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Patient-Oriented Strategies for the Prevention of Drug Interactions

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Abstract

Drug interactions are a common and serious problem arising from polypharmacy. Strategies to reduce the likelihood of the co-prescription of hazardous drug combinations are likely to enhance the quality of care provided for patients requiring polypharmacotherapy. Drugs for which patient-oriented information strategies may decrease the likelihood of drug interactions tend to be those of low therapeutic index, and have interaction potential with other drugs commonly prescribed or available without prescription.

Drug interactions are a common and serious problem arising from polypharmacotherapy. In some cases, drug interactions have a pharmacokinetic basis, arising as a result of the effects of one drug upon the absorption, distribution or elimination of another. In other situations, drug interactions result from pharmacodynamic synergism or antagonism, with the coadministration of 2 drugs leading to pharmacological effects which may not have been observed with monotherapy with either agent. In a seminal paper underpinning the development of the pharmaceutical care movement, Strand et al.[1] identified drug interactions as 1 out of 8 types of 'drug related problems' amenable to remedial intervention.

Research suggests that drug interactions are responsible for considerable patient morbidity and mortality. A study of admissions to an Australian hospital found that drug interactions accounted for 4.4% of drug-related problems encountered.[2] Other researchers found clinical evidence of a serious drug-drug interaction in 1.5% of a 200-patient cohort, although this proportion was substantially less than the number of potential interactions (37%) identified in screening.[3] In the same study, the investigators examined a series of 150 spontaneous adverse drug reaction reports, finding that drug interactions accounted for 8% of these.[3] However, in a review of drug interactions as a cause of hospital admissions, Jankel and Fitterman[4] found that the incidence of admissions attributable to drug-drug interactions in 9 studies ranged from 0 to 2.8%, leading these authors to suggest that the number of drug interactions as a cause of hospital admissions should be viewed within the context of the large number of medications prescribed by physicians and taken by patients.

Other research has specifically addressed the issue of drug interactions in at-risk populations. Goldberg et al.[5] found that the risk of adverse drug interactions increased dramatically with increasing polypharmacy. Potential drug interactions were identified in 27% of a sample of elderly patients assessed by Costa,[6] with factors such as increasing age, multiple illnesses, and female gender iden-

tified as risk factors. Polypharmacy itself has been identified as a risk factor for drug interactions, particularly in the elderly.[7]

Certain drugs, notably those of low therapeutic index, are most likely to be implicated in drug interactions producing adverse health outcomes and undesirable pharmacoeconomic consequences. Marik and Fromm[8] studied a cohort of patients with a serum digoxin concentration in excess of the recommended therapeutic range, identifying drug interactions in approximately 12% of patients. Hamilton and Gordon[9] found that admission to hospital as a result of drug interactions with theophylline was uncommon, but was associated with considerable expense. Other research has demonstrated that drug interactions with warfarin increase length of hospital stay, increase the use of laboratory investigations, and result in higher treatment costs.[10]

Notwithstanding the variability in the reported incidence and clinical significance of drug interactions described in the international medical and pharmaceutical literature, the fact remains that certain drug combinations are indisputably hazardous. Strategies to reduce the likelihood of the co-prescription of these drugs are likely to enhance the quality of care provided for patients requiring polypharmacotherapy. One approach that can be applied for this purpose is the use of medication alert strategies which provide information about drug combinations that should be avoided.

1. General Strategies to Reduce Adverse Drug Reactions and Interactions

Most clinicians will be familiar with medication alert strategies used as a means to reduce the likelihood of reproducing previous adverse drug reactions. In the hospital setting, the most common medication alert strategy is the use of systems to prominently record a previous allergy or hypersensitivity to a drug, meaning that the likelihood of inadvertent future administration of the same drug to that patient can be decreased. Other strategies of this type include the use of personal jewellery or other means to document drug allergy (e.g. the Medic-Alert™ system) allowing information about previous adverse drug reactions to be relayed to health professionals who may be dealing with a patient who is unconscious or otherwise uncommunicative.

Patient-held medication record cards are sometimes used in an effort to provide complete and comprehensive information to healthcare professionals about the current list of medications taken by patients. These medication records actually serve 2 functions: to provide assistance to the patients in the identification, organisation and self-administration of their medications, and to provide clinicians with a list of the medications taken by the patient. The rationale for their use in the latter function is that patients may not provide complete or up-to-date information about their medication therapy, and that by obtaining this information from healthcare workers, the likelihood of obtaining all of the current and relevant information is increased. This premise is by no means universally accepted, with some researchers suggesting that as few as 25% of patients present medication record cards with details consistent with actual medication intake.[11,12] The utility of these medication records as a means to prevent drug interactions is further limited by the fact that even if a complete record of medication use is available to both patients and clinicians, there is no guarantee that either would necessarily recognise all clinically significant interactions present. This being the case, the utility of patient-held medication cards appears to be greater if measured in terms of enhanced patient compliance, in itself a worthwhile goal.

