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Drug-related problems and factors influencing acceptance of clinical pharmacologists' alerts in a large cohort of neurology inpatients

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Summary

QUESTIONS UNDER STUDY/PRINCIPLES: Data regarding the prevalence and types of drug-related problems (DRPs) among neurology inpatients is sparse. The objective of this study was to characterise the types of DRPs seen among neurology inpatients and furthermore to study factors affecting the acceptance of clinical pharmacologists' and pharmacists' recommendations for improving drug safety.

METHODS: 1,263 consecutive inpatient cases in a Swiss university hospital neurology unit were assessed for the presence of DRPs over 12 months. Treating neurologists' acceptance of the resulting recommendations was also recorded. Primary outcome measures were types of DRP, recommendations made by clinical pharmacologists and number of recommendations accepted. Factors potentially associated with acceptance were studied using univariate and multivariate generalised estimating equation modelling.

RESULTS: Twenty-nine percent of cases demonstrated one or more DRPs. DRPs were the cause of admission in 10 cases (0.8%). In total 494 DRPs were identified and 467 recommendations given, of which 62% were accepted. Factors associated with an increased likelihood of acceptance were prescriptions involving regularly administered drugs (odds ratio [OR] 2.57 95% confidence interval [CI] 1.73–3.80), adverse drug events (OR 2.5; 95% CI 1.29–5.06), known drug side-effect (OR 1.85; 95% CI 1.06–3.22), high-risk drug-drug interactions (OR 3.22; 95% CI 1.07–9.69) and interventions involving changing a drug (OR 2.71; 95% CI 1.17–6.25).

CONCLUSION: Clinical pharmacologists and pharmacists can play an important role in identifying DRPs among neurology inpatients. Their recommendations for optimising medication-safety are most likely to be accepted for regular prescriptions, prescriptions associated with an adverse drug event and high-risk drug combinations.

Key words: *drug-related problems; neurology; clinical pharmacology; clinical pharmacy; drug-safety; hospital; acceptance*

Introduction

Clinical pharmacologist- and clinical pharmacist-led services for improving medication-safety in hospitals and in the community have been shown to improve both patient- and cost-related outcomes [1–3]. These services have been well described for ambulatory and hospitalised internal medicine, intensive care unit, family practice, surgery, psychiatry and geriatric patients. The success of such services depends on a number of factors including the accurate identification of drug-related problems (DRPs), appropriate suggestions about how these might be avoided and the acceptance and implementation of these suggestions by the treating medical practitioners. Clinical pharmacologists and pharmacists must concentrate on all three of these aspects to ensure a benefit for patients.

The nature of DRPs among patients hospitalised with neurological conditions has not been previously documented. Furthermore, little is known about factors affecting the acceptance of clinical pharmacologists' and clinical pharmacists' recommendations by treating physicians. We have previously shown that the use of electronic prescription charts is one factor which aids both in the identification of DRPs and the subsequent implementation of recommendations for improving drug safety among hospitalised patients [4].

We therefore conducted a study in neurology inpatients for which electronic prescribing was exclusively employed with an aim to characterise the types of DRPs and to study additional factors which might affect the acceptance of recommendations for improving drug safety.

Patients and methods

Neurology inpatients on two separate wards in a large Swiss university hospital were assessed for drug-related problems (DRPs) on weekly consultant neurologist ward rounds by two clinical pharmacologists and a pharmacist between September 2009 and September 2010. All patients were cared for using integrated electronic medical records (with electronic prescribing). An additional feature of the electronic prescription chart was the electronic drug interactions check programme supplied by Pharmavista® [5]. This programme assessed potential drug-drug interactions and graded these according to required intervention (based on the Operational Classification of Drug Interactions by Hansten et al. [6]) only when requested to do so by the prescriber; it did not flag up potential problems automatically. It was not possible to determine whether or how often the interactions programme was used by the prescribing physicians. Other than the voluntary drug interactions check, no electronic clinical decision support (regarding dosing, for example) was embodied in the electronic prescription chart. Patients who remained in hospital for more than one week or who were readmitted were assessed each time, however, only new DRPs were commented upon. DRPs which had previously been commented upon, but the suggested intervention not implemented, were not commented upon again. This was to avoid over-alerting and also had the advantage that the same problems were not counted twice (and therefore not over-represented) at the time of data analysis. Unlike in our previous study where only regularly administered medication was commented upon [4], this study assessed for DRPs in both "regular" and "as required" medication (given on a "*pro re nata"* or "PRN" basis).

DRPs were defined according to the Pharmaceutical Care Network Europe (PCNE) Classification for Drug-related problems version 6.2 (revised 14.01.2010), which defines a drug-related problem as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" [7]. DRPs were identified and proposals for optimising drug safety were given to the treating neurologists face-to-face on the ward round and again later the same day in the form of electronic notes (checked by the two senior clinical pharmacologists in the team) in the patient records. Clinical pharmacologists and pharmacists accessed internet based databases including Swiss, German and American product information, PubMed, the Pharmavista® tool and Micromedex® Healthcare Series [8].

