PRESS RELEASE

EDITOR'S CHOICE

Inappropriate drug combinations in adult versus geriatric patients in a psychiatric setting

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ABSTRACT

Introduction The objective of this study was to assess the reliability of drug–drug interaction software in monitoring prescriptions in psychiatric settings.

Method A 1 day cross sectional analysis of the ongoing drug regimens in the inpatient population was carried out.

Results This study showed a relatively high prevalence of hazardous or contraindicated drug combinations (approximately 15%). Three major categories of interactions were found: (1) those requiring diagnostic tests; (2) those requiring dosage adjustments, an appropriate drug choice or pharmacological class; and (3) those whose risk–benefit ratio was positive in the treatment indication.

Discussion The findings demonstrate that without access to biological test results and indications, the most prevalent interactions cannot be validated by the pharmacist. These results suggest that the availability of these data is essential, and that interactions with prescribers should be facilitated in order to increase the quality of clinical pharmacy in psychiatry.

INTRODUCTION

Among the diverse and numerous tasks of the pharmacist in a psychiatric hospital, analysis and validation of prescriptions are crucial.[1] Computerisation of prescriptions in many French mental health hospitals now facilitates pharmacists' supervision as it provides a safety analysis by automatically detecting significant drug interactions.

The information provided by these software programs is essential for pharmacists who work in psychiatric settings, but considered alone, it is insufficient. In their daily work, pharmacists have limited time to visit departments in order to obtain the additional information they need, and physicians are not always readily available by telephone at the time of prescription validation. Thus drug–drug interaction software programs are often a good tool for validation of prescriptions although biological data and the patient's entire medical records are seldom available through such programs.

In psychiatric settings, reminders available at the time of drug ordering may have a positive impact on the appropriateness of drug prescriptions.[2] An optimised interaction detection method can therefore provide pertinent recommendations.[3 4] However, Sandson *et al*[5] and Strain *et al*[6] explain that the most widely used drug–drug interaction software programs may lead to ignorance of inappropriate drug combinations because for many psychiatrists these systems provide irrelevant information. In this context, it is the pharmacist's role to assess the relevance of the information concerning inappropriate drug combinations.

The medical information system in our 470 bed psychiatric hospital includes a computerised physician order entry system with an embedded program that automatically screens inappropriate drug combinations during the drug ordering process (the French software program Cariatides). The screening tool used by the automated drug interaction detection program is the database of the French Agency for Medicinal Products. A warning is displayed to the prescriber every time a hazardous or contraindicated drug combination (HCDC) is being ordered, with a reminder on both the nature and degree of severity of the iatrogenic risk entailed by the drug interaction.

In the present study, first, we evaluated the prevalence and patterns of HCDC in the elderly (≥65 years) versus the non-elderly adult inpatient population of a 470 bed psychiatric hospital. Second, we analysed the clinical relevance of this detection, and we estimated whether the drug–drug interaction software program alone is sufficient for the pharmacist to make an appropriate decision.

METHOD

A 1 day cross sectional analysis of all ongoing drug regimens was carried out by the pharmacy department and was repeated after 1 year, after all patients whose data were collected in the previous year were excluded (analysis was conducted on 5 October 2010 and 5 October 2011). This method was used in order to detect a significant number of interactions. Only inpatients were included in the analysis; duration of hospitalisation (short and long stay units) was variable. Patients were 18 years or older. The Student's t-test was used for comparisons.

The drug interaction database of the French Agency for Medicinal Products was the screening/rating tool used by the pharmacy department for assessing drug regimens. Only drugs prescribed on a regular schedule were considered ('as needed' were not included).

The number of physicians and psychiatrists involved in the psychogeriatric and psychiatric inpatient units was comparable. All clinicians showed similar levels of clinical experience even though most of those working with elderly patients (EP) had an additional qualification in geriatric care.

Finally, in light of the interactions detected, we aimed to propose a classification of the different types of interactions.

