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Incidence and Possible Causes of Prescribing Potentially Hazardous/ Contraindicated Drug Combinations in General Practice

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Abstract

Background: Preventing the use of medications where there is the potential for serious drug-drug interactions or drug-disease interactions (contraindications) is essential to ensure patient safety. Previous studies have looked at the incidence of prescribing contraindicated drug combinations, but little is known about the underlying reasons for the co-prescribing events. The objectives of this study were to estimate the incidence of prescribing contraindicated drug combinations in general practice and to explore the clinical context, possible causes and potential systems failures leading to their occurrence.

Methods: A list of contraindicated drug combinations was compiled according to established references. A search of computerised patient medication records was performed, followed by detailed chart review and assessment. The patient records from four general practices in an area of England were searched for a period of 1 year (1 June 1999–31 May 2000) to identify contraindicated drug combinations. All patients registered with the four participating practices during the study period were included (estimated n = 37 940). Medical records of the cases identified by the computer search were reviewed in detail and relevant information was extracted. Each case was then independently assessed by a pharmacist and a physician who judged whether the co-prescribing was justified and whether it was associated with an adverse drug event. Proximal causes and potential systems failures were suggested for each co-prescribing event.

Main outcome measures and results: Fourteen patients with potential drug-drug interactions and 50 patients with potential drug-disease interactions were identified. Overall, these represent an incidence of 1.9 per 1000 patient-years (95% CI 1.5, 2.3) or 4.3 per 1000 patients being concurrently prescribed ≥2 drugs per year (95% CI 3.2, 5.4). 62 cases involving 63 co-prescribing events were reviewed. Two-thirds of these events involved medications that were initiated by hospital doctors. Awareness of the potential drug-drug or drug-disease interactions was documented in one-third of the events at the time of initial co-prescribing. Within

the study period, the co-prescribing was judged to be not justified in 44 events (70%). Potential drug-drug interactions possibly resulted in two adverse drug events. The majority of contraindicated co-prescribing related to drug-disease interactions involved the use of propranolol or timolol eye drops for patients receiving bronchodilators and the use of amiodarone for patients receiving levothyroxine sodium.

Conclusion: The prescribing of contraindicated drug combinations was relatively rare in this study. Multiple possible causes and systems failures were identified and could be used to develop strategies for the prevention of prescribing errors involving contraindicated drug combinations in primary care.

Background

The avoidance of potentially hazardous drug-drug interactions and contraindications (drug-disease interactions) is one of the most important factors to be considered regarding safety in prescribing decision making. The prescribing of these drug combinations or contraindicated drugs increases the risk of adverse drug events, either because of enhanced adverse effects or because of reduced therapeutic effects. In addition to the potential harm to the patient, there are legal implications when adverse events actually occur.

Epidemiological studies in general populations and community settings have generated a wide range of estimates regarding the occurrence of potential drug-drug interactions[1-7] and drug-disease interactions.[8-10] Comparisons are difficult as methodology varies substantially between studies, particularly with regard to the drug interactions that are included and the denominators used to calculate the prevalence or incidence. In addition, many of the drug combinations included in these studies might have been used beneficially if appropriate precautions had been taken. As most studies did not investigate the clinical context in which the hazardous drug combinations were prescribed, it remains unknown whether they were given as a result of careful consideration by the prescribing doctors or whether they represented errors in the medication prescribing process.

The objectives of this study were: (i) to estimate the incidence of prescribing contraindicated drug combinations in general practices; (ii) to examine the documentation of awareness regarding the potential drug interactions or contraindications; (iii) to assess whether the co-prescription was justified and whether an adverse drug event was involved; and (iv) to explore possible causes and systems failures leading to the co-prescription.

Rather than using the theoretical definition of drug interactions such as "the phenomenon of two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more of the drugs is altered",[11] we have used the term 'potentially hazardous/contraindicated drug combinations' to encompass not only potential drug-drug interactions but also some drug-disease interactions that can be identified by drug combinations in which one of the drugs is contraindicated to patients with a disease condition that is usually treated with another drug. We have focused on drug combinations contraindicated by manufacturers or drug safety agencies as the potential drug interactions or contraindications could result in life-threatening events or therapeutic failures. They should, therefore, have been avoided in most circumstances.

Methods

Study Design

We conducted a retrospective search of computerised patient medication records for contraindicated drug combinations, followed by detailed chart review and assessment. The overall study design is shown in figure 1.