All the detected DRPs, their causes and proposed interventions were then retrospectively classified according to the PCNE classification system for reporting purposes. The PCNE classification system has a number of limitations, however. The large number of variables (n = 64 for problems, causes and interventions) makes statistical analyses and comparisons difficult and it does not include the exact nature of the intervention proposed by the clinical pharmacologist or pharmacist to ameliorate or minimise the DRP. We therefore devised a simpler classification system based on the PCNE for the purposes of determining factors which were positively and negatively associated with the implementation of clinical pharmacologists' proposals (table 1).

The outcome measures were the types of DRP, the recommendations made by clinical pharmacologists and the number of these recommendations which were implemented by the treating neurologists. Factors at the prescription-, DRP-, causality- and intervention-levels potentially associated with proposal acceptance were studied. Drug-drug interactions were categorised according to Pharmavista®, where "1" and "2" denote interactions with a high potential for subsequent adverse outcome (so called "severe" interactions) and "3", "4" and "5" represent interactions of lesser clinical importance [5]. Univariate analyses taking clustering by patient and ward into account were performed using generalised estimating equations (GEE) and odds ratios generated. Each patient within each ward was treated as a separate cluster and we included clinic and ward as explanatory variables. Robust standard errors from the GEE model were then extracted to compute a confidence interval for the resulting odds ratio of interest. Of note, standard errors from a GEE are also valid if the underlying correlation structure is not correctly specified by our model assumptions. Factors which were positively associated with the primary outcome measure were then used to build a multivariable logistic regression model to assess for the independent effects of these factors on increasing proposal acceptance. A second model, using factors which were negatively associated with the primary outcome measure was constructed in a similar fashion. Both multivariable models were adjusted for dependence on patient and ward using GEE, and also adjusted for ward as an explanatory variable in order to remove any potential source of bias by ward. The latter was important as the patients on the two wards were cared for by different neurologists and their DRPs were consistently assessed by one clinical pharmacologist on one ward and another clinical pharmacologist together with a pharmacist on the other ward. All analyses were performed using R (R Development Core Team, 2010) using the package "geepack" [9].

Results

Eighty-four ward rounds were attended and 1263 inpatient cases assessed for the presence of drug-related problems (fig. 1). In total 494 DRPs involving 704 individual drug prescriptions in 367 inpatient cases (median age 68.7 years, interquartile range 57.0–77.8 years) were identified. The principal diagnoses at admission were confirmed or suspected cerebral ischaemia or intracerebral bleeding (n = 145, 40%), Parkinson's syndrome or extrapyramidal symptoms (n = 32), epilepsy (n = 29), primary or secondary brain tumours (n = 20), multiple sclerosis (n = 9), infectious nervous system disorders (n = 8), dementia (n = 7), essential tremor (n = 6), gait disturbance (n = 5), chronic headaches (n = 4) and chronic pain syndrome (n = 4). The remaining 98 patients had rarer diagnoses (less than 4 cases per diagnosis).

Twenty-nine percent of the studied inpatient cases demonstrated one or more DRPs. Interventions were proposed for 467 (95%) DRPs. No intervention was proposed for the remaining 27 DRPs, as these were either related to serious adverse drug reactions for which the offending drug had already been discontinued (n = 15) or related to the need for additional information regarding individual pharmacotherapy (n = 12) (fig. 1).

There were 17 cases where an adverse drug reaction (ADR) was judged to have occurred, representing 1.3% of the cases studied. Fourteen of these were classified as non-allergic and 3 allergic. The ADRs were intracerebral bleeding (phenprocoumon n = 2, aspirin n = 2), sinus vein thrombosis (hormonal contraception n = 3) and one case each of retroperitoneal bleeding (valproate and phenprocoumon), acute renal failure (acyclovir), hepatotoxicity (amoxicillin/clavulanic acid), lithium toxicity, stroke (celecoxib), herpes simplex meningoencephalitis (etanercept), rash and liver enzyme increase (lamotrigin), unclear weakness (H1N1 vaccination), haemolytic anaemia (human immunoglobulin) and extrapyramidal syndrome (risperidone). Drug-related problems were the cause of admission to the neurology unit in 10 cases (representing 0.8% of all cases studied).

The drugs most frequently implicated are listed in table 2 and included analgesics, antiplatelet agents, anticonvulsants, lipid-lowering medication, proton-pump inhibitors and night-sedation. The types of DRPs, their causes and the resulting interventions carried out by the treating physicians classified according to the Pharmaceutical Care Network Europe (PCNE) Classification for Drug-related problems version 6.2 (revised 14.01.2010) [7] are shown in

Table 1: Acceptance of proposed interventions grouped according to the type of prescription, type of drug-related problem, underlying cause and proposed intervention. Odds ratios are adjusted for potential dependence on ward and patient.

