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Recognizing and preventing unacknowledged prescribing errors associated with polypharmacy

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Abstract

Background Prescribing errors put an enormous burden on health and the economy, claiming implementation of effective methods to prevent/reduce them. Polypharmacy regimens (five or more drugs) are highly prone to unacknowledged prescribing errors, since the complex network of drug-drug interactions, guidelines and contraindications is challenging to be adequately evaluated in the prescription phase, especially if different doctors are involved. Clinical decision support systems aimed at polypharmacy evaluation may be crucial to recognize and correct prescribing errors.

Methods A commercial clinical decision support system (Drug-PIN®) was applied to estimate the frequency of unrecognized prescribing errors in a group of 307 consecutive patients accessing the hospital pre-admission service of the Sant'Andrea Hospital of Rome, Italy, in the period April-June 2023. Drug-PIN® is a two-step system, first scoring the risk (low, moderate or high) associated with a certain therapy-patient pair, then allowing therapy optimization by medications exchanges. We defined prescribing errors as cases where therapy optimization could achieve consistent reduction of the Drug-PIN® calculated risk.

Results Polypharmacy was present in 205 patients, and moderate to high risk for medication harm was predicted by Drug-PIN® in 91 patients (29.6%). In 58 of them (63.7%), Drug-PIN® guided optimization of the therapy could be achieved, with a statistically significant reduction of the calculated therapy-associated risk score. Patients whose therapy cannot be improved have a statistically significant higher number of used drugs. Considering the overall study population, the rate of avoidable prescribing errors was 18.89%.

Conclusions Results suggest that computer-aided evaluation of medication-associated harm could be a valuable and actionable tool to identify and prevent prescribing errors in polypharmacy. We conducted the study in a Hospital pre-admission setting, which is not representative of the general population but represents a hotspot to intercept fragile population, where a consistent fraction of potentially harmful polypharmacy regimens could be promptly identified and corrected by systematic use of adequate clinical decision support tools.

Keywords Medication errors, Prescribing errors, Polypharmacy, Drug-drug interactions, Drug-PIN®

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Text box 1. Contributions to the literature

- Polypharmacy, defined as the simultaneous use of five or more drugs, is associated with increased rates of adverse drug reactions, hospitalization, poor adherence and compliance.
- The medication harm associated with polypharmacy represents a serious social and economic burden.
- Novel approaches using bioinformatics decision support tools to improve appropriate prescription of polypharmacy are presently actionable. They are expected to improve significantly the efficacy and the safety of polypharmacy.

Background

The World Health Organization (WHO) initiative "Medication Without Harm" [1], launched in 2017, highlights the urgency to reduce the burden of patient's injury related to medication errors (MEs).

MEs have been defined by the US National Coordinating Council for Medication Error Reporting and Prevention [2] as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health-care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use."

Although the rate of MEs varies in different settings, and just a minor fraction causes patient harm, they have been claimed as a non-registered cause of lethal events estimated to be the third cause of death in the USA [3]. In the clinical environment, MEs have been reported to affect up to 50% of prescriptions during hospitalization, to increase healthcare costs by billions of dollars annually, and to occur at increased rates in older people, fragile patients, and polypharmacy regimens (e.g. including five or more drugs) [4–6]. The WHO identified three main critical areas of intervention to reduce harmful MEs, which are the transition of care phase, high-risk situations (such as infancy/elderly) and polypharmacy [1].

Prescription errors (PEs) in polypharmacy are peculiar MEs which may remain unacknowledged by basic inspection of the medication regimen, reducing the appropriateness of the treatment. Defining the optimal drug combination for each patient is complicated by the wide network of pharmacological indications, contraindications and potential drug-drug interactions (DDIs) [7–9]. DDIs happen when a drug alters the pharmacokinetic and/or the pharmacokinetic profile of co-administered drugs, and are mainly due to multiple molecular effects played on human proteins acting as drug targets, drug transporters and drug metabolizing enzymes (DMEs), mainly the cytochrome P450 (CYP450) enzymes [10]. CYP450s are key effectors of DDIs, since drugs can induce/inhibit their drug metabolizing activity, affecting the circulating level of substrate drugs.

Since so many interacting variables determine the appropriateness of polypharmacy, bioinformatics support is needed to consistently screen and interpret a huge bulk of drug-related information, including thousands of potential DDIs. Otherwise, PEs causing inappropriate treatment would likely remain unacknowledged, until a patient's injury is recorded.