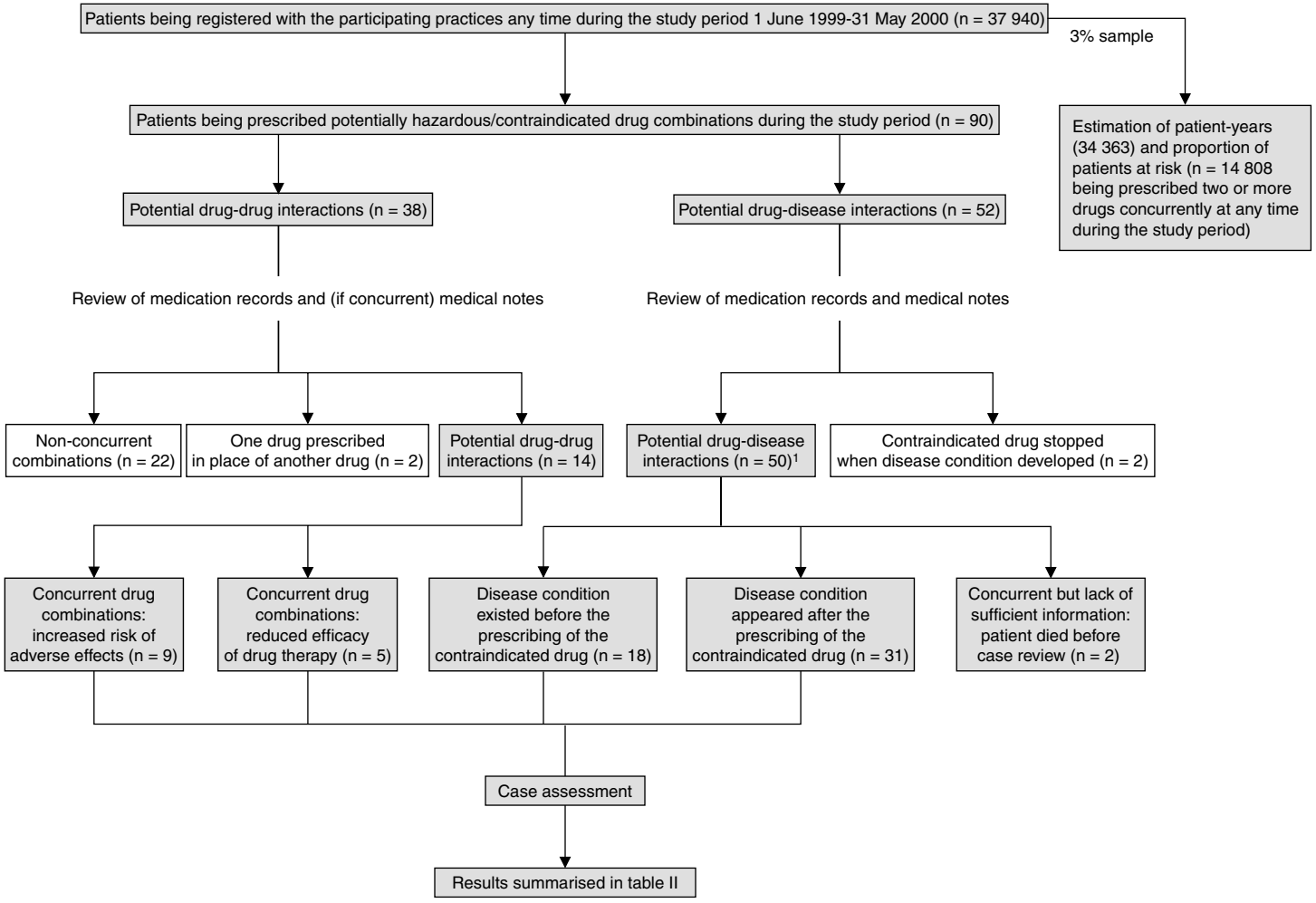

Fig. 1. Study design and overall results of case review. **1** = one patient with on-going timolol eye drops was treated with a bronchodilator for shortness of breath and then was subsequently given propranolol. Therefore, the total number of co-prescribing events among the 50 patients was 51.

Settings and Patient Group Studied

Ethical approval for the study was obtained from the local research ethics committee. All six general practices in a suburban area in Nottingham, UK were invited to participate in the study. Five agreed but one of the practices was excluded because their computerised medication records contained only repeat prescriptions at the time when the computer search was performed. Computerised medication records for all patients in the remaining four participating practices (they all had multiple practitioners), which covered approximately 80% of the local population, were searched for a study period of 1 year (1 June 1999–31 May 2000) using the list described in the next section. After initial exclusion of patients who died or left the practices before the study period and those who registered with the practices after the study period, a 3% random sample (n = 1135) was drawn to estimate the population covered by the participating practices over the study period in terms of overall patient-years and the proportion of the population at risk (being prescribed two or more drugs concurrently at any time during the study period). Medications were judged as being concurrent if the duration of therapy for one drug (calculated according to dose instructions and quantities prescribed) overlapped the duration of therapy for the other drug. The duration of therapy was defined as 1 month for drugs prescribed with 'as needed' direction unless the quantity was exceptionally large or small.

