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ORIGINAL RESEARCH ARTICLE

Comparative Performance of Two Drug Interaction Screening Programmes Analysing a Cross-Sectional Prescription Dataset of 84,625 Psychiatric Inpatients

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Abstract

Background Clinical decision support software (CDSS) solutions can automatically identify drug interactions and thereby aim to improve drug safety. However, data on the comparative performance of different CDSS to detect and appropriately classify interactions in real-life prescription datasets is limited.

Objective The aim of this study was to compare the results from two different CDSS analysing the pharmacotherapy of a large population of psychiatric inpatients for drug interactions.

Methods We performed mass analyses of cross-sectional patient-level prescriptions from 84,625 psychiatric inpatients using two CDSS – MediQ and ID PHARMA CHECK®. Interactions with the highest risk ratings and the most frequent ratings were reclassified according to the Zurich Interaction System (ZHIAS), a multidimensional classification that incorporates the OpeRational ClassificAtion of Drug Interactions (ORCA) and served as a reference standard.

Results MediQ reported 6,133 unique interacting combinations responsible for 270,617 alerts affecting 63,454 patients. ID PHARMA CHECK® issued 5,400 interactions and 157,489 alerts in 48,302 patients. Only 2,154 unique interactions were identified by both programmes, but overlap increased with higher risk rating. MediQ reported high-risk interactions in 2.5 % of all patients, compared with 5 % according to ID PHARMA CHECK®. The positive predictive value for unique major alerts to be (provisionally) contraindicated according to ORCA was higher for MediQ (0.63) than for either of the two ID PHARMA CHECK® components (0.42 for hospINDEX and 0.30 for ID MACS). MediQ reported more interactions, and ID PHARMA CHECK® tended to classify interactions into a higher risk class, but overall both programmes identified a similar number of (provisionally) contraindicated interactions according to ORCA criteria. Both programmes identified arrhythmia as the most frequent specific risk associated with interactions in psychiatric patients.

Conclusions CDSS can be used for mass-analysis of prescription data and thereby support quality management. However, in clinical practice CDSS impose an overwhelming alert burden on the prescriber, and prediction of clinical relevance remains a major challenge. Only a small subset of yet to be determined alerts appears suitable for automated display in clinical routine.

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1 Introduction

For the prevention of adverse drug reactions (ADRs) and their associated morbidity, mortality and costs, drug interactions are a target of particular interest [1–3]. Although only a variable fraction of ADRs is related to interactions, most clinically relevant interactions are known and should therefore be avoidable given sufficient

awareness at the time of drug prescription [4, 5]. Consequently, a number of Clinical Decision Support Software (CDSS) systems that are able to identify concomitantly prescribed interacting drugs and alert the prescriber were developed in recent years.

Such CDSS are promoted as valuable tools to achieve safer prescribing, but they are also subject to important limitations that undermine their acceptance and efficacy in clinical practice [6–9]. Typically, their design focuses on high sensitivity to detect interacting drugs [10–13]. However, the unavoidable trade-off is that highly sensitive CDSS based on comprehensive interaction databases impose an overwhelming alert burden on the prescribing physician. This may lead to 'alert fatigue', meaning that CDSS-triggered alerts are indiscriminately given little attention or even completely disregarded [5, 14–17]. Therefore, the classification and subsequent selection of drug interactions according to their clinical relevance and management implications is a major challenge for CDSS. Furthermore, available CDSS show major differences in their system architecture, underlying knowledge databases and classification systems, and few studies evaluated and compared different CDSS using real-life patient data [13, 18–20]. Therefore, two aspects of CDSS deserve particular attention: first, the development of classifications that focus on clinical relevance and management implications of drug interactions; and second, the development of methods that allow an objective comparison of the performance of different CDSS using real-life data.

In order to address these issues, we recently developed an extended multidimensional operational classification system, the Zurich Interaction System (ZHIAS). It builds on the widely recognized OpeRational ClassificAtion of Drug Interactions (ORCA) that focuses on clinical management and identification of interactions that require medical interventions or monitoring [19, 21]. ZHIAS extends ORCA by another three dimensions that contain information on mechanisms of interaction, management options and expected adverse outcomes in the format of dichotomous variables. ZHIAS also specifically considers the need to include information on individual patients into alert algorithms. ZHIAS was successfully applied in studies that evaluated interactions identified by CDSS [22–24], and in a small pilot study where we used ZHIAS also as a 'silver standard' for the comparison of different CDSS [25].

Besides improving the specificity of CDSS through studies that use real-life patient data for an evaluation of their performance, such studies also allow an analysis of local safety problems and may therefore aid in the customized development of preventive measures according to specific local needs. The frequency of critical medication errors varies between different medical specialties and settings, and within that context psychiatric patients are a population of special interest [26]. Many new psychopharmacologic drugs have been introduced in recent years, and although some may have improved safety profiles, previous studies reported that drugs acting on the CNS are among those most frequently implicated in ADRs [1, 4]. Ageing of the psychiatric population and associated polypharmacy may also contribute to higher incidence of critical drug interactions [26, 27]. Few studies specifically addressed medication safety in psychiatry and the role of CDSS in improving it [26, 28]. In a previous study, we therefore evaluated the frequency and clinical relevance of drug interactions in a large population of psychiatric inpatients based on the CDSS MediQ [24]. The current study extends our previous work through the use of another CDSS in order to evaluate and compare for the first time the identification and grading of drug interactions by two CDSS in a large real-life prescription dataset.

