Potential for drug interactions involving cytochromes P450 2D6 and 3A4 on general adult psychiatric and functional elderly psychiatric wards

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Aims

To assess the potential for interactions involving cytochromes P450 2D6 (CYP2D6) and 3A4 (CYP3A4) between drugs prescribed in a city in-patient psychiatric service.

Methods

Prescription information was obtained from all 236 patients in general adult wards and all 87 patients in functional elderly wards under a city psychiatric service. The frequencies with which combinations of drugs expected to interact via CYP2D6 or CYP3A4 were documented and compared between these two settings.

Results

All 2089 drug prescriptions, of which 1237 (59%) were administered, were analyzed. One hundred and seventy-two patients (73%) on adult wards and 59 (68%) on functional elderly wards were prescribed at least one drug metabolized by and/or inhibiting CYP2D6, the difference being nonsignificant (95% confidence interval on the difference -6.3%, 16.4%). Anticipated interactions from 62/82 CYP2D6-related combinations prescribed on adult wards (27/100 patients) and 19/30 prescribed to elderly patients (22/100 patients) were judged to be clinically important or potentially clinically important. The proportion of patients on functional elderly wards prescribed at least one drug interacting with CYP3A4 (87%) was significantly greater than that for patients on adult wards (57%, $P < 0.001$). The frequency of interactions involving CYP3A4 was significantly greater on functional elderly than adult wards (43/100 vs 22/100 patients, $P < 0.025$, 95% confidence interval on the difference 4, 38/100).

Conclusions

Our findings confirm extensive polypharmacy on general adult psychiatric and functional elderly psychiatric wards. A substantial proportion of patients were receiving combinations of drugs that interact with CYP2D6 and/or CYP3A4, many of which are known to produce clinically important interactions. Doctors practising in old age psychiatry should be aware that patients on functional elderly wards are at increased risk of clinically important CYP3A4 interactions. Psychiatrists should consider the pharmacokinetic implications of drugs prescribed for use 'as needed', because of the potential for unpredictable interactions.

Introduction

The use of combined drug treatments in psychiatry has increased progressively. Among the factors contributing to this are the proliferation of new psychotropic agents thought to be better tolerated than previously available drugs, the broader range of psychiatric indications for existing drugs, the increasing tendency to treat partial response by introducing additional agents, and increased use of drugs to alleviate adverse effects caused by existing psychotropic drug prescriptions [1]. Polypharmacy in the elderly psychiatric population is likely to be even greater, since many in this group receive additional drug treatment for physical illnesses [2].

A further practical issue which may predispose to polypharmacy is the phenomenon of 'p.r.n. prescribing', which is common practice in hospital psychiatry. The term is derived from the latin '*pro re nata*' (literally 'for the thing born'), and is used to mean 'as needed'. P.r.n. medication may be administered at the request of patients, or following assessment by the nursing staff. In one survey, p.r.n. medications were prescribed in the acute phase of 82% of admissions [3]. Similarly, prescription charts are designed to allow doctors to make drugs available for administration to patients at the nurses' discretion, especially antipsychotic, anxiolytic and sedative drugs, analgesic medication and drugs combating side-effects of psychotropic agents (e.g. anticholinergic compounds).

A major concern with the practice of polypharmacy is the potential for drug–drug interactions. The mechanistic basis of many drug–drug interactions is well established [4]. They can occur as a result of changes in pharmacodynamics and/or pharmacokinetics, the latter through effects on absorption, distribution, metabolism or excretion. One of the most clinically important causes of drug interactions is the inhibition or induction of the activity of cytochrome P450 [5], a superfamily of enzymes catalyzing the metabolism of a large number of drugs. Most agents used in psychiatry are metabolized by or interact with only a small number of isoforms of cytochrome P450 (CYP) [6]. In this context the most important forms are CYP2D6 and CYP3A4. Concern over the consequences of drug interactions mediated by CYP has increased in recent years, especially after the withdrawal of the calcium antagonist mibefradil (an inhibitor of CYP3A4 activity) [7], and the restricted use of the antihistamine terfenadine (a substrate of CYP3A4) as a result of life-threatening interactions [8]. In psychiatry, clinically important interactions between the SSRIs fluoxetine and paroxetine (both potent inhibitors of CYP2D6 activity) and tricyclic antidepressants have been widely reported [9].