	Entire group	Accepted (%)	Not accepted	Odds ratio for acceptance (95% confidence interval)
N	467	289 (62)	178	
Type of drug prescription involved in the proposed intervention:				
“Regular” prescriptions only	274	195 (71)	79	2.57 (1.73–3.80)
At least one “as required” agent	193	94 (49)	99	0.39 (0.26– 0.58)
Homeopathic or herbal remedies	6	6 (100)	0	Infinity
At least one anticoagulant or antiplatelet agent	50	38 (76)	12	1.98 (1.02– 3.84)
At least one antihypertensive agent	46	30 (65)	16	1.11 (0.61– 2.02)
At least one antidiabetic agent	11	7 (64)	4	1.29 (0.49–3.42)
Problems				
Lack of efficacy	13	10 (77)	3	2.04 (0.60–6.92)
Potential lack of efficacy	66	45 (68)	21	1.32 (0.78–2.22)
Adverse drug event	59	47 (80)	12	2.56 (1.29–5.06)
Potential adverse drug event	319	184 (58)	135	0.58 (0.38–0.89)
Cost-issue	10	3 (30)	7	0.32 (0.09–1.19)
Causes				
Known side-effect of drug(s)	76	56 (74)	20	1.85 (1.06–3.22)
Dose problem	69	39 (57)	30	0.77 (0.46–1.03)
Duplication of therapeutic class	8	4 (50)	4	0.69 (0.15–3.21)
Prescribing error	26	16 (62)	10	1.03 (0.45–2.37)
Error in documentation of allergies	33	14 (42)	19	0.45 (0.19–1.05)
Suboptimal choice of drug formulation	20	8 (40)	12	0.44 (0.18–1.07)
Interaction	182	119 (65)	63	1.23 (0.84–1.80)
– Proposed intervention involved alteration of a drug combination graded as level 1 or 2*	24	20 (83)	4	3.22 (1.07–9.69)
– Proposed intervention involved alteration of a drug combination graded as level 3, 4 or 5*	110	69 (63)	41	1.02 (0.65–1.6)
Indication (untreated indication or indication for a current treatment requiring reassessment)	14	10 (71)	4	1.48 (0.45–4.83)
Contraindicated	38	22 (58)	16	0.88 (0.43–1.78)
Unknown cause	1	1 (100)	0	n/a
Proposed intervention				
Change drug	40	32 (80)	8	2.71 (1.17–6.25)
Change drug formulation	21	8 (38)	13	0.40 (0.16–0.97)
Documentation of allergies	34	14 (41)	20	0.32 (0.15–0.72)
Dose reduction	119	72 (61)	47	0.97 (0.63–1.51)
Patient monitoring	71	48 (68)	23	1.23 (0.74–2.05)
Start drug	14	8 (57)	6	0.78 (0.28–2.23)
Stop drug	114	77 (68)	37	1.39 (0.86–2.14)
Therapeutic drug monitoring	17	10 (59)	7	0.85 (0.32–2.22)
Timing of drug administration	37	20 (54)	17	0.72 (0.35–1.45)

* Pharmavista did not report on 48 additional interactions which were detected by the clinical pharmacologists.

table 3. The table also shows the distribution of these parameters according to implementation of proposed recommendations. 289 (62%) of the 467 proposed interventions were implemented by the treating neurologists. The commonest drug-drug interactions are given in table 4 along with interaction severity grade and implementation. Drugs for which all, none, greater than 50% or less than 50% of recommendations were carried out are listed in table 5.

Factors potentially influencing the implementation of recommendations could be grouped into the following categories: (1.) type of medication-prescription, (2.) nature or type of DRP, (3.) cause of DRP and (4.) recommended intervention for minimising the DRP (table 1). Univariate analysis taking potential clustering around patient and ward into account showed prescriptions involving only regularly administered drugs, prescriptions involving at least one anticoagulant or one antiplatelet agent, DRPs which were adverse drug events, DRPs which caused manifestation of a known drug side-effect, DRPs caused by a grade 1 or 2 drug-drug interaction and interventions involving changing a drug were all associated with an increased likelihood of implementing the clinical pharmacologists' and pharmacists' recommendations (table 1). Similarly, factors associated with a reduced chance of implementation were prescriptions involving a drug given on an "as required" basis, a DRP which had the potential to cause an adverse drug event, recommendations to change the administered drug formulation and recommendations to document drug allergies and intolerances in the appropriate place (table 1 – see Methods for definition of interaction grades).

