SHORT COMMUNICATION

Drug Saf 2010; 33 (12): 1089-1096
0114-5916/10/0012-1089/$49.95/0

An Algorithm for Integrating Contraindications into Electronic Prescribing Decision Support

Robin E. Ferner[1,2] and *Jamie J. Coleman*[2,3]

1 West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham, UK
2 School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK
3 University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Abstract

Background: Contraindications to medicines define circumstances in which the medicines must not be given. Computerized prescribing systems with decision support should display alerts to warn prescribers of contraindications. However, for such systems to be effective, alerts should only be displayed when relevant.

Objective: We set out to construct an algorithm that would classify contraindications according to the data available to a computerized system, and allow them to be displayed in context as far as possible.

Method: We drafted an initial algorithm from first principles, refined it by classifying further datasets, and then tested it on a further set of 95 phrases for contraindications.

Results: We were able to classify 94 of the 95 phrases; 13 related to age or sex and four related to allergies, but the majority depended on co-morbid conditions.

Conclusions: We have constructed a practicable algorithm for classifying alerts to contraindications. The classification used will allow alerts to be displayed when relevant. However, most contraindications relate to co-morbid conditions, and prescribing systems will only be able to display these in context if they have access to relevant clinical data.

Background

The balance between the benefits of a medicinal treatment and the harm it causes depends on the intrinsic properties of the medicine and the circumstances in which it is used. No benefit will accrue if the medicine is prescribed, for example, for a condition in which it is ineffective. The *indication(s)* for a medicine direct the prescriber towards uses for which its efficacy has been demonstrated. The harm that a particular medicine can cause varies according to the dose, time factors and the susceptibility of the patient.[1] Susceptibility factors include age, sex, genetic make-up, co-morbid conditions, physiological state and other factors. Sometimes, a regulator will deem that a particular subgroup of patients is so susceptible to harm that the risk of prescribing the

medicine outweighs any reasonable probability of benefit. The factor or factors that identify susceptible patients in this circumstance constitute *contraindications* to the use of the medicine. The European Medicines Agency states "4.3 Contraindications: Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include particular clinical diagnosis, concomitant diseases, demographic factors (e.g. sex, age) or predispositions (e.g. metabolic or immunological factors, prior adverse reactions to the medicine or class of medicines). The situations must be unambiguously, comprehensively and clearly outlined. Other medicines or classes of medicine, which must not be used concomitantly or consecutively should be stated, either based on data or strong theoretical reasons … Hypersensitivity to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients (see guideline on excipients in the label and package leaflet of medicinal products for human use). For herbal medicinal products, hypersensitivity extended to other plants of the same family or to other parts of the same plant should be labelled as a contraindication, where applicable."[2]

Contraindications are important, since they represent the regulator's decision that the risk is too high in all contraindicated circumstances to prescribe the medicine. However, they are also sometimes complex, and there may be many contraindications to some medicines. We consider here how to analyse official statements for contraindications to classify them so that – given patient information – the warnings need only to be displayed for subsets of patients according to patient information recorded in electronic systems.

The effectiveness of clinical decision support systems can be compromised by displaying alerts indiscriminately.[3] The extent to which alerts can be tailored to the patient's circumstances depends on the data available to the system.[4] This can be simple demographic information, such as sex and age; many systems will also record known allergies and current therapy. Where data on clinical state, laboratory measurements and past medical history are available it may be possible to substantially reduce the number of alerts displayed to warn of contraindications.

We do not consider in detail whether the decision support is provided as alerts to all prescribers for any patient ('show-all' alerts), or tailored according to other factors such as the expertise of the prescriber. Nor do we consider in detail which alerts 'must' be displayed regardless of circumstances. Our objective is to construct an algorithm that will classify contraindications according to the data available to a computerized system, and allow them to be displayed in context as far as possible.

Method

We set out a draft scheme for an algorithm that could be used to arrange data on contraindications for medicines in such a way that – where linkage was possible – alerts could be provided on the basis of personal information within the system.

We then examined a large series of statements on contraindications from the ABPI *eMedicines Compendium*[5] and the *British National Formulary (BNF)* No. 57, March 2009[6] that had not previously been coded for in the local electronic prescribing system (Prescribing, Information and Communication System [PICS])[7] and amended the draft scheme so that all of the information in the *BNF* contraindication alerts could be categorized. We only considered those phrases regarded by the *BNF* as indicating contraindications and falling within the European Medicines Agency definition of contraindications.

We then examined the set of contraindication alerts prepared for the forthcoming revision of the *BNF* No. 58[8] that had not previously been coded and, using the amended draft algorithm, introduced further changes to it.