Drug Combinations Searched For

A list of contraindicated drug combinations was compiled according to established reference books.[12,13] A drug combination was included on the list if all the following criteria were met:

- The use of the drug combinations or contraindicated drugs increased the risk of adverse effects that were potentially life threatening or the drugs were prescribed in a combination that was pharmacologically contradicted.
- There had been solid scientific evidence for the interaction or contraindication according to comments in the reference books.[12,13] However, occasionally the evidence for certain drug interactions was weak but the manufacturers suggested that concurrent use of the interacting drugs was contraindicated. These agents were included on the list in view of the possible legal implications.
- Each drug or drug group in an interacting pair was likely to be prescribed at least one item per 10 000 patients per year in general practices, according to the prescribing data from the Nottingham Health Authority (population 600 000) for the period of April–September 1999.

The following interactions were excluded because of the limitation of medication records from general practices: interactions with food or alcohol, vaccines, over-the-counter (OTC) drugs, herbal medicines, specialist drugs such as isotretinoin and drugs used to treat HIV infection. Topical preparations for skin conditions and drugs already withdrawn from the UK at the beginning of the study, such as astemizole, were also excluded.

The final list (which can be obtained from the authors on request) included 210 drug-drug interaction pairs involving 124 drugs. In addition, three drug-disease interactions were included: (i) non-selective β-adrenoceptor antagonists (β-blockers) with asthma or chronic obstructive pulmonary disease (COPD), using bronchodilators as a proxy for the disease conditions; (ii) amiodarone with hypothyroidism, using thyroid hormones as a proxy; and (iii) sumatriptan with ischaemic heart disease, using nitrates as a proxy. Bronchodilators, thyroid hormones and nitrates were used as proxies as their use was fairly specific to the treatment of these conditions. Although this approach was well suited to our focus on contraindicated drug combinations, it has to be emphasised that a comprehensive screening of drug-disease contraindication was not our intention and would require the use of diagnostic information.

Case Review

The computer search identified all patients being prescribed contraindicated drug combinations over the study period. Computerised medication records of the identified cases were examined to determine if the potentially interacting drugs were prescribed

concurrently as defined earlier. The full medical records of the patients with concurrent interacting drug combinations and of all the patients with potential drug-disease interactions were then reviewed in detail by one of the investigators (AA, CJ: general practitioners; KN: pharmacist) and checked by another (YC: pharmacist). Particular attention was paid to any documentation in paper or computer records regarding the potential drug interactions or contraindications, whether the initial prescribers of the contraindicated drugs were from primary or secondary care, the dates when the medications started and stopped, laboratory or other test results related to the use of the drug combinations and relevant disease and drug history. The information was extracted to a data collection form for subsequent assessment. The computer search results were fed back to the participating practices for ethical reasons and cases with on-going contraindicated drug combinations at case review were brought to their general practitioners' (GPs) attention when considered necessary by the reviewers.

Case Assessment

Case assessment was carried out independently by two of the investigators (AA, KN). The assessors independently evaluated the following according to subjective judgement: (i) the justification for co-prescribing the drug combinations during the study period; and (ii) the appropriateness of patient monitoring (if the drug combination was still on-going at the time of the case review). In addition, the occurrence of any suspected adverse drug events possibly attributable to the use of the drug combinations or contraindicated drugs was assessed by using the algorithm developed by Naranjo et al.[14] Disagreements were discussed in subsequent meetings of three of the investigators (AA, KN, YC) to try to reach a consensus but were allowed if there was a genuine difference in opinions rather than a difference in the understanding of the cases or assessment tools.

A list of proximal causes possibly leading to the contraindicated co-prescribing and associated systems failures was compiled after the case review. We adopted the definitions by Leape et al.[15] and defined proximal causes as "the apparent reasons for the co-prescribing of contraindicated drug combinations; they are broad categories that are useful for focusing further inquiry and may not be true causes". Systems failures were defined here as "failures in an interdependent group of people or processes with a common purpose to prevent unnecessary co-prescribing of the contraindicated drug combinations". Proximal causes and systems failures definitely or possibly associated with the contraindicated co-prescribing were suggested by the assessors for each co-prescribing event according to information gathered during case review, with additional causes or failures added if they were not on the list.

Data Screening and Data Analysis

The Egton Medical Information Systems (EMIS) was used in all the participating practices, although this was not a requirement for study participation. Both acute and repeat prescriptions in the participating practices were routinely generated by the EMIS, which automatically registered all prescribed medications on to patient medication records. These records were used to screen for contraindicated drug combinations.

