SHORT COMMUNICATION

Using INTERCheck® to Evaluate the Incidence of Adverse Events and Drug–Drug Interactions in Out- and Inpatients Exposed to Polypharmacy

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Abstract

Background Polypharmacy exposes patients with comorbidities (particularly elderly patients) to an increased risk of drug-specific adverse events and drug–drug interactions. These adverse events could be avoided with the use of a computerized prescription support system in the primary care setting. The INTERCheck® software is a prescription support system developed with the aim of balancing the risks and benefits of polytherapy and examining drug–drug interactions.

Objectives This observational study used the INTERCheck® software to evaluate the incidence of adverse events and of drug–drug interactions in outpatients and inpatients receiving multiple medications.

Methods Patients were randomly enrolled from the outpatient department ($n = 98$) and internal medicine ward ($n = 46$) of S. Andrea Hospital of Rome. Polypharmacological treatment was analyzed using INTERCheck® software, and the prevalence of risk indicators and adverse events was compared between the two groups.

Results Polypharmacy (use of five or more drugs) applied to all except three cases among outpatients and one case among inpatients. A significant positive correlation was found between the number of medications and the INTERCheck® score ($\rho = 0.67$; $p < 0.000001$), and a significant negative correlation was found between the drug-related anticholinergic burden and cognitive impairment ($r = -0.30$ $p = 0.01$). Based on the INTERCheck® analysis, inpatients had a higher score for class D (contraindicated drug combination should be avoided) than did outpatients ($p = 0.01$). The potential class D drug–drug interactions were associated with adverse events that caused hospitalization ($\chi^2 = 7.428$, $p = 0.01$).

Conclusions INTERCheck® analysis indicated that inpatients had a high risk of drug–drug interactions and a high percentage of related adverse drug events. Further prospective studies are necessary to evaluate whether the INTERCheck® software may help reduce polypharmacy-related adverse events when used in a primary care setting and thus potentially avoid related hospitalization and severe complications such as physical and cognitive decline.

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Key Points

INTERCheck® provides a score of the risk of potential drug interactions or inappropriate medications, helping physicians to avoid related adverse drug events.

Inpatients with severe adverse drug events had a higher total number of drug–drug interactions, with more than one contraindication in a drug combination and a higher anticholinergic burden.

1 Introduction

Polypharmacy is increasing among patients with comorbidities [1], with a significant risk of inappropriate medication, drug-specific adverse events and potential drug–drug interactions (pDDIs) [2–4]. The multiple negative outcomes of polypharmacy include cognitive impairment/delirium, weight loss and malnutrition, falls with hip fractures, urinary incontinence, functional impairment and reduced mobility, hospitalization, reduced quality of life, death and increased costs for the health system [5, 6]. Computerized prescription support systems (CPSS) may help to prevent inappropriate medication, minimizing the occurrence of adverse drug events (ADEs) and subsequent negative outcomes [7].

To minimize pDDIs and assist clinicians with information readily available at the time of prescription, the CPSS INTERCheck® was developed by the Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) Istituto di Ricerche Mario Negri of Milan and has been associated with a significant reduction in potentially inappropriate medication in patients with comorbidities and polypharmacy [8, 9].

The aim of this observational study was to use the INTERCheck® software to evaluate the incidence of adverse events and of drug–drug interactions in outpatients and inpatients receiving multiple medications.

2 Methods

2.1 Study Population, Study Design and Data Sources

This observational study was performed in the Internal Medicine Unit of S. Andrea Hospital of Rome, from January 2017 to September 2018. We enrolled (as an unselected sample of patients consecutively admitted) 144 patients: 98 from the outpatient department and 46 from the internal medicine ward. All ADEs presented by the patients were collected.

We hypothesized a sequence of steps leading to ADEs: $1 \rightarrow 2 \rightarrow 3 \rightarrow 4$, in which 1 = polypathology, 2 = polypharmacy (five or more drugs), 3 = risk of adverse events for drug–drug interactions (identified by INTERCheck® analysis) and 4 = development of the specific adverse event with minor or more severe outcome (e.g., hospitalization).

