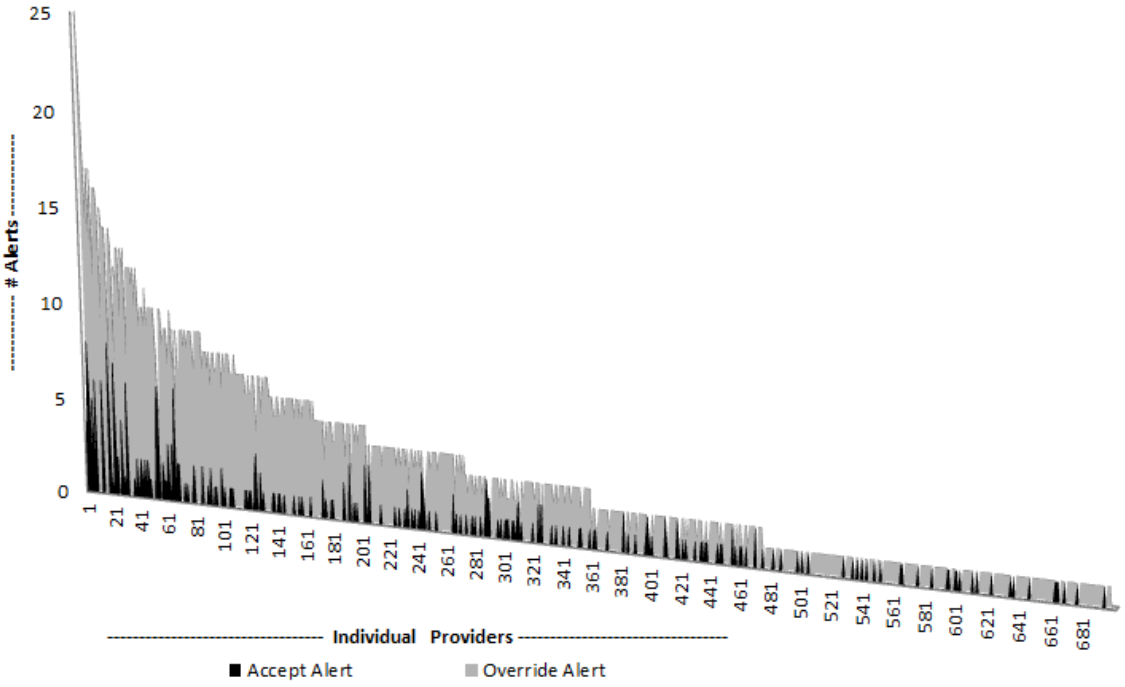
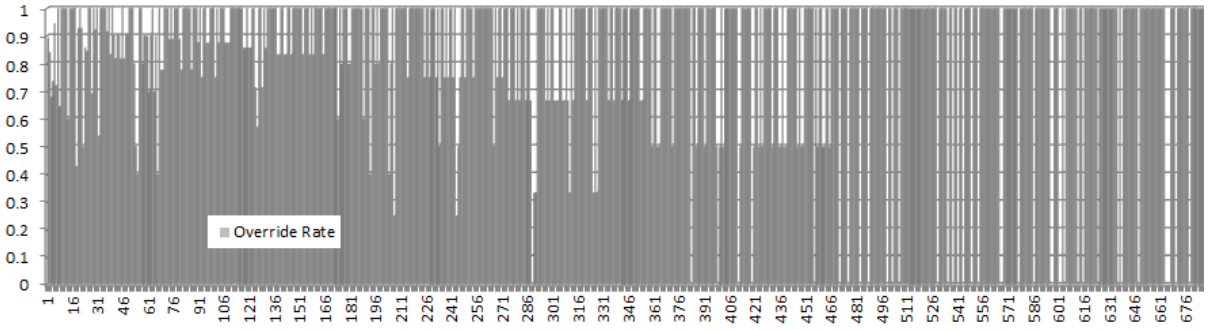


Figure 4.4 Patient's First Opiate Alert Override Rate by Provider ID



4.4.1 Development of GEE models to examine influences on alert override

Parameters for prescribing provider role (APN, Physician), reason for first admission (Medical, Procedural), Allergy reaction type (NALS, NoNALS, Unknown),

Patient gender (M,F), Race (B,W,O) and age as a covariate were put into the initial model as possible predictors of opiate allergy alert override. The following is a discussion of the goodness of fit analyses and how the final model was selected.

GEE goodness of fit is based on a generalization of the likelihood function. There are two goodness of fit measures used: (1) Quasi-likelihood under Independence Model Criterion (QIC), and the (2) Corrected Quasi-likelihood under Independence Model Criterion (QICC). The QIC helps to choose between correlation structures, given a set of model terms. The QICC helps you choose between sets of model terms, given a correlation structure. Table 4.5 shows the QIC and QICC for 18 models initially tested first using the SPSS default Independent correlation matrix, which was appropriate for the within subject data. That is, each patient was assumed to be independent of other patients relating to provider (subject) overrides. The models were ranked in ascending order by QICC as smaller values are better for both QIC and QICC. Of particular interest were the highest ranked model (#1), the conceptual study model (#7), and the null intercept model (#12).

In the second pass through the data models, age as a covariate was entered, which did not change the output for any parameter. However, it increased the QIC statistic to 10539.706, an unacceptably high value and age was then eliminated future models.

There were three correlation matrices evaluated for the 3 models (#1, #7, #12): (1) Independent, (2) Exchangeable, and (3) Unstructured. The unstructured correlation matrix would not converge, and was terminated after 4 hours. The independent correlation matrix was then compared against the exchangeable correlation matrix. The independent correlation matrix structure had the desirable smaller QIC and QICC values

as compared to the exchangeable matrix and was used in the final GEE model. Table 4.6 shows the comparison between these two matrices.