We intended only two iterations, but after the second iteration it was considered that there was scope for further improvement. So we finally tested the performance of the algorithm using a further dataset of 95 uncoded contraindication

alerts prepared for a previous revision of the *BNF* No. 56.[9]

Results

The factors that we considered were, in order, sex, age, recorded allergy or hypersensitivity, genetic or phenotypic trait, concurrent ingestions, co-morbid conditions, specified physiological states and anatomical state or variation. This provided a set of eight classes with a total of 20 subdivisions.

A small number of contraindication alerts could not be incorporated readily into the initial draft version of the algorithm. These included 'Anectine® (suxamethonium) has no effect on the level of consciousness and should not be administered to a patient who is not fully anaesthetized'; 'congenital or acquired abnormality of the uterus (Mirena® levonorgestrel coil)'; and 'the development of oliguria or anuria during treatment of severe progressing [*sic*] renal disease (Burinex® bumetanide).'

The *BNF* No. 58[8] revision included 56 new phrases for contraindications. All but five of these could readily be classified by the algorithm. Two unclassified phrases related to disease in household contacts and one to radiotherapy. Two other phrases – 'vaccines intravenously' and 'volume expansion' – did not fit the European Medicines Agency definition of contraindication and were not considered further. We modified the algorithm again. The final algorithm is shown in table I, together with example phrases from the *eMedicines Compendium*[5] and *BNF* No. 58.[8]

The final validation set, *BNF* No. 56 revision, consisted of 95 uncoded phrases indicating contraindications. We were able to classify all but one of these phrases. The unclassifiable phrase was 'patients unvaccinated against *Neisseria meningitidis*'. Some contraindications were complex: one required the presence of two of four risk factors, which translated to three classes within our algorithm.

Six alerts depended primarily on sex, seven on age, four on allergy or hypersensitivity, seven on hereditary traits and six on concomitant or past exposure to drugs or other substances. Sixty-three contraindications fell into the category of 'contraindicated in patients suffering from or with a history of a co-morbid condition'. One related to anatomical abnormality.

Several contraindications referred to patients who fell into more than one class. For example, 'history of unexplained jaundice following exposure to halothane' was classified as 'past exposure to halothane' and 'past history of jaundice' and qualified by 'unless otherwise explained.' In total, 24 contraindications required qualification; for example, they applied only to a specific route of administration or formulation of drug. The most complex phrase was 'history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable'.

Discussion

Computerized decision support is best when it is targeted, using the greatest amount of available information, and so displays cogent and relevant alerts, while avoiding a plethora of unnecessary, irrelevant and distracting alerts.[3] There is, in essence, a balance to be struck between increasing the number of warnings displayed, which entails paying the price of 'crying wolf' so that important warnings are lost in the noise of irrelevant warnings, and reducing the number of warnings displayed, which can permit harms to go unremarked. It is not clear what the strategy is to optimize harm prevention, and that should be the focus of continuing study. Kuperman et al.[10] imply that drug-allergy checking and dose-range checking are more straightforward than checking for abnormal medication-associated laboratory tests, drug-disease interactions or drug-pregnancy interactions. All can be implemented if relevant data are available to the system, but we found that – for the contraindications we examined – the number of alerts that could be predicated on knowledge of the age or sex of the patient was small, and knowledge of drug allergies also contributed rather little to reducing the burden of alerts. By far the most important data were those on current or past co-morbid conditions. Although we were able to assign them to this class, the descriptor of the co-morbidity was often not a recognized term in standard coding systems, e.g. Systematised Nomenclature of Medicine Clinical Terms

