



BMJ Open Potentiality of algorithms and artificial intelligence adoption to improve medication management in primary care: a systematic review

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ABSTRACT

Objectives The aim of this study is to investigate the effect of artificial intelligence (AI) and/or algorithms on drug management in primary care settings comparing AI and/or algorithms with standard clinical practice. Second, we evaluated what is the most frequently reported type of medication error and the most used AI machine type.

Methods A systematic review of literature was conducted querying PubMed, Cochrane and ISI Web of Science until November 2021. The search strategy and the study selection were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Population, Intervention, Comparator, Outcome framework. Specifically, the Population chosen was general population of all ages (ie, including paediatric patients) in primary care settings (ie, home setting, ambulatory and nursery homes); the Intervention considered was the analysis AI and/or algorithms (ie, intelligent programs or software) application in primary care for reducing medications errors, the Comparator was the general practice and, lastly, the Outcome was the reduction of preventable medication errors (eg, overprescribing, inappropriate medication, drug interaction, risk of injury, dosing errors or in an increase in adherence to therapy). The methodological quality of included studies was appraised adopting the Quality Assessment of Controlled Intervention Studies of the National Institute of Health for randomised controlled trials.

Results Studies reported in different ways the effective reduction of medication error. Ten out of 14 included studies, corresponding to 71% of articles, reported a reduction of medication errors, supporting the hypothesis that AI is an important tool for patient safety.

Conclusion This study highlights how a proper application of AI in primary care is possible, since it provides an important tool to support the physician with drug management in non-hospital environments.

INTRODUCTION

The Institute of Medicine's (IOM) Roundtable on Evidence-Based Medicine defined patient safety as 'the prevention of harm to

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ To our knowledge, this is the first systematic review of literature evaluating the impact of artificial intelligence (AI) on medications error in a primary care setting.
- ⇒ Rigorous and reproducible methodology according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
- ⇒ Multidisciplinary approach to the investigated topic.
- ⇒ Small number of included studies and high heterogeneity across them.
- ⇒ Difficulties in evaluating the most suitable medication class for AI applications due to missing data.

patients',¹ placing attention on the necessity to take precautions to protect a patient's safety during the course of care. Healthcare systems are accountable for reducing the occurrence and effects of adverse events in clinical practice.² The IOM Roundtable was cautious to distinguish between adverse occurrences resulting from pharmaceutical usage and error, but the adverse events category ended up serving as a common starting point for discussions about patient safety as a quality component. In this case, the objective of the patient safety assurance procedure is made to be comparable between adverse events and medication errors. In fact, an adverse event is harm brought on by medical therapy rather than the patient's underlying ailment. Error is defined as the failure to carry out a planned activity as planned or the execution of the incorrect plan to achieve a goal.³ An 'adverse incident that could have been prevented' is one that is traceable to error.⁴ Any mistake that happens during the administration of a medication qualifies as a medication error. Therefore, it is reasonable to assume that



medication errors and error-related adverse drug events (ADEs) are frequent occurrences that cause significant patient harm, including morbidity, hospitalisation, higher healthcare expenses and, in some circumstances, death.⁵ Few research actually address adverse events that occur during primary care; the majority of studies conducted focus mostly on secondary care.⁶ In order to provide initial contact for acute conditions and care (access and continuity of care) for chronic conditions,⁷ primary care is a system of relationships between patients and the communities⁸ that involves a variety of experts and healthcare services. The continuation or commencement of pharmacological therapy occurs in over 75% of outpatient visits by family doctors and general practitioners, mostly in patients 65 and older.⁶ In comparison to the hospital setting, the potential risk of an adverse event resulting from a mistake in medicine use or prescription is much higher in the primary care setting.⁹ This is because patients over 65 years old frequently have polypharmacy, which is harder to monitor, making caregivers' attention to drug management essential to ensuring patient safety.¹⁰ Over the past 20 years, the influence of technology in this setting has increased dramatically.¹¹ By developing new diagnostic procedures and therapies, the use of omics technology, machine learning and artificial intelligence (AI) is expanding our understanding of disease.¹² AI is a growingly applied approach that uses learning (mathematical) algorithms that change many parameters. According to the Encyclopedia of Artificial Intelligence, AI is a discipline of science and engineering devoted to the computational understanding and reproducibility of intelligent behaviour.¹³ This methodology is crucial for achieving the objective of personalised medicine (PM) based on an individual's profile, taking into consideration each patient's unique circumstances since it can be adjusted to the patient's demands. The ability of PM resides in both therapy and prevention targeted at enhancing patient safety.¹⁴ Home-based AI systems may enhance patients' quality of life through treatment optimisation,¹⁵ particularly in the case of prevalent but complex diseases. On the other side, AI-assisted management solutions may also reduce the time and money spent on logistics on a bigger scale.¹⁶ The innovative idea of 'precision health' is made possible by the use of AI to customise treatments to individual needs.¹⁷

Clinical decision support systems and computerised physician order entry are already being used more frequently in e-prescribing techniques to increase patient safety.¹⁸ AI-dependent decision support systems have previously been proved to increase patient safety by enabling error detection, patient stratification and drug management at all stages (eg, prescription, administration and dispensing), despite the fact that it might be argued that they are immature machines.¹⁹ Our initial aim was to focus only on AI-based interventions. Nonetheless, due to the lack of sufficient scientific literature on this specific topic, we decided to expand our investigation to algorithms adopted in drug management as well,

starting from the assumption that AI uses algorithms to support clinical practice. This statement does not imply that algorithms and AI might be considered synonyms but highlights our interest in investigating tools that might ease medical workflow in primary care.