Table 4.5QIC and QICC GEE Goodness of Fit Statistics for the Study Model

#	Ranked Model	Independent Correlation structure QIC	Model terms QICC
1	**Role + Sex**	**1903.877**	**1899.583**
2	Role + Allergy + Sex	1904.658	1900.405
3	Role + Allergy + Sex + MP1	1905.881	1900.811
4	Role	1905.053	1901.418
5	Role + MP1	1906.715	1902.186
6	Role + Allergy	1905.846	1902.249
7	**Role + Allergy + Sex + MP1 + Race**	**1909.319**	**1904.158**
8	Role + Race	1908.750	1904.964
9	Sex + MP1	1920.742	1916.957
10	Sex	1919.722	1916.977
11	Allergy + Sex	1920.100	1917.427
12	**Intercept (Null)**	**1920.041**	**1918.068**
13	MP1	1921.154	1918.131
14	Allergy + MP1	1921.165	1918.296
15	Allergy	1920.436	1918.535
16	Sex + Race	1922.836	1919.847
17	Race	1923.391	1921.128
18	Allergy + Race	1923.550	1921.401

Table 4.6 Comparison of Model Correlation Structures

	QIC		QICC	
Ranked Model	Exchangeable	Independent	Exchangeable	Independent
#1 Role, Sex	1905.035	1903.877	1901.592	1899.583
#7 Role, Allergy, Sex, MP1, Race	1911.177	1909.319	1907.647	1904.158
#12 Intercept (Null)	1919.657	1920.041	1918.291	1918.068

To support the final model terms selection, a GEE relevant deviance statistic was calculated and compared across the 3 models. Deviance was calculated using the following formula: Deviance = Independent QICC –2(p), where p= # parameters (variables, scale, intercept). A Chi square test on the model deviance statistic was used to examine the significance of the differences in fit between models. Results showed that there was no statistical difference between Model 1 and Model 7, however they both were statistically better than the null intercept Model 12. Key statistics are displayed in Table 4.7 below.

Table 4.7 Comparison of Model Term Structures

Model Comparisons	Deviance	df diff	χ^2 Critical value	sig.
Model 12 vs. Model 1	22.485	2	7.378	sig
Model 12 vs. Model 7	27.91	7	16.013	sig
Model 7 vs. Model 1	-5.425	5	12.833	n.s.

* χ^2 p=.025 Model 12=Intercept; Model 1=age + sex only, Model 7 = all study variables

Therefore, the planned study Model 7 (excluding age) was retained. In review, the type of first admission (medical versus procedural) was important to the conceptual model since it would likely reflect the reason for opiates (medical vs. procedural pain). It also may reflect that clinical service to which the provider belongs. Gender and Race were also important as it might reflect cultural differences in how opiate allergies were reported and possible genomic influences that reflect opiate intolerances. Allergy reaction type (NALS) is the focus of this research. In consideration of the above, the study model (#7) was accepted, and GEE parameter results are displayed in the adjusted model column in Table 4.8b.

Table 4.8a Unadjusted Results of GEE Modeling of Opiate Allergy Alert Override

Opiate Allergy Alert Override	Unadjusted			
	B	Std error of Beta	Wald Chi-Square	p-value
Intercept				
Reaction/severity				
NALS vs NoNALS	.346	.177	3.811	.051
Unk vs NoNALS	.040	.150	.072	NS
Provider role				
APN vs Phys	-.793	.241	10.859	.001
Type of adm1				
Med vs Proc	.174	.157	1.238	NS
Patient gender				
Female vs Male	-.236	.160	.077	NS
Patient race				
Black vs White	.117	.205	.325	NS
Other vs White	-.252	.354	.505	NS

Note. NS=Not Significant; Scale=1; [a] Model fit QIC = 1909.319, QIC=1904.158

Table 4.8b Adjusted Results of GEE Modeling of Opiate Allergy Alert Override

	Adjusted

Opiate Allergy Alert Override	B	Std error of Beta	Wald Chi-Square	p-value	Exp (B)	C.I.
Intercept	2.253	.261	74.496	<.001		
Reaction/severity						
NALS vs NoNALS	.343	.177	3.755	.053	1.410	.996-1.995
Unk vs NoNALS	.005	.149	.001	.973	1.005	.750-1.346
Provider role						
APN vs Phys	-.778	.243	10.292	<.001	.459	.285-.739
Type of adm1						
Med vs Proc	.158	.155	1.032	.310	1.171	.864-1.586
Patient gender						
Female vs Male	-.273	.153	3.185	.075	.761	.564-1.027
Patient race						
Black vs White	.101	.204	.246	.620	1.106	.742-1.650
Other vs White	-.208	.348	.359	.549	,812	.410-1.606

When each of the 5 factors (allergy, role, sex, race, med/proc) was put into the model individually, only role was significant for P < .05 (β=-.779, p=.001). However, allergy reaction/severity closely approached significance (GEE β= .346, p=.051). In addition to each variable (role, allergy, sex, MP1, race) being put into the model as main effects, and all possible 2 factor (e.g. role*sex) and 3 factor (e.g. allergy*MP1* race)

combinations of interaction effects was were analyzed. Role remained the only significant factor throughout.

4.5 Summary of Aims

Opiate allergy override rate was 93% for all admissions and re-admissions. It was 89% for the first admission's alert. For the first alert only, APN's had an override rate of 80%, and physicians had a 90% override rate. In the GEE analyses, provider role was the most significant variable in predicting alert overrides. Study findings showed that on average, compared to physicians, APNs generally were 54% less likely to override first opiate allergy alerts,

Exp (B) =.459, p=.001, 95% Wald CI [.285-.739] all else being equal. There may be a number of reasons that could explain why APN's are less likely to override first alerts. They may cancel the order based on the first alert, get more information and re-order the medication which would have fired a second alert that was not captured. Or, they may have ordered an alternative, non-opiate medications for pain control.