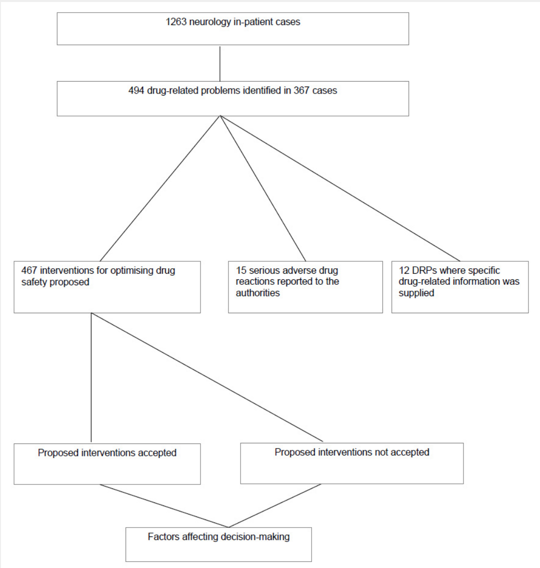

Figure 1

Study flow-chart.

While 71% of recommendations involving "regular" medication were implemented, only 49% of recommendations involving at least one "as required" medication were accepted. Multivariate analysis showed the type of prescription (whether for "regular" or "as required" medication) was the sole independent determinant of acceptance. After adjustment for the factors positively associated with implementation shown in table 1 and adjustment for ward, the odds ratio for "regular" medication was 2.31 (95% CI 1.51–3.53). After adjustment for the factors which were negatively associated with implementation (table 1) and adjustment for ward, the odds ratio for "as required" medication was 0.47 (95% CI 0.3–0.73) (table 6). The entire multivariable model and the associated adjusted odds-ratios and p-values are shown in table 6.

There were 38 cases where a contraindicated drug-therapy was prescribed. In twenty-two cases prescriptions were changed on the basis of our recommendations and included all recommendations regarding contraindicated drug-drug combinations. Recommendations which were not implemented were where the product information cited underlying conditions or diseases as precluding drug use such as tramadol or metoclopramide in epilepsy (n = 5), ACE inhibitor, nonsteroidal anti-inflammatory drugs, eplerenone or metformin in renal impairment (n = 6), anticoagulation in the setting of thrombocytopenia or recent history of bleeding (n = 2), metamizole in the setting of agranulocytosis (n = 1), domperidone in the setting of QTc prolongation (n = 1) and reserpine in the setting of depression (n = 1).

Although not systematically examined for the purposes of this study, there were examples where implementation of the proposed intervention led to a clear benefit for the patient during the period of hospitalisation. This included a case where symptomatic hypoglycaemia developed after the introduction of a fibrate to on-going glibenclamide therapy. On conversion of the fibrate to a statin as recommended, no further hypoglycaemic events occurred. In a further case an elevation in serum transaminases norm-

Table 2: Top 10 drugs featuring in the 494 drug-related problems (in total 704 drug prescriptions were involved in the drug-related problems).

Drug	Class	Number	Percentage of prescriptions
Zolpidem	Sedative	62	8.8%
Paracetamol	Antipyretic/analgesic	48	6.8%
Aspirin	Antiplatelet agent	28	4%
Phenytoin	Anticonvulsant	23	3.3%
Atorvastatin	Lipid lowering agent	22	3.1%
Diclofenac	Antipyretic/analgesic	21	3%
Clopidogrel	Antiplatelet agent	20	2.9%
Esomeprazole	Proton pump inhibitor	18	2.6%
Ibuprofen	Antipyretic/analgesic	17	2.4%
Carbamazepine	Anticonvulsant	16	2.3%
Domperidone*	Antiemetic	16	2.3%