Clinical decision support systems (CDSS) aimed at reliable and pre-emptive estimation of polypharmacy are increasingly available. They apply specifically developed algorithms and automated knowledgebase consultation to generate prescription warnings and to guide informed drug selection and co-prescription [11–13]. It is noteworthy to note that inappropriate drug combinations often is caused by prescriptions from two or more specialists engaged in caring for the same patient, with poor doctor-doctor and doctor-patient communication. To ensure proper poly-pharmacy evaluation and harmonization, it is recommended to perform systematic medication reconciliation (MedRec), that is, the process of accurately compiling the medication history of a patient and comparing the list(s) of prescribed drugs with the list of used drugs, including over-the-counter medications and dietary supplements [14–18].

We previously tested the clinical utility of the Drug-PIN® system, a CDSS developed to evaluate and improve the polypharmacy appropriateness supporting informed drug selection, finding improved clinical outcomes in patients whose polypharmacy prescription was Drug-PIN®-guided [19–21]. Drug-PIN® is based on a deep-learning algorithm performing a multi-pass analysis and increasing the polynomial order of calculation for each factor added to the patient's record [22, 23]. The algorithm integrates data from different knowledgebase (clinical recommendations, drug labels and DDIs profiles), patient data as demographics (age, gender), habits (smoking, alcohol and caffeine consumption), clinical history (co-morbidities, hepatic/renal function) and pharmacogenomic data, if available. Reference sources used by the algorithm include the PRISCUS list and the Beers criteria, reporting age-related recommendations for drug prescription [24, 25]. Given the list of used drugs and the patient's data, the Drug-PIN® algorithm generates a numerical index, representing a theoretical therapy-associated risk score (TARS): the greater the TARS, the higher the risk of medication harm, intended as inefficacy and/or safety. According to TARS values, medication regimens are classified as low, moderate or high risk of medication harm for a given patient. In the case of moderate or high-risk therapies, the CDSS allows the selection of alternative drugs from a ranked list of medications

fitting the same therapeutic group, thus enabling therapy improvement (e.g. a TARS reduction).

In this study, we used Drug-PIN® in the frame of a formal MedRec process ongoing at the University Hospital Sant'Andrea of Rome, with the aim to evaluate the rate of unacknowledged PEs detectable by the system (defining PEs as the fraction of therapies with moderate- or high- TARS) and the fraction of such PEs which could be prevented by Drug-PIN®-guided polypharmacy selection. The study retrospectively analyzed medication regimens in 307 consecutive patients accessing the hospital pre-admission service, preceding their elective hospital admissions.

Methods

Study design and population

This is a retrospective, observational study analyzing anonymized data collected from 307 consecutive patients accessing the pre-admission service of the University Hospital Sant'Andrea of Rome, Italy, from April to June 2023. The hospital pre-admission process consists of an in-person patient appointment within two to three weeks before the elective (planned) hospital admission. During the appointment, nurses/doctors collect information about patient's current health status and medical condition, perform medication reconciliation, make the preanesthetic assessment, conduct tests such as basic metabolic blood tests, blood pressure test, electrocardiogram, and inform the patient about the programmed medical procedures. Data anonymization by data masking has been performed by appointed authorized personnel dedicated to the pre-admission service.

The patient data collected for the study were: gender, age, body mass index (BMI), the complete list of used drugs obtained by the MedRec process and biochemical parameters obtained at the pre-admission blood sampling: glomerular filtration rate (GFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST).

Medications evaluation/optimization by Drug-PIN®

The commercial software Drug-PIN® was used to calculate a therapy-associated risk score (TARS). Briefly, the risk of inefficacy/toxicity of a given therapy is obtained by inserting available patient data (gender, age, BMI, GFR, ALT, AST) and the list of used drugs. The TARS value is associated with a risk class as follows: low-risk (LR, TARS$<$50); moderate-risk (MR, 50$\leq$TARS$<$70); high-risk (HR, TARS$\geq$70). This first-pass step also produces a more detailed report listing age-related contraindications, other major contraindications (as duplicate prescriptions and not recommended co-prescriptions), warnings related to impaired renal/hepatic function and the drugs-CYP450 interaction profile (e.g. substrate, inducer, inhibitor) involved in the medication regimen.