Therefore, this study aims to assess how AI and algorithms affect medication management in a primary care context. Second is to examine the kinds of therapeutic errors prevented and the degree of autonomy attained by used AI devices.

METHODS

The synopsis for this systematic review was published in the *BMJ Open*.²⁰ This systematic review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews,²¹ and the Synthesis Without Meta-analysis checklist was filled out and is provided as online supplemental material.

Patient and public involvement

The involvement of patients or the public in the design, conduct or reporting of the survey was not suitable for this kind of investigation.

Literature search strategy

A Boolean search string was created using the elements of the PICO model (P, population/patient; I, intervention/indicator; C, comparator/control; O, outcome) to search for relevant articles in Cochrane Library, Web of Science and PubMed databases.²² For the search strategy the following synthetic PICO criteria were addressed:

1. Population: general population of all ages (ie, including paediatric patients) in primary care settings (ie, home setting, ambulatory and nursery homes).
2. Intervention: analysis AI and/or algorithms (ie, intelligent programs or software) application in primary care for reducing medications errors.
3. Comparator: general practice.
4. Outcomes: reduction of preventable medication errors (eg, overprescribing, inappropriate medication, drug interaction, risk of injury, dosing errors or in an increase in adherence to therapy).

References of individual studies were also back-checked. Articles were retrieved from the inception of each database until November 2021. Following are some of the investigated search terms:

1. Terms related to population: 'primary care', 'ambulatory care', 'outpatient care', 'general practitioner', 'general paediatrics'.
2. Terms linked to intervention: 'artificial intelligence', 'algorithms', 'machine learning', 'deep learning', 'neural networks'.
3. Terms related to measured outcomes: 'medication error', 'adverse event', 'prescribing error', 'dispensing error', 'administration error', 'monitoring

error', 'medication errors reporting', 'medication reconciliation'.

The full search string is provided in online supplemental material 1.

Inclusion criteria

The inclusion of relevant studies was based on the following criteria: (1) randomised controlled trials (RCT) developed in primary care settings; (2) studies comparing the application of AI and/or algorithms to usual clinical practice; (3) studies applying AI and/or algorithms to drug management; (4) studies quantitatively analysing the effectiveness of the intervention in terms of medication error reduction.

In order to be included, articles had to clearly state the application of AI and/or algorithms in the text. A double check of the intervention methodology was performed to ensure the effective application of AI and/or algorithms, according to the Encyclopedia of Artificial Intelligence definition²³ and the further stated Hintze classification of AI types.²⁴

We focused on primary studies reporting efficacy results. Only articles written in English and with full texts available and published in peer-reviewed journals were included. After removing duplicate results, f

our researchers (MS, MTR, SG, GAL) independently screened the title and abstract to outline the most appropriate articles. Then, the four researchers performed a full-text screening of each article to determine eligibility.

First, the four researchers screened few of the potentially eligible articles, with the aim to fine-tune the screening process and solve eventual misalignments. Second, the four researchers independently read the abstracts and proceeded with the selection of the pertinent ones.

During the screening process, the researchers solved any ambiguous situation or bias by discussing together the inclusion or exclusion of the article based on the eligibility criteria identified and their expertise on the topic. The agreement was handled with tailored group meetings.

Data extraction and quality assessment

Data extraction was independently completed by five researchers (GAL, MCN, FC, GAU, MZ), adopting a standard data entry electronic form. Data on study characteristics (ie, author name, country or region of study, year of publication, study design), participant-related aspects (ie, sample size, role, type of specialist, type of patient), intervention-related aspects (ie, name of the intervention, target and provider of intervention, duration of intervention, type and description of intervention, type of AI, complexity level of the machine, type of medication, type of error) and outcome-related aspects (ie, outcome measurement tools) were extracted from each included study. The methodological quality of included studies was appraised adopting the Quality Assessment of Controlled Intervention Studies of the National Institute of Health for RCTs recommended by the National

Institute of Health, US Department of Health and Human Services. The tool consists of 14 criteria that are used to assess quality, including whether the study was described as randomised, whether the outcome assessors were blinded, and an assessment of the dropout rate. The criteria were classified as 'yes', 'no' or 'not reported'. Quality rates were good, fair or poor as judged by two independent observers (MCN and GAU) following the instructions given by the National Institute of Health and US Department of Health and Human Services. If disagreements occurred, the final decision was reached by team consensus. One of the suggested questions, question number 8, 'Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?', was not included in the assessment process since not applicable to all the included studies. To achieve a summary score for the proposed questions, a threshold was identified. A potential risk of bias was considered if the answers 'no' or 'not reported' were selected for the items by the reviewer. The quality of an article was considered 'good' if the 'yes' answers were $\geq 75\%$ of the total; if they were $< 75\%$ but $\geq 50\%$, an article was scored as 'fair'; if they were $< 50\%$, the article was scored as 'poor'.²⁵

Data synthesis

The main features of the articles were extracted and narratively described, then displayed in a tabular format. The type of applied AI in the included RCTs was described using Hintze classification,²⁴ which allows to differentiate between reactive machines, the most basic type of AI; limited memory, containing machines that can look into the past; theory of mind, with machines able to understand that people, creatures and objects in the world can have thoughts and emotions that affect their own behaviour; finally, self-awareness, with machines having consciousness. After an extensive literature search, Hintze classification was chosen based on the following considerations: it offered the most pertinent graduation for our study, it detailed the specifics of the investigated categories and it was already applied to internationally recognised digital health studies.