2 Subjects and Methods

2.1 Data Source and Study Population

AMSP ('Arzneimittelsicherheit in der Psychiatrie' = Drug Safety in Psychiatry) is an ongoing international multicentre drug safety programme that has been collecting data on pharmacotherapy and ADRs from psychiatric hospitals in a naturalistic setting since 1993. Its methods have been described in detail elsewhere [29, 30]. Briefly, AMSP collects drug prescriptions and adverse events from more than 80 hospitals in Germany, Switzerland, Austria and, for some time, Belgium and Hungary. All participating hospitals survey psychiatric inpatients on two reference days per year. The drugs administered on these days are recorded along with the patients' age, sex and leading psychiatric diagnoses. For the current study we used the cross-sectional prescription data from patients surveyed between 1994 and 2008.

2.2 Study Design and Data Processing

We conducted a retrospective analysis of drug interactions in the anonymized AMSP prescription dataset using the CDSS MediQ and ID PHARMA CHECK®. The ethics committee had approved the study with a waiver of authorization.

Processing and recoding of the raw data for interaction analyses have been described in detail in our previous study [24]. The original AMSP dataset contained cross-sectional data of 88,029 psychiatric inpatients with a total of 334,056 prescriptions. After exclusion of patients with unidentifiable prescriptions and expansion of multi-ingredient preparations into individual constituents, 84,625

patients with 361,112 prescriptions remained suitable for automated mass analysis with ID PHARMA CHECK®. For mass analysis with MediQ we also had to exclude substances not comprised in the MediQ database, thus leaving 84,607 patients with 359,207 prescriptions. The most highly graded ('major') and most frequent drug interactions identified by the two CDSS were subsequently reclassified according to ZHIAS. Interactions resulting in decreased efficacy were also identified as such by both CDSS and were further evaluated.

2.3 Clinical Decision Support Software (CDSS) for Mass Analysis of Drug Interactions

2.3.1 MediQ

MediQ is a CDSS designed as a web-based stand-alone interaction analysis solution. Mass analysis with MediQ has been described in our previous studies [22–24]. Briefly, we developed a customized web interface that allowed us to perform mass analysis and automated identification of drug interactions with MediQ. MediQ uses a four-level hierarchical severity classification system of interactions (Table 1). All interactions with the MediQ 'high danger' grading were defined as 'major' in the current study.

2.3.2 ID PHARMA CHECK®

ID PHARMA CHECK® is a CDSS designed for integrated use with computerized physician order entry and clinical information systems. It has been described in our previous pilot study in a small population of neurological inpatients [25]. ID PHARMA CHECK® uses several information sources to determine possible drug interactions. Because each source has its own classification system, it can display a multitude of various alerts, where each is assigned an ID PHARMA CHECK® three-level, color-coded risk grade and an optional free text comment. The underlying information sources are: (i) hospINDEX drug interaction database, which assigns interactions to one of six categories, including risk assessment and management recommendations; (ii) ID MACS® medical semantic network, which comprises two main mechanisms for drug interaction detection–a *database* that contains interactions between certain drug groups and assigns them to one of three risk categories, and an *algorithm* that automatically detects interactions between cytochrome P450 (CYP) inhibitors or inducers and substrates, as well as QTc-prolonging drugs. Interactions are assigned to one of three color-coded risk categories, depending on the type of interaction and the number of simultaneously interacting substances. In order to compare the ID PHARMA CHECK® output with the one from MediQ, ID PHARMA CHECK® warnings were grouped according to their color codes. The classification systems of ID PHARMA CHECK® and the definition of 'major' interactions for the comparative purposes of this study are presented in Table 1.

2.4 ZHIAS Reclassification of Interactions Identified by CDSS

We selected the following interactions for ZHIAS reclassification: all interactions that were identified by either MediQ or ID PHARMA CHECK® and had received the highest rating of the respective programmes ('major'), the top 25 most frequent alerts identified by each programme,

Table 1 Classification of drug interactions by the clinical decision support software solutions MediQ and ID PHARMA CHECK®, and our definition of 'major' interactions that were selected for ZHIAS reclassification in the current study

CDSS	Classification of interactions
MediQ	**3 = 'strong', high danger of ADRs**
	2 = 'clinically relevant', average danger of ADRs
	1 = 'relevant in exceptional cases', low danger of ADRs
	0 = 'no interaction' or favourable combination
ID PHARMA CHECK®	
hospINDEX database (originally features six risk and management categories)	**Red = 'likely to or can cause serious consequences'**
	Orange = 'monitoring or dose adjustment may be required'
	Yellow = 'monitoring advised'
	Blue = 'usually no action required'
ID MACS database	**Red = 'absolute contraindication', 'contraindication'**
	Orange = 'relative/conditional contraindication'
	Yellow = 'use with caution'
ID MACS algorithm for interactions via CYP450 enzymes and QTc prolongations	**Red = 'substantially increased risk'**
	Orange = 'increased risk'
	Yellow = 'slightly increased risk'

Bold text indicates 'major' interactions

ADRs adverse drug reactions, *CDSS* Clinical Decision Support Software, *CYP450* cytochrome P450

and all interacting drug pairs that were simultaneously identified by MediQ, hospINDEX and each of the two ID MACS components ($n = 166$). Altogether this accounted for 648 unique interacting pairs. In addition, another 819 interactions detected in this patient dataset had previously been reclassified as part of our previous studies, and this information was also available for our analyses.