Aim 2 GEE modeling of patient race, sex, or admission type (medical/procedural) showed no significant ($p < .05$) effect on opiate allergy alert overrides. While not significant at $P < .05$, the study variable of non-allergic/low severity gastrointestinal reactions (GI NALS) was in the right direction of being more likely to be overridden. (NALS, $\beta = .343$, $p = .053$). Conceptually, this fits what is known about these factors. GI NALS reactions like nausea are likely to be overridden if strong pain medication like opiates are needed and nausea symptom control can be ordered. However, the other categories (skin, nervous/mood, other) likely have a high number of non-allergic/low

severity alerts that represent other, non-gastrointestinal types of alerts (i.e. makes me sleepy). This would support the assumption that there is much variability in how reactions and severity is or is not captured across all categories.

In summary, the descriptive results from Aim 1 were as, or more important, than the results of the GEE predictive modeling results for Aim 2. The descriptives reinforced the importance of opiate and related allergy alert research because of the significant prevalence of recorded opiate allergies, opiate allergy alerts and the high override rates of opiate allergy alerts. Of concern, is the alert reaction detail missing in three quarters of the alerts. Severity too is poorly described. This significantly reduces the ability of the provider to make an informed decision about the alert.

Due to the complexity of the patient condition, clinical environment, provider experience and current CPOE systems, it is still difficult to predict what allergy alerts will be consistently overridden, and should be removed across all situations. However, identifying and removing non-allergic, low severity gastrointestinal reactions may help reveal new information about the remaining alerts.

5.0 Discussion, Limitations, Additional Research

5.1 Summary of Findings and Overview of Chapter

The study revealed two related phenomena in the evaluation of patient opiate allergy alerts. The first being that there was a high prevalence of opiate allergies recorded and alerted on for a reportedly rare occurrence. This might reflect a true rise in hypersensitivities due to the high volume of opiate use in hospitals, but was outside the scope of this study. Particularly problematic were allergies to codeine, which trigger alerts to many other opiate orders. Findings suggest that this is due, in part, from inappropriately broad allergy definitions and use of the allergy data collection field to alert the prescriber to other non-allergy clinical concerns such as previously experienced side effects.

The second phenomenon was the high volume of common opiate side effects recorded as allergic reactions. Of particular importance was the high volume of overridden opiate allergy alerts triggered by non-allergic/low severity gastrointestinal reactions. Eliminating this group of triggers, would have resulted in a 9% reduction in opiate allergy alerts at the study site. It also opens for discussion that proactive management of drug side effects may be needed.

Analysis of patient attributes such as age, race, gender and the type of admission (medical vs. procedural) had no significant effect on provider opiate allergy override rates. While physicians were more likely to override alerts (90%) than advance practice nurses (80%), alert rejection rates were unacceptably high.

Building clinical alerts that have the right balance of sensitivity and specificity require clearly articulated goals and the data concepts that drive them. This study shows that the results of allergy data collection, processing and related displays have not been well purposed for CPOE drug alerts.

This chapter outlines the opportunities and challenges that flow from the study that could improve opiate allergy alerting. These are organized along each phase in the alert trajectory: data collection, alert data processing, and enhanced alert presentation for provider evaluation of the alert and execution of the order. Lessons learned are applicable to the improvement of many types of alerts that rely on human collected, machine processed, and human interpreted clinical data.

5.2 Data Collection Opportunities

There is growing support and regulatory incentives to use clinical decision support that is based, in part, on the patient's EMR data. However, the sensitivity, specificity and overall clinical value of that decision support is dependent upon the quality of the EMR data upon which CDS algorithms are built. In the one example examined in this study, opiate allergy, data have been shown to be loosely defined, subjective and incomplete. High override rates of this type of CDS attest to the problem. Lessons learned may be applied to some of the other CPOE drug allergy CDS algorithms or those that depend upon other manually entered data such as height, weights, vital signs, and/or recall of past medical history. Data collected should be clearly defined, purposed and tested for its usefulness by decision support algorithms – particularly when those collecting it are unaffected by its low quality.

Review of the literature revealed no universally agreed upon definitions for collecting allergy data well purposed for CPOE allergy alerts. Current allergy screen use has outgrown its design intent, appearing to be a catch-all for any adverse and unpleasant drug experiences. Clerical staff or clinicians unfamiliar with discriminating allergies from side effects are guided to enter allergy information based on local computer screen design and data field attributes. If codeine and nausea are prominently displayed, as in this study, one might think them to be common answers to the allergy question.

Use of the allergy screen comments field to note that the patient has a history of addiction, liver failure, or needed rescue meds like Narcan may have been clever attempts at getting this information to the provider during opiate ordering. Newer alerting algorithms may better handle them as coded elements that are part of the Drug: Disease alerts rather than Drug:Allergy alerts.