2. Patient-Oriented Medication Alert Strategies

A variety of strategies have been used to help engage patients in a partnership approach to the safe use of medicines. These strategies are not only relevant to healthcare providers and patients, but are also of interest to other parties such as regulatory authorities, the pharmaceutical industry and patient support groups.

The use of 'ancillary' or 'cautionary' labelling of medicines as a supplement to primary labelling and verbal counselling from pharmacists or doctors is one mechanism to direct the attention of patients to the specific issue of drug interactions. In Australia, guidance for dispensing pharmacists in relation to the use of ancillary labels is provided in the Australian Pharmaceutical Formulary and Handbook.[13] Ancillary labels specifically relating to drug-drug interaction potential include those describing potential adverse interactions with alcohol, as well as more specific interactions such as those seen with nonselective monoamine oxidase inhibitors.[13] Another label cautions patients in relation to the interaction between polyvalent cations (e.g. iron, magnesium, calcium, aluminium) and some antibacterials such as tetracycline and quinolones.[13] Previous ancillary label guidelines have not distinguished between the interaction potential of high dose aspirin (acetylsalicylic acid) and that seen with the same drug used in low, antiplatelet doses, but this distinction is now outlined in the most recent guidelines.[13] Other recent additions to the range of advisory labels include one designed to minimise the likelihood of coadministration of terfenadine, astemizole or cisapride with inhibitors of hepatic microsomal cytochrome P450 (CYP) 3A4 isoenzymes (e.g. erythromycin or itraconazole), and another label cautioning against the consumption of grapefruit and grapefruit juice whilst taking cyclosporin or some calcium antagonists.[13]

For many years drug products have been accompanied by package inserts with content primarily directed at healthcare professionals. This information has also been accessible to consumers of medications, at times generating confusion and possibly causing a detrimental effect upon patient compliance. More recent times have seen the introduction of package insert materials specifically designed for use by consumers. An example of this type of patient-specific medication information is consumer medicines information, previously referred to as consumer product information. Consumer medicines information must now accompany all drug products newly introduced to the Australian market, with a 'grandfather' clause presently applying to drugs introduced before the advent of the relevant legislation.[14] Consumer medicines information provides a plain language explanation of issues such as precautions and contraindications, adverse effects and potential drug interactions.

The implementation of consumer medicines information usage in specialised settings such as hospitals presents various logistical difficulties which are yet to be fully resolved.[14] Interprofessional tension between doctors and pharmacists in relation to role delineation in the use of consumer medicines information has also been identified,[15] and it is important that this issue should be addressed through appropriate education and training to facilitate cooperation. Representatives of the consumer health movement have greeted the introduction of consumer product information legislation with enthusiasm, citing advantages such as the availability of written materials as a back-up to verbal counselling, the uniformity of information provided, and the practical nature of the information.[16] Notwithstanding the consumer orientation of consumer medicines information materials, some early research suggested that this material performs poorly when tested with objective readability instruments such as the Flesch Reading Ease formula.[17]

Another strategy which can be used to minimise the risk of drug-drug interactions is the use of medication alert cards and other, similar patient-oriented information. This type of material has been in use for some considerable time, and includes information such as educational booklets and leaflets covering issues such as potential adverse drug reactions, drug-drug and drug-food interactions.[18-20] Examples include the various booklets and other information produced for patients treated with oral anticoagulants, nonselective monoamine oxidase inhibitors and the psychotropic drug lithium.[18-20] Each of these agents have several factors in common: they are drugs of low therapeutic index (i.e., the dose producing serious adverse ef-

fects is similar to that which can be used to produce therapeutic effects); they are implicated in a range of important drug interactions with other drugs which are relatively commonly prescribed or available without prescription; and the consequences of their interactions with other drugs is often of major clinical significance (resulting in death or major enduring disability). In view of these issues, it is not surprising that healthcare professionals, notably pharmacists, have focused attention upon the development of written materials which can be used to supplement verbal counselling when dispensing these drugs.