2.2 Assessments

After providing informed consent, every subject underwent a multidimensional assessment, including the Cumulative Illness Rating Scale, Charlson Comorbidity Index and Elixhauser Index; cognitive function was evaluated using the Mini-Mental State Examination (MMSE) [10–13]. The clinical evaluation included anthropometric measurements (body mass index and metabolic syndrome using Adult Treatment Panel III criteria), hemodynamic parameters (systolic and diastolic blood pressure, heart rate, electrocardiography with QTc interval measurements), blood chemistry tests with complete blood count, sodium, potassium, creatinine with estimation of glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation, albumin, glycaemia, vitamin D, pharmacological history (drug number and dosage), the Anticholinergic Cognitive Burden (ACB) scale (2012 update) [14, 15] and drug–drug interaction risk analyzed using the INTERCheck® software (http://www.intercheckweb.it) [7]. The information provided by INTERCheck® includes drug interactions (database of interactions created and updated by the Mario Negri IRCCS Institute for Pharmacological Research); potentially inappropriate drugs in the elderly according to criteria from the scientific literature such as Beers and START (Screening Tool to Alert to Right Treatment)/STOPP (Screening Tool of Older Persons' Prescriptions); evaluation of the anticholinergic load (ACB scale); GerontoNet adverse drug reaction risk score algorithm (for identifying patients at greater risk of unwanted drug effects). In particular, the INTERCheck® software describes the interactions between drugs according to their clinical relevance as "class A" (minor, no known clinical relevance), "class B" (moderate, interaction associated with an uncertain or variable event), "class C" (major, interaction associated with a serious event, but which can be managed, e.g., by reducing the dose) and "class D" (contraindicated or very serious, interaction associated with a serious event for which it is appropriate to avoid coadministration or to establish careful monitoring) [16]. The total INTERCheck® score was considered as the sum of all obtained interactions. For example, in a single patient, INTERCheck® may find the following interactions: $n = 0$ in class A, $n = 14$ in class B, $n = 4$ in class C and $n = 3$ in class D (total score = 21). The mean score in each class of

drug interactions was measured in the two groups of patients (inpatients and outpatients). Data about drug interactions and ACB scores are presented as mean ± standard deviation.

We assessed the presence of DDIs (class of risk evaluated with INTERCheck®) and ADEs at the time of enrollment in the outpatient department or hospital ward. The causality assessment was evaluated on the basis of the mechanisms of potential DDIs as indicated by the software. ADEs were classed as minor or severe (requiring hospitalization).

2.3 Statistical Analysis

The statistical analyses were performed using the one-way analysis of variance to compare data between two groups. Associations between two variables were assessed using the Chi-squared (χ^2) test and Spearman's rank correlation coefficient (rho [ρ]). A p value < 0.05 was considered statistically significant. Primer of Biostatistics Version 7 (McGraw-Hill, 2011) was used as statistical software.

3 Results

3.1 Clinical Features

Table 1 presents the clinical features of the outpatient and inpatient groups. Polypharmacy (five or more drugs) was recorded for 97% of outpatients (two subjects were taking four drugs and one subject was taking three drugs) and 98% of inpatients (subject was taking three drugs).

The INTERCheck® total score, class A, B, C, D, C + D and ACB scores of outpatients and inpatients (with or without ADEs) are reported in Fig. 1 and Table 2 (outpatients vs. total inpatients: class D $p = 0.01$, class C + D $p = 0.025$, ACB $p = 0.00001$).

None of the patients taking fewer than five drugs presented as class D in the INTERCheck® analysis.