5.2.1 Clarifying adverse drug reaction versus allergy

One recommendation would be to rename the *Allergy* input screen to the *Adverse Drug Reaction History (ADR Hx).* This would be more accurate and help frame the right onscreen cues to differentiate clinically significant hypersensitivities and important patient comments not elsewhere captured. Hypersensitivity, which includes both allergies and non-allergies is also a more precise term. Previously described as causing "objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects" (Johansson I, 2005). Discussion of reaction severity suggested that those classified as low/mild should quickly abate when the drug is discontinued, while moderate to severe reactions require medical intervention. Recent

history of drug reactions may be more significant information than those recalled from childhood through second hand memories. The questions implicit in these definitions are missing from current data collection screen designs. These might include variations on the following ADR Hx intake questions :

Allergy History Intake Form:

1. Did the reaction go away soon after you stopped taking the drug? If no, did you need medical attention? [severity] If yes, did a physician say it was life-threatening or could cause permanent damage to you? [High severity]

2. Describe the reaction in your own words – i.e. Patient states "morphine makes him crazy" [subjective considerations]

3. Has this happened to you more than once when you take this drug? [reproducibility]

4. How much of the drug did you take when you had these symptoms? [dose & duration]

5. Did a doctor confirm this allergy? How long ago did this reaction occur? [recall trustworthiness, immune status changes]

6. Would you take this drug again if you were in pain? What do you usually take and/or do for moderate to severe pain? Comments? [patient preferences or proxy for genomic variations]

5.2.2 Capturing adverse drug reaction detail

In this study, 16% of the opiate alerts had no reaction documented, and 74.3% of the alerts had no severity assigned. The absence of reaction detail has been identified as a significant hindrance in provider evaluation of alerts. Data intake screens must be designed to make it easier to capture <u>accurate</u> data, rather than "guess" or ignore these data fields.

Well-intended efforts to facilitate capture of this data through drop-down lists, frequently used checkboxes (☑ N/V) or highly visible rare but severe reaction types (anaphylaxis) may inadvertently cause over-capture of questionable clinical data. Previous study by Ariosto (2008) showed higher than expected rates of overrides for "anaphylaxis" alerts, suggesting that this life-threatening allergy may have been miscoded. Data entry staff may translate a patient statement like "I felt hot and faint" into "hypotension" if there are field length restrictions, or coded selection lists. Once in a system, these are extremely difficult to remove. Since reaction data have not reached a reasonable level of accuracy and usability, free text capture of the patients' own words may better inform the provider. This would allow the provider to clarify using the patient's own words. For example, a provider may comment "You said that morphine made you feel 'crazy' – tell me more.."

5.2.3 Capturing individual intolerances

There has been little discussion of capturing patient individual tolerances and pain management preferences. The high incidence of *GI upset* recorded "allergies" may reflect, in part the spectrum of individual physiological and psychological intolerances to opiates. To some patients, nausea may be worse than a little pain and should be part of the opiate ordering decision. More research on the patient experience, and pain management preferences might help to inform the ordering decision. Subjective ranking of the ADR event from mild (not too bad, would take this drug again) to severe (worst imaginable, will never take this drug again) may be of value. Simply asking the question "What usually works for your pain management" may make the alert evaluation easier.

Future research that compares differences in how these hypersensitivity attributes are collected with alert volumes, measures of comfort management, and patient satisfaction would be valuable. This approach is consistent with recent initiatives to focus on care and outcomes that are important to patients. Real-time correlation of known side effects or past reaction experience with patient's current GI state may avoid further upset or increased pain with existing constipation. A dehydrated, constipated patient is more susceptible to the effect of opiates on the GI tract. Bringing existing EMR data to the point of ordering would be valuable.

Another consideration for future research is how to use the patient maintained personal health record (PHR). A robust hypersensitivity history is often difficult to get during the acute phase of the patient admission, or the fast pace of the outpatient clinic. Increasingly patients have the ability to access their clinical information online as well as have the ability to update and correct information captured. Designing PHR screens that help the patient understand why an accurate hypersensitivity history is important, and giving them the capability to update same will be important.

5.3 Alert Processing Opportunities

The allergen/drug databases and alerts rule engines that connect data entry with order entry also offers opportunities for improving upstream data collection and subsequent allergy alerting through enhanced computing. Suggested research opportunities include: analyzing (1) the effect of adding logic to segregate known side effects from hypersensitivies; (2) exploring different logic for class based hypersensitivities and secondary drug ingredients; (3) separating low value ADR data; (4)

improving ADR surveillance and prevalence reporting; and (5) using other types of CDS to "learn" from user override responses and patient outcomes to reduce alert volume. These are described in greater detail below.

5.3.1 Adding logic to segregate known side effects from hypersensitivies.

Known side effects, by drug, are currently not displayed during data input or drug ordering. Data collection previously described could be enhanced by displaying known side effects to the allergen entered, and provide additional prompts to determine if this patient's reaction is a side effect or a true hypersensitivity. As drug databases and patient outcomes are correlated and coded, there is increasing opportunity for CDS to suggest symptom management at the time of the opiate order, especially for high volume medications like opiates.

5.3.2 Exploring different logic for class based sensitivities

Sophisticated rules engines may be over-engineered in their current state – tagging a person as allergic to all of the drugs ingredients as well as its class. A prescriber whose patient is allergic to Percocet is alerted for every opiate and every Tylenol ordered. Many of the opiate drug formulations include commonly used drugs such as acetaminophen or aspirin that may significantly contribute to alert volume. Opportunities may exist at data entry when a multi-ingredient drug is entered, the logic should present "Acetaminophen (Tylenol) is an ingredient of Percocet. Are you able to tolerate acetaminophen (Tylenol)?" If the question is not answered at data entry, opportunities could be provided at ordering or administration. Ingredients in drugs from

different classes should also be suggested for further evaluation. A patient allergic to Nyquil, Darvocet and Percocet maybe only hypersensitive to acetaminophen or have been overdosed due to hidden presence of common ingredients. A person taking Nyquil and Tylenol may not realize they both contain acetaminophen. The potentiating effects of other drugs can increase side effects such as antihistamines and anticholinergics. While that research is typically considered within the domain of drug:drug alerting, there may be some crossover and some of the reported side effects may have been a result of concurrent use of other medications.