Applying the criteria described above, it is possible to develop a list of drugs for which patient-oriented medication alert information may be useful in decreasing potential for drug-drug interactions. This approach can be oriented from the perspective of particular drugs or classes of drugs, or alternatively can be designed around groups of agents used in particular therapeutic applications. Examples of both approaches are outlined in tables I and II.

Table I. Specific drugs for which patient-oriented alert materials may decrease drug interaction potential

Drug	Rationale
Astemizole, terfenadine, cisapride	Potentially fatal prolongation of QT interval after coadministration with inhibitors of hepatic microsomal cytochrome P450 3A4 isoenzymes. Commonly prescribed examples include erythromycin and azole antifungal drugs. Astemizole has been available without prescription in many countries
Lithium	Toxicity resulting from drug interactions may result in death or permanent neurological damage. Thiazide diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed, and many NSAIDs are available without prescription
Oral anticoagulants	Serious adverse health outcomes can result from failure of anticoagulation due to concurrent hepatic microsomal enzyme inducers, or from over-anticoagulation and bleeding resulting from coadministration of drugs such as cotrimoxazole (trimethoprim-sulfamethoxazole) or amiodarone
Theophylline	Serious CNS toxicity resulting from elevated serum concentrations after coadministration of macrolide or quinolone antimicrobial agents

The principles referred to above have been used in the development of a series of medication alert cards designed to minimise the potential for drug interactions with antidepressants.[21] The cards have been developed on the basis of evidence suggesting that physical comorbidities and polypharmacy are common amongst patients with mental illness.[22] New generation antidepressants have the ability to inhibit the metabolic activity of a variety of the hepatic CYP450 isoenzymes, resulting in the potential for interactions with drugs such as astemizole, terfenadine, theophylline, carbamazepine, methadone, warfarin, alprazolam, metoprolol and many others.[23] Research suggests that pharmacokinetic drug interactions resulting from inhibition of the CYP450 isoenzymes by psychotropic drugs are a significant issue amongst medically ill patients, supporting the need for strategies to minimise this type of drug-related problem.[24] Medication alert cards have been developed to reflect the range of potential interactions expected on the basis of the known clinical pharmacology of drugs such as fluoxetine, fluvoxamine, nefazodone and paroxetine.[21] In addition to drug-related harm resulting from pharmacokinetic drug interactions, the cards also seek to minimise the likelihood of the development of the serotonin syndrome from coadministration of more than 1 antidepressant. Feedback suggests that the cards may have averted several potentially interactions during the initial implementation period.[21]

3. Potential Disadvantages of Patient-Oriented Medication Alert Strategies

Although many arguments can be advanced to support the positive aspects of the use of patient-oriented medication alert strategies to reduce drug interactions, it is important to maintain a perspective of potentially negative aspects for patients and healthcare providers.

In Section 2 of this discussion, the possible interprofessional tensions arising from role-delineation disputes amongst health care providers have been alluded to.[15] Medical practitioners, pharma-

Table II. Drug classes for which patient-oriented alert materials may decrease drug interaction potential

Drugs	Rationale
Antidepressants	Wide range of potentially serious interactions mediated by antidepressant-associated inhibition of cytochrome P450 (CYP) isoenzymes
	Examples include interactions with hypolipidaemic agents, analgesics, antipsychotics and cardiac drugs
Drugs used for management of HIV/AIDS	Antiretroviral agents, antifungal drugs and antitubercular drugs are all associated with a wide range of important drug interactions
Immunosuppressants	Cyclosporin, tacrolimus and mycophenolate mofetil all have significant interactions with inhibitors of CYP3A4. Azathioprine interacts with allopurinol. Serious adverse effects ± loss of allograft may result

cists, nurses and representatives of the pharmaceutical manufacturing industry can all lay claim to a legitimate role in the provision of patient information, but the training of these stakeholders in disciplines relevant to this work function varies vastly. Although formal legislation such as that enacted in Australia to facilitate the implementation of consumer medicines information can serve to promote uniformity and consistency in the content of written consumer drug information, materials developed informally in individual settings have the potential to cause confusion if communication between members of the healthcare team is not clear. Furthermore, there is also a possibility that a third party supplying drug information to a consumer, but who is not directly involved in the care of that patient, may undermine the positive relationship which exists between a patient and their primary healthcare provider.

The rapidly expanding range of health and drug information sites found on the internet serves to underscore the importance of this issue. The reliability of information from sources such as the internet may be less then ideal. For example, McClung et al.[25] examined internet-derived information about the management of childhood diarrhoea, finding that the extent of compliance with guidelines of the American Academy of Paediatrics was poor.