RESULTS

The 711 inpatients present in the wards during the 2 study days were included, among whom 152 were EP and 559 non-elderly patients (NEP) (see table 1 for details on distribution of inappropriate combinations). It is noteworthy that in the first cross sectional analysis, 103 EP and 395 NEP were included and no relevant differences were found for the pattern of HCDC between the two cross sectional analyses. The prevalence of HCDC in EP was similar to that recorded in NEP (p=0.42): 17.1% (n=26) in EP and 14.5% (n=81) in NEP. Patterns of HCDC were strongly influenced by the high prevalence of antipsychotic drug prescriptions: 107 of 152 (70%) EP and 464 of 559 (83%) NEP were treated with at least one antipsychotic drug. Antipsychotic containing HCDC accounted for 65% (n=17) and 74% (n=60) of HCDC recorded in EP and NEP, respectively (p=0.39). Involvement of polypharmacy with a QT prolonging antipsychotic was significantly higher in the HCDC recorded in NEP; it accounted for 65.4% (n=53) of HCDC in NEP and 23% (n=6) of HCDC in EP (p=0.002). Among these interactions, the combination of haloperidol plus phenothiazine was the most frequently found in the two subpopulations (67% and 75% of HCDC involving polypharmacy with an antipsychotic in EP and NEP, respectively) . The combinations of (1) QT prolonging antipsychotic with bradycardia inducing drugs, (2) angiotensin converting enzyme inhibitors plus potassium sparing diuretics or potassium supplement, (3) antipsychotic plus levodopa and (4) haloperidol plus lithium were more frequent in EP: 8%, 35%, 23% and 11% of HCDC in EP, respectively, versus 4%, 2%, 1% and 1% of HCDC in NEP, respectively. In contrast, some HCDC were exclusively found in NEP, and two of them accounted for 9% of HCDC in NEP (the combination of lamotrigine plus valproate and the combination of antiepileptic drugs plus oral contraceptives). Finally, other minor HCDC exclusively observed in NEP were: the combination of carbamazepine with clozapine and dextropropoxyphen (4% of HCDC in NEP) and the combination of naltrexone with codeine and non-steroidal anti-inflammatory drugs plus low molecular weight heparin (1% of HCDC in NEP).

Table 1 Distribution and types of the 107 hazardous or contraindicated drug combinations recorded in the elderly and non-elderly patients

	EP	NEP
Type of HCDC		
Polypharmacy with QTAP	6	53
Haloperidol–phenothiazines	4	40
Haloperidol–benzamides	0	4
Benzamides–phenothiazines	2	6
Phenothiazines–phenothiazines	0	2
Benzamides–benzamides	0	1
QTAP plus bradycardia inducing drugs	2	3
QTAP–pyridostigmine	0	3
QTAP–amiodarone	2	0
ACE inhibitors plus potassium sparing diuretics or potassium supplement	9	2
AP plus levodopa	6	0
Haloperidol plus lithium	3	1
Lamotrigine plus valproic acid	0	7
AED plus oral contraceptives	0	7
Clozapine plus carbamazepine	0	3
Carbamazepine plus dextropropoxyphen	0	3
Naltrexone plus codeine	0	1
LMW heparin plus NSAID	0	1
Total	26	81
Types of iatrogenic risk carried by the HCDC recorded		
Cardiotoxicity (torsade de pointe)	8	56
Additive	6	53
Potentiated	2	3
Therapeutic inefficacy	6	8
Antagonistic interaction at the receptor level	6	1
Antagonistic interaction through increased clearance mechanisms	0	7
Hyperkalaemia	9	2
Dermatologic toxicity (epidermal neurolysis)	0	7
Neurotoxicity (delirium)	3	4
Haematopoietic toxicity (agranulocytosis)	0	3
Bleeding	0	1
Total	26	81

ACE inhibitors, angiotensin converting enzyme inhibitors; AED, antiepileptic drugs; AP, antipsychotics; EP, elderly patients; HCDC, hazardous or contraindicated drug combination; LMW heparin, low molecular weight heparin; NEP, non-elderly patients; NSAID, non-steroidal anti-inflammatory drug; QTAP, QT prolonging antipsychotics.

DISCUSSION

EP are often exposed to polypharmacy because of the co-occurrence of multiple chronic conditions[6]; therefore, the lack of difference in the prevalence of interactions between NEP and EP can be explained, at least in part, by the patient and by the experience of doctors working in these units.

Our work also highlights different types of iatrogenic risks associated with HCDC (see table 1).

The main risk found in NEP (69% of HCDC) was cardiotoxicity, with increased risk of torsades de pointes. This risk was lower in EP (31% of HCDC). Indeed, the combination of two antipsychotics with intrinsic risks of inducing QT prolongation can result in additive cardiotoxicity. In our study, the most frequent antipsychotic combination was haloperidol plus a phenothiazine (eg, cyamemazine). Another mechanism for increased risk of QT prolongation is the potentiation of the antipsychotic related intrinsic risk by the bradycardia induced by another drug (QT prolonging antipsychotic plus pyridostigmine or amiodarone in our study). The second most prevalent iatrogenic risk in our study was therapeutic inefficacy resulting from an antagonistic interaction at the receptor level or through increased clearance mechanisms: a combination of levodopa plus antipsychotic was encountered exclusively in EP while a combination of antiepileptic drugs with oral contraceptives exclusively in NEP. Another important iatrogenic risk, exclusively found in NEP, was the danger of toxic epidermal necrolysis potentiation produced by the combination of valproate plus lamotrigine.