Descriptive statistics were compiled using SPSS 9.0. Ninety-five percent CIs were calculated based on binomial distribution for the estimate of population at risk and Poisson distribution for the occurrence of contraindicated co-prescribing events. The 95% CI for the incidence of co-prescribing events was estimated using computer simulation based on these distributions.

Main Outcome Measures and Results

Estimation of Population at Risk

A 3% random sample (n = 1135) was drawn from patient records in the participating practices after initial exclusion of patients who were not registered with the participating practices over the study period. Eighty-two percent (936) of the patients in the sample were registered with the practices for the

whole study period and the remaining patients joined/left the practices or died during the study period. The total number of patient-years registered with the practices for the 1135 patients was 1028. Excluding skin preparations and vaccines, 63% (95% CI 60, 66%) of the sample were prescribed at least one drug and 39% (95% CI 36, 42%) were prescribed ≥2 drugs concurrently in the study period. Extrapolating from the sample, the estimated study population (number of patients being registered with the practices at any time during the study period) was 37 940, with 34 363 patient-years registered (95% CI 33 661, 34 984). The estimated number of patients at risk of being prescribed two or more drugs concurrently was 14 808 (95% CI 13 727, 15 911).

Occurrence of Contraindicated Drug Combinations

The drug combinations identified by computer search are listed in table I and the occurrence of potentially contraindicated co-prescribing are summarised in figure 1. Excluding non-concurrent cases, 14 patients with potential drug-drug interactions and 50 patients with potential drug-disease interactions were identified. Together they represent an incidence of 1.9 per 1000 patient-years (95% CI 1.5, 2.3) or 4.3 per 1000 patients being concurrently prescribed two or more drugs per year (95% CI 3.2, 5.4).

Case Review and Assessment

Two cases were excluded from the case review and assessment as the patients died prior to the case review and the available information was insufficient. All the other cases were reviewed in detail and were subsequently assessed. The results of case review and assessment are summarised in table II. The 62 cases reviewed included 63 events of contraindicated co-prescribing. Two-thirds (42) of the events involved drugs initiated by hospital doctors and in three-quarters (31) of these events one of the drugs was initiated in primary care. Documentation of awareness of the drug-drug or drug-disease interactions at initial co-prescribing was found in only one-third (21) of the events. These included 11 of 15 co-prescriptions of levothyroxine sodium and amiodarone, and 5 of 11 co-prescriptions of propranolol with bronchodilators. Awareness was documented in only 3 of the 15 events involving timolol (mostly eye drops) and bronchodilators at initial co-prescribing. Including any initial or subsequent consultations and communications, documentation regarding the drug-drug or drug-disease interactions was found in about half (29) of all events.

Within the context of the study period, the co-prescribing of the contraindicated drug combinations was judged by the assessors to be justified in 14 events (22%) and not justified in 44 events (70%). Twelve of the justified cases involved amiodarone/levothyroxine sodium combinations and two involved amiodarone/sotalol combinations. Where the contraindicated drug combinations were still ongoing at the time of case review (37 cases), the monitoring of the patient was felt appropriate in seven cases and inappropriate in 21 cases. No consensus was reached by the assessors in nine cases; seven of which involved amiodarone/levothyroxine sodium combinations. The major unresolved issue was the acceptability of regular monitoring with frequencies lower than 6 monthly as recommended by the British National Formulary.[16]

Among the 49 co-prescription events associated with potential drug-disease interactions, the prescribing of the contraindicated drug pre-dated the identification of the disease condition in 31 events. The disease conditions were classified as *probable* adverse drug events caused by the contraindicated drugs in fifteen cases and *possible* adverse drug events in fourteen cases (as assessed by the Naranjo algorithm). The *probable* adverse drug events involved hypothyroidism caused by amiodarone (n = 11) and breathing problems caused by non-selective β-blockers including propranolol (n= 2), nadolol (n = 1) and timolol eye drops (n = 1). The *possible* adverse drug events included breathing problems possibly associated with timolol eye drops (n = 9), propranolol (n = 3) and levobunolol eye drops (n = 1), and chest pain possibly associated with sumatriptan (n = 1).