The type of avoided error was described using Williams classification,²⁶ defining three categories of medication error, namely prescription errors, the incorrect drug selection for a patient; dispensing errors, including selection of the wrong strength or product, and administration errors, when a discrepancy occurs between the drug received by the patient and the drug therapy intended by the prescriber.

The target populations of the interventions were classified according to Assiri *et al's*²⁷ definition of patient at risk of medication errors in community care contexts. In this study, authors reported as risk factors the number of medications used by the patient, increased patient age, comorbidities, use of anticoagulants, cases where more than one physician was involved in patient care and care being provided by family physicians/general practitioners.

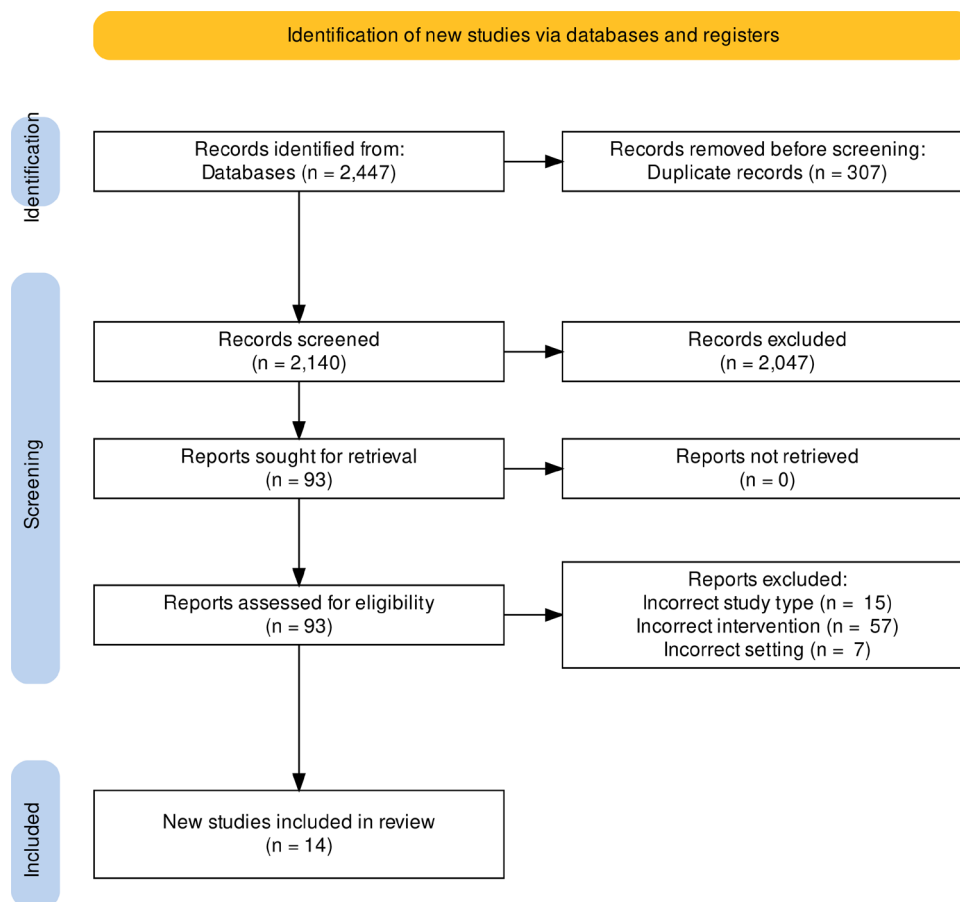


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of different screening rounds.

A quantitative synthesis was not applied due to heterogeneity issues. The heterogeneity was assessed based on the structural diversity (ie, different settings, populations targeted, type of intervention, and outcomes) among the studies.