The aim of the present study was to assess the potential for the occurrence of clinically important drug interactions mediated by CYP2D6 and 3A4, through a survey of prescribing on general adult psychiatric and functional elderly psychiatric wards in the city of Sheffield. The results of this study represent a 'snapshot' of psychiatric prescribing practice in one city in the United Kingdom.

Methods

Survey population

All five general adult psychiatry wards (receiving patients aged 18–65 years at the onset of illness) and both of the two functional elderly psychiatric wards (receiving patients becoming unwell psychiatrically after the age of 65 years, but not those with dementia) in the city of Sheffield were included in the survey. General adult and old age psychiatry inpatient rehabilitation units that receive patients progressing from periods of treatment on the above general adult and functional elderly psychiatric wards, were also included. Wards predominantly used for the treatment of elderly patients with dementia were excluded, because there is no general adult equivalent. Psychiatric Day Centres were also excluded, since for most patients attending such Centres, control of drug prescribing will have reverted to the general practitioner.

The study was defined as an audit. The data were collated for analysis in an anonymized and untraceable fashion. Permission to analyze prescription data was obtained from consultant psychiatrists attached to each ward. Under the terms of this audit, no demographic data were recorded nor were diagnoses documented.

Data collection

A case record form based on the drug cards used on the wards, was completed for each patient. Individual wards were visited on two separate days 5 months apart (to allow for seasonality in illness and prescribing profiles, and to provide adequate power for statistical comparisons). During these visits, details of all currently prescribed medication was recorded, namely (a) drugs prescribed for regular administration, (b) drugs prescribed for once-only administration, (c) p.r.n. drugs prescribed for use at the ward nurses' discretion in response to requests from patients, or the occurrence of symptoms, and (d) depot injections (provided the injection had last been given within the prescribed administration interval period). For each p.r.n. prescription listed, it was noted whether the drug had been administered to the patient within the last 24 h. Similarly, for

once-only prescriptions it was noted whether the drug had been administered.

Classification of prescription information

Drug prescriptions were classified in two ways 1) *Prescribed drugs* comprising all of the above prescription categories (1a, 1b, 1c and 1d) and additionally any p.r.n. drugs listed on the prescription chart but recorded as not having been administered within the previous 24 h, and any once-only drugs entered on the prescription chart in this period but not administered, and 2) *Administered drugs*, namely (a) regularly prescribed medication listed on the chart as being given every day or every 2 days, (b) drugs prescribed and given as a single once only dose within the previous 24 h, (c) p.r.n. medication that had been administered during the previous 24 h, and (d) depot medication administered within the prescribed administration interval period.

Assessment of drug interaction potential

The likelihood of a CYP2D6 or CYP3A4 mediated interaction between individual drug combinations was assessed based on a search of established databases (Web of Science, PubMed, http://www.gentest.com/human_p450_database/index.html), the latest edition of the textbook 'Drug Interactions' [4] and the authors' personal files. They were categorized as follows:

Clinically important interaction, for which there is *in vitro* metabolic evidence and/or *in vivo* pharmacokinetic and clinical evidence that a drug–drug interaction occurs or could occur. For example, both fluoxetine and paroxetine are potent inhibitors of CYP2D6 activity *in vitro*

[10], and *in vivo* cause two to four-fold increases in the plasma concentration of tricyclic antidepressants resulting in anticholinergic and other adverse reactions (reviewed by Stockley [4] and Mitchell [11]).

Potentially clinically important interaction, for which there is a theoretical basis for an interaction, but for which experimental evidence is lacking. For example, haloperidol is an inhibitor [12] and amitriptyline a substrate of CYP2D6 [13], but there have been no reports of *in vitro* or *in vivo* interactions between the two drugs.

Unlikely interaction for which there is either evidence against or no theoretical basis for an interaction.

Details of the published data used to assess the significance of individual drug interactions can be obtained from the corresponding author.

Statistical analysis

The Student's *t*-test or the chi square test was used to compare the frequency of prescription and administration of CYP2D6 and CYP3A4 interacting combinations between patients on general adult and functional elderly wards. The Yates correction was used in all chi square tests. A *P* value of <0.05 (two-sided) was considered to be of statistical significance.

