

Review Paper ■

Medication-related Clinical Decision Support in Computerized Provider Order Entry Systems: A Review

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Abstract While medications can improve patients' health, the process of prescribing them is complex and error prone, and medication errors cause many preventable injuries. Computer provider order entry (CPOE) with clinical decision support (CDS), can improve patient safety and lower medication-related costs.

To realize the medication-related benefits of CDS within CPOE, one must overcome significant challenges. Healthcare organizations implementing CPOE must understand what classes of CDS their CPOE systems can support, assure that clinical knowledge underlying their CDS systems is reasonable, and appropriately represent electronic patient data. These issues often influence to what extent an institution will succeed with its CPOE implementation and achieve its desired goals.

Medication-related decision support is probably best introduced into healthcare organizations in two stages, basic and advanced. Basic decision support includes drug-allergy checking, basic dosing guidance, formulary decision support, duplicate therapy checking, and drug-drug interaction checking. Advanced decision support includes dosing support for renal insufficiency and geriatric patients, guidance for medication-related laboratory testing, drug-pregnancy checking, and drug-disease contraindication checking. In this paper, the authors outline some of the challenges associated with both basic and advanced decision support and discuss how those challenges might be addressed. The authors conclude with summary recommendations for delivering effective medication-related clinical decision support addressed to healthcare organizations, application and knowledge base vendors, policy makers, and researchers.

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Introduction

Medications are powerful and commonly used modern therapies that can yield many benefits. Yet, they can also cause considerable harm,^{1,2,3,4} especially if prescribing clinicians fail to consider relevant patient characteristics. For example, renal insufficiency and advanced patient age call for lower than usual medication doses, and drug-drug interactions are sometimes lethal. Electronic health record (EHR) systems can improve the reliability, quality, and safety of medication use.^{5,6}

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Computerized provider order entry (CPOE) with clinical decision support (CDS) can improve medication safety and reduce medication-related expenditures because it introduces automation at the time of ordering, a key process in health care. Electronic order communication can occur instantly, accurately, and reliably and computer-generated orders are more legible than those written by hand. A knowledge-based CDS review can assure that the order is safe and compliant with guidelines.^{7,8} For CDS to be effective, adequate expertise must go into defining and representing medical knowledge. Also, data that are critical for CDS, such as the patient's weight and allergy status, must be captured and made available to the CDS system. CDS systems must support, rather than impede, clinical workflows through speedy, available, and usable algorithms that provide parsimonious, clear, concise, and actionable warnings and advice.^{8,9}

To help understand the state of the art of the capability of CDS to improve medication safety, efficiency, and health care quality, the authors convened a CPOE conference in San Francisco in June of 2005. Participants reviewed the common categories of medication-related CDS within CPOE. For each category of CDS, we considered: How does it work? What is the potential benefit? What (if any) are the results of studies that have documented the benefits and/or undesirable side effects? What are outstanding issues (e.g., knowledge-base

management, user interface issues) that prevent the benefit from being realized to its fullest? And what are some next steps that might help the evolution of the specific category of decision support?

This review provides a literature-based summary of the discussions. Rather than exhaustively reviewing the literature on these topics, we selected papers that reflect exemplary current practice and have direct actionable relevance to system designers working to implement these features in today's technical environment. We also identified papers that illustrate the limitations of today's technology and can help point the way forward for future developments in the field. For each category of decision support, we make recommendations for how the effectiveness of the feature can be optimized and we conclude the paper with summary recommendations to healthcare organizations, application and knowledge-base vendors, policy makers, and researchers for how to advance the delivery of effective medication-related clinical decision support.

We divided the CDS categories into two stages—basic and advanced. The issues associated with basic CDS are more straightforward than the advanced categories, and may represent a suitable starting point for most health care organizations. In basic CDS, we included drug-allergy checking, basic dosing guidance, formulary decision support, duplicate therapy checking, and drug–drug interaction checking. Advanced decision support includes dosing support for renal insufficiency and geriatric patients, guidance for medication-related laboratory testing, drug–disease contraindication checking, and drug–pregnancy checking.

Categories of Basic Medication-Related Decision Support

Drug-Allergy Checking

Drug-allergy checking, an important patient safety feature,¹⁰ presents an alert when a provider orders a medication to which the patient has an electronically documented allergy. Matching a documented drug allergy and an ordered medication requires that both medications and allergies be represented with a consistent coding scheme, with medications organized in antigenically related classes.¹⁰ Potential harm to patients can occur if allergy checking is inadequate—either by missing important alerts or by generating so many unimportant alerts that clinicians ignore even important alerts.

Drug-allergy checking is inconsistent across CPOE applications and major shortcomings plague many drug-allergy checking features. For example, some applications do not require structured, coded entry of allergens and allergic reactions. Drug-allergy checking then becomes close to impossible. Nuances of drug-allergy checking vary across applications—for example, whether the system provides cross-sensitivity checking (e.g., triggering a drug-allergy alert on a cephalosporin order when the patient is allergic to penicillin) and checking the active medication list for interactions when a provider enters a new allergy (“reverse allergy checking”).¹⁰ Also, many applications do not distinguish between a drug allergy and a drug sensitivity, depriving the physician of important information when faced with difficult, limited therapeutic options.¹⁰

Excessive drug-allergy alerting in clinically irrelevant circumstances is highly prevalent and a major disruptor of clinicians' workflows. In one study, physicians accepted less than 20% of drug-allergy alerts.¹¹ Another study showed that almost all overrides of alerts were clinically appropriate and that overrides rarely caused serious adverse outcomes.¹² A major reason for over-alerting is that drug prescribing knowledge bases often include drug-allergy rules that are of questionable clinical value. For example, cross-sensitivity rules in commercial medication knowledge bases tend to be overly inclusive and generate many alerts with low clinical relevance. Currently, drug-“allergy” alerts based on narcotic sensitivities comprise an especially high number of unhelpful alerts.¹² For example, an allergy alert will trigger upon ordering morphine in a patient with an “allergy” to codeine for which the documented reaction is nausea and vomiting, which is in fact a sensitivity rather than a true allergy. Also, cross-sensitivity rules that alert when furosemide is ordered on a sulfa-allergic patient generate numerous clinically insignificant alerts.¹¹ Local effort by institutions implementing such systems to inactivate some of these cross-sensitivities from the drug-allergy knowledge base can eliminate a large number of “nuisance” alerts.^{12,13} Another technique for decreasing excessive alerts would be to suppress an alert when a provider previously has seen and overridden a drug-allergy alert for the same medication in the same patient.