3.2 Correlation Analysis

The correlation analysis revealed a significant positive correlation between number of medications and the total

Table 1 The clinical features of inpatients ($n = 98$) and outpatients ($n = 46$)

Characteristics	Inpatients	Outpatients	p value
Age (years)	81.6 ± 8.4	80.0 ± 6.6	
Females	58	71	
CIRS-SI	2.6 ± 0.7	2.4 ± 0.5	
CIRS-CI	7.0 ± 2.5	7.2 ± 2.3	
Charlson Comorbidity Index	4.4 ± 2.1	3.9 ± 1.8	
Elixhauser Index	5.5 ± 2.0	5.3 ± 1.8	
MMSE	19.4 ± 10.7	22.2 ± 5.3	
Drugs (N)	8.0 ± 2.7	8.6 ± 2.8	
BMI	25.9 ± 6.8	28.3 ± 5.6	
Metabolic syndrome (ATP-III) (%)	52	48	
SBP (mmHg)	126.1 ± 22.9	132.6 ± 19.8	0.01
DBP (mmHg)	69.9 + 13.0	77.1 + 11.2	0.001
HR (bpm)	80.3 + 18.5	76.5 + 12.5	
QTc (ms)	454.1 + 45.1	410.7 + 82.4	0.025
GFR by CKD-EPI (ml/min)	53.8 + 26.1	66.6 + 21.4	0.05
Albumin	48.7 + 5.0	56.0 + 4.8	< 0.000001
Hb (g/dl)	11.5 + 2.0	13.1 + 1.6	0.000001
Blood glucose (mg/dl)	144.2 + 106.4	104.2 + 26.5	0.001
Na (mmol/l)	137.3 + 6.7	141.2 + 3.5	0.00001
K (mmol/l)	4.1 + 0.8	4.5 + 0.4	0.001
Vitamin D (ng/ml)	14.8 + 10.3	26.7 + 12.6	0.00001
Polypharmacy	98	97	

Data are presented as mean ± standard deviation or percentage

ATP-III Adult Treatment Panel III (ATP-III criteria for metabolic syndrome), *BMI* body mass index, *CI* comorbidity index, *CIRS* Cumulative Illness Rating Scale, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration equation, *DBP* diastolic blood pressure, *GFR* glomerular filtration rate, *Hb* hemoglobin, *HR* heart rate, *MMSE* Mini-Mental State Examination, *QTc* corrected QT interval, *SBP* systolic blood pressure, *SI* severity index

Fig. 1 INTERCheck® scores (total and divided in risk classes A, B, C, D, C + D, ACB scale) in **a** outpatients (*n* = 98) and inpatients (*n* = 46) and **b** inpatients with (*n* = 21) and without (*n* = 25) severe ADEs. The software describes the interactions between drugs according to their clinical relevance from class A (minor, no known clinical relevance) to D (contraindicated, drug combination should be avoided). *ACB* anticholinergic cognitive burden. Data are presented as mean ± standard deviation