ZHIAS is a four-dimensional drug interaction classification system that was developed during the conduct of our previous studies [22–24]. ZHIAS is primarily based on the well-established and documented five-level grading according to the ORCA criteria [19, 31]. Briefly, ORCA's five operational levels are defined as follows: Grade 1 = 'contraindicated combination' (the risk associated with the drug interaction always outweighs the benefit); Grade 2 = 'provisionally contraindicated' (the combination should be avoided unless the interaction is desired or no alternative is available, monitoring may be necessary); Grade 3 = 'conditional risk' (monitoring or alternatives should be considered); Grade 4 = 'minimal risk' (no special action is needed, unless additional risk factors are present); Grade 5 = 'no interaction'. The other three major dimensions of ZHIAS use dichotomous variables that relate to patient management, interaction mechanisms and expected adverse effects (see also Sect. 3; Table 4). An expert panel consisting of clinical pharmacologists, pharmacists, neurologists and psychiatrists discussed the ZHIAS classifications of identified interactions until common agreement was achieved. For our assessments we referred to original and secondary literature, including but not limited to Hansten and Horn's *Drug Interactions: Analysis and Management* [31], *Stockley's Drug Interactions* [32], and the list of QTc-prolonging drugs maintained by the Arizona Center for Education and Research on Therapeutics (AzCERT) [33].

2.5 Data Analysis

Data analysis was primarily descriptive with presentation of results in text, tables and figures, and calculation of medians, means and proportions as appropriate. Correlation of drug interaction grading systems was assessed using Spearman's non-parametric rank correlation coefficient. The positive predictive value for a unique major interaction identified in the given population by a CDSS was calculated as the proportion of interactions classified as ORCA level 1 or 2 among all unique major interactions detected by the respective CDSS. Data management and analyses were performed with STATA Version 11.2 for MacOS X (Stata Corporation, College Station, TX, USA) and SPSS Version 19 for Windows (SPSS, Inc., Chicago, IL, USA).

3 Results

Demographics, medical diagnoses and pharmacotherapy of the study population have been described in detail in our previous study [24]. Median age of the patients was 51 years (range 9–108), nearly 55 % were female, and schizophrenia (34.3 %) and mood (affective) disorders (30.5 %) were the leading primary diagnoses. Antipsychotics and antidepressants were the most frequently prescribed drug classes, followed by cardiovascular agents and sedatives/anxiolytics. Patients had a mean of 3.9 concomitant drugs (median = 3); 5 % of all patients had concomitant prescriptions for nine or more substances.

3.1 Identification and Classification of Drug Interactions by CDSS

An overview of the interaction alerts generated by MediQ and ID PHARMA CHECK® is presented in Table 2. MediQ generated a total of 270,617 drug interaction warnings that affected 63,454 patients, excluding additional comments. Only 2,305 interactions in 2,156 patients (2.5 %) were classified as 'high danger'. ID PHARMA CHECK® issued fewer alerts, i.e. 157,489 affecting 48,302 patients, but a 2-fold higher proportion of patients (5,842 interactions in 4,235 patients; 5.0 %) had combinations classified as 'red'.

Identification of *unique* interacting drug pairs in the study population and their overlap between MediQ and ID PHARMA CHECK® are presented in Fig. 1. Altogether both CDSS issued alerts relating to 9,379 unique interacting drug combinations, MediQ identified 6,133 unique interactions, and ID PHARMA CHECK® identified 5,400 unique interactions. Only 2,154 (23.0 %) of these were identified by both programmes. Among the 5,400 unique combinations identified by ID PHARMA CHECK®, quantitative contributions from its underlying sources HospINDEX (3,310 combinations) and ID MACS (3,169 combinations) were similar and showed only a moderate overlap (1,079; 20.0 %). Further analysis of the 3,169 interactions contributed by ID MACS showed that its database component had identified 1,370 unique interacting pairs, of which 370 overlapped with hospINDEX and 342 pairs were labelled 'red' (contraindicated). The ID MACS algorithm component, responsible for detection of CYP450-mediated interactions and combinations of QTc-prolonging drugs, identified another 2,350 potentially interacting combinations (756 overlapping with other sources within ID PHARMA CHECK®): 1,217 were combinations of inhibitors or inducers and substrates of various CYP450 enzymes, 968 of QTc-prolonging drugs and another 165 involved both of those mechanisms.