A second reason for over-alerting is poor quality allergy data in the clinical database. When the coded reason for an allergy alert override is “patient tolerates this medication,” the quality of the clinical data is suspect and removal of such allergies from the patient record can be considered. In one study, removal of allergy documentation in such circumstances happened less than 20% of the time.¹² Institutions should consider strategies to improve allergy removal, while retaining a record of such “outdated” allergies. Strategies to improve allergy removal should be further explored, as well as cultural issues around clinicians' hesitance to remove allergy data, even of dubious accuracy, from the electronic medical record.

Another factor impeding optimal drug-allergy alerting is lack of knowledge, from a human factors standpoint, about the best way to present specific types of alerts to providers.¹⁴ Important questions include: how to present highly clinically significant warnings as readily identifiable and easily distinguished from other warnings. How to define “high clinical significance” alerts. Would coding the severity (e.g., anaphylaxis vs. hives) of past reactions for the patient's allergy address the problem, or confound it with more noise? More research needs to be done to determine the most effective ways to differentiate high-severity alerts.

Research suggests that medication CDS should include a number of specific allergy-related features.^{10,12} These include:

1. All clinicians who customarily document allergies should be allowed to contribute to a common allergy database.¹⁰ Organizations that cannot provide a single allergy database should link multiple ones.¹⁵

2. Allergy documentation should require a coded allergen and coded reaction (discriminating between true allergies and sensitivities/intolerances).
3. Drug-allergy checking should include evidence-based cross-sensitivity checking (clearly indicating, and possibly not alerting, if reported cross-sensitivities occur rarely).
4. Applications should include “reverse allergy checking” (defined above).
5. Knowledge developers should avoid over-alerting by improving specificity of alerts and by improving allergy data quality. Removal of an allergy from the allergy list should be facilitated when a physician overrides a drug-allergy alert.
6. Analyses of override reasons should occur as part of system quality improvement efforts, and contribute to further reduction of non-essential alerts.
7. Once over-alerting is under control, systems should ask the clinician to provide a coded override reason whenever he or she overrides drug-allergy alert. The override reason should allow nurses and pharmacists to understand the rationale for the override.
8. Research should continue into how to make drug-allergy alerting as effective as possible. The way alerts are presented to providers should be improved in part through differential display based on the severity of the anticipated event.

Basic Dosing Guidance for Medications in CPOE

In non-automated and some automated ordering environments, dosing mistakes comprise the most common type of medication error leading to preventable adverse drug events (ADEs).^{3,16–19} In one inpatient study, over 60% of prescribing errors involved wrong medication doses or improper administration frequencies.²⁰ Susceptible patient populations, particularly pediatric and geriatric age groups, are at risk of serious dosing errors, especially over-dosing.^{2,21–24} Pathophysiological conditions and comorbidities, such as renal insufficiency, may further complicate the patient’s medication dosing requirements, putting him or her at increased risk for preventable injury. Medications with low margins of safety, such as nephrotoxic antibiotics, oncologic agents, sedatives, and narcotics create opportunities for serious dosing errors.

CPOE with CDS can improve medication dosing through multiple mechanisms. A simple, minimally intrusive method is to offer the clinician a list of patient-appropriate dosing parameters for each specific medication, and to facilitate through defaults the selection of the most appropriate initial dose.²⁵ This can dramatically decrease variability in initial dosing.²⁵ Another approach to CPOE dosing enhancement includes provision of lists of complete order sentences, defined as “complete pre-written medication orders that include dose, dose form (when necessary), route of administration, frequency, and a PRN flag and reason (if necessary)” (see Figure 1). Alternatively, the system may provide separate recommendations for dose and frequency.⁷ Choosing from pre-defined lists decreases errors due to a mental “slip,” a misplaced decimal point, or using the wrong dosing unit (e.g., grams instead of milligrams).^{17,19} One study determined that pre-defined order sentences might prevent over 75% of 1,111 dosing errors.²⁰ Another study of outpatient prescribing determined that default dose

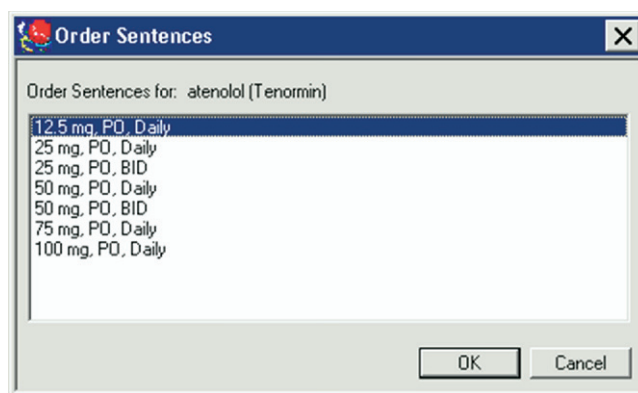


Figure 1. Order sentence pick list for atenolol.

and frequency suggestions might have eliminated 42% of prescribing errors and 53% of potential adverse drug events.¹⁹ Providing constrained lists of dosing options both delivers dosing guidance and improves user acceptance of the system by enhancing workflow.⁸

Another, potentially more intrusive, way of providing dosing decision support is to review the order (invisible to the user, by algorithm) after obtaining the user’s dosing parameters, and to alert the clinician only when reasonable dosing parameters have been exceeded.²⁶ See Appendix 1, available as an online data supplement at www.jamia.org, for a case report of how one institution prepared for basic dosing decision support.