In the second step, the inputted medication regimen can be optimized by exchanging a drug with an alternative medication within the same therapeutic class. Exchanging drugs, the TARS is updated, and the best medication regimen can be defined by reiterating the drug-exchanging step until achieving the lower TARS. The clinician performing optimization can preliminarily set eventual drugs not to substitute for.

Statistics

Data were analyzed using the SPSS software version 27 (IBM Statistics). The normality of continuous data were assessed by the Kolmogorov–Smirnov test. As data were non-normally distributed, they were reported as median and inter-quartile range (IQR) and analyzed by non-parametric testing. The Wilcoxon signed-rank test was applied to analyze differences between TARS values, before and after therapy optimization. The Kruskall-Wallis test was applied to analyze differences between patients whose TARS could be reduced by Drug-PIN® therapy optimization and patients whose TARS could not be reduced.

All patients were also categorized, according to TARS values, as patients with low-risk (LR), moderate-risk (MR) or high-risk (HR) for therapy-associated harm (TARS$<$50, 50$\leq$TARS$<$70, TARS$\geq$70, respectively). Frequencies of categorical variables were analyzed by χ-square testing. Post-hoc power calculation was performed using the online calculator ClinCalc.com [26].

Results

The study analyzed anonymized data from 307 patients' records consecutively collected at the hospital pre-admission service of the Sant'Andrea University Hospital of Rome, Italy. Most patients (63.8%) had planned access to surgical areas, whereas the remaining patients had planned access to other wards including internal medicine, cardiology, gastroenterology, neurology, and urology.

Continuous data were non-normally distributed and thus analyzed by non-parametric testing. Table 1 reports patient characteristics in the overall cohort and in groups of patients stratified according to TARS value calculated by Drug-PIN®, as follows: low risk (LR group, TARS$<$50); moderate risk (MR, 50$\leq$TARS$<$70); high risk (HR, TARS$\geq$70). No statistically significant differences in gender distribution among LR, MR and HR groups (χ-square testing) were detected.

Polypharmacy ($\geq$5 drugs) was present in 205 patients (66.8%). All therapies including$<$5 drugs were classified by Drug-PIN® as LR except for 2 therapies (both including 4 drugs) classified as MR. Among polypharmacies, 116 (56.58%) were classified as LR, 35 (17.07%) as MR and 54 (26.34%) as HR. Comparing LR, MR and HR patients,

Table 1 Comparison of patient characteristics and number of used drugs in subjects classified as LR, MR or HR by Drug-PIN® therapy evaluation. Data are reported as median and inter-quartile range (IQR). Data were collected at the Sant'Andrea Hospital of Rome, Italy, during pre-admission service from April to June 2023

Risk group	Gender	Age (IQR)	BMI (IQR)	GFR (IQR)	AST (U/l) (IQR)	ALT (U/l) (IQR)	Drugs (IQR)
LR (*N* = 216)	M: 47.4%	66 (58–73)	26.2 (23-30.8)	89.4 (74.8–99.1)	24 (20–29)	22 (17-31.5)	5 (4–6)
MR (*N* = 37)	M: 62.2%	73 (65.5–78)	26.2 (24.3–32.1)	79.3 (65.1–87.4)	25 (20-29.5)	18 (14–25)	7 (7–9)
HR (*N* = 54)	M: 50%	73.5 (66–80)	28 (24.7–30.8)	66.3 (45.2–84)	24 (19-30.5)	19 (13–31)	9.5 (8-12.2)
Overall (*N* = 307)	M: 49.8%	68 (61–75)	26.4 (23.4–31.1)	84.5 (67.7–95.2)	24 (20-29.7)	21.5 (15–29)	6 (4–8)

BMI: body mass index; GFR: glomerular filtration rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Table 2 Examples of TARS minimization using Drug-PIN® guided medication exchange/deprescription. The reported polypharmacies concern two subjects accessing the pre-admission service, Sant'Andrea Hospital of Rome, Italy, in the period April-June 2023