Table 2 Overview of the output of the drug interaction analyses by MediQ and ID PHARMA CHECK®

CDSS	Risk category	Total alerts (n)	Patients affected [n (%)]	Alerts per patient	
				Mean	Max
MediQ	High to low	270,617	63,454 (75.0)	3.20	52
	High to average	73,308	37,752 (44.6)	0.87	19
	High only	2,305	2,156 (2.5)	0.03	4
ID PHARMA CHECK®	Red to yellow	157,489	48,302 (57.1)	1.86	29
	Red to orange	86,242	38,292 (45.2)	1.02	20
	Red only	5,842	4,235 (5.0)	0.07	9

CDSS clinical decision support software

Stratification of unique interacting drug pairs reported by hospINDEX and MediQ over the identifying source and severity grades assigned by each source is presented in Table 3. Looking at 'major' interactions, MediQ classified 198 out of 6,133 (3.2 %) interactions as 'high danger' and hospINDEX classified 210 out of 3,310 (6.3 %) as 'likely to or can cause serious consequences'. Overall, we observed only a moderate correlation of severity grading between MediQ and hospINDEX for those 1,559 interactions that were identified by both sources (Spearman's rank correlation coefficient $r = -0.43$, $p < 0.001$; negative r is due to the inverse grading conventions). However, the proportion of interactions missed by either hospINDEX or MediQ steadily decreased with increasing severity grades, i.e. from 94.1 to 30.1 % for hospINDEX, and from 83.7 to 25.3 % for MediQ. In other words, the probability that *both* sources identified an interaction was higher if either programme had classified the interaction to a higher severity grade. Nevertheless, even for 'major' interactions the overlap was far from complete, i.e. only 72 interactions received a 'major' rating from MediQ *and* hospINDEX.

3.2 ZHIAS Reclassification of Interactions

An analysis of all reclassified interactions showed that the ORCA classification, used as the core component of ZHIAS and a 'silver standard' in this study, correlated more closely with MediQ danger rating than with hospINDEX rating ($|r| = 0.72$ vs. 0.41, $p < 0.001$). Correlation between ORCA classification and ID MACS database was even lower

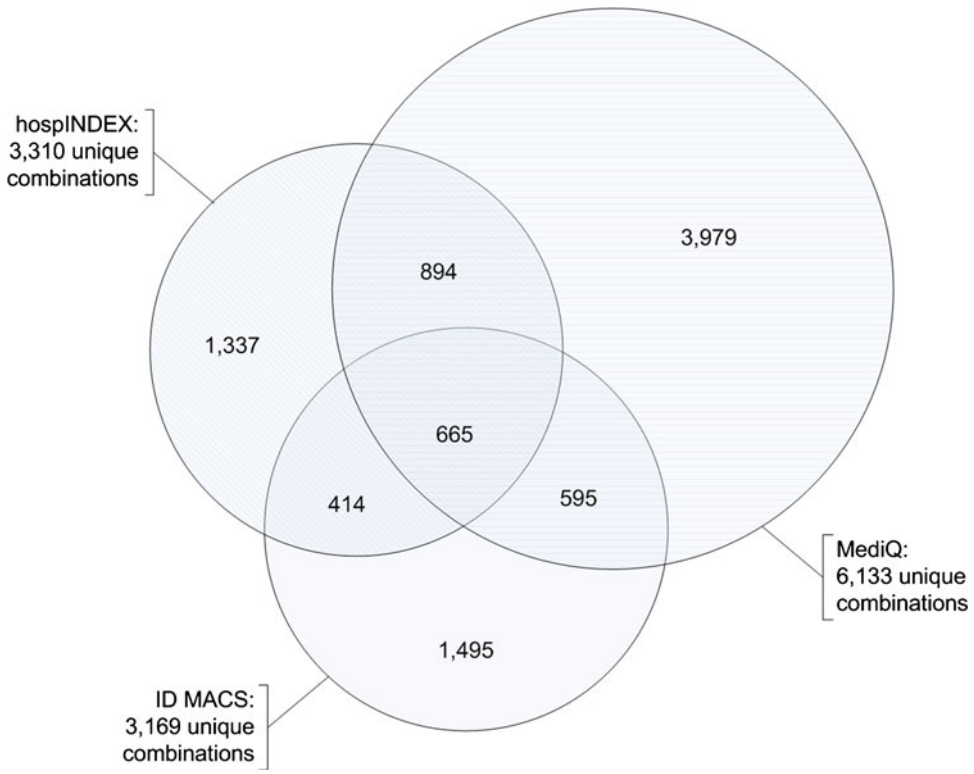

Fig. 1 Overlap between unique combinations identified by MediQ and either of the two major ID PHARMA CHECK® information sources

Table 3 Simultaneous stratification of unique interacting drug pairs reported by hospINDEX and MediQ over the identifying source and severity grades assigned by each source