RESULTS

Study selection and characteristics

Out of 1731 articles retrieved from the search string launched in July 2021, seven articles resulted suitable to be included as meeting the inclusion criteria. An update of the same string in November 2021 brought to a total of 716 new articles to be evaluated. A total of 2447 articles were thus retrieved, of which 93 were screened. The total final number of included articles was 14. The following PRISMA flow diagram reports the systematic review's search and selection process of studies for inclusion (figure 1).²¹ All articles evaluated the risk reduction in medication use achieved by the application of AI in primary care. Four out of 14 studies^{28–31} were performed in the USA, three^{32–34} in Canada, one³⁵ between Canada and the USA, two^{36–37} in Germany, one³⁸ in France, one³⁹ in Spain, one⁴⁰ in Ireland and one⁴¹ in England. Articles were published in between 1993³⁸ and 2020.³⁷ Most of the included articles^{29–32–34–36–38–40–41} referred to RCTs

conducted in primary care ambulatories (64%) administered by physicians or pharmacists; four studies^{28–31–35–39} (29%) were carried out in primary care clinics, both for long stay and short stay. Finally, one study was carried out in patient homes³⁰ (7%). Six studies^{33–37–42} were addressed to physicians (50%), four^{30–31–38–41} to patients (29%), three studies^{28–32–40} involved both physicians and patients (14%) and one study²⁹ involved pharmacists (7%). Online supplemental material 2 shows additional characteristics of the included studies.

Quality assessment

The quality of included studies was evaluated applying the Quality Assessment of Controlled Intervention Studies of the National Institute of Health for RCTs. Six studies^{28–29–34–36–38} were found to be of 'good quality', four studies^{33–39–41} of 'fair quality' and four studies^{30–32–35} of 'poor quality'. Results of the quality assessment process for each included study and details on the quality assessment questionnaire are available in online supplemental material 3.

Outcome categories and measures

The type of avoided error was evaluated adopting Williams classification of errors in the use of drugs. Most of the articles^{28–31–37–39–41} (79%) evaluated trials avoiding prescribing

errors. Two studies^{30 38} referred to AI application to avoid administration errors (14%), one study²⁹ (7%) avoided dispensing errors.

Hintze classification was used to define the level of autonomy reached by AI machines used in the trials. Seven out of 14 studies^{28 32 35–38 41} described machines that reached level I, seven^{29–31 33 34 39 40} out of 14 studies described machines that reached level II of autonomy. No studies adopted AI technologies belonging to levels III and IV.

Studies reported in different ways the effective reduction of medication error. Ten out of 14 included studies^{28 29 32–35 37 39–41} reported a reduction of medication errors. Four studies^{30 31 36 38} did not report any significant reduction of medication error.

The most frequently applied machine category was 'computerised decision support system' (CDSS).^{28 29 31–37}

Assiri *et al's* definition of patient 'at risk' was applied to the target populations of the interventions. Fifty-seven per cent of interventions^{28 29 31 35–38 41} were conducted on subjects at risk of medication error, 43% of studies^{30 32–34 39 40} referred to general primary care populations with an average risk of error.

Overprescribing

A total of four studies^{32 33 37 40} evaluated the changes that AI application induced in excessive prescribing. One study³⁷ reported a decrease in prescribed drugs in the intervention group compared with control group (adjusted mean difference -0.45 , 95% CI -0.63 to -0.26 ; $p < 0.001$). One study⁴⁰ found a reduction in proton pump inhibitor prescribing in the intervention group (adjusted OR=0.30, 95% CI 0.14–0.68; $p=0.04$). One study³² described a reduction in therapeutic duplication problems in the intervention group (OR=0.55; $p=0.02$), no difference in the overall prevalence of prescribing problems. One study³³ reported a significant 57% (OR=1.43; $p < 0.0001$) reduction in prevalence of therapeutic duplications in the computer-triggered alert group.

Inappropriate medication

A total of four studies^{28 30 31 36} defined risk reduction considering inappropriate medication prescription reduction. One study²⁸ reported significantly lower mean proportion of cases per physician with unsafe prescriptions for the intervention group compared with the control group after adjustment for baseline rates ($F_{5,4,24}$; $p < 0.05$, effect size 5, 0.54). One study³⁰ reported an 18.6% reduction of the use of inappropriate medications in the intervention group compared with 27% of the control group. One study³⁶ adopted the Medication Appropriateness Index (MAI sum score).²⁷ Results showed that the mean MAI sum scores decreased minimally in both groups 6 months after baseline—by 0.3 points in the intervention group and 0.8 points in the control group—revealing a non-significant adjusted mean difference of 0.7 (95% CI -0.2 to 1.6) points in favour of the control group. One article³¹ adopted the Patient Assessment of Care for

Chronic Conditions (PACIC) score.⁴³ Results showed that a greater proportion of patients who received the intervention than control patients reported a PACIC score of 11 or 12, but this difference was not significant (29.7% vs 15.6%; $p=0.06$).

Drug interaction

A total of two studies^{35 39} esteemed the risk reduction evaluating reported drug interaction before and after the intervention. One study³⁵ reported that comparing intervention and control units, in a post hoc analysis limited to events that might have been prevented as a result of one or more of the alerts, the rate was 1.55 preventable ADEs per 100 resident-months on the intervention units and 1.72 preventable events per 100 resident-months on the control units, for an adjusted rate ratio of 0.89 (95% CI 50.61–1.28). One study³⁹ after the follow-up period registered 4353 potential clinically relevant interactions (5.3 interactions per 100 patients, 95% CI 5.2–5.5) for a 21% reduction in comparison to baseline.