Results

Prescription information from 236 patients on general adult psychiatric wards and 87 patients on functional elderly psychiatric wards is summarized in Table 1. A mean of 6.5 drugs was prescribed to each patient. The total number of drug prescriptions per patient was greater on functional elderly than general adult psychi-

Table 1

Drugs prescribed and administered to patients on general adult psychiatry and functional elderly psychiatry wards by prescription type

	General adult wards (236 patients)		Functional elderly wards (87 patients)		Total (323 patients)	
	Prescribed	Administered	Prescribed	Administered	Prescribed	Administered
Total drugs	1405	761 (54%)	684	476 (70%) ^c	2089	1237 (59%)
Drugs per patient	6.0	3.2	7.9 ^a	5.5 ^b	6.5	3.8
Drugs for regular administration	688	688	430	430	1018	1018
Drugs for p.r.n. administration	744	99 (13%)	253	44 (17%)	997	143 (14%)
Drugs for once only administration	13	12	0	0	13	12
Depot injections	60	60	1	1	61	61

^a*P* < 0.01 for comparison of patients on general adult and functional elderly wards (95% CI on the difference 1.2, 2.6),

^b*P* < 0.001 for comparison of patients on general adult and functional elderly wards (95%CI on the difference 1.6, 2.9),

^c*P* < 0.001 (95%CI on the difference 11%, 20%).

atric wards (Table 1). This can be explained by the prescription of considerably more nonpsychotropic drugs to the elderly. The total number of psychotropic agents prescribed and administered were similar in the two settings, although there were some differences with respect to individual drug classes. In the functional elderly setting, more prescribed drugs were administered than on the general adult wards. This difference was attributable to p.r.n. prescribing.

Seventy-three per cent of the patients on adult wards, and 68% of those on functional elderly wards were prescribed at least one drug metabolized by and/or inhibiting CYP2D6, the difference being nonsignificant (Table 2). One hundred and twelve combinations of drugs that interact with CYP2D6 were prescribed to the 323 patients studied. Patients in the functional elderly setting were subject to a similar frequency of CYP2D6 combinations. About three quarters of the CYP2D6 combinations were judged to represent clinically important or potentially clinically important interactions. These combinations were prescribed to 19% of our total patient sample (Table 2). There were no significant differences in prescribing drugs that interact with CYP2D6 between the elderly and adult wards. Four prescribed combinations of drugs interacting with CYP2D6 were identified as being of proven clinical significance supported by published evidence. The CYP2D6 combinations all involved coprescription of a tricyclic antidepressant with an SSRI antidepressant (Table 3).

With respect to administered drugs, 35% of patients on adult wards, and 52% of patients on functional elderly wards had taken at least one drug interacting with CYP2D6 in the previous 24 h (or were subject to the ongoing action of a CYP2D6 interacting drug given by depot injection), a difference that was significant (Table 2). The relative frequencies of CYP2D6 interacting combinations administered to patients on general adult and functional elderly wards were similar to those for prescribed drugs (Table 2). About two thirds of the CYP2D6 combinations administered to the 323 patients in the survey were judged to represent clinically important or potentially clinically important interactions.

Eighty-eight combinations of drugs that interact with CYP3A4 were prescribed to the 323 patients studied, and one fifth of our sample had been prescribed combinations of drugs that interact with CYP3A4 (Table 2). The proportion of patients (87%) on functional elderly wards prescribed at least one drug metabolized by and/or inducing/inhibiting CYP3A4 was significantly greater than that for patients on adult wards (57%) (Table 2). There was also a significantly greater frequency of combinations of drugs that interact with

CYP3A4 in the elderly compared with the adult setting. Overall, 40% of the CYP3A4 combinations were judged to represent clinically important or potentially clinically important interactions, and these combinations were prescribed to 8% of our total patient sample.

Six drug combinations interacting with CYP3A4 were identified as being of proven clinical significance supported by published evidence. Five of these involved carbamazepine, prescribed with diazepam to three patients, with fluoxetine to one patient and with the antipsychotic agent sertindole to one patient (Table 4). The sixth combination was that of diazepam with the proton pump inhibitor omeprazole.

The relative frequencies of CYP3A4 interacting combinations administered to patients on general adult and functional elderly wards were similar to those for prescribed drugs (Table 2), and again the differences between the two settings were significant or approaching significance. Nearly one half of the CYP3A4 combinations administered to the 323 patients in the survey were judged to represent clinically important or potentially clinically important interactions.

Discussion

The results of this study represent a 'snapshot' of prescribing practice on all general adult psychiatric and functional elderly psychiatric wards in Sheffield. Our findings confirm those from numerous other studies going back to the 1970s ([14, 15] and references therein) that treatment of psychiatric in-patients is associated with considerable polypharmacy. Our patient population was relatively small and centred on one city in the United Kingdom. However, since data were included from the prescription chart of every in-patient, on all eligible general adult and functional elderly psychiatry wards including rehabilitation units, there is no reason to believe that the findings cannot be extrapolated to the wider psychiatric in-patient population.