MediQ alerts	hospINDEX alerts					
	In MediQ				Not in MediQ [n (%)]	Total
	High danger	Average danger	Low danger	Total		
In hospINDEX						
Interaction likely to cause serious consequences	30	19	2	*51*	22 (30.1)	*73*
Interaction can cause serious consequences	42	28	9	*79*	58 (42.3)	*137*
Monitoring or dose adjustment required	72	512	266	*850*	860 (50.3)	*1,710*
Monitoring or dose adjustment may be required	0	49	56	*105*	107 (50.5)	*212*
Monitoring advised	4	162	305	*471*	656 (58.2)	*1,127*
Usually no special precautions required	0	0	3	*3*	48 (94.1)	*51*
Total	*148*	*770*	*641*	*1,559*	*1,751 (53.0)*	*3,310*
Not in hospINDEX [n (%)]	50 *(25.3)*	1,239 *(61.7)*	3,285 *(83.7)*	*4,574 (74.6)*		
Total	198	2,009	3,926	6,133		

(r = 0.163). Accordingly, also the positive predictive value for unique major alerts to be (provisionally) contraindicated according to ORCA was higher for MediQ (0.63) than for either of the two ID PHARMA CHECK® components (0.42 for hospINDEX and 0.30 for ID MACS). This means that compared with ID PHARMA CHECK® a unique 'major' risk alert from MediQ was more likely to be contraindicated or provisionally contraindicated according to ORCA.

ZHIAS reclassification of all 'major' *unique* interactions reported by MediQ and ID PHARMA CHECK® is presented in Table 4. Also for this subset of 'major' alerts only, MediQ rating displayed a closer correlation with ORCA, i.e. we assigned a higher proportion of 'major' alerts from MediQ than from ID PHARMA CHECK® to ORCA classes 1 or 2 (62.7 % for MediQ vs. 42.4 % for hospINDEX and 29.8 % for ID MACS). The presented additional ZHIAS components provide further information on management, mechanisms and expected possible adverse events of those interactions. In most cases, a therapeutic alternative with a lower risk may be available, and/or intense monitoring may be an acceptable option. Pharmacodynamic mechanisms of interaction were more frequent than pharmacokinetic mechanisms, and sometimes both contributed simultaneously to an interaction. Depending on the identifying source, between 38.9 and 60.2 % of interactions caused increased drugs effects. MediQ as well as both sources of ID PHARMA CHECK® indicate that arrhythmias, mostly related to QTc prolongations, are the single most frequent expected ADRs: within the studied population, 3,908 patients (4.6 %) had an interacting prescription with an elevated risk of arrhythmia rated as ORCA 1 ($n = 52$) or 2 ($n = 3{,}856$).

Among 38 warnings classified as 'major' by MediQ, hospINDEX and ID MACS, one combination was 'contraindicated' according to ORCA, i.e. amiodarone and domperidone, affecting one patient. Twenty-eight were provisionally contraindicated after reclassification; of those, 15 were combinations of monoamine oxidase (MAO) inhibitors with serotonergic agents or carbamazepine, and 13 combinations of QTc-prolonging antipsychotics with other QTc-prolonging agents. The remaining nine combinations had a conditional risk according to ORCA.

Among all drug interactions detected by MediQ and/or ID PHARMA CHECK®, and subsequently reclassified according to ZHIAS, 58 individual drug pairs were classified as contraindicated (ORCA 1), and 193 as provisionally contraindicated (ORCA 2). Tables 5 and 6 present the top 15 most frequently occurring interactions in the study population for each of these categories, respectively. Contraindicated combinations not identified by ID PHARMA CHECK® included those of mefenamic acid with ibuprofen or diclofenac, and that of lithium with rofecoxib. The first is a combination of two NSAIDs, i.e. a therapeutic duplication, and was found in 13 patients. The second was found in eight patients; rofecoxib has meanwhile been withdrawn from the market because of its unfavourable cardiovascular safety profile. In turn, MediQ did not report the therapeutic duplication of celecoxib with ibuprofen, and the QTc-prolonging combination of fluvoxamine with thioridazone. Regarding provisionally contraindicated combinations not in ID PHARMA CHECK®, the most prominent is the concomitant administration of two different benzodiazepines (11 unique pairs, found in 1,315 patients). This is followed by the combination of olanzapine with carbamazepine that was prescribed to 550 patients. Of note, in those two cases, as well as in the most frequent ORCA 1 combination (ginkgo biloba with antithrombotics or aspirin), ORCA classification

Table 4 Results of the reclassification of all highest-ranked ('major') *unique* interactions identified by MediQ and each ID PHARMA CHECK® source according to ZHIAS