*Dopamine antagonist, not licensed in USA

Table 3: Classification of the 494 drug-related problems according to Pharmaceutical Care Network Europe Classification for Drug-Related Problems Version 6.2.				
Characteristic	**Entire group**	**No proposal made**	**Proposal accepted**	**Proposal not accepted**
Number of drug-related problems	494			
Number of proposals	467	27	289	178
The Problem				
P1: Treatment effectiveness: There is a (potential) problem with the (lack of) effect of the pharmacotherapy.				
P1.1 No effect of drug treatment/therapy failure	5 (all manifest)	2	3	0
P1.2 Effect of drug treatment not optimal	78 (2 manifest)	10	47	21
P1.3 Wrong effect of drug treatment	0	0	0	0
P1.4 Untreated indication	8	0	5	3
P2: Adverse reactions: Patient suffers, or will possibly suffer, from an adverse drug event.				
P2.1 Non-allergic	27 (14 manifest)	8	14	5
P2.2 Allergic	41 (3 manifest)	2	16	23
P2.3 Toxic	321	5	199	117
P3: Treatment costs:				
P3.1 Drug treatment more costly than necessary	10	0	3	7
P3.2 Unnecessary drug treatment	4	0	2	2
The Cause				
C1: Drug selection				
C1.1 Inappropriate drug (including contra-indicated)	61	0	38	23
C1.3 Inappropriate combination of drugs	50	0	34	16
C1.4 Inappropriate duplication of therapeutic group or active ingredients	30	0	19	11
C1.5 Indication for drug-treatment not noticed	5	0	3	2
C1.7 More cost-effective drug available	10	0	3	7
C1.8 Synergistic/preventive drug required and not given	8	0	6	2
C1.9 New indication for drug treatment presented	1	0	0	1
C2: Drug form				
C2.1 Inappropriate drug form	11	0	5	6
C3: Dose selection				
C3.1 Drug dose too low	1	1	0	0
C3.2 Drug dose too high	22	0	17	5
C3.3 Dosage regimen not frequent enough	1	0	0	1
C3.4 Dosage regimen too frequent	5	0	2	3
C3.5 No therapeutic drug monitoring	15	0	8	7
C3.6 Pharmacokinetic problem requiring dose adjustment	120	9	66	45
C5: Drug use process				
C5.1 Inappropriate timing of administration and/or dosing intervals	28	0	18	10
C8: Other				
C8.1 Other cause* C8.2 No obvious cause	126	17	70	39
The Intervention				
I0.0: No intervention	27	27	–	–
I1. At prescriber level				
I1.1 Prescriber informed only	12	–	–	–
I1.2 Prescriber asked for information	0	–	–	–
I1.3 Intervention proposed, approved by Prescriber	289	–	–	–
I1.4 Intervention proposed, not approved by Prescriber	178	–	–	–
I1.5 Intervention proposed, outcome unknown	0	–	–	–
I3: At drug level				
I3.1 Drug changed	34	–	34	–
I3.2 Dose changed	70	–	70	–
I3.3 Formulation changed	8	–	8	–
I3.4 Instructions for use changed	19	–	19	–
I3.5 Drug stopped	78	–	78	–
I3.6 New drug started	8	–	8	–
I4: Other intervention or activity				
I4.1 Other intervention**	72	–	72	–
I4.2 Side effect reported to authorities	15	–		–

* Predictable adverse reactions were classified under this heading
** Other interventions consisted of therapeutic drug monitoring, documentation of allergies and patient monitoring.
There were no DRPs in the following categories: *The Problems:* P4 Other problems: P4.1 Patient dissatisfied with therapy, P4.2 Unclear problem; *The Causes* C1 Drug selection: C1.2 No indication for drug, C1.6 Too many drugs prescribed for indication, C3.7 Deterioration/improvement of disease state requiring dose adjustment, C4: Treatment duration: C4.1 Duration of treatment too short, C4.2 Duration of treatment too long; C5: Drug use process: C5.2 Drug underused/under-administered (deliberately), C5.3 Drug overused/over-administered (deliberately), C5.4 Drug not taken/administered at all, C5.5 Wrong drug taken/administered, C5.6 Drug abused (unregulated overuse), C5.7 Patient unable to use drug/form as directed; C6. Logistics: C6.1 Prescribed drug not available, C6.2 Prescribing error (necessary information missing), C6.3 Dispensing error (wrong dose or drug dispensed); C7: The Patient: C7.1 Patient forgets to use/take drug, C7.2 Patient uses unnecessary drug, C7.3 Patient takes food that interacts, C7.4 Patient stored drug inappropriately; C8 Other: C8.2 No obvious cause; *The Interventions* I2: At patient/carer level I2.1 Patient (medication) counselling, I2.2 Written information provided only, I2.3 Patient referred to prescriber, I2.4 Spoken to family member/caregiver.

alised after the recommended atorvastatin dose reduction was carried out.

Discussion

Drug-related problems

This study describes the role of clinical pharmacologists and clinical pharmacists in the detection and avoidance of DRPs among neurology inpatients. Twenty-nine percent of cases demonstrated at least one DRP. This compares more favourably with the 80% seen in a large study of 827 patients hospitalised with internal medical or rheumatological conditions [10] and a study of geriatric inpatients which found a DRP prevalence of 78% [11]. Both these latter studies defined DRPs according to the PCNE system as in the current study, however, DRPs were solely detected through chart reviews and not attendance on ward rounds. It is likely that attendance on ward rounds enables a more accurate identification of clinically relevant DRPs, which could be an explanation for the lower DRP prevalence seen in our study. In attending ward rounds, clinical pharmacologists and pharmacists are able to gain an insight into the patient case as a whole and can thereby provide patient-specific recommendations and avoid false positive DRP detection.

It is well known that the vast majority of DRPs are avoidable, as we also found in this study. Root causes of the DRPs in this patient group were not specifically analysed but were likely to have been due in part to continued prescription of problematic drug regimes initiated prior to hospital admission, switching to "hospital list" medication and thereby causing a new drug-drug interaction and use of standardised prescriptions for "as required" medication (a function facilitated by electronic prescribing). This latter aspect accounts for the high number of DRPs arising from "as required" prescriptions for zolpidem and paracetamol for example, in which dose adjustment for age or the presence of concomitant enzyme-inducing agents are not automatically carried out.