Formulary Decision Support

Through committees such as the Pharmacy and Therapeutics Committee (P&T), hospitals and pharmacy departments constantly struggle to control the rising costs of drugs while providing essential medications to support safe and effective care. Each institutional drug formulary captures the best clinical judgments of local physicians, pharmacists, and other experts.²⁷ Formularies promote clinically appropriate, safe, and cost-effective drug therapy, and may include “restricted medications”—drugs that may be used only for a particular indication or require a specialist consult.

CPOE-based CDS can improve formulary compliance by guiding clinicians in various ways preferentially towards formulary options over non-formulary options. One such method is to include only formulary medications in the CPOE order catalog. However, this should be avoided because it may delay administration of critical medications.^{18,28} In one extreme example, a CPOE-based hospital required 6 days to deliver a non-formulary medication used to prevent organ rejection.²⁹ A better approach is to display a non-formulary or restricted designation with the medication name or within the provided order sentences (see Figure 2). A third, more disruptive but probably more effective method is to display a pop-up alert when the clinician attempts to order a non-formulary drug, while providing a selectable list of alternative formulary medications (Figure 3).^{25,30,31} Teich and colleagues demonstrated wide success, sustained at 2 years, using a pop-up alert to increase formulary compliance of drugs such as histamine₂-blockers.²⁵ Success factors for such guidance include clearly written “to-the-point” guidelines with links to additional information if desired, and offering a non-controversial

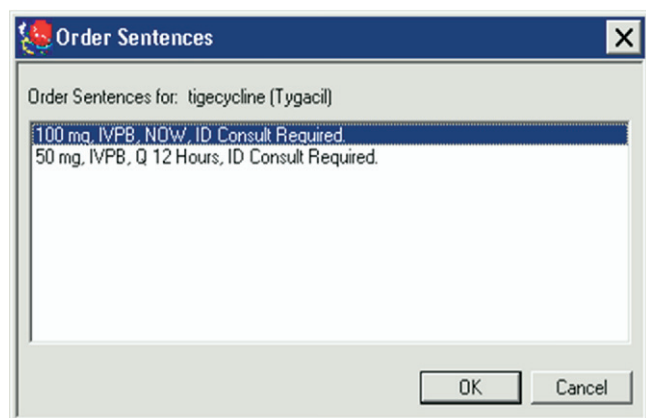


Figure 2. Formulary status of “restricted to infectious disease consult” embedded into order sentence.

suggested alternative within the alert window.^{23,32} Factors associated with poor compliance are the lack of an offered alternative, or strong provider beliefs about the medication, even if those beliefs are not necessarily supported by the available evidence.²⁵

An organization that wishes to improve formulary compliance should have in place an educational program to accompany clinical decision support.¹⁴ Providers will bypass prompts that they do not understand or do not agree with. Recommendations for making optimal use of formulary decision support include:

1. The organization should consider CDS for medication substitution after addressing decision support for patient safety and clinical quality needs.
2. Strong P&T support and good communication constitute a vital part of the plan.

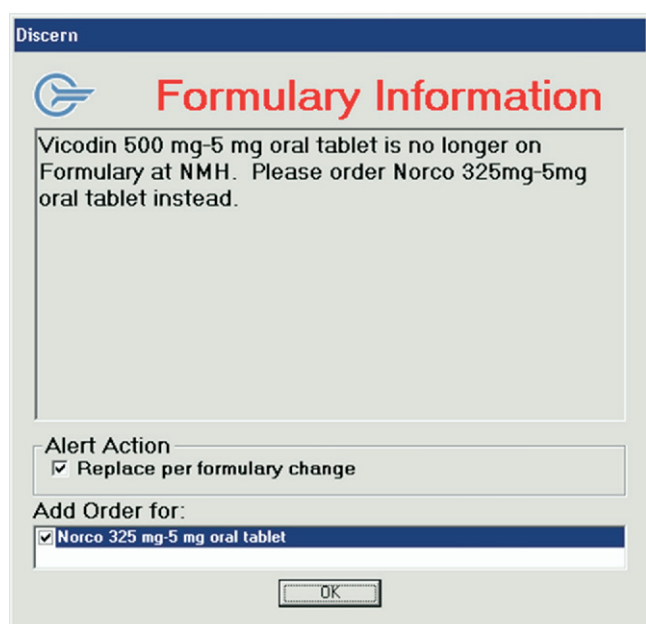


Figure 3. Alert to inform the prescriber of change in formulary status and take him or her to the replacement formulary item.

3. CDS is not effective when a recommendation is controversial or not valued by clinicians. Screen recommendations with expert local clinicians first.
4. The alert screen should include a link to information describing institution-specific guidelines for restricted medications.
5. Pharmacists should personally review on a frequent periodic basis the ignored formulary alerts, including interviews with clinicians to understand why. Formulary alerts should be monitored and modified or removed if the desired outcome is not being achieved.
6. In certain situations, formulary-related alerts can achieve a desired outcome by educating the users, for example, in:
 - Formulary changes for a drug class, e.g., H₂ blockers.
 - Medication shortages.
 - New safety alerts issued by the FDA.