Reclassification	MediQ (high danger) [n (%)]	hospINDEX (serious consequences likely/possible) [n (%)]	ID MACS (contraindication, substantially increased risk) [n (%)]
Total unique combinations	*198 (100.0)*	*210 (100.0)*	*309 (100.0)*
ORCA level			
1: Contraindicated	32 (16.2)	18 (8.6)	12 (3.9)
2: Provisionally contraindicated	92 (46.5)	71 (33.8)	80 (25.9)
3: Conditional risk	70 (35.4)	105 (50.0)	173 (56.0)
4: Minimal risk	4 (2.0)	16 (7.6)	44 (14.2)
Management			
Desired, risk-benefit ok	38 (19.2)	34 (16.2)	93 (30.1)
Alternative available	155 (78.3)	136 (64.8)	136 (44.0)
Monitoring recommended	159 (80.3)	175 (83.3)	262 (84.8)
Mechanism of interaction[a]			
Pharmacokinetic	87 (43.9)	83 (39.5)	93 (30.1)
Pharmacodynamic	149 (75.3)	161 (76.7)	272 (88.0)
Expected adverse effects associated with the interaction[b]			
Drug effect increased	77 (38.9)	113 (53.8)	186 (60.2)
Drug effect decreased	21 (10.6)	29 (13.8)	18 (5.8)
CNS—sedation, respiratory depression	17 (8.6)	36 (17.1)	80 (25.9)
CNS—serotonin syndrome	42 (21.2)	38 (18.1)	53 (17.2)
CNS—extrapyramidal syndrome	8 (4.0)	21 (10.0)	21 (7.1)
CNS—seizures	11 (5.6)	12 (5.7)	5 (1.6)
CNS—other	38 (19.2)	32 (15.2)	70 (22.7)
Nephrotoxicity	1 (0.5)	0 (0.0)	1 (0.3)
Hepatotoxicity	1 (0.5)	0 (0.0)	0 (0.0)
QTc prolongation/Torsade de pointes	97 (49.0)	88 (41.9)	159 (51.5)
Arrhythmia	103 (52.0)	113 (53.8)	169 (54.7)
Thrombosis	1 (0.5)	9 (4.3)	0 (0.0)
Bleeding	0 (0.0)	3 (1.4)	2 (0.6)
Hypertension	17 (8.6)	14 (6.7)	25 (8.1)
Hypotension	18 (9.1)	38 (18.1)	33 (10.7)
Other cardiovascular effects	1 (0.5)	2 (1.0)	5 (1.6)
Hyperkalaemia	9 (4.5)	2 (1.0)	0 (0.0)
Hypokalaemia, hyponatremia	5 (2.5)	2 (1.0)	3 (1.0)
Metabolic and endocrine effects	3 (1.5)	5 (2.4)	13 (4.3)
Gastrointestinal toxicity	1 (0.5)	0 (0.0)	0 (0.0)
Blood glucose up	2 (1.0)	0 (0.0)	0 (0.0)
Blood glucose down	1 (0.5)	0 (0.0)	0 (0.0)
Muscle toxicity	3 (1.5)	2 (1.0)	2 (0.7)
Bone marrow toxicity	3 (1.5)	7 (3.4)	11 (3.6)
Other	10 (5.1)	7 (3.4)	11 (3.6)

ORCA Operational Classification of Drug Interactions

[a] Pharmacokinetic and pharmacodynamic mechanisms can be involved concomitantly; combined total may therefore exceed 100 %

[b] Categories are not mutually exclusive and may therefore overlap

is not necessarily driven by a high resulting risk, but rather by the consideration that these combinations are unjustified due to a lack of (additional) efficacy. Nevertheless, in the case of benzodiazepines, different pharmacokinetic properties may sometimes justify their concomitant administration.

4 Discussion

The current study evaluated the performance of two CDSS using cross-sectional prescription data of psychiatric inpatients. Other previous studies also compared drug interactions and their classification between various compendia

Table 5 The 15 most frequent ORCA level 1 (contraindicated) combinations

Drug combination	Frequency in 84,625 patients [n (%)]	Danger rating			Expected adverse effects
		MediQ	hosp-INDEX	ID MACS	
Ginkgo biloba and antithrombotics or aspirin (acetylsalicylic acid)	102 (0.12)	Average	Monitoring/DA required	–	Bleeding
Cisapride—tricyclic antidepressants	17 (0.02)	High	–	*	QTc prolongation
Mefenamic acid—ibuprofen, diclofenac	13 (0.02)	Average	–	–	GI bleeding
Celecoxib—ibuprofen	9 (0.01)	–	–	Caution	GI bleeding
Rofecoxib—lithium	8 (0.01)	High	–	–	Lithium intoxication
Amiodarone—digoxin	7 (0.01)	High	Monitoring/DA required	–	Arrhythmia, digoxin toxicity
Carbamazepine—clarithromycin	7 (0.01)	High	May cause SC	*	Carbamazepine toxicity
Carbamazepine—midazolam	7 (0.01)	High	Monitoring/DA required	*	Loss of midazolam efficacy
Fluvoxamine—thioridazine	7 (0.01)	–	Likely to cause SC	AC[a]	QTc prolongation
Atazanavir—pantoprazole	6 (0.01)	Average	Likely to cause SC	–	Loss of antiviral activity
Fenoterol, salmeterol—non-selective β-blockers	6 (0.01)	High	Monitoring/DA required	–	Bronchospasm
Fentanyl—tramadol	5 (0.01)	Average	–	–	Serotonin syndrome, seizures
Haloperidol—erythromycin	5 (0.01)	High	Monitoring/DA required	RC[a]	EPS, QTc prolongation
Levodopa—tiapride	5 (0.01)	High	May cause SC	–	Loss of levodopa efficacy
Sibutramine—SSRI, other serotonergic drugs	5 (0.01)	Varies	Likely to cause SC	–	Serotonin syndrome

N-dash indicates not identified by software, asterisk indicates identified by software (without further danger rating)