5.3.3 Separating low value adverse drug reactions (ADR)

Low value alerts have been identified as being particularly problematic in this study. Creating logic to separate and handle these types of alerts differently is warranted. A codeine allergy with no other opiate hypersensitivities, not coded as moderate or severe, and/or experienced longer than 10 years ago might be demoted to a passive (FYI) status. For example, show the information as part of the opiate ordering screen, but do not specifically prompt the user to acknowledge it.

5.3.4 Improving ADR surveillance

This study has identified significant prevalence of recorded opiate allergies. While these high volumes are not likely to be true allergies, this was not validated in this study and is worth further analyzes. World Health Organizations' pharmaco-vigilance focuses on new and emerging hypersensitivity patterns. This is achieved through standardized terms and collaborative surveillance efforts and analysis. Vendors and local

developers should be encouraged to use standard terminology and report on the type and volume of alerts internally as well as to external oversight bodies. At the local level, hospitals should identify emerging sensitivity patterns that may occur with high use of drugs like opiates.

5.3.5 Using non-knowledge based CDS

This study has looked at knowledge based CDS which has used information about hypersensitivity reactions recorded in the EMR correlated with drug information databases. Exploration of non-knowledge based CDS should be explored using the past alert responses – the user experience. These include Darwinian "survival of the fittest" approaches or neural networks that give more weight to accepted alerts. Conversely, if a specific alert/patient combination is always overridden it will be demoted and eventually not fire at all for an individual patient or patient population. This may be especially helpful for eliminating alerts that fire based on class based, cross-reactivity algorithms.

5.4 CPOE Alert Presentation Opportunities

5.4.1 Alert severity level presentation

At the presentation stage, there are opportunities to reduce the cognitive load of drug:allergy alert evaluation and execution by adapting the 3-tiered structure applied by Paterno et al. (2009) for drug:drug alerts. As summarized in Table 5.1, the tiered allergy alert response would be: Level 1 - Stop drug (high severity), Level 2 - State reason for override (e.g. has tolerated, no alternative, will monitor) and Level 3 – No response

needed (mild). Eliminating the override response requirement for Level 3 alerts would significantly reduce the overall number of alert overrides.

Table 5.1 Potential Tiered CPOE Allergy Alert Response Levels

Alert Response	*Drug:Allergy Criteria*
Level 1 (red alert) Requires stop order or co-sign	High/Severe = Life-threatening; disability or death if untreated (e.g. anaphylaxis)
Level 2 (orange alert) Requires a reason for override	Intermediate/Moderate = Neither low nor high severity (all else, including unknown)
Level 3 (yellow alert) No response required (FYI)	Low/Mild = Reaction disappears when the drug is stopped – no medical attention required. Patient has had an unpleasant experience, but agrees to take if necessary

Using standardized response definitions for Level 1-3 for all types of alerts (drug: drug, drug:allergy, drug:condition, etc.) would eliminate the needs to learn and process different alert styles. Use of color that reflects industry standard warning hues (red alert, orange alert, yellow alert) may also be of value.

There is increasing momentum to engage patients in their care decisions, especially comfort care. Making patient comfort preferences (drug, non-drug) explicit to the provider at the point of ordering may help facilitate this care partnership. For example, a patient with a very poor psychological tolerance for mild nausea may bump a Level 3 alert to Level 2. Where pain is anticipated during the treatment course, patient preferences for mild, moderate, and severe pain drugs and non-drug interventions should be displayed. Additional research on patient outcomes is needed to see what would best fit into each level.

5.4.2 Alert reaction detail presentation

At the point of ordering, the provider must acquire and/or mentally fill in missing data to complete their decision to order or cancel the drug. If new or complete information is acquired, interrupting the CPOE process to update ADR data for the next user is unlikely. Future alert systems should consider designs that include and encourage easy updating of missing, incomplete or erroneous data at the point of ordering.

5.4 Personalized alerts

Less discussed and researched has been how to inform the provider of the patient's preferences for pain and comfort management. Personal tolerances and preferred treatment for pain or nausea may vary widely across patients and are dependent upon current health status. Coupling patient preferences from the allergy or pain management history with concurrent documentation from nursing and other disciplines could enrich the comfort management order evaluation and execution. In the case of opiate alerts, the greatest cause of ADRs was GI upset, a known side effect. Further research on how to visualize current pain, GI status, and other relevant body systems would help inform ordering decisions. A sample, personalized alert is displayed in Figure 5.1.

Figure 5.1 Sample Personalized Alert

Current Status:

GI: Constipated

Pain: Mod-Severe (7 out of 10) Location: Abdominal

Patient reports these have worked in the past:

- *Mild – Moderate Pain: Tylenol 650 x3 daily*
- *Moderate – Severe Pain: Morphine & Reggae music*
- *Constipation: M.O.M.*

Other Patient Comments: I had a hard time getting off Percocet after my 1980 back surgery

Revisiting the study definition of hypersensitivity as causing "objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects" suggests that we can identify "normal". As the industry strives to embrace the concept of personalized medicine, the alert types displayed in Table 2.1 consider morbidities such as renal disease, conditions like pregnancy, lab values such as renal function, and age groups like the fragile elderly. And while there has been alert work with conditions and dosing guides based on vital signs, urinary output, and comorbidities, there has been no specific discussion of incorporating current , non-pathology based diagnoses such as constipation into alerts.

For medical centers with CPOE and electronic clinical documentation there could be great value in the real time integration of relevant nursing assessments and order alerts. In the case of opiate ordering, real-time processing (by computer or provider) of the patient's current GI status (nausea, vomiting, constipated, diarrhea, etc.) may be helpful with dose adjustment and/or symptom control – and might result in fewer reporting of these types of these types of adverse drug reactions. Expanding this to all drugs causing GI upset, of which there are many, might have significant impact on improving the clinical value of drug alerts.