Duplicate Therapy Checking

Drug duplication consists of prescribing more than one regimen of a single drug, or multiple regimens of different medications with similar therapeutic effects (e.g., multiple sedatives or multiple narcotic analgesics). Duplicate orders for medications can occur when multiple clinicians provide care for the same patient, or when orders co-exist for a medication to be administered by different routes, for example, when a prescriber forgets to discontinue the IV form of the medication when switching to the oral form. Medication errors can result from unintentional drug duplication, with the consequence of preventable adverse toxicity events.^{3,16,18,33} Therapeutic duplication is uncommon, comprising less than 6% of all prescribing-related errors.^{3,16,18}

Duplicate therapy warnings inform the prescriber when the patient is already receiving the exact medication just ordered or a different drug in the same therapeutic category. Such alerts, typically in the form of pop-up interruption, may not always be clinically relevant. Examples of medication orders that might trigger a duplicate drug alert but would in fact be appropriate are orders for antimicrobials, immunosuppressants, opioids, insulin, drug tapers, different doses for the same drug, and boluses in the presence of a regular administration. Issuing alerts under such circumstances can interrupt clinicians' workflow and cause frustration when the “duplicate” was already considered and not deemed to be a problem. In some CPOE systems, a new inpatient order can trigger a duplicate alert if the order matches a drug on the patient's ambulatory medication list. Other systems treat an order as active at the time of entry and will trigger a duplicate alert for a future order even if the current medication order will expire before the future order begins. Excessive inappropriate alerting may lead to desensitization to all classes of alerts. Too many false positive alerts for duplicate medication classes have caused at least one organization to inactivate duplicate checking altogether,³⁴ although others have found them to be effective if used selectively.³⁵

Although vendor CPOE and e-prescribing systems frequently include duplicate drug checking CDS, few outcome studies document their effect. Three studies evaluating reasons for pharmacist interventions after CPOE implementations identified increases in duplicate therapy events—presumed to occur after prescribers ignored duplicate ther-

apy alerts.^{36,37,38} One institution documented that ordering clinicians accepted 77% of such warnings as appropriate after restricting duplicate medication class alerts to those with high risk for adverse events (analgesic, cardiac, psychiatric, and endocrine medications).³⁵

Recommendations for best duplicate therapy checking practices include:

1. Organizations should customize duplicate checking to decrease the number of clinically insignificant alerts.
2. Duplicate alerts should fire selectively. For example, a heparin bolus and a heparin drip entered within the same ordering session are likely intentional duplications.

Drug-Drug Interaction Checking

Many drugs interact with the metabolism or action of other drugs, causing untoward effects that are best avoided. Appendix 1, available online at www.jamia.org, presents an example of a drug-drug interaction scenario. A number of sources, including commercial vendors, supply drug interaction databases to support automated drug-drug interaction checking and thereby potentially reduce harm to patients. Though attractive in its promise, this form of decision support has several important limitations when installed within CPOE systems. Similar to drug duplication alerting, drug interaction checking can generate large numbers of clinically insignificant (low severity) alerts that clinicians ignore. Payne found that 11% of medication orders generated a drug-drug, drug-allergy or other interaction and that clinicians continued with the order for 88% of even "critical" drug-drug interaction warnings.³⁹ Spina found that clinicians categorized only 1 in 9 potentially relevant interaction alerts as helpful when surveyed at the time of the warning.⁴⁰ Weingart documented override rates for high-severity drug-drug interactions at 89%.⁴¹ Clearly, clinicians do not consider most serious drug-drug interaction messages as meritorious of a change in behavior, and perhaps deservedly so. In one study, adverse consequences almost never occurred even when the highest level drug-drug interactions were overridden.⁴² However, some clinically relevant drug-drug interactions will occur and such important messages may be buried in a sea of unimportant messages.⁴³

Some provider organizations edit vendor-supplied drug interaction knowledge bases to tailor warning messages and even remove some alerts.⁴⁴ In one study, a significantly restricted, locally adapted commercial drug-drug knowledge base achieved a 42% acceptance rate.³⁵ However, the ability to customize commercial systems' alerts is very crude because vendor-supplied software allows limited flexibility for modifications, for example, by selecting from only a few predetermined, broad severity levels.¹³ Finally, when a clinician overrides an alert, it does not uniformly indicate that the alert had no value. An alert may prompt ordering clinicians to monitor therapy more carefully, and to discuss the possibility of an interaction with the patient.

Several factors contribute to an excessive number of drug interaction alerts. One reason is flawed logic. For example, some interaction checking systems will trigger an alert when one of the offending medications is a topical agent with negligible systemic absorption. Also, as noted previously, many commercially available drug interaction knowledge bases include minor interactions of low clinical relevance,

and do not adequately flag them as being different than clinically significant ones. Effective drug-drug interaction checks require accurate information about which drugs a patient is taking. Ambulatory medication lists are often incomplete, lacking over-the-counter medications, herbal drugs, various supplements, and medications prescribed at other sites.^{45,46} Another limitation of drug interaction alerting is faulty warning design. Screens or pop-up windows may fail to clearly convey the intended message, and confuse the clinician. Alerts should present the names of the interacting drugs, a brief (one-line) description of the interaction, optional links to more detailed information, and a menu for potentially appropriate actions in response to the alert. These requirements present challenges in human factors engineering.

The value of drug-drug interaction alerts will increase as these limitations are addressed. Sites implementing drug-drug interaction alerts should monitor override rates to measure the impact of alerts. More thoughtful user interface design may convey to clinicians cautionary information that enables better-informed and more appropriate responses.