AC absolute contraindication, *DA* dose adjustment, *EPS* extrapyramidal symptoms, *GI* gastrointestinal, *ORCA* Operational Classification of Drug Interactions, *RC* relative contraindication, *SC* serious consequences, *SSRI* selective serotonin reuptake inhibitor

[a] Combination was also automatically flagged as an interaction between cytochrome CPY450 inducer/inhibitor and substrate or a concomitant administration of two QTc-prolonging substances

and CDSS [10–12, 18, 20, 34–39]. However, few studies used real-life prescription data for this purpose and therefore also considered the prevalence of potentially interacting prescriptions in the target population [13, 25]. This approach provides a different and more realistic picture of CDSS performance in clinical practice. Furthermore, the high efficiency of the applied automated mass analyses, first presented in our previous study in the same population and now extended to another CDSS [24], enables us to conduct such studies in very large populations.

MediQ generated 1.7-fold more warnings for the studied population than ID PHARMA CHECK®. This may indicate higher sensitivity, but high sensitivity for low-risk interactions also implies excessive alert burden that undermines the acceptance and therefore efficacy of CDSS in clinical practice [14, 17]. ID PHARMA CHECK® generated 2.5-fold more 'major' interaction alerts than MediQ. At first glance this suggests high sensitivity, particularly for high-risk interactions. However, MediQ showed better correlation with ORCA severity ranking, and after ZHIAS reclassification the number of identified interactions classified as ORCA 1 or 2 was similar for both programmes. In a previous study with a much smaller population we were able to reclassify all identified interactions according to ZHIAS and were therefore able to formally calculate comparative sensitivity and positive predictive value against ZHIAS as a 'silver standard' [25]. In this study, MediQ had a higher sensitivity to detect interactions classified as ORCA 1 or 2, but because the number of low-risk alerts was also higher, the positive predictive value with regard to presumably relevant ORCA class 1 or 2 interactions was similar between both programmes. In contrast, the current study calculated the positive predictive value for major alerts only, and this was now higher for MediQ. Overall it appears that both programmes are able to effectively identify high-risk interactions at the price of a very high alert burden.

The low overlap of identified interactions between the two programmes is remarkable and unexpected, although it concerns mainly low-risk interactions of questionable relevance in clinical practice. In order to reduce the alert burden, one may select the display of high-risk interactions only. However, we found only a moderate correlation between different risk classifications. Previous studies that compared different interaction classification systems also reported significant disagreements in the inclusion and severity rating of interactions [12, 18, 20], and none of the currently available classifications can be considered as a gold standard. ORCA may be one of the most management-oriented and widely accepted classifications and was

Table 6 The 15 most frequent ORCA level 2 (provisionally contraindicated) combinations

Drug combination	Frequency in 84,625 patients [n (%)]	Danger rating			Expected adverse effects
		MediQ	hosp-INDEX	ID MACS	
Any two benzodiazepines	1,315 (1.55)	Average	–	–	Sedation
Haloperidol—clozapine	822 (0.97)	Average	–	RC[a]	QTc prolongation, sedation
Haloperidol—olanzapine	687 (0.81)	Average	–	RC[a]	QTc prolongation, metabolic, CNS
Haloperidol—carbamazepine	650 (0.77)	Average	Monitoring advised	[a]	Loss of haloperidol efficacy
Haloperidol—levomepromazine	624 (0.74)	Average	–	Caution	EPS, QTc prolongation
Carbamazepine—olanzapine	550 (0.65)	Average	–	–	Loss of olanzapine efficacy, metabolic
Carbamazepine—risperidone	500 (0.59)	Average	Monitoring advised	–	Loss of risperidone efficacy, other CNS
Clozapine—fluvoxamine	402 (0.48)	High	Monitoring/DA required	[a]	Bone marrow toxicity
Haloperidol—tricyclic antidepressants	232 (0.27)	Average	Monitoring/DA required	RC[a]	QTc prolongation, seizures
MAO inhibitors—tricyclic antidepressants	212 (0.25)	High[b]	Monitoring/DA required	AC	Serotonin syndrome
Lithium—hydrochlorothiazide	190 (0.22)	High	Monitoring/DA required	–	Lithium intoxication
Carbamazepine—clozapine	183 (0.22)	Average	Likely to cause SC	AC[a]	Agranulocytosis
Clozapine—olanzapine	177 (0.21)	High	–	[a]	QTc prolongation, metabolic
Clozapine—quetiapine	168 (0.20)	Average	–	[a]	QTc, bone marrow toxicity, hypotension, sedation

En-dash indicates not identified by software

AC absolute contraindication, *DA* dose adjustment, *EPS* extrapyramidal symptoms, *GI* gastrointestinal, *MAO* monoamine oxidase, *ORCA* Operational Classification of Drug Interactions, *RC* relative contraindication, *SC* serious consequences, *SSRI* selective serotonin reuptake inhibitor

[a] Combination was also automatically flagged as an interaction between CYP inducer/inhibitor and substrate or a concomitant administration of two QTc-prolonging substances

[b] Some combinations were missing from MediQ

therefore used as a 'silver standard' in this study, being the major component of ZHIAS, but is also subject to inter-rater variability. Indeed, there were also some discrepancies with our assessments vs. those, for example, from Hansten and Horn's ORCA classifications [24, 31]. Reasons for disagreements include the weighting of therapeutic alternatives and risks vs. benefits, patient-specific factors that play an important but difficult to standardize role for the risk of a potential interaction in individual patients, and risks due to interactions between more than two interacting drugs, e.g. 'triple interactions'.