Table I. Number of patients being prescribed potentially hazardous/contraindicated drug combinations during the period 1 June 1999–31 May 2000 in four general practices in Nottingham, UK (total number of patients [estimated] = 37 940)

Drug A	No. of patients receiving drug A (% total patients)	Drug B	No. of patients receiving drug B (% total patients)	No. of patients receiving both drugs over study period	No. of patients receiving both drugs concurrently[a]
Drug-drug combinations					
Increased risk of adverse effect: QT prolongation					
amiodarone	69 (0.2)	Sotalol	80 (0.2)	4	2
cisapride	30 (0.1)	Erythromycin[b]	1080 (2.8)	3	1
		Clarithromycin	462 (1.2)	1	0
		Amitriptyline	535 (1.4)	1	0
		Quinine	320 (0.8)	1	0
terfenadine	167 (0.4)	Erythromycin[b]	1080 (2.8)	5	2
		Amitriptyline	535 (1.4)	3	1
		Lofepramine	148 (0.4)	1	1
		Clarithromycin	462 (1.2)	4	0
		Dosulepin	777 (2.0)	1	0
		Imipramine	75 (0.2)	1	0
Increased risk of adverse effect: miscellaneous					
sildenafil	111 (0.3)	Nitrates	779 (2.1)	1	1
tramadol	220 (0.6)	Phenelzine	3 (0.008)	1	1
adrenaline (epinephrine)[c]	23 (0.06)	Amitriptyline	535 (1.4)	1	0
Reduced efficacy of drug therapy					
betahistine	117 (0.3)	Antihistamines[d]	2446 (6.4)	4	3
		Cinnarizine	70 (0.2)	4	2
		Cyclizine	27 (0.07)	1	0
cabergoline[e]	9 (0.02)	Domperidone	140 (0.4)	1	0
Drug-drug combinations subtotal				*38*	*14*
Drug-disease combinations					
amiodarone	69 (0.2)	Thyroid hormone[f]	784 (2.1)	17	17 [4]
levobunolol	9 (0.02)	Bronchodilators	3472 (9.2)	1	1
nadolol	2 (0.005)			1	1
propranolol	246 (0.6)			12	11 [6]
sotalol	79 (0.2)			4	3 [3]
timolol	211 (0.6)			15	15 [3]
sumatriptan	160 (0.4)	Nitrates	779 (2.1)	3	3 [2]
Drug-disease combinations subtotal				*52*[g]	*50*[g]
Total				**90**[g]	**64**[g]

a Numbers in brackets indicate the number of cases in which drug A was prescribed after the patient had been prescribed drug B.

b Excluding gel and topical solution.

c Excluding cream.

d Including acrivastine, azatadine, brompheniramine, cetirizine, chlorphenamine, clemastine, cyproheptadine, fexofenadine, hydroxyzine, loratadine, mizolastine, promethazine, terfenadine and alimemazine.

e Only applies to the hypoprolactinaemic effects.

f Including levothyroxine sodium and liothyronine.

g One patient was prescribed bronchodilators with both timolol and propranolol, and thus the total number of patients receiving contraindicated drug combinations equals the total number of co-prescribing events −1.

In 18 events the contraindicated drugs were prescribed to patients with pre-existing disease conditions. Five patients experienced exacerbation of their disease conditions *possibly* attributable to the

Table II. Results of case review and case assessment for events of co-prescribing contraindicated drug combinations

Item reviewed or assessed	Results	Drug-drug interactions (n = 14)		Drug-disease interactions (n = 49)		Total (n = 63)
		Increased risk of adverse effects (n = 9)	Reduced efficacy of drug therapy (n = 5)	Disease condition existed before the prescribing of the contraindicated drug (n = 18)	Disease condition appeared after the prescribing of the contraindicated drug (n = 31)	
Case review						
Initial prescribers (doctors who made initial	Both drugs initiated by GP	4	2	6	8	20 (32%)
decisions to start the drug treatment)	One drug initiated by GP, another initiated by hospital doctor	1	2	11	17	31 (49%)
	Both drugs initiated by hospital doctor	4	0	1	6	11 (17%)
	Unknown (insufficient information)	0	1	0	0	1 (2%)
Documentation of awareness of the drug	Yes	1	0	6	14	21 (33%)
interactions or contraindications at the time	No	8	4	11	15	38 (60%)
of initial co-prescribing	Unknown (insufficient information)	0	1	1	2	4 (6%)
Documentation of awareness at any	Yes	2	1	8	18	29 (46%)
consultations or communications	No	7	3	9	11	30 (48%)
(including initial co-prescribing)	Unknown (insufficient information)	0	1	1	2	4 (6%)
Case assessment						
Justification of co-prescribing during	Justified	2	0	2	10	14 (22%)
the study period, as judged by	Not justified	7	4	15	18	44 (70%)
the assessors	No consensus	0	0	1	1	2 (3%)
	Unknown (insufficient information)	0	1	0	2	3 (5%)
Appropriateness of monitoring as judged	Appropriate	0	0	2	5	7 (11%)
by the assessors, if the contraindicated	Not appropriate	4	1	5	11	21 (33%)
drugs were still being co-prescribed at	No consensus	1	0	3	5	9 (14%)
the end of the study period	Unknown (insufficient information)	0	0	0	1	1 (2%)
	Not applicable (contraindicated drug(s) stopped)	4	4	8	9	25 (40%)
Potential adverse drug events caused	Probable	1	0	0	15	16 (25%)
by the contraindicated drugs or drug	Possible	0	1	5	14	20 (32%)
combinations, assessed by Naranjo	Doubtful	0	0	2	0	2 (3%)
algorithm	Not assessed (no evidence of suspected adverse drug events)	8	4	11	2	25 (40%)