Categories of Advanced Medication-related Decision Support

Advanced medication-related decision support should be implemented only after basic decision support is in place and working well, with good user acceptance. Nonetheless, many of the most important financial and safety benefits of CPOE will be realized only after advanced CDS features are implemented.⁴⁷

Advanced Dosing Guidance in CPOE

Even in CPOE with basic dosing CDS—standard default lists for medication doses and frequencies—researchers found a 55% decrease in serious dosing errors and a decrease from 2.1% to 0.6% of doses exceeding the recommended maximum dose.^{3,25,48} However, dosing errors continued to be relatively common (21.3/1000 patient-days) and many of the preventable adverse drug events that occurred were still related to dosing errors.⁴⁸ Another study also found that preventable adverse drug events (ADEs) remained common with a CPOE system that lacked dosing decision support.⁴⁹

Dosing decision support systems sometimes assume that patients are non-geriatric adults and have normal physiologic function, but these assumptions can lead to inappropriate dosing suggestions. Advanced medication dosing decision support tools that take into account patient variation are complex. To determine confidently what will be a safe and appropriate dose of a medication for a particular patient may require many factors to be considered. These factors include: the indication for the drug; patient characteristics such as age, weight, height, physiologic status (e.g., renal function, liver function, and fluid status), and comorbidities; other medications the patient may be currently taking; and the patient's previous response to the drug, though not all are needed for every drug. In addition, a medication may have a single dose limit, a daily dose limit, and/or a cumulative "current course" or lifetime dose limit. Prescribing applications exist that provide specific dosing suggestions when renal impairment is present, the patient is

elderly, or the patient is a child.^{23,50–52} Each of these conditions affects large numbers of patients, for example, in one study, 42% of inpatients had some degree of renal insufficiency.⁵⁰ In patients with renal insufficiency, the percent of orders with an appropriate dose and frequency increased from 30% to 51% after a renal function-specific dosing decision support system was implemented; length of stay was shorter as well, by 0.5 days.⁵⁰ A study of decision support for dosing of psychotropic medications in geriatric patients showed a 34% improvement in agreement with recommended dosing guidelines and a concomitant decrease in in-hospital fall rate.²³ Some organizations are experimenting with providing renal and geriatric dosing decision support in the outpatient setting.^{53,54}

Evans and colleagues described a highly sophisticated decision support system for antibiotic prescribing that offers recommendations for both medication and dose⁵⁵ while taking into account parameters such as the patient's renal function and age, and cultured organisms' sensitivity patterns (or, in the case of empiric therapy, local antibiograms). The "Antibiotic Assistant" has been shown to substantially decrease adverse events and costs, as well as days of unnecessary therapy.⁵⁵

Clinicians may reasonably disagree with a CPOE system's specific dosing suggestions. Compliance with suggestions is far less than 100%.^{25,50,52} Dosing decision support modules that can be used as CPOE or EMR "plug-ins" are not yet available commercially. Therefore, healthcare organizations must decide how much local effort to expend in developing dosing decision support capabilities. Online Appendix 1 presents options for institutions to consider when implementing advanced medication dosing support.

Future dosing decision support research should focus on:

1. Determining the most effective way to deliver dosing decision support (e.g., when are default suggestions or post-hoc critiques more effective).
2. Developing robust dosing knowledge for the general population as well as special populations (pediatrics, geriatrics, oncology, renal impairment).
3. Determining how best to increase compliance with dosing suggestions.
4. Identifying medications that are most likely to be incorrectly dosed and/or have narrow therapeutic windows that could be the target of high-priority, advanced efforts.
5. Determining how best to disseminate dosing knowledge broadly so that each institution does not have to "reinvent the wheel."
6. Determining the best ways to reconcile when multiple factors are present that may impact on optimal dose (e.g., more than one of advanced age, impaired renal function, and impaired liver function).

Advanced Guidance for Medication-associated Laboratory Testing

Failure to take into account important physiologic parameters when a medication is initiated, or improperly monitoring those parameters over time, can result in morbidity, such as unnecessary hospital admissions due to drug toxicity or under-dosing, and even mortality.⁵⁶ Several categories of drugs, including anticoagulants,⁵⁷ digoxin,⁵⁸ and antiepileptic drugs,⁵⁹ are poorly monitored. To minimize risk to

patients for certain drugs, laboratory tests should be done prior to the initial administration of the drug and at regular intervals during drug treatment (Table 1).^{60,61} For some medications, monitoring means keeping track of the level of the drug itself (e.g., digoxin levels, antiepileptic drug levels); for other medications, monitoring may involve tracking physiologic parameters that the medication can adversely affect (e.g., angiotensin-converting enzyme inhibitors can raise serum potassium and creatinine levels). Some medications, such as aminoglycoside antibiotics, require monitoring of both drug levels and physiologic status (creatinine levels).

Reminders in CPOE can assist physicians with medication monitoring to keep, for example, aminophylline, aminoglycosides, and oral anticoagulants, within the therapeutic range.⁶² Chen et al. showed that anti-epileptic drug levels, frequently ordered too soon after a dosing change, can be optimized through reminders issued at the time of ordering, decreasing the rate of inappropriate ordering from 54% to 14.6%.⁶³ Overhage et al. showed that prompts at the time of ordering could double physicians' rates of compliance with a variety of guidelines, including drug monitoring.⁶⁴ Bates et al.⁶⁵ showed that rates of ordering unnecessarily redundant tests, including unnecessary drug levels, can be reduced with computerized prompts. Online Appendix 1 provides additional examples of how computerized reminders can help to optimize medication-associated laboratory test ordering.

Robust CPOE-based medication test monitoring involves important prerequisites. First, the CPOE application must have access to the patient's previous laboratory results. Second, an alerting system that may exist outside of CPOE per se might be needed to inform providers when a patient is due or overdue for a medication monitoring test. Third, ideally, the knowledge bases upon which monitoring recommendations are made should be evidence-based, with documentation of benefits.⁶⁶ However, rigorous evidence is rarely available now, and most recommendations for medication monitoring are based on expert opinions or package inserts that are often non-specific or vague (e.g., "periodic laboratory testing is recommended"),^{60,67} complicating the implementation of the CDS.

CDS related to medication monitoring could be improved as follows:

1. As much as possible, systematic reviews and, if needed, primary research, should be carried out to establish the benefits of medication-related laboratory testing. When the evidence-base is unclear, developers should supplement existing knowledge with expert consensus-building to determine safe monitoring intervals that are acceptable to clinicians.
2. Ensure that recommended monitoring intervals are reviewed and updated whenever new evidence occurs or when specified inter-review intervals elapse.
3. Improve alerting capabilities to detect when patients are overdue for testing and to notify the patient or clinicians appropriately.