Risk of injury

Two studies^{34 41} evaluated the risk of adverse events before and after intervention. One study³⁴ reported a reduction of 1.7 injuries per 1000 patients (95% CI 0.2/1000 to 3.2/1000; $p=0.02$) after the follow-up phase. The effect of the intervention was greater for patients with higher baseline risks of injury ($p < 0.03$). One study⁴¹ reported an incidence of recorded transient ischaemic attack higher in the intervention practices (median 10.0 vs 2.3 per 1000 patients with atrial fibrillation; $p=0.027$) but, at 12 months, a lower incidence of both all-cause stroke ($p=0.06$) and haemorrhage ($p=0.054$). No adverse effects of the software were reported.

Adherence

One study³⁸ evaluated the adherence to therapy, finding no statistically significant difference in the non-adherence rates in both groups when comparing pill count data (35%) in the control group with data in the intervention group (60%).

Dosing

One study²⁹ outlined over the 15-month intervention period a proportion of medication dosing errors in the intervention group significantly lower than the usual care group (33% vs 49%; $p < 0.001$).

DISCUSSION

This systematic review of literature identified 14 papers respecting all inclusion criteria. To our knowledge, this is the first systematic review evaluating AI application to medication management in a primary care setting. In our study, we evaluated whether the use of intelligent algorithms reduced medication errors by avoiding human mistakes. Within the interventions, the most frequently applied machine category was 'computerised decision support system',^{28 29 31–37} a technological software that



uses and analyses patient data (including treatments and outcomes) for clinical decision-making.⁴⁴ Seven out of nine studies applying this machine^{28 29 32–35 37} registered a statistically significant decrease in medication errors. This evidence suggests the need for further larger scale research on the evaluation of CDSS for clinical practice in primary care. Only nine articles reported the class of drugs the experimentation focused on. In four out of 14 studies,^{28 34 38 41} the machine was applied to one single class of medications (respectively non-steroidal anti-inflammatory drugs, psychotropic agents, hypoglycaemic agents and oral anticoagulants). All four of the above articles reported a statistically significant reduction of medication error, arguably suggesting the importance of taking targeted actions in the process of digital health innovation with the aim of progressively achieving a ‘precision health’ system.⁴⁵ The remaining five articles^{29–31 35 46} reported the evaluation of AI application on four or more medication classes. The heterogeneity of the application fields and the lack of information on drug classes in four out of 14 articles did not allow to detect which type of drugs might be most suitable for AI-mediated management. Most of the trials were carried on by introducing computer devices into physicians’ routines. Some of the articles^{29 37 38} were able to assess the detected compliance in the intervention groups. In one of the three articles,³⁷ the investigators reported a low level of compliance mainly due to the difficulties encountered by physicians in interfacing with the software. AlQudah *et al*⁴⁷ found that perceived usefulness, ease of use and increased work efficiency—in these cases related to the use of technology—can positively affect employee attitudes. Therefore, user-friendly solutions in the healthcare should be supported.⁴⁸ In around 80% of the studies, AI prevented prescribing errors. According to Williams classification, a prescribing error (eg, wrong indication, dosing) is the incorrect choice of a drug for a patient.²⁶ The Food and Drug Administration reported that problems associated with prescription are a common cause of medical errors.⁴⁹ de Araújo *et al*⁵⁰ investigated solutions, including the promotion of training courses, the implementation of digitised tools and the inclusion of the patient in the care process to reduce medical errors. In 2013, Ross *et al*⁵¹ reported that excessive workload and overpressure can lead to clinical mistakes. Therefore, as inadequate theoretical preparation, senescent tools and management deficiencies have been identified as sources of clinical errors, most solutions to this problem involve training, digitalisation and reorganisation of work. About 20% of the included studies applied AI to processes usually related to administration errors. Williams defined administration errors as those occurring when there is a discrepancy between the drug received by the patient and the drug therapy intended by the prescriber.²⁶ As the second most frequent type of error, several studies have analysed it and tried to find a solution. Keers *et al*⁵² focused on nurses’ role as the least link of the administration chain. Three main causes of error were identified, namely

misinterpretations, lack of knowledge and violations. Two out of the three hypotheses (ie, the educational and management topics) have already been discussed above, hence the need to emphasise these issues, especially in a primary care setting where caregivers may be responsible for the administration process.⁵³ Some studies⁵⁴ highlighted the importance of implementing computerised tools to support the administration process. One intervention allowed the avoidance of dispensing errors, which Williams describes as errors occurring at any stage of the dispensing process, from the receipt of the prescription in the pharmacy to the supply of a dispensed medicine to the patient, primarily with drugs that have a similar name.²⁶ Parand *et al* in 2018⁵⁵ suggested the inclusion of pharmacists in the process of care from prescription understanding to drug storage, patient premonitoring, drug preparation, drug administration and patient post-monitoring. For example, Bhardwaja *et al*²⁹ reported a significant reduction of dispensing errors through the application of a computerised tool for pharmacists.²⁹ Similar interventions^{28 29 31 35–38 41} were conducted on populations at risk of medication errors, for example, elderly people. Moreover, some studies also evaluated patients’ compliance to AI technologies,⁵⁶ as well as the correlation between compliance and health status.⁵⁷ Future studies might investigate a possible association between patients’ compliance and risk of medication error. Medication errors represent a relevant problem in terms of patient damage and health systems sustainability.⁵⁰ Those most frequently related to patient harm occur in the prescription (56%) and administration (34%) phases, which respectively account for 56% and 34% of reported errors according to Bates and Slight.⁵⁸ Elliott *et al*⁵⁹ reported that most errors lead to minor consequences (72%), whereas about one in four (just under 26%) have the potential to cause moderate harm and 2% could potentially cause serious harm. The scientific literature provides many reports on medicolegal consequences of the errors in primary care,⁶⁰ that is, civil actions, criminal charges and medical board discipline.⁶¹ The evidence of the current study supports the hypothesis that AI is a safe and efficient tool. However, the potential issues associated with AI-based interventions should be considered. Indeed, Oliva *et al*⁶² identified the lack of personal data protection as the main related issue. Also, the lack of transparency of the decisional process of many algorithms (especially if unsupervised) and the reliability of AI devices depends on the quantity and the quality of the training data, not guaranteeing the quality of the machine.⁶² Thus, it should be a political priority to reinforce AI regulation and guidelines to prevent the development of AI-related errors, with the intention of becoming a support rather than an obstacle to the clinical practitioner. After an overall assessment of the issue from physician and patient’s point of view, the economic impact on the public health system should also be evaluated. Worldwide, the cost of medication errors is estimated to reach US\$42 billion per year.⁵⁰ In 2017, Walsh *et*