*p=0.025   **p=0.01   ***p=0.00001

*p=0.05   **p=0.025   ***p=0.01   ****p=0.001   *****p=0.00001
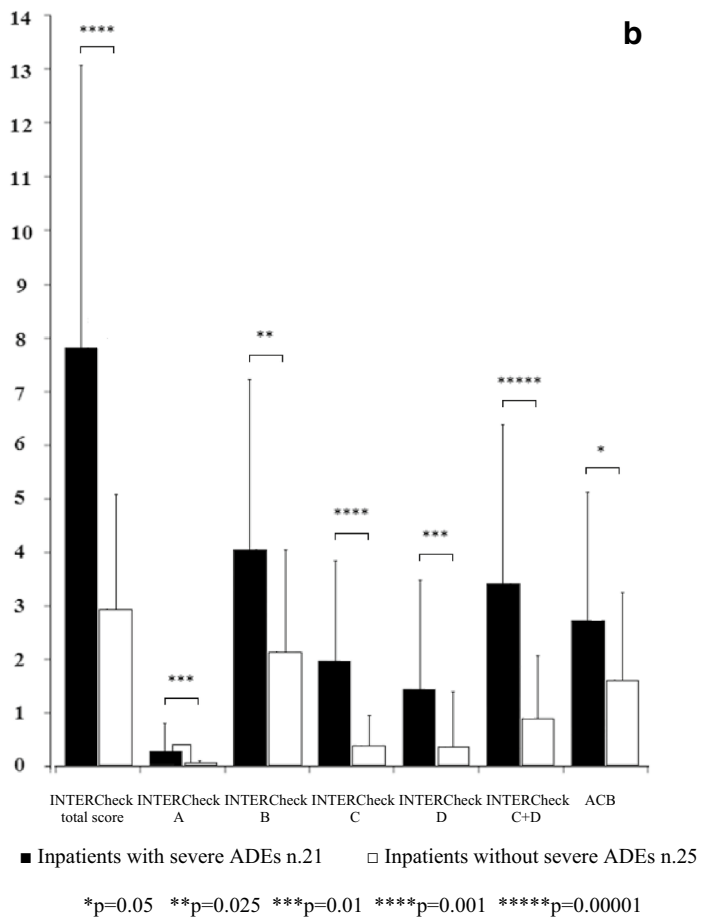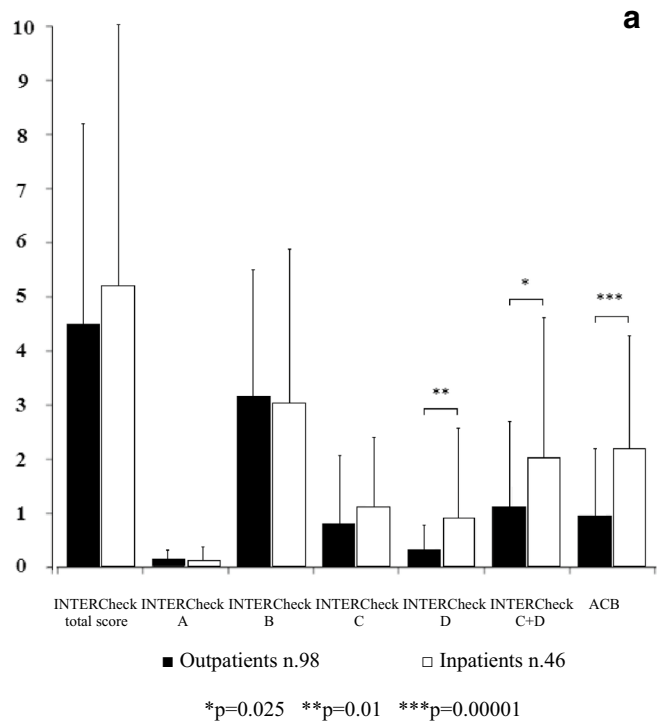
Table 2 INTERCheck® scores (total and divided in risk classes A, B, C, D, C+D, ACB) in outpatients ($n=98$) and inpatients ($n=46$) without ($n=25$) and with ($n=21$) severe ADEs

	Total score	Class					ACB
		A	B	C	D	C+D	
Outpatients	4.5±3.8	0.1±0.3	3.2±3.8	0.8±1.2	0.3±0.6	1.1±1.6	0.9±1.3
Inpatients	5.2±4.8	0.1±0.3	3.0±2.9	1.1±1.5	0.9±1.6	2.0±2.5	2.2±2.1
Inpatients without severe ADEs	2.9±2.6	0.0±0.0	2.2±2.0	0.4±0.6	0.4±0.9	0.8±1.4	1.6±1.7
Inpatients with severe ADEs	7.9±5.3	0.3±0.5	4.1±3.4	2.0±1.9	1.6±2.0	3.6±2.8	2.9±2.4

Outpatients vs. total inpatients class D $p=0.01$, class C+D $p=0.025$, ACB $p=0.00001$; inpatients with vs. without severe ADEs, INTERCheck® total score $p=0.001$, class A $p=0.01$, class B $p=0.025$, class C $p=0.001$, class D $p=0.01$, class C+D $p=0.00001$, ACB $p=0.05$; inpatients with severe ADEs vs. outpatients INTERCheck® total score $p=0.001$, class A $p=0.025$, class C $p=0.0001$, class D $p<0.000001$, class C+D $p<0.000001$, ACB $p<0.000001$. The INTERCheck® software describes the interactions between drugs according to their clinical relevance in class A (minor, no known clinical relevance), class B (moderate, interaction associated with an uncertain or variable event), class C (major, interaction associated with a serious event, but which can be managed, e.g., by reducing the dose), and class D (contraindicated or very serious interaction associated with a serious event for which it is appropriate to avoid coadministration or to establish careful monitoring). Data are presented as mean±standard deviation