We envisaged that patients in old age psychiatry settings may be more likely to be prescribed interacting drug combinations, since they may require a broader range of drug treatments for physical symptoms and illnesses. Our findings confirmed this hypothesis specifically for CYP3A4 based interactions, as a result of the more frequent use of cardiovascular and hypnotic drugs.

Nearly 20% of both adult and elderly patients were prescribed two or more drugs that are metabolized by and/or inhibit CYP2D6 in clinically important or potentially clinically important combinations (see Methods for definitions). The drugs involved were antipsychotics, antidepressants and codeine. Ten combinations (prescribed on a total of 29 occasions) included either

Table 2

Prescription of drugs and drug combinations interacting with CYP2D6 and CYP3A4 on general adult and functional elderly psychiatric wards

	Adult (<i>n</i> = 236)	%, or number per 100 patients	Elderly (<i>n</i> = 87)	%, or number per 100 patients	Total (<i>n</i> = 323)	%, or number per 100 patients
CYP2D6 interactions						
<i>Drugs prescribed</i>						
Patients prescribed one or more CYP2D6 interacting drugs	172	73% ^a	59	68%	231	72%
Number of CYP2D6 combinations	82	35/100	30	34/100	112	35/100
Patients prescribed CYP2D6 combinations	62	26%	20	23%	82	25%
Number of clinically important or potentially clinically important CYP2D6 combinations	63	27/100	19	22/100	82	25/100
Patients prescribed clinically important or potentially clinically important CYP2D6 combinations	46	19%	16	18%	62	19%
<i>Drugs administered</i>						
Patients administered one or more CYP2D6 interacting drugs	83	35%	45	52%**	128	40%
Number of CYP2D6 combinations	27	11/100	12	14/100	39	11/100
Patients administered CYP2D6 combinations	25	11%	12	14%	37	11%
Number of clinically important or potentially clinically important CYP2D6 combinations	19	8/100	7	8/100	26	8/100
Patients administered clinically important or potentially clinically important CYP2D6 combinations	17	7%	7	8%	24	7%
CYP3A4 interactions						
<i>Drugs prescribed</i>						
Patients prescribed one or more CYP3A4 interacting drugs	135	57% ^b	76	87%***	211	65%
Number of CYP3A4 combinations	51	22/100 ^c	37	43/100*	88	27/100
Patients prescribed CYP3A4 combinations	39	17%	29	33%**	68	21%
Number of clinically important or potentially clinically important CYP3A4 combinations	18	8/100 ^d	17	20/100† (<i>P</i> = 0.055)	35	11/100
Patients prescribed clinically important or potentially clinically important CYP3A4 combinations	15	6% ^e	12	14%† (<i>P</i> = 0.057)	27	8%
<i>Drugs administered</i>						
Patients administered one or more CYP3A4 interacting drugs	73	31%	49	56%***	122	38%
Number of CYP3A4 combinations	29	12/100	23	26/100*	52	16/100
Patients administered CYP3A4 combinations	21	9%	19	22%**	40	12%
Number of clinically important or potentially clinically important CYP3A4 combinations	12	5/100	12	14/100† (<i>P</i> = 0.066)	24	7/100
Patients administered clinically important or potentially clinically important CYP3A4 combinations	10	4% ^f	10	11%*	20	6%

P* < 0.05, *P* < 0.01, ****P* < 0.001 for the comparison between patients on general adult and functional elderly wards.

†Difference approached statistical significance (*P* value stated). ^a95%CI on the difference between adult and elderly −6.3%, 16.4%, ^b95%CI 21%, 40%, ^c95%CI 4/1100, 38/100, ^d95%CI 0.4/100, 15.3/100, ^e95%CI −0.4%, 24.2%, ^f95%CI 0.1%, 14%.