The content of patient-oriented medication information may well be open to criticism. The incorporation of information into the approved product information for drug products is strictly governed by principles laid down by various national and international regulatory authorities – this type of governance does not necessarily guide the development of practice-based, locally produced patient information materials. On the other hand, the rate of development of knowledge regarding drug interactions in the postmarketing surveillance period commonly outstrips that observed during clinical trials conducted under tightly controlled circumstances. Officially sanctioned patient information may not necessarily keep pace with the development of new knowledge about drug interactions, nor may the sponsors of clinical trials necessarily be inclined to seek to ensure that this is the case. Other problems underpinning difficulties with the content of patient-oriented drug information may include inaccurate generalisations across drug classes, and undue emphasis upon single case-reports or open studies relative to data obtained from well controlled trials. Overall, a multidisciplinary and essentially cautious approach is warranted in relation to the development of consumer drug information materials.

Even when the content of patient-oriented medication information is well researched and accurate, there is no guarantee that the information will be presented in a format which facilitates the effective transfer of knowledge to the patient. Baker demonstrated the poor readability of some patient-oriented drug information materials,[17] and other research also confirms that factors such as complexity of information and the level of a patient's education may influence the utility of written health education materials.[26]

Critics of Baker's research point out that significant progress in this area has occurred since the time of the research, and that the use of diagnostic testing enables the identification of readability problems in consumer product information.[27,28]

Also critical of the Baker study, Sless contends that readability formulae do not necessarily predict readability.[29] Baker responds to these criticisms by pointing out that despite improvements in consumer medicines information, it is unlikely that this strategy will be effective for all patients, and thus should not be relied upon as a sole means to impart information to patients about their medications.[30]

Patient literacy also has a profound effect upon the utility of written patient information – Lasater and Mehler point out that with illiteracy thought to affect over 20% of adults in the US, alternative communication strategies may often be needed.[31] Similarly, although a patient may indeed be literate, this literacy may in fact be in a language other than that in which the patient information is presented.

Although doctors or pharmacists may well have appropriate training and background to enable them to convey drug-related knowledge to other health professionals, many may not have formal training in communication or editorial skills relevant to the production of patient education materials. Moreover, it is possible that health professionals may attach a different importance or emphasis to various aspects of information – a factor of minor clinical significance to a healthcare worker may have major lifestyle implications for the patient.

Another criticism sometimes levelled at the practice of providing patient-oriented drug information materials is that presenting a patient with a raft of potentially alarming information about adverse effects or drug interactions may adversely affect compliance with prescribed treatment regimens. Fogarty[32] discusses the so-called 'reactance theory' in relation to noncompliance, suggesting that a perceived threat to an individual's freedom results in motivation to recapture that freedom and to prevent the loss of others. The tenets of reactance theory suggest that if a patient perceives a loss of individual freedom of behaviour options as a result of potential drug interactions with a prescribed medication, the reaction may be to elect not to take that medication. Feste and Anderson[33] have examined differences between empowerment and compliance, pointing out that the former strategy is based upon the premise that human beings have the capacity to make choices and are responsible for the consequences of these. Patient-oriented alert materials can be viewed as a means by which patients are empowered as a result of the provision of information. On this basis, the consumer can choose the course of action acceptable to them, aware of the consequences of the choices made. In view of the medico-legal implications of the failure to warn patients of the potential for adverse outcomes or consequences of treatment, the empowerment approach offers a practical option for healthcare providers seeking to enable patients to make informed decisions about their health.

Although providing information which highlights possible negative effects of drug therapy may result in an individual electing not to pursue treatment in a particular instance, this is not necessarily reflected in the findings of research. For example, Chaplin and Kent[34] examined the effects of educating patients about the risk of tardive dyskinesia associated with antipsychotic treatment, concluding that this approach was associated with a low risk of noncompliance.

4. Conclusions

In view of the known morbidity and mortality associated with drug interactions, it would seem intuitively obvious that healthcare practitioners should explore all possible avenues for their prevention. Even so, it is necessary to be judicious and cautious about the production and usage of patient-oriented alert materials – as with many healthcare interventions, the consequences of their use may not be as clear as first thought. What is plain is that the amount of high quality, focused research into this specific issue is small, especially when viewed in the context of the vast amount of patient information materials that has been produced.[35] Until such time as this research has been undertaken, it is incumbent upon healthcare providers to care-

fully select appropriate ways to convey information to patients about potential drug interactions and other important consequences of drug therapy.

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