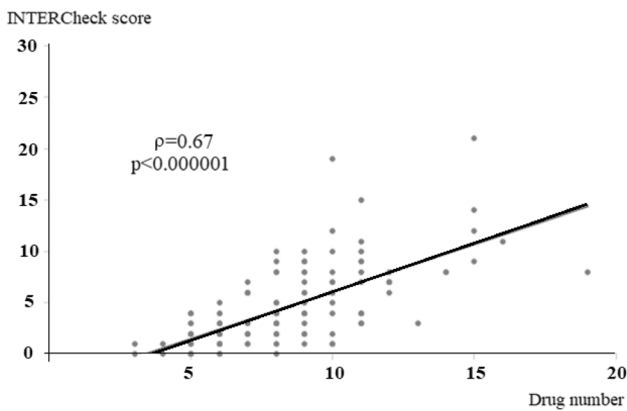*ACB* anticholinergic cognitive burden scale, *ADE* adverse drug event

Fig. 2 Spearman's rank correlation (rho, ρ) analysis between the number of drugs and the total INTERCheck® score

INTERCheck® score ($\rho=0.67$, $p<0.000001$) (Fig. 2) and a significant negative correlation between the anticholinergic burden according to ACB score and cognitive impairment evaluated with MMSE ($\rho=-0.30$ $p=0.01$) (Fig. 3).

3.3 Prevalence of Adverse Drug Events

A high risk (class D combined with any other class) was recorded for 41% of inpatients and 24% of outpatients, with inpatients having a significantly higher class D score ($p=0.01$) (Fig. 1a). ADEs were found in 45% ($\chi^2=7.428$, $n=21$) of inpatients (17/21 = 81% with DDIs of class D) and 11% ($n=11$) of outpatients ($\chi^2=6.732$, $p=0.001$) (Fig. 1b and Table 3). The ADEs in outpatients were all minor. For inpatients, the class D DDIs were associated with the adverse events that caused the
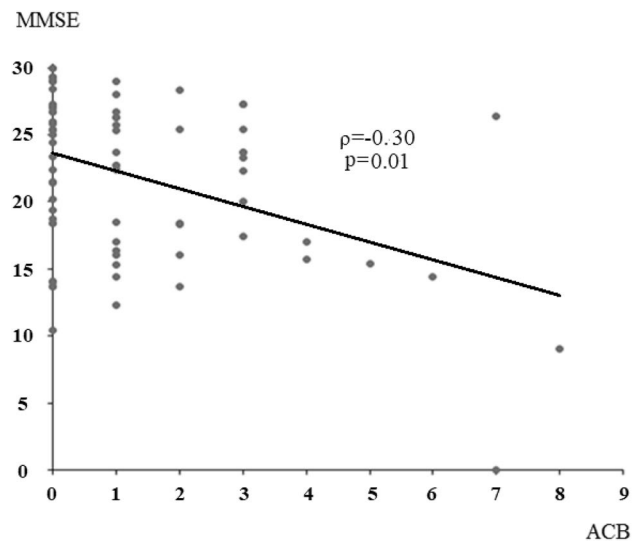

Fig. 3 Spearman's rank correlation (rho, ρ) analysis between Anticholinergic Cognitive Burden scale (ACB) and Mini-Mental State Examination (MMSE) score

Table 3 Adverse drug events for class D drug–drug interactions

		ADE	
		With hospitalization	Without hospitalization
Class D DDIs	With	17	3
	Without	4	8