Table 1 ■ Examples of Pre- and Post-drug Administration Tests^{60,61}

Drug	Pre-administration Tests	Post-administration Tests*
Cardiovascular		
Angiotensin-converting enzyme inhibitors and angiotensin-II inhibitors	Renal function, potassium	Repeat at 1 week after initiation and following dose increases. Consider checking renal function and potassium periodically once patient stabilized on medication
Amiodarone	LFTs, TFTs, potassium, CXR	LFTs and TFTs every 6/12. Consider periodic lung function tests, CXR, eye examination
Diuretics	Renal function and electrolytes	Repeat within a month of initiation. Consider long-term monitoring, particularly in the elderly
Digoxin	Renal function, potassium. Consider TFTs	Repeat at least annually and whenever there is a risk of change in potassium levels. Consider checking digoxin levels
Oral anticoagulants	Prothrombin time, APTT, LFTs	Check INR as regularly as needed to keep levels within the therapeutic range
Statins (see product inserts for specific guidance, e.g., for atorvastatin, rosuvastatin)	Lipid profile, LFT, CK	Repeat within 1–3 months. Check LFT and lipid profile at 6 and 12 months. Consider longer-term monitoring
Respiratory		
Theophylline		Theophylline levels every 6–12 months after initial stabilization. Consider checking potassium if severe asthma or use of interacting drugs
Anti-epileptic drugs		
Carbamazepine	CBC, LFTs	CBC “periodically” (according to product insert)
Phenytoin	Consider CBC, LFTs	Check CBC (according to product insert). Consider checking LFTs and folate levels
Sodium valproate	CBC, clotting profile, LFTs	LFT “periodically” during first 6 months of treatment
Antipsychotic and anti-manic drugs		
Atypical antipsychotics (excluding clozapine)	See product inserts. Likely to include CK, CBC, renal function and electrolytes, LFT, TFT, BP, weight. May include glucose, prolactin, ECG	See product inserts
Clozapine	See PI: All of the above plus WBC > 3.5 × 10 ⁹ /L with normal differential and EEG	See product inserts
Lithium	Urinalysis, renal function, TFTs	Once stabilized: renal function and lithium levels (e.g., 3 monthly), TFTs (e.g., 6 monthly)
Antimicrobials		
Minocycline		If used for longer than 6 months, check every 3 months LFTs and signs of SLE
Aminoglycosides (administered parenterally)	Creatinine clearance	Regular serum peak and trough levels depending on age and renal function
Vancomycin (administered parenterally)	CBC, renal function (creatinine clearance), urinalysis	Regular vancomycin levels
Endocrine		
Thyroxine	TSH, T4	Once stabilized, repeat yearly or following a dose change
Metformin	CBC, renal function	CBC annually and renal function “regularly” (according to product insert)
Thiazolidinediones, e.g., pioglitazone, rosiglitazone	LFTs	LFTs every 2 months for the first year and then “periodically” (according to the product insert)
Disease-modifying anti-rheumatic drugs		
Azathioprine	CBC, renal function and electrolytes, LFT	After initial intensive monitoring, CBC and LFTs monthly
Hydroxychloroquine	Renal function, LFTs, and ophthalmological examination	Ophthalmological examination at least yearly
Leflunomide	CBC (with differential white count), LFTs (including ALT)	See product insert—regular checks of BP, CBC, and LFTs (including ALT)
Methotrexate	Renal function, CBC, LFTs, and CXR	Once stabilized on treatment, check CBC and LFTs at least “2–3 monthly” (according to product insert)
Penicillamine	CBC, renal function, urinalysis	Once stabilized, check CBC and urinalysis monthly
Sodium aurothiomalate	CBC, renal function, urinalysis, LFTs	CBC and urinalysis before each injection

*Where possible, specific monitoring intervals are given. These are not available, however, for some drugs and in these cases terms such as “consider checking” and “periodically” appear. If in doubt, it is suggested that the reader consult relevant product inserts, but it should be noted that these are not always specific in their advice.

Advanced Checking of Drug–Disease Interactions and Contraindications

When prescribing, clinicians should avoid contraindicated drugs based on pre-existing morbidities and other patient-related conditions. For example, the use of non-selective

beta-blocking drugs should not be prescribed for patients with asthma, and a number of drugs are contraindicated that exacerbate myasthenia gravis. Nevertheless, prescription of contraindicated drugs continues,⁶⁸ and causes avoidable morbidity and costs in the form of hospital admissions.⁵⁶

CPOE applications can help clinicians to avoid contraindicated medication prescribing by alerting them at the time of ordering about relevant underlying conditions. To enable such checking is non-trivial. First, one must obtain or develop an adequate knowledge base of drug-disease contraindications. Many vendors and healthcare organizations have developed these based on contraindications listed in package inserts. A review of drugs available in the British National Formulary revealed around 1,500 contraindications between drugs or drug groups and morbidities or clinical states.⁶⁰ Important categories of contraindications included hepatic impairment, renal impairment, and a range of other conditions. Often the information provided in package inserts regarding drug-disease contraindications is vague and unhelpful. Many product inserts refer vaguely to a wide range of “absolute contraindications” presenting significant challenges for those attempting to code computerized alerts. For example, streptokinase is contraindicated in “all conditions that are likely to be associated with existing or very recent hemorrhage.”⁶⁹

Second, contraindication alerts can only work only when patients’ diagnoses and conditions have been accurately and comprehensively entered as structured data into the EHR. A major problem is that “final” diagnoses for an admission or a patient visit are usually established at time of discharge. One might attempt to use, for example, diagnosis codes from previous encounters generated as part of billing procedures, although such information is notoriously unreliable and of questionable accuracy. Some electronic medical records applications allow the clinician to maintain a coded problem list that might be relevant for this purpose, but coding may vary among clinicians.^{70,71} Finally, recent laboratory test results may indicate the presence of disease states such as renal or hepatic impairment. Importantly, alerts for documented “renal insufficiency” or “hepatic impairment” often depend on the degree of impairment. Different alerts should be presented depending on whether the patient has mild renal insufficiency, untreated uremia, or is actively undergoing dialysis. Creative approaches to communicating alerts may help, for example, by placing information about renal and hepatic function “non-interruptively” on usual data entry screens rather than displaying them in separate “pop-up” screens.³⁵

Also, although it is expedient to focus on commonly encountered contraindications, clinicians may be less aware of contraindications for rare but important conditions, such as porphyria. Finally, in situations in which the alerting system does not cover the domain completely, clinicians should be aware of what is *not* covered by the alerting system.