Table I. Algorithm for contraindications and examples

Algorithm for contraindications	Examples from *eMedicines Compendium*, section 4.3[5][a]
1. Contraindications differ between sexes? **YES: Consider by sex; signal if contraindicated in one sex; go to 1.1**	
NO: go to 2	
1.1 In females, differing according to reproductive status: menarche, menopause, pregnancy? **YES: signal by status; go to 2**	Tritace® (ramipril) pregnancy Aromasin® (exemestane) should not be administered to women with pre-menopausal endocrine status
NO: go to 2	
2. Contraindicated by age? **YES: Consider by age; signal; go to 3**	Kaletra® (lopinavir and ritonavir) oral solution is contraindicated in children below the age of 2 years
NO: go to 3	
3. Contraindicated by allergy or hypersensitivity to any ingredient or any class of which any ingredient is a member? **YES: go to 3.1**	
NO: go to 4	
3.1 By allergy or hypersensitivity to a class to which the primary drug or drugs belong? **YES: identify which class or classes; signal; go to 3.3**	CosmoFer® (iron[III] hydroxide-dextran complex). Drug hypersensitivity including iron mono- or disaccharide complexes and dextran
NO: go to 3.2	
3.2 By allergy or hypersensitivity to primary drug or drugs? **YES: signal; go to 3.3**	Betaferon® (recombinant interferon-β). Patients with a history of hypersensitivity to natural or recombinant interferon-β
NO: go to 3.3	
3.3 By allergy or hypersensitivity to a class to which excipient, diluents, colourant or other secondary ingredients (including contaminants) belong? **YES: identify which class; signal; go to 4**	Betaferon® (recombinant interferon-β). Patients with a history of hypersensitivity to … human albumin or to any excipients
NO: go to 3.4	
3.4 By allergy or hypersensitivity to excipient, diluents, colourant, or other secondary ingredients (including contaminants)? **YES: signal; go to 4**	Aggripal® (influenza vaccine): hypersensitivity to the active substances, to any of the excipients and to residues
NO: go to 4	
4. Contraindicated by genetic or phenotypic trait? **YES: go to 4.1**	
NO: go to 5	
4.1 Contraindicated by known, inferred, or suspected genetic trait? **YES: signal; go to 4.2**	Sevoflurane is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia
NO: go to 4.2	
4.2 Contraindicated by observed or suspected phenotypic trait (including ethnic group)? **YES: signal; go to 5**	Concerta® XL (methylphenidate) in patients with a family history or diagnosis of Tourette's syndrome
NO: go to 5	
5. Contraindicated in patients taking or having taken exogenous substances? **YES: go to 5.1**	
NO: go to 6	
5.1 Contraindicated in patients taking or having taken medicines? **YES: go to 5.1.1**	
NO: go to 5.2	

Continued next page

Table I. Contd

Algorithm for contraindications	Examples from *eMedicines Compendium*, section 4.3[5][a]
5.1.1 Contraindicated in patients taking medicines now? **YES: signal drug or drug class; go to 5.1.2**	Adalat® (nifedipine) should not be administered concomitantly with rifampicin (rifampin) since effective plasma levels of nifedipine may not be achieved owing to enzyme induction. Adenoscan® (adenosine). Concomitant use of dipyridamole
NO: go to 5.1.2	
5.1.2 Contraindicated in patients having taken medicines in the past? **YES: signal time interval and drug or drug class; go to 5.2**	Nardil® (phenelzine) should not be administered at the same time as, or within 14 days of, treatment with other monoamine oxidase inhibitors, buspirone or dibenzazepine derivative drugs (including tricyclic antidepressant agents, perphenazine or carbamazepine)
NO: go to 5.2	
5.2 Contraindicated in patients taking or having taken non-medicinal substances? **YES: go to 5.2.1**	Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking Aptivus® (tipranavir) due to the risk of decreased plasma concentrations and reduced clinical effects of tipranavir
NO: go to 6	
5.2.1 Contraindicated in patients taking non-medicinal substances now? **YES: signal non-medicinal substances; go to 5.2.2**	Vertab SR® (verapamil) concomitant ingestion of grapefruit juice
NO: go to 5.2.2	
5.2.2 Contraindicated in patients having taken non-medicinal substances in the past? **YES: signal time interval and non-medicinal substances; go to 6**	None found
NO: go to 6	
6. Contraindicated in patients suffering from or with a history of a co-morbid condition? **YES: go to 6.1**	
NO: go to 7	
6.1 Contraindicated in current co-morbid conditions? **YES: go to 6.1.1**	
NO: go to 6.2	
6.1.1 Contraindicated in general conditions or pathology not related to one physiological system (even if localized), including trauma, radiotherapy and cancer? **YES: signal; go to 6.1.2**	Acnocin® (cyproterone acetate and ethinylestradiol). Severe diabetes mellitus with vascular changes Administration of Gardasil® (human papilloma virus vaccine) should be postponed in individuals suffering from an acute severe febrile illness Anectine® (suxamethonium) causes a significant transient rise in intraocular pressure, and should therefore not be used in the presence of open eye injuries or where an increase in intraocular pressure is undesirable unless the potential benefit of its use outweighs the potential risk to the eye
NO: go to 6.1.2	
6.1.2 Contraindicated in current co-morbid conditions related to specific pathology by system? **YES: signal in order – CVS, RS, GI tract, CNS, Skin, Endoc, MSS, GUS, RES; signal within system by symptoms, signs, tests; go to 6.1.3**	Coracten XL® (nifedipine) during or within 1 month of a myocardial infarction
NO: go to 6.1.3	
6.1.3 Contraindicated in current co-morbid conditions demonstrated only by investigations? **YES: signal in order – biochemistry, haematology, immunology, electrocardiography, pulmonary function tests, other; go to 6.2**	Adcal D3® (calcium carbonate). Absolute contraindications are hypercalcaemia resulting, for example, from myeloma, bone metastases or other malignant bone disease, sarcoidosis, primary hyperparathyroidism and vitamin D overdosage