GP = general practitioner.

contraindicated prescribing (four of these involved non-selective β-blockers and one involved amiodarone). Two potential adverse drug events might have been related to drug-drug interactions: the tramadol/phenelzine combination *probably* resulted in confusion in one patient, and a *possible* decrease in the efficacy of betahistine because of concurrent use of cinnarizine was also identified.

Proximal Causes and Systems Failures

Proximal causes which may have contributed to the co-prescribing of the contraindicated drug combinations and associated systems failures are listed in table III. For the majority of the co-prescribing events, multiple proximal causes and systems failures were suggested. However, in four events involving the prescribing of levothyroxine sodium to treat hypothyroidism probably or possibly caused by amiodarone, both assessors felt the co-prescribing

Table III. Common proximal causes and systems failures for the prescribing of potentially hazardous/contraindicated drug combinations

Proximal causes and systems failures associated with the co-prescribing of contraindicated drug combinations, as suggested by at least one of the assessors[a]	No. of cases definitely associated	No. of cases possibly associated	No. (%) of all cases possibly or definitely associated (n = 62)
Proximal causes			
Lack of knowledge of the drug Example: the prescribing doctor was not aware of the drug interactions, contraindications, possible adverse drug reactions or their seriousness	14	33	47 (76)
GP has continued a drug or a combination prescribed by hospital doctor	31	7	38 (61)
Lack of knowledge of the patient Example: the prescribing doctor was not aware of the medications that the patient was taking or not aware of the patient's past disease history	3	32	35 (56)
Necessary treatment of adverse drug effect/ no better alternative available	5	10	15 (21)
Patient's informed decision to take the risk	6	6	12 (19)
No firm diagnosis for the contraindication	3	7	10 (16)
Patient did not accept or comply with GP's recommendation	5	3	8 (13)
Medications were not intended to be used together Example: GP prescribed the drug combination concurrently but warned the patient not to take the drugs together	3	4	7 (11)
Medication was not removed from repeat prescription list although GP had intended to stop it	3	2	5 (8)
Systems failures			
Drug knowledge dissemination	20	38	58 (94)
Completeness of medication records and documentation of clinical decision	41	13	54 (87)
Inadequate review of repeat prescriptions	8	24	32 (52)
Communication between primary and secondary care	17	13	30 (48)
Communication between the prescribing doctor and the patient	7	23	30 (48)
Summary and display of patient information and important clinical messages	3	23	26 (42)
Monitoring of patients	7	8	15 (24)
Communication between hospitals, between clinics in the hospital or between general practices	4	7	11 (18)

a Definition and classification of proximal causes and systems failures adapted from Leape et al.[15]

GP = general practitioner.

was necessary but one indicated a lack of systems failure while another suggested there was insufficient documentation and/or monitoring.

We were unable to assess two potential sources of systems failures (both were error defence systems: computer alerts for prescribing doctors and dispensing pharmacists regarding potential interactions, and the pharmacists' interception of prescribing errors involving contraindicated drug combinations) because it was not possible to verify their occurrence using information from patients' records.

Discussion

Occurrence of Contraindicated Co-Prescribing

The results of this study show that the prescribing of contraindicated drug combinations was relatively rare, with only 4.3 instances per 1000 patients being concurrently prescribed two or more drugs per year. The incidence reported here is not directly comparable to previous studies that included all potentially hazardous drug combinations[2,3,5-7] as our study focused only on contraindicated drug combinations, which are a subset of hazardous drug combinations included in those studies.

The co-prescribing events identified in this study reflect a range of scenarios that involve balancing between the benefit and risk of prescribing – situations that clinicians regularly face in daily practice. For example, amiodarone is contraindicated for patients with a history of thyroid dysfunction because it can have an unpredictable adverse effect on thyroid function. Nevertheless, when a previous euthyroid patient develops hypothyroidism after being stable on amiodarone treatment the discontinuation of amiodarone is not usually feasible and the co-prescribing of levothyroxine sodium with amiodarone may be the best option.[17,18] In these special cases, clear documentation of the clinical decision and adequate monitoring are important. The co-prescribing of other contraindicated drug combinations was rarely justifiable and was likely to represent failures in the prescribing process that warranted further investigation.