Future developments in drug-disease interaction checking should address:

1. Developing a standardized, comprehensive source of contraindication information that could be used by all CPOE systems.
2. Building consensus among healthcare organizations about which contraindications to include in CPOE systems, especially for contraindications with difficult-to-code trigger conditions, such as when the contraindication depends on the degree of morbidity. Healthcare organizations should explore how to share such knowledge amongst themselves.

3. Developing methods to ensure that all patient “triggering” morbidities for contraindications can be accessed by CPOE systems during ordering sessions. For example, physicians might code morbidities electronically as they record details of consultations and interventions. Alternatively, coding after the fact by non-medical staff would provide a less reliable and less timely approach.

Advanced Drug-Pregnancy Alerting

Drug-pregnancy alerts represent an important category of advanced decision support. A small number of drugs are high teratogenic, and should never be given to a woman who is, or might be, pregnant. Many other drugs are relatively contraindicated, to varying degrees, in pregnancy. A closely related issue is that many drugs are absolutely or relatively contraindicated during lactation.

Among organizations implementing drug-pregnancy checking, the greatest challenge involves the determination of whether a female patient is or might be pregnant. Urine tests, serum beta HCG, and more expensive ultrasound imaging can be used to determine current pregnancy status. However, pregnancy tests are not routinely performed on admission, and many systems do not contain the results of recent pregnancy tests, even when they were performed (for example, at home, or at another institution). Furthermore, a recent negative pregnancy test does not absolutely guarantee that the patient is not currently pregnant. Conversely, systems that do contain pregnancy information do not often update the information when a pregnancy has ended. A final complication is that patients who have had total hysterectomies cannot become pregnant at any age, so that issuing pregnancy and lactation-related alerts becomes inappropriate. Electronic health records should allow clinicians to document explicitly whether a woman is known to be pregnant, whether she might be pregnant, and whether she is lactating. Because some drug-pregnancy alerts depend on the stage of the pregnancy, an estimated due date, or estimated date of conception would also be valuable to capture electronically. Some alerts should appear only for patients who are believed to be pregnant, whereas others should appear for all women of child-bearing age.

Institutions activating drug-pregnancy alerts use highly selective criteria to select “trigger” medications.³⁵ Those medications carrying the Food and Drug Administration’s current “Category X” specification in the pregnancy section of the drug label⁷² clearly merit displaying drug-pregnancy alerts as pop-up warnings—not doing so can be catastrophic. In one outpatient CDS application, drug-pregnancy alerts for Category A drugs also were implemented as a pop-up alert, whereas Categories B and C were implemented as passive, non-interruptive messages on the usual ordering screens. Even though this approach minimized the total number of pop-up drug-pregnancy alerts, the alert acceptance rate, i.e., the rate with which alerts were canceled in response to the alert, was only 10%, reflecting the inability of the computer to know with certainty whether the patient is pregnant.³⁵

Future work on drug-pregnancy decision support should include:

1. Improved methods and standards for electronic health records to indicate pregnancy, expected due date, potential pregnancy, lactation, and the impossibility of pregnancy.
2. Better delineation of when to interrupt the provider with specific alerts.

Recommendations for Future Work

Clearly, medication-related decision support has achieved many benefits. Yet, many issues remain for future work. Recommendations follow below for individuals and organizations involved in applying information technology to improve pharmacotherapy quality and safety within patient care.

Recommendations to Healthcare Provider Organizations

Healthcare organizations should actively adopt medication-related clinical decision support safeguards. Each organization should have an appropriate organizational structure (including administrators, clinicians, and informaticians) in place to actively seek out medication-related decision support capabilities and to review the suitability of purchasing vendor clinical decision support offerings vs. developing them locally (when appropriate expertise exists). Provider organizations should employ local personnel who understand the CDS-related technical capabilities of their CPOE applications, human factors involved in CDS development, issues in creating the knowledge for CDS systems, and workflow considerations critical to clinical system implementation. Organizational staff must be capable of reviewing and editing, and perhaps even creating, alerts.

Healthcare institutions should be aware that different alerts may be presented in different ways, for example, some may be presented at the time of ordering, others at the time of logging on, and others perhaps as automated e-mail messages. Organizations should have personnel who work with the CPOE application vendor to find the best way of using clinical decision support features to achieve the organization's medication safety goals. Organizations should be aware that most CPOE applications will have implemented only some of the clinical decision support features described in this article, so they must lobby for desired features that may not yet be available.

Healthcare organizations that implement CDS must monitor its effectiveness locally. Leadership should know how often alerts are firing and how often clinicians are responding to the alerts (i.e., what proportion of the alerts are "accepted").

Recommendations to CPOE Application Vendors

Vendors of clinical information systems and EHR software should implement as many proved, effective medication-related decision support features as possible. Vendors should be especially attentive to the user interface (UI) for clinical decision support because, by design, alerts interrupt clinicians' intended workflows. The CDS UI should present information clearly and concisely, allow clinicians to act on alerts directly from the alert screen when possible, and then return clinicians to their previously intended workflows. In addition, vendors should support the development of more detailed knowledge bases that facilitate alerting and can differentiate among anticipated severities of conditions so that the most appropriate warning mechanism can be used.