Patient 1 (Female, aged 66, BMI: 33.3, creatinine: 0.72 mg/dl; ALT: 19 U/L; AST: 19 U/L)								**TARS**
Polypharmacy	Cortisone	Levothyroxine	Amitriptyline	Simvastatin	Esomeprazole	Calcitriol	Cholecalciferol	74.66
Drug-PIN-optimized polypharmacy	Cortisone	Levothyroxine	Amitriptyline	**Pitavastatin**	**Roxatidine**	Calcitriol	**eliminated**	**22.47**
Patient 2 (Female, aged 74, BMI: 27.3, creatinine: 0.70 mg/dl; ALT: 61 U/L; AST: 38 U/L)								
Polypharmacy	Acetylsalicylic acid	Hydrochlorothiazide	Bisoprolol	Amlodipine	Atorvastatin	Valsartan		56.75
Drug-PIN-optimized polypharmacy	Acetylsalicylic acid	Hydrochlorothiazide	**Celiprolol**	**Lacidipine**	**Pitavastatin**	**Olmesartan Medoxomil**		**17.3**

BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase

a statistically significant difference in median age, glomerular filtration rate (GFR) and number of used drugs has been detected by the Kruskall-Wallis test ($p<0.001$), as expected (Table 1).

Drug-PIN®-guided optimization was performed for all therapies scored as MR and HR (thus considered potentially harmful). In this group of patients, including 91 of 307 patients (29.6%), optimization reduced the median TARS from a value of 79.5 (IQR: 61.9-104.1) to a value of 55.6 (IQR: 33.1–94.9), a statistically significant change (Wilcoxon Signed-Rank Test, $p<0.001$).

Table 2 shows two examples of polypharmacy optimization. The medication regimen of patient 1 was classified as high risk (TARS = 74.77) and was composed of 7 drugs, including cholecalciferol and calcitriol, both forms of vitamin D. The Drug-PIN® report highlighted that such co-prescription has major contraindications due to toxicity of excess vitamin D [27]. Further, the report showed multiple interactions of each medication with the same metabolic enzyme: all of them affect the CYP450 isoform 3A4, 6 medications affect the 3A5 isoform, 4 medications affect the 2C19 isoform and 3 medications affect the 2C9 and 2D6 isoforms. The TARS was lowered to 22.47 by exchanging the cholesterol-lowering drug simvastatin with pitavastatin and the proton pump inhibitor esomeprazole with roxatidine, and deprescribing cholecalciferol, thus decreasing the number of CYP450s engaged by multiple drugs and removing major contraindications.

The polypharmacy taken by patient 2 was classified as moderate risk (TARS = 74.77) and was composed of 6 drugs, including four antihypertensive medications (amlodipine, bisoprolol, valsartan, hydrochlorothiazide). In this medication regimen, the Drug-PIN® report highlighted a moderate contraindication for bisoprolol and valsartan co-prescription, due to a possible increase of blood potassium [28]. Further, 4 drugs are shown to inhibit the CYP450 isoforms involved in bisoprolol metabolism. Selection of alternative drugs, as shown in Table 2, lowered the TARS to 17.3, thanks to the elimination of contrasting drug-CYP450 interactions.

Figure 1 (panel A) shows the distribution of the risk group before and after therapy optimization: 63.7% ($N=58$) of MR and HR therapies could be improved, changing the patient's classification to a lower risk class (MR to LR and HR to MR or LR class), whereas 36.3% ($N=33$) therapies could not be improved at all.

We further evaluated if gender, age, BMI, GFR, ALT, AST and the number of used drugs were eventually associated with unsuccessful TARS minimization, finding a statistically significant association between unsuccessful polypharmacy optimization and a higher number of drugs, with a median of 11 drugs (IQR: 8.5–15) compared to a median of 8 (IQR: 7–9) in the group where TARS were effectively reduced ($p<0.001$) (Fig. 1, Panel B).

The prevalence of the most prescribed medications in the group of polypharmacies associated with successful optimization did not differ significantly from the prevalence observed in the group of polypharmacies which could not be optimized (Fig. 2), except for ramipril and gabapentin, though post-hoc power calculation shown