Following our detailed case reviews, it became apparent that many of the co-prescribing events shared similar patterns, with common proximal causes and systems failures emerging as summarised earlier (table III). An understanding of how these events occur could result in the development of strategies to prevent future occurrence and may help to avoid the need for regulatory bodies and manufacturers to withdraw drugs such as cisapride because of contraindicated co-prescribing.[19-22]

Documentation and Awareness

Our findings show that the majority of contraindicated co-prescribing involved medications initiated by hospital doctors and many of these events involved prescribers from both primary and secondary care. However, documentation of awareness of the potential drug-drug and drug-disease interactions was found in only half of the cases in any consultations or communications. We cannot rule out the possibility that in some cases the prescribing doctors were aware of the interactions or contraindications but they did not document the awareness in the medical records. However, in most cases we suspect doctors were not fully aware of the potential hazards of the contraindicated prescribing, most notably the use of timolol eye drops in patients having breathing difficulties, despite the potential adverse effects being known for several years prior to the study period.[23-29]

Even if the prescribing doctors documented the awareness of the drug interactions or contraindications, some of the prescribing decisions might have exposed the patient to unnecessary risk. For example, a doctor co-prescribed erythromycin and terfenadine while asking the patient not to take them together. Prescribing a non-interacting drug combination would have been a safer alternative. In another case, a doctor prescribed propranolol on the patient's request while acknowledging that the patient was also using a bronchodilator. A greater sense of caution regarding the use of contraindicated drugs or drug combinations still seems to be needed.

It is also worth mentioning that documentation does not guarantee attention from future or alternative prescribers. Important clinical messages could be buried among piles of notes as illustrated in several of the cases that we reviewed. Hence, the effective summary of information is necessary in addition to good documentation. Computerised medical and medication records have great potential to improve the storage, retrieval and display of important clinical information.

Communication

As half of the co-prescribing events involved both hospital doctors and GPs, the poor documentation also reflected deficiencies in communication between primary and secondary care. Our study identified several failures in communication that could result in the co-prescribing of contraindicated drug combinations and subsequent harm to the patients. On their referral letters to secondary care, GPs sometimes omitted information on medications such as eye drops and bronchodilators. Hospital discharge letters and outpatient letters sometimes did not give clear information on prescribing decisions and the need to monitor newly prescribed medication. The lack of information provided to GPs makes it difficult to understand and challenge hospital prescribing decisions and treatment initiated by hospital specialists is often continued without query.

Similar problems in the transfer of information between primary and secondary care settings have been reported previously.[30-33] Our findings serve as a call for the improvement in communication and sharing of information at the primary/secondary care interface, without which patient safety will be difficult to assure. Given the legal responsibility held by the actual prescribers of medications, GPs should be encouraged to communicate with hospitals if there is any doubt regarding the safety of any prescribing decision when patients or the prescribing tasks are transferred from secondary to primary care. In addition, improvement of communication between the patient and the prescribing doctor could also help to prevent contraindicated co-prescribing as a result of incomplete information.

Monitoring of Patients and Repeat Prescriptions

Where the use of contraindicated drug combinations is judged to be necessary, such as the use of levothyroxine sodium to treat hypothyroidism caused by amiodarone, appropriate monitoring of the patient is essential. Current guidelines for patient monitoring were largely based on expert consensus but they were usually not well observed in real practice. The development of evidence-based guidelines to inform clinicians of the most cost-effective practices for the monitoring of patients taking high-risk medications should be promoted and their implementation encouraged.

Inadequate review and control of repeat prescribing has been observed in a couple of recent studies.[34,35] Our study highlighted the importance of addressing this issue as most of the co-prescribing events involved repeat prescribing and would have been identified earlier had the patients been carefully reviewed. In a few cases the patients obtained the contraindicated medications even though the prescribing doctors had intended to discontinue these agents. Therefore, not only clinical review but also the administrative and managerial aspects of the whole repeat prescribing systems should be taken into account.

Error Defence Systems

Computerised drug interaction alerts and community pharmacists' screening of prescriptions are two important safety nets to prevent contraindicated co-prescribing in primary care. The GPs in this study had access to computerised drug interaction alerts and it is likely that they over-rode these alerts when prescribing many of the hazardous drug-drug combinations that are identified in this study. In another study we found that GPs admit to overriding computerised drug interactions alerts without properly checking them.[36] Further research is needed to help understand why GPs over-ride interaction alerts so that more effective systems can be devel-

oped. Also, the computerised drug interaction alert systems used by GPs in this study provide alerts only at the point of the initial prescription of a drug-drug combination. If the systems were redesigned to give alerts whenever prescriptions were reviewed, this would give further opportunities for correcting erroneous co-prescriptions. In addition, it was observed that the practice computer systems did not trigger alerts to all contraindicated drug combinations, particularly for those representing drug-disease interactions. A recent study on pharmacy drug interaction software packages in Washington State in the US also found that the performance of these packages on detecting drug-drug interactions was sub-optimal and they varied in the ability to check drug-disease interactions.[37] Healthcare professionals should be aware of this potential problem and further work is required to assess the completeness of drug interaction and contraindication alerts produced by current computer systems used in general practices and community pharmacies.