al systematically reviewed a total of 16 economic evaluations on this specific topic. Mean cost per error per study ranged from €2.58 to €111 727.08, suggesting a difficult and not accurate estimate of the global economic burden of this issue.⁶³ At the same time, the economic evaluation of AI machines is particularly difficult due to the lack of data on direct and indirect costs. Among the included articles, in 2011 Lopez-Picazo *et al* tried to build a cost-effectiveness model of the analysed intervention,³⁹ estimating the incremental cost incurred to reduce the mean of potential interactions. The machine was applied to three different interventions, with a mean cost ranging from US\$4.2 to US\$32.1 per 1% of improvement in 100 patients beyond the control group. Therefore, given the documented large economic impact associated with the cost burden of medication errors, policymakers might steer choices focused on the proper allocation of the upcoming funds, related to post-COVID-19 recovery plans, to promote a wider adoption of AI machines in the clinical practice. The adoption of a similar instrument by further studies on AI machines might become a fundamental decisional tool. The main strength of this study is its unique value: to our knowledge, there is currently no similar systematic review of literature evaluating the impact of AI on medication error in a primary care setting. In addition, a rigorous methodology was applied to every phase of this article development. Furthermore, the current topic was analysed from a medicolegal point of view to contextualise the error in healthcare, allowing further reflection on the issues of safety and the applicability of AI. There are several limitations to this systematic review. First of all, the small number of papers could not be representative of all different machines currently used in healthcare. The missing attitude in events reporting characterising primary care might be the main cause of this. Moreover, the great heterogeneity in results reporting we found in the included articles did not allow a quantitative synthesis of evidence for a meta-analysis. Finally, most of the articles did not report specifications regarding the medication classes involved in the intervention, hence not allowing to define which class was more easily managed through AI application. Further research is needed to evaluate the potential association between patients' compliance and risk of medication error. Additionally, future studies might focus on the application of AI machines on a specific medication class. Moreover, the accuracy, sustainability and cost-effectiveness of implementing AI-based digital health solutions in clinical practice should be investigated. Further research is also claimed to clarify the technical characteristics of single computer-based interventions for each type of involved technology.

CONCLUSIONS

The current study tries to partially fill an important literature gap regarding AI application in primary care. The ambitious aim to systematically approach such an

innovative theme brought this review to be particularly difficult to realise and did not allow to end up with a detailed quantitative synthesis. Nevertheless, it was able to strengthen the evidence regarding the aid that AI is able to provide to physicians in managing patients' medication and to encourage a wider application of machines even in less controlled environments, such as the ones in which primary care specialists operate.

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Contributors The study concept was developed by AO, GD, GDM and MC. The manuscript was drafted by GAI, MCN, SG, MZ, FC, GAU and D.3.2 group and critically revised by AO, GD, GDM, MC and AHA. AO, GD, GDM and MC developed and provided feedback for all sections of the review and approved the final manuscript. The search strategy was developed by GAI, MCN, SG, MZ, FC, GAU and D.3.2 group. Study selection was performed by FC, GAI, MZ, AHA and D.3.2 group. Data extraction and quality assessment was performed by GAI, MCN and GAU, with SG as a fourth party in case of disagreements. GDM acted as guarantor. All authors have approved the final version of the manuscript.

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Supplementary Materials

The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

Supplementary materials 1: Full search string.