5.5 Study Limitations

Multiple limitations of the study design must be acknowledged. This study is limited to only one university medical center with advanced capacity to build and continuously tune its CPOE system. There may have been changes to the data collection screen design and alert logic during that period that this researcher is unaware of,

however, it is expected to have been a relatively consistent experience across users captured.

The ability to generalize findings to other hospital CPOE systems may be limited. The alert trajectory is complex and involves many systems and disciplines which may differ across institutions. Those systems include the allergy data collection tools, allergy processing algorithms, and CPOE alert displays. Some facilitates may have built in help text, required fields, or variations in how alerts are displayed. Some hospitals may rely more or less on physician assistants or nurse practitioners who may react differently as a group. Independent physician groups may respond differently to low value, time consuming alerts than faculty based providers who are employed and incentivized by the university medical center culture.

This study is limited to a retrospective analysis of only opiate allergy alerts. Interviewing clinicians immediately after the alerts could give a better sense as to why they overrode an alert, which information was needed, and what information was used in making decisions. A retrospective audit of opiate allergic patients who actually received the opiates, to evaluate and confirm and update their true reaction status would have been valuable. Limiting the study to opiates was necessary but also limits generalizability to other drugs. While many patients experience GI upset from taking medication, they may have a wider severity range and/or affect body systems differently.

This retrospective alert analysis could not show what else may have affected the alert override decisions at the time or whether the provider initiated other measures. There may have been team or patient discussions and/or subsequent ameliorative measures initiated (i.e. nausea medications, crackers with opiates, monitoring). It is a

standard care practice to evaluate the unpleasant and known adverse effects of medications by nursing staff – and request symptom control as needed.

The creation of the NALS variable was difficult and based on evaluation of reaction data present. The presumptive assignment of known opiate GI side effects, such as nausea and vomiting, with no coded severity to the NALS group is a weakness of this study. This was based on the coupling of N/V in a data entry checkbox which did not discriminate between the two, and the presumption that if the severity was not mild - it would likely been have recorded. This was supported by the higher override rate in this group.

This study likely underestimated the number of non-allergic/low severity reactions because it focused only on the GI subset. Many skin reactions could have been assigned to the NALS category – as there are histamine responses from taking opiates that are not allergic reactions.

There was a small, but significant difference between APN and physician override rates. At the target facility, there is no standardized governance in how the various roles that made up the APN category were entered. Therefore, the treatment of the APN roles in a single group may not be as homogenous as assumed. However, this did not change the final study recommendations. Another consideration was that in some settings, APN's treat the more complex patients which might have had accounted for the lower alert override rates – however patient level severity was not captured.

Several assumptions were made in developing the study design and in conducting the study which require further validation. That is, that most recorded opiate "allergies" are actually known drug side effects and not true allergies. The assumption that excluding

low or no severity opiate GI reactions (nausea, constipation) that were not true allergic responses (rash, swelling), would significantly reduce alerts volumes without additional patient risk. The logic of "no new risk is introduced by eliminating alerts that have always been ignored" is not a strong one, and needs to be tested.

5.6 Conclusion

Drug allergy alerting was one of the earliest and supposedly simplest forms of CPOE CDS, yet still has unacceptably high override rates. While alert logic may be simple, the complex environment in which it exists is not. This dissertation highlights unintended consequences that can occur when computerized clinical decision support logic is not tightly aligned with the electronic medical record data upon which it depends. Much of our recorded healthcare data is influenced by human factors such as memory, personal experience, and varied interpretation by patients, clinicians and support staff. Our computer systems are programmed by humans with their own sets of experiences who make seemingly logical assumptions in the lab that don't always match up to the complexities in the clinical setting. Without explicit definitions, connecting people and systems without a clear sense of purpose, will result in suboptimal decision support.

The volume of side effects, recorded as allergies, should not be ignored or completely attributed to vague allergy definitions, human error or the influences of data entry screen design. Moreover, this reflects the need for better symptom management of opiates and all medications that are known to cause distressing side effects. Increased education and engagement of patients in understanding the use and effects of opiates, accurate reporting and partnering with their providers in comfort management is fundamental.

This research also highlights the need for continuous feedback and analysis of alerts in clinical practice, to identify opportunities to improve systems and reveal emerging healthcare patterns as more people use computers to record, deliver and improve care. The high use opiates over time may be introducing new hypersensitivities in susceptible individuals that have yet to be fully revealed. More than half of all inpatients had opiates ordered. Of these, 9% of the patients triggered over 25,000 opiate alerts based on how their allergy history was recorded and how often opiates were re-ordered for the visit. This count could be tripled when you consider that the same alert that may be presented to the pharmacist on dispensing, and the nurse on administering. Allergy alerting will continue to increase as we connect allergy records from paper records in the clinics and physician offices and codify existing free text entries of allergy information elsewhere in the medical record.

In this study, CDS enhanced data entry could be as important as the CDS that fires the alert or the CDS that suggests alternative pain management. Eliminating inappropriate or ambiguous data from the beginning alert trajectory could have huge downstream effects on reducing alert volume and override rates.