The adverse drug reaction frequency of 1.3% was smaller than in our previous study of medical inpatients admitted to the same hospital (3.7%) [4] but in keeping with a previous study in internal medicine and surgery inpatients (1.7%) [12]. A recent review of DRPs in hospitals has collated data from a number of studies reporting the frequency of ADRs detected and found a range of 1.3 to 60.7% [13]. The data presented here clearly lie at the lower limit of this range and may reflect the fact that the patients were being cared for in a specialist unit. Adverse drug reactions as the cause for admission (0.8%) were also fewer than in other observational studies conducted in Switzerland (4.1% of admissions to internal medicine wards in a study conducted between 1996 and 2000) [14]. Another large study conducted in the UK found 5.2% of all hospital admissions to be directly related to an ADR with the most common cause for an ADR-related admission being gastrointestinal bleeding [15]. The lower prevalence of ADRs as the cause of admission in our study most likely reflects the fact that adverse drug events less commonly present as an isolated neurological problem requiring specialist neurologist care (sinus vein thrombosis in association with hormonal contraception being a notable exception).

DRPs arose mainly in medication not specifically licensed for the treatment of neurological conditions (table 2). Seventy-nine percent of the drugs where all recommendations were implemented (15 out of 19) were not ones primarily prescribed for the treatment of a neurological condition (table 5). These observations not only provide evidence for good pharmaceutical practice in the speciality but also provide evidence that clinical pharmacologists and pharmacists can contribute significantly to non-speciality aspects of patient pharmacotherapeutics.

Acceptance

The acceptance of recommendations for improving medication-safety in this study of neurology inpatients was 62% which is in line with our previous study of hospitalised medical inpatients cared for using electronic prescription charts [4]. For drugs administered regularly, the ac-

Table 4: Ten commonest drug-drug interactions and implementation of the resulting suggestions. The total number of detected drug-drug interactions for which interventions were proposed was 182.

Interacting drugs	Potential consequence	Severity grade*	Number of cases (% total interactions)	Number of proposals accepted
Clopidogrel – esomeprazole	Reduction in clopidogrel efficacy	2	15 (8.2)	14
Aspirin – ibuprofen	Reduction in aspirin efficacy	3	13 (7.1)	8
Phenytoin – paracetamol	Increased paracetamol-induced hepatotoxicity	4	12 (6.6)	7
Zolpidem – lorazepam	Over-sedation	**	9 (4.9)	5
Levothyroxine – cations (calcium, magnesium)	Reduction in levothyroxine absorption	3	8 (4.4)	4
Carbamazepine – paracetamol	Increased paracetamol-induced hepatotoxicity	4	7 (3.8)	3
Domperidone – atypical neuroleptics	Increased risk of Torsades de Pointes	3	7 (3.8)	4
Amiodarone – atorvastatin	Increased atorvastatin toxicity (rhabdomyolysis)	3	5 (2.7)	4
Ciprofloxacin – olanzapine	Increased risk of Torsades de Pointes	5	3 (1.6)	2
Phenobarbital – paracetamol	Increased paracetamol-induced hepatotoxicity	4	2 (1.1)	0
Valproate – topiramate	Risk of hyperammonaemia	3	2 (1.1)	2
Metformin – radioopaque contrast medium	Risk of acute renal failure and lactic acidosis	**	2 (1.1)	2

* Grade 1 = Contraindicated drug combination; grade 2 = relatively contraindicated drug combination; grade 3 = this drug combination requires dose adjustment and/or monitoring for adverse drug reactions; grade 4 = in patients with risk factors, this drug combination requires dose adjustment and/or monitoring for adverse drug reactions; grade 5 = this drug combination requires monitoring for adverse drug reactions.
** Interaction not rated by Pharmavista®.

ceptance was 71%, while for drugs administered on an "as required" basis the acceptance was significantly lower at 49%; this association remained after adjustment for other univariate factors, most likely reflecting the study power for this variable conferred by the large numbers (247 regular prescriptions and 193 "as required"). Nonetheless, examination of factors which were associated with increased acceptance and those associated with decreased acceptance provide interesting information. Recommendations regarding a potential adverse event, for example, were less likely to be implemented and could signal over-alerting. High-risk drug-drug interactions, on the other hand, were more likely to be implemented and are a good example of where a clinical pharmacologist can bring specialist knowledge to patient care.

It is known from studies of electronic clinical decision support systems that over-alerting is associated with overriding of recommendations for improving drug safety, particularly as the alerts are often not clinically relevant [16–18]. Indeed as many as 91% of electronically generated alerts pertaining to drug-drug interactions may be ignored [16]. The danger in such cases is that important, clinically relevant drug-related problems are missed and the appropriate action to stop or prevent adverse events is not taken when it should be. By providing a physician- and/or pharmacist-led service for flagging-up relevant drug-related problems and providing suggestions for avoiding these, situations such as the latter should hopefully be avoided. Indeed, while electronic decision support appears to have a very low implementation, face-to-face clinical pharmacist interven-

Table 5: Acceptance of recommendation according to the drugs involved in the drug-related problems. Only drugs which featured in more than 1 drug-related problem are shown.