We were not able to properly assess the role of community pharmacists in error detection in this study. This was because we could not rely on the medical records having documentation of any queries raised by community pharmacists. A previous study showed that communications between community pharmacists and general practices regarding drug interactions and contraindications was infrequent.[4] One possible reason for this may be that community pharmacists do not have access to important clinical information to assess the seriousness of potential hazards. Sharing such information with community pharmacists might strengthen their role in error prevention.

Strengths and Limitations of the Study

This study provides population estimates of the exposure of primary care patients to contraindicated drug combinations while systematically investigating the clinical context of individual co-prescribing events. Therefore, it fills the important gap between population studies derived from analysis of large databases in which contextual information is usually not available and spontaneous case reports and studies on hospital admissions in which population estimates cannot usually be made. The investigation of possible causes and systems failures associated with contraindicated co-prescribing also allows a better understanding of prescribing errors in primary care, information on which is scarce.

Our study also has several limitations. First, it was carried out in a small geographical area in the UK. The general practices involved in the study were not unusual in terms of their list sizes and their use of computers for prescribing. Nevertheless, the practices could not be considered representative of all practices in the UK given the small number of participating practices and the voluntary nature of study participation. Second, the information that we collected during the case review may not have been complete because of the retrospective nature of the study. However, our investigators spent half an hour on average to review each case in the first instance and the data was meticulously validated, with further information added by a second investigator. Therefore, it is unlikely that we have missed any important information that the GPs would notice during their consultations, which usually last around 10 minutes. However, the identification and assessment of potential adverse drug events might have been restricted by the completeness of the documentation. In addition, although the completeness of prescription records in practices using the same computer system has been demonstrated in a previous study,[38] a number of hazardous/contraindicated drug combinations involving OTC medications (such as dextromethorphan), herbal medicines, specialist drugs (such as isotretinoin, immunosuppressants and HIV drugs) and other drugs mainly used in hospitals could not be screened in this study because of the lack of information in the practice records. Since our study has demonstrated that incomplete patient records and lack of documentation are important systems failures likely to be associated with contraindicated co-prescription, it would be prudent for the future practice computer systems to include these OTC and specialist drugs as well as relevant drug interaction alerts and for the GPs to systematically record the use of these drugs by the patient.

We have described only the factual presence of documentation regarding contraindicated drug combinations and have assessed the justification of co-prescribing during the study period. We have not attempted to assess initial prescribing decisions as many of them date back several years and could have been made in hospital settings, which would make the collection of sufficient information extremely difficult, if not impossible. For example, a few amiodarone/levothyroxine sodium and amiodarone/sotalol combinations were judged to be justified by the assessors because the potential risk of stopping the drug(s) during the study period may have been greater than the risk of continuing the drug combination, but the information available would not allow appropriate assessment of the initial prescribing decision. For the same reasons we were unable to conclude which of the identified possible causes and systems failures were 'true'. Nevertheless, they have provided a useful template for future studies, which could prospectively involve prescribers and adopt methods such as incident-monitoring techniques and root-cause analysis to obtain further insight. Finally, although the attitude among healthcare professionals towards medication errors and patient safety has been changing in the past few years, the investigation of potentially negative events remains a sensitive issue. We commend the participating practices for their courage and openness, which made this research possible. This study has examined potential systems failures from the perspective of GPs; exploration from the perspective of hospital doctors, pharmacists and patients would allow the development of more comprehensive strategies to reduce potential prescribing errors and to enhance patient safety.

Conclusion

The prescribing of contraindicated drug combinations was relatively rare in this study. Where such events occurred, awareness of hazards associated with the drug combinations was often not documented in either the general practice records or correspondence between primary and secondary care. Several possible causes and potential systems failures associated with contraindicated co-prescribing were identified. Our findings suggest that adequate knowledge of drug interactions and contraindications and complete information on the patients and their medications at the time of prescribing are crucial to prevent contraindicated co-prescribing. Improving documentation and awareness of contraindicated drug combinations through drug knowledge dissemination and computer prescribing decision-support systems, facilitating communications and information flow among healthcare professionals and patients, and closer monitoring of patients and repeat prescribing systems might be the focus for the development of preventive strategies to reduce these types of medication error.

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