Appendix A Top Summary Service Database Reactions (75%) for All Allergy Types

Highlighted text shows GI Reactions

Rank		
1	rash	16.32%
2	UNKNOWN	15.68%
3	hives	4.70%
4	INTOLERANCE	3.34%
5	anaphylaxis	3.18%
6	NAUSEA	2.80%
7	itching	2.34%
8	swelling	1.71%
9	VOMITING	1.59%
10	N/V	1.37%

Rank	(< 1.0%)
11	hallucinations
12	urticaria
13	rash;
14	cough
15	diarrhea
16	intolerance;
17	myalgias
18	gastrointestinal symptoms
19	GI upset
20	headache
21	RASH URTICARIA
22	Shortness of breath
23	anaphylaxis;
24	TACHYCARDIA
25	DIZZINESS
26	breathing difficulties
27	angioedema
28	n/v;
29	nausea/vomiting
30	STOMACH PAIN
31	seizures
32	edema
33	blisters
34	HYPERACTIVITY
35	Raised Rash, Hives
36	Throat swelling
37	palpitations
38	Nausea and Vomiting
39	upset stomach
40	tongue swelling
41	rash, itching
42	FACIAL SWELLING
43	anxiety
44	AGITATION
45	confusion
46	unsure
47	chest pain
48	urticaria;
49	nausea, vomiting
50	sob
51	whelps
52	HYPOTENSION
53	itch
54	rash, swelling
55	rash; urticaria;
56	Pruritis
57	difficulty breathing
58	GI Disturbances
59	N/V RASH
60	anaphylaxis rash
61	rash;, rash
62	rash, hives
63	intolerance n/v
64	leg cramps
65	syncope
66	flushing
67	insomnia
68	rash/hives
69	STOMACH UPSET
70	rash and itching
71	Fatigue
72	constipation
73	?
74	headaches
75	itching, rash
76	INTOLERANCE RASH
77	BLEEDING
78	unk
79	joint pain
80	depression
81	mental status changes
82	n & V
83	hives, rash
84	abdominal pain
85	THROAT SWELLS
86	muscle aches
87	fever
88	migraines
89	cramps
90	lip swelling
91	sneezing

92	wheezing
93	severe rash
94	SWELLING, RASH
95	hives, swelling
96	redness
97	weakness
98	Nightmares
99	seizure
100	sick
101	muscle pain
102	yeast infection
103	Dyspnea
104	rash/itching
105	dizzy
106	Rash,Itching
107	WELTS
108	hives, itching
109	emesis
110	asthma
111	rash/swelling
112	rash and swelling
113	Bradycardia
114	skin irritation
115	unknown reaction
116	HYPERTENSION
117	HYPERKALEMIA
118	passed out
119	GI DISTRESS
120	muscle cramps
121	Shock
122	respiratory distress
123	unkown
124	nausea, n/v
125	muscle weakness
126	myalgia
127	skin rash
128	jittery
129	N&V
130	vomitting
131	sinus
132	stomach cramps
133	tremors
134	hives, urticaria
135	RENAL FAILURE
136	nausea & vomiting
137	itching/rash
138	Nausea / Vomiting
139	welps
140	SEVERE NAUSEA
141	BURNING
142	congestion
143	rash,swelling
144	gi bleed
145	migraine
146	Altered Mental Status
147	rash, nausea
148	heart racing
149	heart races
150	HALLUCINATION
151	HEART PALPITATIONS
152	rash swelling
153	convulsions
154	muscle spasms
155	psychosis
156	itching, hives
157	intolerance; n/v;
158	Unsure of reaction
159	Thrombocytopenia
160	pancreatitis
161	dystonia
162	rash, Vomiting
163	rash and hives
164	eye swelling
165	`
166	RED MAN SYNDROME
167	sedation
168	hyponatremia
169	N/V; RASH;
170	vertigo
171	nervousness
172	anaphalaxis
173	hives/rash

174	abd pain
175	dystonic reaction
176	hyper
177	N/V, nausea
178	Rash, INTOLERANCE
179	not sure
180	HIT
181	MOUTH SORES
182	red rash
183	Skin Reaction
184	swelling, itching
185	sensitivity
186	shakes
187	fainting
188	HTN
189	gi
190	RESPIRATORY
191	pass out
192	trouble breathing
193	swelling/rash
194	increased heart rate
195	SEVERE ITCHING
196	throat closes
197	cardiac arrest
198	FLU LIKE SYMPTOMS
199	swelling, hives
200	childhood
201	anaphylaxis; rash;
202	does not remember
203	lethargy
204	renal dysfunction
205	shaking
206	anaphylactic
207	RESP DISTRESS
208	rash, fever
209	BLURRED VISION
210	Elevated liver enzymes
211	hair loss
212	not given
213	hyperactive
214	irritability
215	nauseated
216	pain
217	weight gain
218	nervous
219	Itchy
220	URINARY RETENTION
221	numbness
222	GI bleeding
223	n/v urticaria
224	severe headache
225	rash, SOB
226	RASH ITCHING
227	ANAPHYLAXIS RASH URTICARIA
228	breaks out
229	lips swell
230	blister
231	bruising
232	mouth ulcers
233	nose bleeds
234	thrush
235	breathing problems
236	nephrotoxicity
237	PRECAUTION
238	swells
239	itching and rash
240	passes out
241	chest tightness
242	DELIRIUM
243	Hives,Itching
244	INTOLERANCE HALLUCINATIONS
245	rash, rash;
246	serum sickness
247	swelling and rash
248	renal disease
249	Rash, N/V
250	unkn
251	swelling of throat
252	stopped breathing
253	burns