All recommendations accepted	At least 50% of recommendations accepted	Less than 50% of recommendations accepted	No recommendations accepted
Aciclovir	Acetaminophen	Citalopram	Amitriptylline
Aldactone	Amiodarone	Dalteparin	Azathioprine
Alendronate	Amoxicillin/clavulanate	Domperidone	Betainterferon
Amiloride	Aspirin	Hydrochlorothiazide	Finasteride
Amphotericin	Atorvastatin	Levothyroxine	Paraffin fecal softener
Escitalopram	Calcium supplements	Phenobarbital	
Folic acid	Captopril	Primidone	
Gingko biloba	Carbamazepine	Trimipramine	
Indapamide	Celecoxib		
Iodine-containing radioopaque contrast medium	Ciprofloxacin		
Levetiracetam	Clopidogrel		
Oxcarbazepine	Clozapine		
Phosphate-based bowel preparation	Diclofenac		
Potassium supplements	Enalapril		
Quetiapine	Enoxaparin		
Saccharomyces boulardii	Esomeprazole		
Simvastatin	Ibuprofen		
Topiramate	Indomethacin		
Valsartan	Lisinopril		
	Lithium		
	Lorazepam		
	Magnesium supplements		
	Metamizole		
	Metformin		
	Metoclopramide		
	Mirtazapine		
	Morphine		
	Olanzapine		
	Perindopril		
	Phenprocoumon		
	Phenytoin		
	Pipamperone		
	Ramipril		
	Rasagiline		
	Tamsulosin		
	Tizanidine		
	Tramadol		
	Trazodone		
	Trimethoprim/sulfamethoxazole		
	Valproate		
	Venlafaxine		
	Zolpidem		

tions have been associated with rates as high as 83% for general medical hospital inpatients [19] and 96% for outpatients attending a specialist hypertension clinic [20]. These studies were however smaller than the current study and it is not clear whether "regular" and "as required" medication or solely "regular" medication was commented upon. The acceptance rate in specialist neurology units has not been formally assessed and reported before.

Clinical pharmacologists' and clinical pharmacists' recommendations for improving medication-safety ought to focus on the likelihood of outcomes in order to alert clinicians appropriately about potential adverse drug events. For drugs which are prescribed to be administered on an "as required" basis, the likelihood of outcomes is by definition low, as the exposure is low compared to drugs which are given daily.

In order to improve the implementation of recommendations for improving medication-safety, the underlying processes need to be considered. De Almeida Neto and Chen have reviewed the likely role of the treating-physicians' psychological "reactance" to recommendations by clinical pharmacists [21]. Reactance is defined as "a reaction to a recommendation to take a certain course of action which is affected by a motivational state compelling a response in which freedom of choice is maintained" [21]. The greater the number of seemingly non-beneficial recommendations, the greater the physicians' reactance to them is likely to be. One method of reducing reactance would be to restrict recommendations to those with the highest clinical relevance and most likely benefit. A further method, as suggested by de Almeida Neto is to provide prescribing physicians with choices, so that their sense of freedom of choice is maintained [21].

Limitations

Being carried out over 12 consecutive months could mean that a learning effect of the neurologists cannot be ruled out. However, we do not think this played a significant role as the junior physicians, who have the main prescribing role, changed positions in 3 to 6 month cycles and their supervising seniors changed positions in 6 to 9 month cycles. A further limitation is the lack of systematic long-term follow-up data regarding the effect of clinical pharmacologist-initiated interventions and patient outcome. Whether the study findings are likely to be generalisable to other patient settings, other clinical pharmacology and clinical pharmacist services and other prescribers is not apparent. There was also a power-dominance of the "regular" and "as-required" prescriptions in the multivariable analysis in this study. Further, larger studies in different settings focussing particularly on regular prescriptions are warranted in order to more accurately determine factors affecting prescriber decision-making to accept or reject clinical pharmacologists' and clinical pharmacists' recommendations.

Conclusions

Clinical pharmacologists and pharmacists can play an important role in identifying DRPs and optimising medication-safety among neurology inpatients. Their recommendations for optimising medication-safety are most likely to be accepted for regular prescriptions, prescriptions associated with an adverse event and high-risk drug combinations.

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Table 6: Multivariate models for factors A) positively and B) negatively affecting implementation of proposed interventions.