Considering such multiple interactions, ID PHARMA CHECK®'s ID MACS algorithm aims to reduce the number of alerts and better quantify risks through recognition of multiple combinations when more than two concomitant drugs are substrates of the same enzyme or are associated with QTc interval prolongation. Instead of issuing several low danger warnings liable to be ignored, ID PHARMA CHECK® produces one high-risk alert that is more likely to catch the prescriber's attention. Indeed, the majority of interactions that received top ratings from MediQ, hosp-INDEX and ID MACS were combinations of MAO inhibitors with selective serotonin reuptake inhibitors or other serotonergic agents, and concomitant use of QTc-prolonging antipsychotics with other QTc-prolonging agents, and these also frequently occur as triple interactions in our real-life prescription data. The extended classification of interaction mechanisms and expected adverse effects used in ZHIAS has the potential to take the concept of multiple risk factors in individual patients even further through integration with other patient-specific information: for example, a combination with hypotension as a possible adverse effect might be assigned a higher priority if this symptom is already present in a given patient.

ID PHARMA CHECK®, optimized for integration into clinical information systems, may also analyse prescription

data together with the information about a patient's diagnoses and other clinical information, and therefore direct a prescriber's attention towards symptoms that are a possible ADR resulting from an interaction. This can support the identification of ADRs as such. In addition, ID PHARMA CHECK® issues alerts relating to single substances and duplicate medications. One should note that those extra features of ID PHARMA CHECK® are not reflected in our comparative quantitative analyses, but may be of additional benefit if ID PHARMA CHECK® is fully integrated into a hospital's clinical information system.

Beyond a comparison of different CDSS, the innovative use of CDSS for mass analyses of real-life pharmacotherapy can also make important contributions to local quality management. Our study demonstrates that CDSS can efficiently identify the most problematic and most frequently occurring interacting prescriptions in a population. This information can subsequently be used for locally customized preventive measures, and an evaluation of the subsequent impact of interventions on prescribing behaviour. For example, both CDSS identified arrhythmias as the single most frequent expected ADRs associated with interactions in this population of psychiatric patients. This potentially lethal risk as well as the frequently identified therapeutic duplications should urge clinicians to be vigilant and avoid such combinations if possible or implement monitoring as appropriate.

Finally, we must also consider some limitations of our study. First, we cannot exclude that some interactions remained undetected even by both CDSS, and we were therefore not able to calculate the true sensitivity and specificity of the CDSS regarding their identification of drug interactions. We cannot formally quantify this limitation but only assume that the very large number of drug interactions identified by both programmes, many of which were not even mentioned in standard full-size reference textbooks, and the increasing overlap in detection with higher severity, makes it unlikely that we missed a high number of high-risk interactions.

Second, the large number of 9,379 identified unique interactions precluded their complete reclassification. It is therefore possible that we missed some interactions that we would have classified into a clinically relevant ORCA risk class. However, we also reclassified those interactions with the highest prevalence in the study population and used classifications from previous studies; our previous smaller studies where we reclassified all interactions identified by CDSS demonstrated that we would miss only a negligible proportion of combinations classified as ORCA 1 or 2 with the approach taken in the current study [22, 23, 25].

Third, because ID MACS is not designed as a standalone source of drug interaction knowledge but rather as a supplement to the information provided by hospINDEX, a direct comparison of drug interaction detection and classification was carried out only between hospINDEX as part of ID PHARMA CHECK® and MediQ, or full ID PHARMA CHECK® output and MediQ, but not with ID MACS separately. Another reason for this is that the severity rating of some ID MACS alerts considers more than two simultaneously interacting substances, whereas a comparison with MediQ must be limited to an analysis of drug pairs.

Finally, one must also keep in mind that the databases of the studied CDSS are constantly updated.

5 Conclusions

MediQ and ID PHARMA CHECK® show major differences in their performance regarding identification and grading of interactions, as well as presentation of their results. MediQ reported more interactions, and ID PHARMA CHECK® tended to classify interactions into a higher risk class, but overall both programmes identified a similar number of interactions classified as high risk according to ORCA criteria. The applicability in clinical routine is limited by an overwhelming alert burden on the prescriber for both programmes. Therefore, the prediction of clinical relevance remains a major challenge, which even improved classifications and integration of additional patient-specific information into an alert algorithm will not be able to fully resolve. Consequently, prescribers may only accept the use of either system for the identification of drug interactions if these are offered as an on-demand option for screening purposes. Therefore, additional development of small subsets of alerts suitable for automated display in clinical routine has recently been proposed, and these can also be co-implemented in CDSS that are integrated into clinical information systems with electronic prescription [13, 40]. Last but not least, our study also demonstrated that CDSS could also be used for mass-analysis of prescription data and thereby play an important role in comprehensive local drug safety and quality management concepts.

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