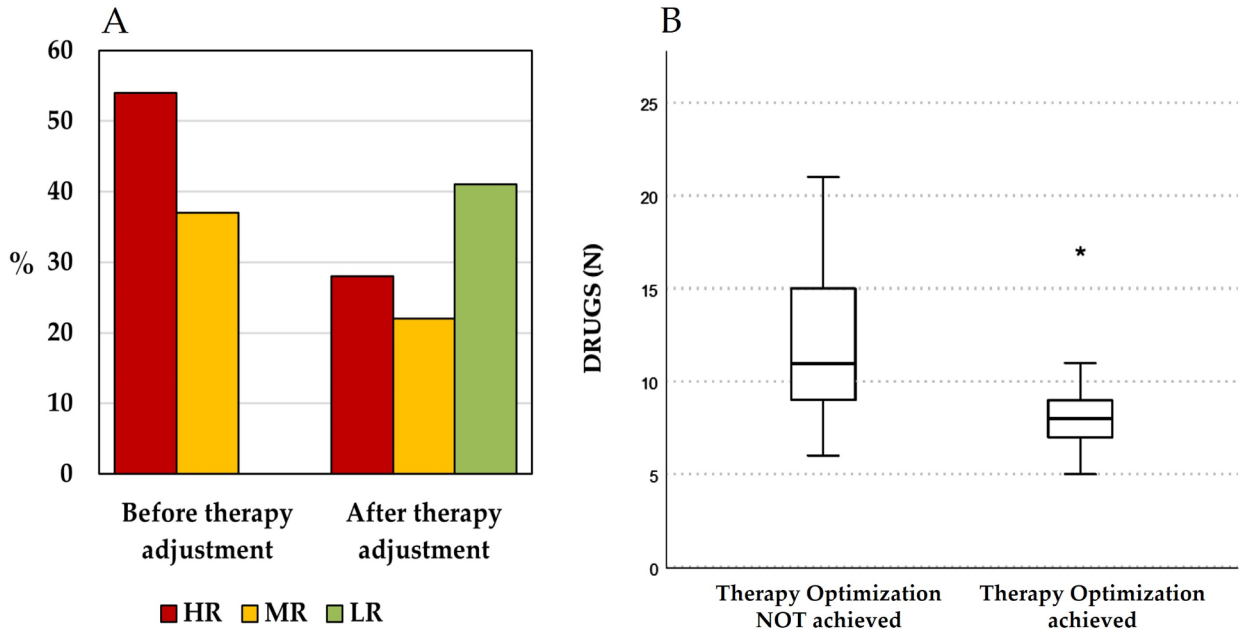

Fig. 1 Panel A: changes in risk class distribution, expressed as a percentage of the total, after CDSS-guided therapy adjustment. Panel B: box plot showing the difference in the number of used drugs between patients whose therapy could be improved and patients whose therapy could not be improved. Patients' therapies were recorded, from April to June 2023, at the pre-admission service, Sant'Andrea Hospital of Rome, Italy

that the sample size has reduced statistical power (<0.8) for the mentioned drugs.

Discussion

Patient harm due to the administration of pharmacological treatments is a well-recognized factor impairing the quality and efficiency of healthcare systems. The implementation of well-designed organizational models, aimed to minimize the occurrence of inadequate drugs' prescribing/administration, is the leading strategy to limit the MEs-associated burden. Thus, healthcare systems are developing surveillance programs aimed at identifying and recording MEs, enabling root cause analysis and problem-solving activities [14–18].

MedRec emerged as a simple but powerful tool to detect specific types of MEs, as transcription errors, discrepancies, missing route/dose/frequency, omissions [17, 18], and should be applied at every transition phase of patient care, when frequent changes in therapy may increase the error rate. However, MedRec activities have limited potential to identify more complex and hidden types of error, such as inappropriate prescription due to drug-drug interactions or poor adherence to indications and contraindications. Bioinformatics support to drug selection, especially in the case of polypharmacy, may greatly contribute to contrast this kind of PEs. Clearly, an integrated strategy using complementary approaches is needed to identify and avoid different sources of MEs, occurring during different phases of the medication process.

In this study, we sought to evaluate the potential utility of a CDSS system aimed at identifying and correcting PEs. The commercial Drug-PIN® software evaluates different factors contributing to the patient-specific therapy-associated risk and allows therapy optimization by medication exchange. In the Drug-PIN® classification system, the MR represents a category where moderate medication problems are detected, that is MR patients deserve careful monitoring and proper communication about the correct use of drugs, since they may be at increased risk of unsafety/inefficacy. Also, MR patients can easily switch to the HR class adding more medications. Concerning HR patients, they can be considered as subjects requiring therapy adjustment, possibly de-prescribing and at least, a closer monitoring of treatment efficacy/safety, since a major risk for medication harm is present.