Table 3

Prescribed combinations of drugs that interact with CYP2D6 and that give rise to clinically important or potentially clinically important interactions (the data refer to the number of patients prescribed or administered each combination)

			Number of combinations			
			Adult wards		Elderly wards	
			Prescribed	Administered	Prescribed	Administered
Amitriptyline	Paroxetine	a	1	1	0	0
Fluoxetine	Nortriptyline	a	0	0	1	1
Nortriptyline	Paroxetine	a	0	0	2	2
Amitriptyline	Haloperidol	b	1	0	0	0
Chlorpromazine	Haloperidol	b	6	2	0	0
Chlorpromazine	Zuclopenthixol	b	2	1	0	0
Clomipramine	Thioridazine	b	1	1	0	0
Codeine/paracetamol	Chlorpromazine	b	3	1	0	0
Codeine/paracetamol	Fluoxetine	b	0	0	3	0
Codeine/paracetamol	Haloperidol	b	4	1	2	0
Codeine/paracetamol	Paroxetine	b	1	0	2	0
Codeine/paracetamol	Propranolol	b	0	0	1	1
Codeine/paracetamol	Zuclopenthixol	b	0	0	1	0
Dextropropoxyphene/paracetamol	Haloperidol	b	1	0	0	0
Dextropropoxyphene/paracetamol	Thioridazine	b	2	0	0	0
Dihydrocodeine	Haloperidol	b	2	1	1	0
Dihydrocodeine	Thioridazine	b	1	0	0	0
Fluoxetine	Thioridazine	b	2	1	0	0
Fluoxetine	Zuclopenthixol	b	1	1	1	1
Haloperidol	Metoprolol	b	0	0	1	1
Haloperidol	Paroxetine	b	6	2	2	0
Haloperidol	Risperidone	b	4	0	0	0
Haloperidol	Thioridazine	b	10	3	0	0
Haloperidol	Zuclopenthixol	b	9	1	1	0
Paroxetine	Thioridazine	b	5	2	0	0
Paroxetine	Zuclopenthixol	b	1	1	1	1
Total			63	19	19	7

a = proven clinically important interaction, b = potentially clinically important interaction. Total number of patients on adult wards studied = 236, total number of patients on functional elderly wards studied = 87.

fluoxetine or paroxetine, which are potent inhibitors of CYP2D6 activity (e.g. [10]). There are reports that these SSRI drugs potentiate the adverse effects of antipsychotic therapy [16–19] through inhibition of CYP2D6-mediated metabolism. In one controlled prospective study, paroxetine was found to cause a profound decrease in the clearance of perphenazine, a substrate of CYP2D6, leading to over sedation and impairment of psychomotor performance and memory [20].

In the present context there may be particular concern about two antipsychotics, thioridazine and zuclopenthixol. Certain antipsychotic drugs cause lengthening of the QTc interval, which may have contributed to cases of sudden unexplained deaths in patients taking thioridazine [21–23]. ECG changes appear to be dose-

and plasma concentration-related [24]. CYP2D6 activity is an important determinant of the clearance of thioridazine, and in the UK the Committee on the Safety of Medicines have severely restricted the indications for thioridazine and issued a warning that co-administration of drugs that inhibit CYP2D6 activity may increase the risk of cardiotoxicity [25, 26]. Zuclopenthixol is also a substrate of CYP2D6 [27]. One of its indications is to control agitated and aggressive behaviour in acutely disturbed psychotic patients [28]. It is given as a slow release intramuscular preparation (Acuphase®) to provide rapid and long lasting tranquilization for this indication. Some patients receiving zuclopenthixol are prescribed an antidepressant (e.g. fluoxetine, paroxetine, both potent inhibitors of CYP2D6 activity). This com-

Table 4

Prescribed combinations of drugs that interact with CYP3A4 and that give rise to clinically important or potentially clinically important interactions (the data refer to the number of patients prescribed or administered each combination)

			Number of combinations			
			Adult wards		Elderly wards	
			Prescribed	Administered	Prescribed	Administered
Carbamazepine	Diazepam	a	3	3	0	0
Carbamazepine	Fluoxetine	a	0	0	1	1
Carbamazepine	Sertindole	a	1	1	0	0
Diazepam	Omeprazole	a	0	0	1	1
Amiodarone	Carbamazepine	b	0	0	1	1
Amiodarone	Temazepam	b	0	0	1	0
Amlodipine	Carbamazepine	b	1	1	2	2
Amlodipine	Fluoxetine	b	0	0	1	1
Buspirone	Carbamazepine	b	1	1	0	0
Carbamazepine	Sertraline	b	1	1	0	0
Carbamazepine	Temazepam	b	2	1	3	1
Carbamazepine	Zopiclone	b	2	1	0	0
Fluoxetine	Lanzoprazole	b	1	0	0	0
Fluoxetine	Temazepam	b	3	1	7	5
Fluoxetine	Zopiclone	b	1	1	0	0
Omeprazole	Temazepam	b	2	1	0	0
Total			18	12	17	12

a = proven clinically important interaction, b = potentially clinically important interaction. Total number of patients on adult wards studied = 236, total number of patients on functional elderly wards studied = 87.

bination may lead to higher than expected plasma concentrations of zuclopenthixol, increasing the risk of adverse effects and cardiotoxicity. Whereas rapid tranquillization protocols advise that the dose of zuclopenthixol should be tailored to the size and weight of the patient, information on key interactions which may cause significant and potentially dangerous increases in plasma concentration is not included in current prescribing advice.