Continued next page

Table I. Contd

Algorithm for contraindications	Examples from *eMedicines Compendium*, section 4.3[5][a]
	Hydrea® (hydroxycarbamide) thrombocytopenia ($<100 \times 10^9$/L), Actilyse® (alteplase) evidence of intracranial haemorrhage on the CT scan Securon® (verapamil) second- or third-degree atrioventricular block (except in patients with a functioning artificial pacemaker)
NO: go to 6.2	
6.2 Contraindicated in patients with a history of a co-morbid condition? **YES: signal with time course if relevant, ordered as for current co-morbidities; go to 6.3**	Actilyse® (alteplase) significant bleeding disorder at present or within the past 6 months Dianette® (cyproterone acetate and ethinylestradiol) jaundice or persistent itching during a previous pregnancy Femodene® (gestodene and ethinylestradiol) Existing or previous arterial thrombotic or embolic processes
NO: go to 6.3	
6.3 Contraindicated where there is illness in others? **YES: go to 6.3.1**	
6.3.1 Contraindicated where there is a relevant family history of illness, not recorded at 4.2? **YES: signal; go to 6.3.2**	Ketek® (telithromycin) is contraindicated in patients with a history of congenital or a family history of long QT syndrome (if not excluded by ECG) and in patients with known acquired QT interval prolongation Varivax® (varicella virus vaccine). Individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated
NO: go to 6.3.2	
6.3.2 Contraindicated where there is contact with others who are ill? **YES: go to 7**	*British National Formulary*[8] warning regarding live poliomyelitis vaccine): the live (oral) vaccine must **not** be used for immunosuppressed individuals or their household contacts
NO: go to 7	
7. Contraindicated in patients in a specified physiological state? **YES: Consider physiological state; signal; go to 8**	Anectine® (suxamethonium) has no effect on the level of consciousness and should not be administered to a patient who is not fully anaesthetized
NO: go to 8	
8. Contraindicated in patients by anatomical state or variation? **YES: Consider anatomical state or variation; signal; go to END**	(Ditropan®, oxybutinin) shallow anterior chamber Menopur® (menotrophin). Structural abnormalities in which a satisfactory outcome cannot be expected; for example, tubal occlusion (unless superovulation is to be induced for *in vitro* fertilization), ovarian dysgenesis, absent uterus or premature menopause
NO: END	

a Examples from *eMedicines Compendium* unless indicated otherwise.

CVS = cardiovascular system; **Endoc** = endocrine system; **GI** = gastrointestinal; **GUS** = genitourinary system; **MSS** = musculoskeletal system; **RES** = reticuloendothelial system; **RS** = respiratory system.

(SNOMED CT®)[11] and *International Classification of Diseases (ICD)-10*. This will make it difficult to apply clinical decision support rules within electronic prescribing systems where co-morbidities are coded using these systems.

The structure of European Summaries of Product Characteristics (SPCs) explicitly separates contraindications, interactions and dosage instructions; warnings, which are weaker than contraindications, can have elements of cautions related to susceptibility, interactions or dosage. The US FDA approves drug labels that have sections on contraindications, warnings and precautions, as well as information on indication, dosage and adverse effects.

It is possible to make the display of a contraindication alert contingent on data already present. For example, the alert 'Andropatch® 2.5 mg (testosterone patch) has not been evaluated in women and must not be used in women' need

only be displayed if the patient is female. Our algorithm allows the decision whether to display an alert to be systematized where data are available. Since, in the absence of relevant data, the default may be to display information on contraindications, we have ordered the checks to consider the most basic data first, and then data less likely to be available.

Where data are missing – for example, where it is unknown whether a woman is pregnant – there are three options. First, the system can display alerts such as 'Arthrotec® 50 (diclofenac and misoprostol) is contraindicated in pregnant women and in women planning a pregnancy' for all female patients, regardless of age. Second, it can make reasonable assumptions – for example, that girls below the age of 10 years and women over the age of 55 years will not be pregnant, and use additional data such as birth date on which to base the decision to display the alert. A third possibility is to enquire of the user whether the patient is pregnant. This has the advantage of prompting the user to consider the question of contraindications, but may constitute an unwanted interruption in workflow.