We found that about 30% of the analyzed patients/therapies were classified as moderate or high risk by Drug-PIN® and that most of them could theoretically be improved by Drug-PIN® – guided therapy optimization. To roughly estimate the significance of this observation for public health, we can calculate the number of potentially inappropriate pharmacological treatments which could be identified by our healthcare structure using bioinformatics support for drug prescription. The Sant'Andrea Hospital of Rome counts about 14,000

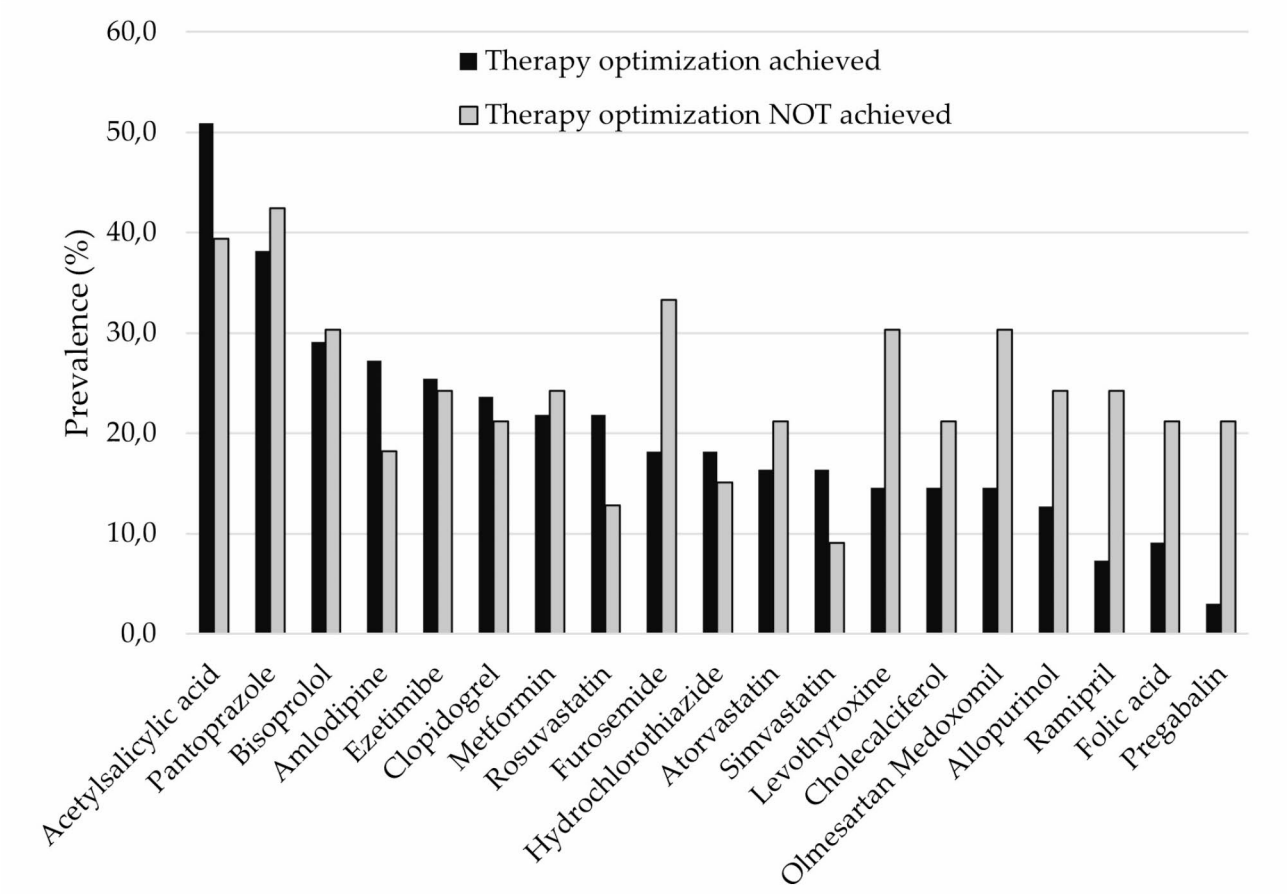

Fig. 2 The prevalence of the top prescribed medications in the polypharmacy group is associated with successful optimization compared to the polypharmacy group, which could not be optimized. Patients' therapies were recorded, from April to June 2023, at the pre-admission service, Sant'Andrea Hospital of Rome, Italy

ordinary admissions/per year, thus systematic evaluation and optimization of medication regimens could identify and correct thousands of PEs annually. Public and private healthcare structures may act as a capillary network intercepting inappropriate prescriptions in different target patient populations (elderly, chronic, acute, fragile), according to the delivered care service.