PubMed

("primary care" OR "ambulatory care" OR "outpatient care" OR "basic health care" OR "basic health-care" OR "basic healthcare" OR "day-to-day health care" OR "first aid" OR "initial medical care" OR "local doctors" OR "local doctor" OR "primary medical care" OR "primary health-care" OR "primary healthcare" OR "general practitioner" OR "general practitioners" OR "GP" OR "GPs" OR "family medicine" OR "general internal medicine" OR "general paediatrics" OR "primary care physician" OR "continuity of care" OR "first aid station" OR "first-aid station" OR "medical station" OR "home care" OR "home assistance" OR "home help")

AND ("artificial intelligence"[MeSH] OR "algorithms" OR "electronic prescribing" OR "Telehealth" OR "machine learning" OR "deep learning" OR "neural networks" OR "Computational Intelligence" OR "Machine Intelligence" OR "Computer Reasoning" OR "telemedicine"[MeSH] OR "m-health" OR "mhealth" OR "mobile health" OR "ehealth" OR "e-health" OR "digital health")

AND ("Medication use" OR "adverse drug events" OR "drug prescription" OR "medication errors"[MeSH] OR "prescription errors" OR "medication error" OR "medication adverse event" OR "drug error" OR "medication administration" OR "medication prescription" OR "medication use" OR "prescribing error" OR "dispensing error" OR "omission error" OR "wrong time error" OR "monitoring error" OR "compliance error")

Web Of Science

("primary care" OR "ambulatory care" OR "outpatient care" OR "basic health care" OR "basic health-care" OR "basic healthcare" OR "day-to-day health care" OR "first aid" OR "initial medical care" OR "local doctors" OR "local doctor" OR "primary medical care" OR "primary health-care" OR "primary healthcare" OR "general practitioner" OR "general practitioners" OR "GP" OR "GPs" OR "family medicine" OR "general internal medicine" OR "general paediatrics" OR "primary care physician" OR "continuity of care" OR "first aid station" OR "first-aid station" OR "medical station" OR "home care" OR "home assistance" OR "home help") AND ("artificial intelligence" OR "algorithms" OR "electronic prescribing" OR "Telehealth" OR "machine learning" OR "deep learning" OR "neural networks" OR "Computational Intelligence" OR "Machine Intelligence" OR "Computer Reasoning" OR "telemedicine" OR "m-health" OR "mhealth" OR "mobile health" OR "ehealth" OR "e-health" OR "digital health") AND ("Medication use" OR "adverse drug events" OR "drug prescription" OR "medication errors" OR "prescription errors" OR "medication error" OR "medication adverse event" OR "drug error" OR "medication administration" OR "medication prescription" OR "medication use" OR "prescribing error" OR "dispensing error" OR "omission error" OR "wrong time error" OR "monitoring error" OR "compliance error")

Cochrane

ID	Search
#1	primary care
#2	ambulatory care
#3	outpatient care
#4	basic health care

#5	basic health-care
#6	basic healthcare
#7	day-to-day health care
#8	first aid
#9	initial medical care
#10	local doctors
#11	local doctor
#12	primary medical care
#13	primary health-care
#14	primary healthcare
#15	general practitioner
#16	general practitioners
#17	GP
#18	GPs
#19	family medicine
#20	general internal medicine
#21	general paediatrics
#22	primary care physician

#23	continuity of care
#24	medical station
#25	home care
#26	home assistance
#27	home help
#28	m-health
#29	mhealth
#30	mobile health
#31	ehealth
#32	e-health
#33	digital health
#34	artificial intelligence
#35	algorithms
#36	electronic prescribing
#37	Telehealth
#38	machine learning
#39	deep learning
#40	neural networks

#41	Machine Intelligence
#42	Computer Reasoning
#43	telemedicine
#44	adverse drug events
#45	drug prescription
#46	medication errors
#47	prescription errors
#48	medication error
#49	medication adverse event
#50	drug error
#51	medication administration
#52	medication prescription
#53	wrong medication use
#54	prescribing error
#55	drug dispensing error
#56	drug omission error
#57	drug monitoring error
#58	drug compliance error

- #59 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
- #60 #28 OR #29 OR #30 OR #31 OR #32 OR #33#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
- #61 #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
- #62 #59 AND #60 AND #61

Supplementary materials 2: Additional characteristics of the included studies

Author, year country	Name of the intervention	Intervention description	Population targeted	Setting	Type of evaluated population	Type of patient or health care specialists	Duration of the intervention
Berner ES, 2006, US	The Intervention Rule (Nonsteroidal Anti-inflammatory Drug Gastrointestinal RISK)	"The Intervention Rule assessed six established risk factors for GI complications from NSAIDs: age, self-assessed health status, diagnosis of rheumatoid arthritis, steroid use, a history of GI hemorrhage or hospitalization for ulcer, and symptoms with NSAIDs. Users enter all six elements into the PDA via pull-down menus and tap a submit button on the PDA screen to receive the score and recommendation."	physicians, patients	primary care residency	at risk	Patients at risk of Gastrointestinal complications	6 months
Fried TR, 2017, US	Tool to Reduce Inappropriate Medications (TRIM)	TRIM (a web tool) extracts data about medications and chronic conditions from the EHR. These data serve as input for automated algorithms identifying medication reconciliation discrepancies, PIMs, and potentially inappropriate regimens.	patients	Primary care clinics	at risk	Patients aged 65 years and older prescribed ≥ 7 medications	12 months
Muth C, 2018, Germany	Prioritising Multimorbidities in Multimorbidity (PRIMUM)	The healthcare assistant conducted a checklist-based interview with patients on medication-related problems and reconciled their medications. Assisted by a computerised decision support system, the general practitioner optimised medication, discussed it with patients and adjusted it accordingly. The control group (CG) continued with usual care.	physicians	General practitioners ambulatories	at risk	Patients aged 60 years and older, with ≥ 3 chronic conditions, under pharmacological treatment with ≥ 5 long-term drug prescriptions with systemic effects	9 months
Gurwitz JH, 2008, US and Canada	Computerized provider order entry with clinical decision support system to prevent adverse drug events	For residents on the intervention units, the alerts were displayed in a pop-up box to prescribers in real time when a drug order was entered. The pop-up boxes were informational; they did not require specific actions from the prescriber and did not produce or revise orders automatically	physicians	Long-term care setting	at risk	In-patients	12 months
Rieckert A, 2020, Germany	Polypharmacy in chronic diseases: reduction of inappropriate medication and adverse drug events in older populations by	The intervention consisted of a computerised decision support tool providing a comprehensive drug review (see appendix figs 1a and 2a) generated from patient data recorded in the electronic case report form.	Physicians	General practitioners ambulatories	at risk	Adults aged 75 years and older using eight or more drugs on a regular basis	24 months