The risk of hyperkalaemia induced by the combination of drug related potassium retention was the most important iatrogenic factor recorded in EP. This finding is also consistent with the high frequency of treatments with angiotensin converting enzyme inhibitors or potassium sparing diuretics in EP, mostly for arterial hypertension. Neurotoxicity associated with drugs increasing the risk of delirium was found equally in both populations: a combination of haloperidol plus lithium, especially in EP, and a combination of carbamazepine plus dextropropoxyphen, exclusively in NEP. Two additional iatrogenic risks were observed in NEP: haematopoietic toxicity by additive risks of agranulocytosis (a combination of clozapine and carbamazepine) and potentiation of the risk of haemorrhage by the co-prescription of drugs that can induce bleeding (ie, a combination of non-steroidal anti-inflammatory drugs and low molecular weight heparin).

Hence the benefits of interaction detection systems are limited. The drug–drug interaction software programs lack sensitivity and specificity in detection.[7] In our study, the main interactions detected

demonstrated that our detection system is not totally useful on its own. Three major categories of interactions can be distinguished: those requiring diagnostic tests; those requiring dosage adjustments, an appropriate drug choice or pharmacological class; and those whose risk–benefit ratio is positive in the treatment indication.

In the first category of interactions, combinations between QT prolonging antipsychotics are usually prescribed with the prescriber's informed consent, hence the combination is thought to be essential to clinical improvement. In this case, preliminary clinical analyses on the QT need to be carried out.

In the second category, the association between an antipsychotic (except clozapine) and levodopa is due to the mutual antagonism of antiparkinsonian and neuroleptic drugs. However, in patients presenting with parkinsonian symptoms, this type of combination may be difficult to avoid, and if it has to be maintained, it is recommended to use the minimum effective doses of both drugs. In addition, the association between CYP3A4 inducing antiepileptic drugs (eg, carbamazepine, oxcarbazepine and phenytoin) and oral contraceptives can lead to contraceptive inefficiency by accelerating liver metabolism. Again, it is possible to circumvent this problem by using high doses of oral contraceptives with an oestrogen compound dose of at least 50 µg (low dose topiramate monotherapy 35 µg) and additional barrier methods of contraception.[8]

In the latter category, the interactions detected between lamotrigine and valproic acid are a hazardous combination associated with increased risks of serious skin reactions. Stevens–Johnson syndrome and toxic epidermal necrolysis remain rare with lamotrigine but the association of lamotrigine with sodium valproate increases the frequency of cutaneous rash.[9 10] Sodium valproate may also reduce lamotrigine metabolism. However, if the association is necessary, this co-prescription can be maintained with close clinical monitoring. Moreover, an additive effect between lamotrigine and valproate has been observed[11–13] with an acceptable incidence rate of side effects.[11–14] This type of combination is recommended for numerous patients with refractory epilepsy in psychiatric hospitals.

In our institution, pharmacists have access to the results of laboratory tests, allowing them to validate the first type of interaction that we discussed. However, if they do not have access to the entire patient record, more specific information, such as diagnosis and treatment indications, is often lacking, which limits their expertise on the other two types of interactions.

These findings illustrate that it is necessary, in addition to any computerised detection system, to promote an optimal collaboration between prescribers and pharmacists in order to accurately assess each case's interactions. Thus rigorous clinical pharmacy work consists of appropriate follow-up of diagnostic tests as well as choosing the appropriate molecule, adjusting its dosage and searching scientific data that can legitimise a potentially dangerous interaction in terms of risk–benefit ratio.

CONCLUSION

This study shows a relatively high prevalence of HCDC (approximately 15%), regardless of patient age. However, the numerous interactions detected are questionable and may in fact be validated by specific therapeutic situations. The drug–drug interaction software program alone is insufficient for the pharmacist to make an appropriate decision. Indeed, in many cases, pharmacists cannot guarantee the validity and clinical safety of the prescription, which can limit their analyses. These preliminary results should be replicated in a longitudinal and multicentre study.

Moreover, future studies should also focus on the objectives of each interaction, which cannot be provided by detection interaction software programs. This long term evaluation, involving biological data and choosing the appropriate molecules in a pharmacotherapeutic class, is part and parcel of the clinical pharmacist's daily work, and requires close collaboration with physicians and easier access to patient records for clinical pharmacists.

Key messages

Impact of findings on practice:

- Iatrogenic risks associated with hazardous or contraindicated interactions in psychiatry are different between elderly and non-elderly patients.
- Despite their apparent utility, drug–drug interaction detection software programs do not help the management of iatrogenic risks in a psychiatric setting.
- A close collaboration between physicians and pharmacists is recommended in clinical pharmacy's daily work for the management of drug interactions.

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