Factor	Adjusted odds ratio (95% confidence interval)*	p value
A Positive model: Proposed intervention involved: A drug which was given regularly	2.31 (1.51–3.53)	0.00011
At least one anticoagulant or antiplatelet agent	1.30 (0.61–2.77)	0.5
A drug which had caused an adverse drug event**	2.08 (0.84–5.17)	0.1
A drug which had caused the patient to suffer a known side-effect of that drug**	0.90 (0.43–1.89)	0.8
A drug which had led to a grade 1 or 2 drug-drug interaction	1.46 (0.42–5.08)	0.6
Changing a drug	2.26 (0.92–5.56)	0.08
B Negative model: Proposed intervention involved: A drug which was given as required	0.47 (0.3–0.73)	0.0007
A drug potentially leading to an adverse drug event	0.76 (0.47–1.21)	0.2
A drug which had led to a grade 3, 4 or 5 drug-drug interaction	0.90 (0.56–1.43)	0.7
Changing the administered drug formulation	0.39 (0.15–1.02)	0.06
Documentation of drug allergies and intolerances	0.50 (0.21–1.21)	0.1

* adjusted for potential dependence on patient ward
** the difference between these two is the level of the parameter – the adverse drug event described the problem itself, while a known side-effect of the drug described the underlying cause of a problem. While there is necessarily large overlap, the parameters are not the same.

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Figures (large format)

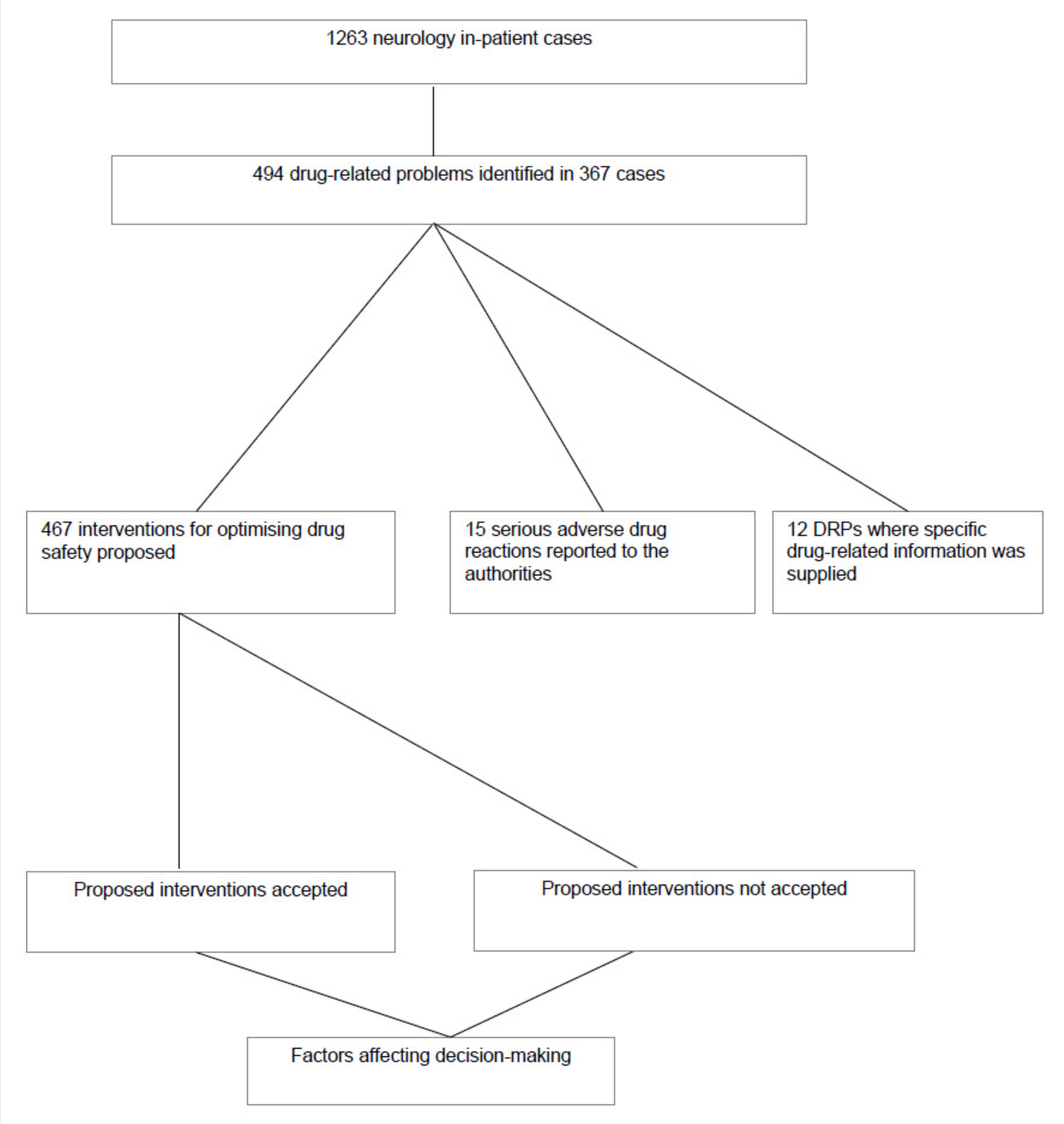

Figure 1

Study flow-chart.