Several antipsychotics are themselves potent inhibitors of CYP2D6 activity [12, 29]. In the present survey, we found potentially clinically important interactions based on this mechanism involving an antipsychotic combined with another antipsychotic, with a tricyclic antidepressant, or with codeine. Eight drug cards contained prescriptions for inhibitors of CYP2D6 activity in combination with medicines containing codeine (e.g. fluoxetine and cocodamol). Codeine is believed to require conversion to morphine for analgesia [30], and this reaction is catalysed by CYP2D6 [45]. Thus, inhibition of CYP2D6 activity by co-administered drugs may lead to ineffective analgesia, which, based on our survey, may be occurring in substantial numbers of

patients. However, the role of CYP2D6 in modulating codeine analgesia requires confirmation in prospective studies of clinical pain, since current opinion is based mostly on data from healthy subjects using experimental pain protocols [31].

Overall, fewer patients were prescribed combinations of drugs that interact with CYP3A4 than with CYP2D6. Of the 16 different combinations observed, carbamazepine was the most commonly coprescribed drug likely to cause clinically important interactions. Carbamazepine is a potent inducer of CYP3A4 [32], leading to decreased blood concentrations of substrates of this enzyme and the risk of therapeutic failure.

Many of the drugs prescribed during this survey have been shown not to be substrates/inhibitors/inducers of CYP2D6 and CYP3A4. However, for a number of the older drugs used, particularly those introduced three or more decades ago, very little if anything is known about the enzymology of their metabolism. In the present survey prescriptions were found for the following 'orphan' drugs: clomethiazole, domperidone, dothiepin, droperidol, fluphenazine, flupentixol, lofepramine, lofexidine, pipotiazine, prochlorperazine, procyclidine, promazine

and trifluoperazine. Inspection of the chemical structures of these drugs suggests that they might be substrates for CYP2D6 and/or CYP3A4. There is preliminary evidence that chlormethiazole, fluphenazine and promazine are metabolized by these forms of cytochrome P450 [33], but there are no published data on the remaining compounds. Thus, there may be many more potential drug interactions involving the metabolism of psychotropic drugs than can be predicted on current knowledge. For example, procyclidine was prescribed on a regular or p.r.n. basis to 38% of patients in our sample. Inhibition of its metabolism by the antipsychotics with which it is usually prescribed, may lead to clinically important interactions if its antimuscarinic effects are plasma concentration-related.

Standard drug charts used on hospital psychiatric wards are designed to allow several different types of prescriptions to be made, namely regularly administered drugs, once-only medication, p.r.n. medication and depot injections. Drug interactions from regular medication can be reasonably well anticipated, since the prescriber knows in advance what drugs will be present in the body at any given time. P.r.n. prescriptions are written by doctors to allow medication to be given when immediate treatment is required and are normally administered by the nursing staff. Thus, the prescriber will not know if or when these drugs are taken, and therefore is less able to predict interactions. When considering future changes in practice, education of prescribers (including nurses) about pharmacokinetic interactions and the unpredictability that p.r.n. prescribing may introduce (perhaps with factual reminders on drugs charts relating to CYP interactions) would seem more achievable than any attempt at more sweeping reform by limiting drug availability under the p.r.n. prescribing system.

In conclusion, our findings confirm extensive polypharmacy on general adult psychiatric and functional elderly psychiatric wards. Over one-third of patients studied were prescribed combinations of drugs that interact with CYP2D6, and almost one-quarter were prescribed drug combinations that interact with CYP3A4. Clinically important or potentially clinically important interactions involving the latter enzyme were significantly more common on functional elderly psychiatric wards. The logical extension of this audit will be to investigate whether the co-administration of these drugs leads to clinically important interactions in individual patients. In the meantime, consideration should be given to the incorporation into prescribing charts of data on cytochrome P450-related drug interactions with particular reference to the p.r.n. and once only medica-

tion sections, and to clinical settings associated with enhanced risk of drug-induced toxicity, such as rapid tranquillization protocols.

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