254	blisters in mouth
255	disoriented
256	itching, swelling
257	intolerance; rash;
258	PRURITUS
259	hives/swelling
260	GI intolerance
261	nausea/vomitting
262	joint swelling
263	vomiting, n/v
264	anaphylaxis urticaria
265	elevated bp
266	crazy
267	hives and swelling
268	hay fever
269	nausea, vomitting
270	nausea,vomiting
271	as a child
272	ANAPHYLAXIS, RASH
273	irritation
274	itches
275	severe vomiting
276	vomit
277	burning sensation
278	Bronchospasm
279	INEFFECTIVE
280	leg pain
281	respiratory arrest
282	rash/itch
283	RASH HIVES
284	coma
285	HIVES/ITCHING
286	hive
287	Paralysis
288	stops breathing
289	breathing difficulty
290	hives, SOB
291	DISORIENTATION
292	FACIAL EDEMA
293	hives and itching
294	panic attacks
295	SEVERE DIARRHEA
296	stop breathing
297	Tongue swells
298	MOUTH SWELLING
299	-rash
300	RASH, urticaria
301	asthma attack
302	n/v;, nausea
303	SEVERE HIVES
304	rapid heart rate
305	sick to stomach
306	arthralgias
307	kidney failure
308	ulcers
309	urticaria;, HIVES
310	- rash
311	Hives, vomiting
312	heartburn
313	nausa
314	itching,rash
315	rash, blisters
316	ras
317	Projectile vomiting
318	rash;, HIVES
319	vomiting, rash
320	EPS
321	hives,swelling
322	leg swelling
323	rash, itch
324	RASH, ANAPHYLAXIS

Appendix B FY10 Opiate Orders –Adult & Pediatric

Triggering Opiate Order	#
ACETAMINOPHEN	22
ACETAMINOPHEN	161
ACETAMINOPHEN	4
ACETAMINOPHEN	697
BELLADONNA-	143
BELLADONNA-	675
CODEINE	30
CODEINE:	101
DARVOCET-N 100:	33
DILAUDID	12
DILAUDID/MARCAI	692
DILAUDID/ROPIVAC	23
FENTANYL 100	299
FENTANYL 12	158
FENTANYL 25	428
FENTANYL 50	392
FENTANYL	25
FENTANYL 75	234
FENTANYL	4
FENTANYL	1388
FENTANYL	3558
FENTANYL	14772
FENTANYL	8
FENTANYL/MARCAI	84
FENTANYL/ROPIVA	97
GLUTAMINE ORAL	1
GLUTAMINE	28
HYDROMORPHONE	25
HYDROMORPHONE	50
HYDROMORPHONE	179
HYDROMORPHONE	20075
HYDROMORPHONE	34
HYDROMORPHONE	6241
HYDROMORPHONE	211
HYDROMORPHONE:	1720
LORTAB 10 / 500	3034
LORTAB 5 / 325	50
LORTAB 7.5 / 325	370
LORTAB 7.5 / 500	7429

Triggering Opiate Order	#
LORTAB ELIXIR:	3492
MEPERIDINE INJ:	769
MEPERIDINE PCA:	16
MEPERIDINE:	683
METHADONE INJ:	941
METHADONE PCA 1	2
METHADONE:	2037
MORPHINE	5
MORPHINE	1195
MORPHINE	197
MORPHINE	78
MORPHINE	16
MORPHINE	27127
MORPHINE ORAL	5
MORPHINE PCA	36
MORPHINE PCA	3362
MORPHINE PCA	174
MORPHINE PF	1041
MORPHINE SR	68
MORPHINE SR: MS	2933
MORPHINE	84
MORPHINE	189
MORPHINE	1
MORPHINE/MARCAI	35
OXYCODONE 1	2244
OXYCODONE 20	34
OXYCODONE	2822
OXYCODONE:	6509
PERCOCET	6932
PERCOCET	15891
PERCOCET TAKE	8
PROPOXYPHENE:	3
REMIFENTANIL	57
SUFENTANIL INJ:	1
TRAMADOL:	1012
TRIZIVIR	12
VICODIN (LORTAB 5	9517
VICODIN (LORTAB	11
TOTAL	153,02

Glossary of Terms

Term	Definition
Documented allergy	Any documented reactions in the EMR allergy field. May be an allergy, non-allergy (non-immune mediated), known or unknown side effect.
ADR –	Adverse Drug Reaction An unintended drug effect
Alert	A computer generated pop-up to a drug order to which the patient may be allergic.
Alert Backout	The prescriber stops or cancels placement of an order after receiving an alert about potential harm from that order
Alert Fatigue	A reported, but unvalidated, effect of too many alerts cause the user to override an alert without fully mentally processing the alert.
Alert Override	Where a CPOE alert is rejected, and the prescriber places the order despite the warning.
Allergy	Hypersensitivity subclass that is immune mediated
Allergy Module/Screen	A data entry screen designed for the purpose of entering hypersensitivity information.
APN Advanced Practice Nurse	Registered nurses with additional education and certification that allow prescribing of medications. These include nurse anesthetists (CRNA), midwives (CNM), nurse practitioners (NP). Clinical nurse specialists are also considered APNs. The State Board of Nursing grants prescriptive authority through certificate of fitness to prescribe controlled substances.

CIS -	Clinical Information System - A network of clinical applications or modules that collect and display information about a patient.
CPOE -	Computerized Provider Order Entry -Data entry of an order (meds, labs, etc.) by a duly licensed prescriber (physician, APN) into a computer system
Documented Severity	The severity of the allergic reaction. These are often subjective designations determined by the patient and the staff member documenting the allergy.
EMR -Electronic Medical Record	Clinical information collected and displayed for a patient.
GI – Gastrointestinal	Affecting the stomach and intestines.
Hypersensitivity	Objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. (Johansson I, 2005).
NALS -	Non-Allergic/Low Severity - An ADR that is classified as mild, and is not immune mediated (itch, rash, swelling).
Not NALS	All other documented “allergy” adr reactions (severity, immune mediated)
Prescriber	Provider that can order medications
Provider	Licensed Independent Practioners (LIP)

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