A major difficulty is that regulatory documents, notably SPCs, have accumulated data on contraindications over 40 years. As a result, there are non-standard phrases, uncertainties in precise terminology and difficulties in mapping terms from the listed contraindications to standard ICD-10 or SNOMED CT® terms. The European Medicines Agency, the FDA and CIOMS should consider demanding that a consistent terminology be used for contraindications labelled in regulatory documents. We also encountered the problem that contraindications were sometimes described in terms of drug classes that are not part of standard classifications, such as 'hepatotoxic drugs' or 'drugs that prolong the QT interval.' There are no canonical lists of these classes, and for computerized alerts to be optimally effective it would be necessary to identify such drugs.

If personal data cannot be used to target the display of alerts, there remains the possibility of showing every contraindication alert. This is, at first, a seemingly safe strategy, since all necessary alerts have been displayed. Unfortunately, the human-machine interface is complex and there is a rapid fatigue of attention to alerts. As a result, many alerts are cancelled by prescribers, even when they are relevant.[12] There is therefore a balance to be struck between displaying every possible alert and displaying a small number of important alerts that will command attention and result in action. By definition, regulators consider contraindications to be important. However, the harm done by prescribing in ignorance of a contraindication is a function of the probability of the contraindication being present as well as of the seriousness of the consequence should it be present. Yet Madopar®, used to treat Parkinson's disease, is contraindicated in 'women of childbearing potential in the absence of adequate contraception.' There are about 600 000 children born each year in the UK, and perhaps 25 000 000 women of childbearing age, so approximately 2–3% of potentially pregnant women will in fact be pregnant. Most prescriptions for Parkinson's disease will not be for women of child-bearing potential, and few women of child-bearing potential are in fact pregnant (whether or not they have Parkinson's disease). It might be thought reasonable to allow prescribing without displaying this warning: the risks may be tolerable. Decisions of this sort will inevitably be required where phrases are unclassifiable, as we found in rare cases, or where relevant data are not available to the system.

Conclusions

Prescribing decision support systems will function best when alerts are displayed if and only if they are relevant. We considered here how to analyse contraindications to classify them so that the warnings need only to be displayed for subsets of patients where relevant information was available. Most contraindications refer to current or past co-morbid conditions. If these are to be used by decision support systems they will have to be described in standard codable terms. Only systems with access to clinical data will be optimal, although even simple demographic data can be used to reduce the burden of unnecessary alerts.

Acknowledgements

Financial support for the submitted work was provided from the National Institute of Healthcare Research as part of the Collaborations for Leadership in Applied Health Research and Care Scheme. Both authors declare no financial relationships with commercial entities that might have an interest in the submitted work.

References

1. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ 2003; 327: 1222-5
2. European Commission, Enterprise & Industry Directorate General. A guideline on summary of product characteristics, October 2005 [online]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-2/c/spcguidrev1-oct2005_en.pdf [Accessed 2010 Feb 20]
3. van der Sijs H, Aarts J, Vulto A, et al. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006; 13: 138-47
4. Bobb A, Gleason K, Husch M, et al. The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry. Arch Intern Med 2004; 164 (7): 785-92
5. Datapharm Communications Ltd. ABPI eMedicines compendium [online]. Available from URL: www.emc.medicines.org.uk [Accessed 2010 Feb 20]
6. BMA/RPS. British national formulary. 57th ed. London: Royal Pharmaceutical Society Publishing, BMJ Publishing Group, March 2009
7. Nightingale PG, Adu D, Richards NT, et al. Implementation of rules based computerised bedside prescribing and administration: intervention study. BMJ 2000; 320: 750-3
8. BMA/RPS. British national formulary. 58th ed. London: Royal Pharmaceutical Society Publishing, BMJ Publishing Group, 2009 Sep
9. BMA/RPS. British national formulary. 56th ed. London: Royal Pharmaceutical Society Publishing, BMJ Publishing Group, 2008 Sep
10. Kuperman GJ, Bobb A, Payne TH, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007; 14 (1); 29-40
11. United States National Library of Medicine. Unified Medical Language System® (UMLS®): SNOMED Clinical Terms® (SNOMED CT®). Bethesda (MD). 2009 [online]. Available from URL: http://www.nlm.nih.gov/research/umls/Snomed/snomed_main.html [Accessed 2010 Sep 10]
12. Weingart SN, Toth M, Sands DZ, et al. Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med 2003; 163: 2625-31

Correspondence: Professor *Robin E. Ferner*, West Midlands Centre for Adverse Drug Reactions, City Hospital, Dudley Road, Birmingham B18 7QH, UK.
E-mail: r.e.ferner@bham.ac.uk