ADEs (requiring hospitalization or not) were found in 45% ($n=21$) of inpatients (17/21 = 81% with class D DDIs) and 11% ($n=11$) of outpatients ($\chi^2=6732$, $p=0.001$)

ADE adverse drug event, *DDI* drug–drug interactions

hospitalization (severe ADEs) ($\chi^2 = 7.428$, $p = 0.01$). Table 2 shows the results of the INTERCheck® analysis in inpatients with ($n = 21$) and without ($n = 25$) severe ADEs (differences between inpatients with and without ADEs, INTERCheck® total score $p = 0.001$, class A $p = 0.01$, class B $p = 0.025$, class C $p = 0.001$, class D $p = 0.01$, class C + D $p = 0.00001$, ACB $p = 0.05$; differences between inpatients with ADEs and outpatients INTERCheck® total score $p = 0.001$, class A $p = 0.025$, class C $p = 0.0001$, class D $p < 0.000001$, class C + D $p < 0.000001$, ACB $p < 0.000001$).

None of the patients taking fewer than five drugs presented with severe ADEs.

4 Discussion

Pharmacological interactions may affect patient health by leading to adverse drug reactions and hospitalization, increasing costs for the healthcare system. A computer-based application, such as INTERCheck®, can be used to review medications in elderly patients, combining their clinical, cognitive and functional status evaluations with an analysis of adverse event risk and drug–drug interactions and improving prescribing quality. In a recent retrospective study, clinicians judged nearly 50% of pDDIs identified by INTERCheck® in the medications on medical record as clinically relevant (because of their potential clinical impact in relation to comorbidity or because their impacts were unknown) [7]. In the presence of multimorbidity (i.e., two or more long-term health conditions), the UK National Institute for Health and Care Excellence suggested a tailored approach to care [17]. The use of a CPSS such as INTERCheck® has been shown to optimize drug prescription for older people in nursing homes and in a geriatric ward [8, 9]. To the best of our knowledge, no other tools with a similar role to INTERCheck® are available for use in primary care.

4.1 Strengths and Weakness of the Study

In the present study, we found adverse events in 45% of hospitalized patients (INTERCheck® analysis reported a high class D score for > 80% of these patients). Our findings are consistent with a previous study in patients aged > 75 years that found hospital admission due to adverse drug reactions was as high as one in every three [18]. The cut-off for the number of drugs for the risk of incurring a serious or very serious interaction was found to be five [18]; the mean number of drugs was above eight in our patients. It is noteworthy that class D must be

considered a contraindicated association between drugs, that should be discontinued or avoided.

Moreover, we observed a high ACB score in inpatients, and the role of cognitive decline on the development of ADEs needs further investigation [16]. Possible cofactors (such as age, education level, number of comorbidities, frailty and dementia) should be considered as a limitation of the study, acting as covariates in the correlation analysis (no adjustment was performed in the present study).

A previous study reported that patients who scored three or more on the ACB scale had about three to six times the risk of delirium than those not taking anticholinergic drugs [19]. In the same study, according to the ACB scale, 377 inpatients (79.0%) received at least one anticholinergic drug [19]. In our study, inpatients with severe ADEs had a significant increase in both ACB scale (mean 2.9) and DDIs (mean total score 7.9, class D 1.6, class C + D 3.6). This high number of drug interactions included more than one contraindication and an anticholinergic burden near the above-mentioned cut-off for delirium.

5 Conclusions

The application of a software program such as INTERCheck® could significantly reduce the incidence of adverse events at every level of healthcare. In a setting of primary care (general practitioners), it could potentially avoid the high-risk drug–drug interactions, related hospitalizations and subsequent complications such as physical and cognitive decline, loss of autonomy, institutionalization or death (particularly in elderly patients). Finally, there could be a significant reduction in hospitalization-related healthcare costs. For these reasons, further prospective studies are necessary to evaluate whether the INTERCheck® software may help to reduce adverse events in patients receiving multiple medications.

Compliance with Ethical Standards

Bruno Laganà, Paolo Martelletti, and Giorgio Sesti have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval All the procedures carried out by this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee.

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