Degree of severity should influence interruptive versus non-interruptive notification methods.

Vendors should implement knowledge management tools for their customers' use.¹³ Healthcare organizations (of sufficient size) that purchase CPOE products should be able to review embedded drug information resources (e.g., drug-drug interactions, drug-lab interactions, etc.) to determine where errors are present (invariably some will be present), and to decide which specific alerting rules they want to implement. Errors should be reported back to the vendor so they can be fixed at the source. Customers may also want to create additional alerts when appropriate. Application vendors' tools should allow provider organizations to make local customizations to the knowledge base, and these customizations should survive vendor product upgrades.¹³ Application vendors should encourage the research required to improve the quality and breadth of currently available drug information databases. Application vendors may need to work with knowledge-base vendors to implement improved medication CDS functionality.

To enable health care organizations to monitor the effectiveness of CDS, vendors should provide reporting functionality that makes this information easy to obtain.

Recommendation to Drug Information Knowledge-base Vendors

Drug information knowledge-base vendors should work with CPOE and pharmacy system vendors to implement knowledge management tools so that provider organizations can customize purchased drug information, and so customizations persist across version upgrades. Application vendors and knowledge-base vendors may need to work together on improving CDS functionality. Wherever possible, vendors should use established and emerging standards, both for knowledge representation as well as for the concepts involved in alerting rules (e.g., standard cross-vendor, nationally accepted identifiers for laboratory, medication, and concepts from the history and physical examination). Knowledge-base vendors should be supportive of standards development efforts.

As much as possible, knowledge-base vendors should try to create clinically meaningful, pragmatic knowledge that can be applied at the point of care. Such knowledge should be evidence-based supported by references; when this is not possible, evidence should be based on experts' consensus opinion about accepted best practices, and referenced as such. Vendors should work to create concise and actionable alert messages (e.g., "starting amiodarone doubles previously stable serum digoxin levels" rather than "digoxin and amiodarone interact"). Links should exist to enable clinicians to review the evidence basis for automated drug information, both as bibliographic references and as text summaries of evidence. Knowledge-base vendors should be sensitive to the concepts of "false positive" and "false negative" alerts, the costs of each, and the performance characteristics of any particular set of alerts. Knowledge-base vendors should recognize the pent-up demand for truly useful CDS knowledge and try to bring new products to market.

Recommendations to Policy Makers

Currently, most of the CDS that has been shown to be useful has been custom developed by the institutions (usually large medical centers, such as academic institutions) that make use of it. Under such circumstances, each organization that wishes to implement a particular knowledge-based feature must craft the knowledge themselves, test the intervention before implementing it, and monitor its effectiveness over time. There are few incentives for a healthcare organization to share knowledge that has been so painstakingly developed and there are significant technical hurdles if it wished to do so. Given that the knowledge-base vendor market still is so immature, organizations wishing to implement CDS must develop it themselves. Most organizations do not have the resources and expertise to do this. A single national repository of executable medication-related alerting rules would be a valuable national resource, and policymakers should provide support to create one. The National Library of Medicine could serve as the custodian for such a repository and has identified such a goal in its long-range plan.⁷³ This should be done in a way that supports and complements commercial efforts rather than supplants them.

Recommendations to Research Community

The area of clinical decision support is replete with opportunities for further research. Examples of CDS-related areas where research is needed include:

- To what extent does alerting impact on clinician behavior and patient outcomes?
- What is the optimal way to present alerts to prescribers?
- How can clinicians' sense of satisfaction with alerts and other kinds of decision support be increased, i.e., so clinicians find decision support useful and not annoying?
- When does "alert fatigue" happen?
- What is the best way for organizations to share alert knowledge?
- How can commercial medication knowledge bases be edited to yield clinically valuable knowledge bases?
- Where there are multiple presentation modes, which mode is most appropriate for any given alert?
- Which member of the health care team—for example, physician, nurse, pharmacist, other—is the best recipient of any kind of alert?
- Should physicians and pharmacists see the same drug-related alerts?

Summary

Prescription-related CDS within CPOE systems can improve the quality and safety of medication prescribing and reduce its costs. However, realizing the benefits of CDS requires that many complexities be addressed, and the responsibility falls to health care provider organizations to assure intended goals are being achieved. Health care organizations must have dedicated staff and create effective processes⁷⁴ to get the most benefit from CDS. The implementation of CDS must be done thoughtfully, taking into account the staff and workflow and needs of the organization. Unfortunately, there is not yet a "one-size-fits-all" approach to CDS.

Creating a clear and concise alert that displays sufficient information so that the clinician understands the rationale for the interruption, as well as makes it easy to take a more appropriate action, presents a substantial human factors

challenge, and current user interface capabilities are limited. Organizations must take this into account when building CDS features.

A health care organization should assure that the CDS it implements is helpful to clinicians and not generating a large number of unhelpful alerts. A large set of definitive medical knowledge that can be implemented as CDS immediately and unambiguously still is largely elusive. To develop the knowledge for CDS, health care provider organizations must use a combination of commercial rule sets, rules that other organizations have developed, and rules about best practice that can be derived from the primary health care literature and national and local consensus on what constitutes best practice. In many cases, more research is needed to determine with more clarity what in fact constitutes "best care."

Finally, the list of potential CDS features is long and health care organizations will need to prioritize the ones they want to implement. Ideally, these choices should complement the overall quality and safety program of the organization.

The complexities of CDS mean that with today's technology, most organizations will realize only a moderate proportion of the potential benefit of CDS. Substantial opportunities exist for increasing the benefit that can be realized by CDS, however, multiple stakeholders in the healthcare system (government agencies, knowledge-base and application vendors, healthcare providers, pharmacies, researchers, and informaticians) will need to collaborate if we are to realize the benefits of CDS and make medication use as safe and effective as possible. The importance of patient safety dictates that all parties should work on these problems expeditiously.

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