Although we detected a consistent fraction of MR and HR therapies which could not be improved, these patients may still gain benefits by closer monitoring prompted by the increased risk awareness. Anyway, it could be supposed that systematic use of polypharmacy prescription support tools may prospectively reduce the fraction of unfixable MR and HR therapies.

Since the causal relationship between the number of used drugs and the rate and severity of medication harms is widely demonstrated, in our vision of a systematic approach to PEs detection, the raw number of administered drugs could represent an "action alert" claiming the activation of a more accurate medication revision process and closer patient monitoring. In this scenario, MedRec and the mere listing of drugs, including over-the-country medications, could represent a first-line and easily actionable screening of the patient population at each level of care, to identify subjects who deserve pharmacological counselling and therapy improvement. Even if, presently, CDSSs performing therapy optimization are not widely diffused, it seems conceivable that few pharmacological counselling facilities could serve a lot of patients there addressed by a capillary, first-pass territorial screening. Considering the annual cost incurred by healthcare payers to front ADRs and MEs [6, 29–31], this strategy seems largely sustainable. Rather, different and serious barriers hamper the implementation of a diffuse system of pharmacological counselling integrated with MedRec activities. Key issues are poor (or absent) doctor-doctor communication, which limits the harmonization of prescriptions from different clinicians involved in treating co-morbidities, and the willingness of physicians to accept recommendations and suggestions about therapy changes by a CDSS. It is noteworthy to note that CDSSs just provide information and options to the

clinicians, who retain the full prerogative to accept or decline such recommendations according to their unique knowledge of the patient history and needs.

Corrective actions toward cultural habits may be the strengthening of communication channels (as shared systems for electronic recording of patients' history) and a broader application of MedRec activities but, above all, an evidence-based engagement of doctors is critical: educational programs focused on the multifaceted and interplaying phenomena of MEs, ADRs, DDIs and their impact on patient health, could greatly contribute to achieving doctors' commitment to novel activities (as CDSS use), making clear that few time spent in doctor-doctor and doctor-patient relationships triggers a burst in the quality of care.

We would lastly comment on the main limit of the present study, that is the therapy optimization process was performed retrospectively, and the clinical effect of therapy optimization could not be recorded. Although some previous reports have shown the clinical efficacy of Drug-PIN® [20, 23], further comparative studies are needed to quantify the impact of CDSS-guided polypharmacy prescription. In particular, evaluating the performance of the process should involve, besides clinical outcome indicators, drug usage indicators (number of prescribed drugs, number of duplicate prescriptions, defined daily dose), patient indicators (adherence level, quality of life), doctors indicators (acceptance, satisfaction). The measured indicators should be representative of each defined level of care and each defined target population and should contribute to assessing the improvement in structure performance and, finally, in healthcare performance, thus supporting public health decision-making.

Conclusions

PEs represent a known burden for healthcare systems, and major efforts should be directed at eradicating the significant fraction of preventable MEs. In our opinion, the time is ripe to consider a more systematic use of CDSSs aimed to support appropriate drug selection in polypharmacy, also considering that their use can be centralized, reducing the costs. Integration of patient-sized polypharmacy evaluation/optimization in extensive MedRec programs could represent a major step toward the improvement of medication safety and efficacy. Comparative and cost-effectiveness studies are surely needed to demonstrate the clinical, societal and economic benefits of the proposed approach.

Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CDSS	clinical decision support system
DDI	rug-drug interaction
GFR	glomerular filtration rate
HR	high risk
IQR	Inter-quartile range
LR	low risk
ME	medication error
MedRec	medication reconciliation
MR	moderate risk
TARS	therapy-associated risk score

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
Professor Robert Preissner and Professor Maurizio Simmaco are members of the Advisory Board of Drug-PIN AG. The Drug-PIN AG is holder of the patent PCT/IB2019/052310. The remaining authors declare no conflict of interest.

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