	electronic decision support (PRIMA-eDS)						
Tamblyn R, 2008, Canada	prescribing alerts generated by computerized drug decision support (CDDS)	Effectiveness of two approaches to medication alert customization: on-physician-demand versus computer-triggered decision support.	physicians, patients	ambulatory care	not at risk	Patients with at least one prescription by the study physician.	6 months
Tamblyn R, 2019, Canada	The medical office of the 21st century (MOXXI)	Physicians in the CDS group obtained information on each patient by downloading updates of dispensed prescriptions from the RAMQ drug-insurance program. These data were integrated into the patient's health record and categorized as having been prescribed by the study physician or by another physician. Alerts were instituted to identify 159 clinically relevant prescribing problems in the elderly, a list established previously by expert consensus:	physicians	Primary care physicians ambulatory	not at risk	Patients aged 66 years and older	13 months
Bhardwaja B, 2011, US	The Drug Renal Alert Pharmacy (DRAP) Program	Patient-specific Clcr data were transferred to the Pharmacy Information Management System (PIMS), enabling PIMS to trigger an alert when a potential medication error was detected—that is, when a target drug was ordered for a patient with a drug-specific Clcr cutoff value. In contrast to alerts that notify the provider at the point of prescription entry, when a potential error was detected in our system, the alert would notify the pharmacist and stop the dispensing process by preventing the prescription label from being printed. In lieu of the prescription label, a medication decision guide was printed for the pharmacist that outlined the process for intervening on the alert. The pharmacist then confirmed if there was an error by using the medication guide, and if needed, contacted the prescribing physician to discuss the potential problem. All pharmacist activities were electronically documented in PIMS.	pharmacists	ambulatory pharmacies	at risk	Patients at least 18 years old, with an estimated creatinine clearance of 50 ml/minute or lower, and not receiving dialysis	15 months

Tamblyn R, 2012, Canada	MOXXI	Intervention physicians received information about patient-specific risk of injury computed at the time of each visit using statistical models of nonmodifiable risk factors and psychotropic drug doses. Risk thermometers presented changes in absolute and relative risk with each change in drug treatment. Control physicians received commercial drug alerts.	physicians	Family physicians ambulatory	not at risk	Patients aged 65 and older who were prescribed psychotropic medication	12 months
Chrischilles, 2014, US	Iowa PHR (personal health record)	Iowa PHR is a web-based application that features a tabbed interface design. Users can enter, view, and print their current and past medicines, allergies, health conditions, and health event tracking over time. An embedded tutorial video provides assistance with the system. Iowa PHR displayed a message when a user entered a medication with an associated ACOVE-3 safety concern. The messages were displayed in three levels of increasing detail and complexity to facilitate tiered information take-up: a brief alert containing the basic reason for concern, a summary level that included recommended actions, and a detailed explanation of the alert.	patients	patient's home	not at risk	Adults age 65+	7 months
Clyne B, 2015, Ireland	OPTI-SCRIPT study (Optimizing Prescribing for Older People in Primary Care, a cluster-randomized controlled trial)	web-based pharmaceutical treatment algorithms for GPs that provided evidencebased alternative treatment options to PIP drugs, and tailored patient information leaflets	physicians, patients	Ambulatory care	not at risk	70 yo patients and older	11 months
Holt, TA et al, 2017, England	Effectiveness of a software tool (AURAS-AF [Automated Risk Assessment for Stroke in Atrial Fibrillation]) designed to identify people at risk of stroke, but not	Screen reminders appeared each time the electronic health records of an eligible patient was accessed until a decision had been taken over OAC treatment	patients	primary care practice	at risk	Patients with Atrial fibrillation but not receiving treatment with Oral Anti Coagulants to prevent stroke	6 months

	receiving treatment, during routine care						
Lopez-Picazo, JJ, 2011, Spain	OMI-ap + PRISMAp	3 different intervention group: delivery of the interaction report (report group), implementation of clinical educational sessions using the report data (session group), and faceto-face interviews between each family physician and a pharmacist who was specially trained to present the results of the report (face-to-face group)	physicians	Primary care centres	not at risk	All patients in the practice who were older than 14 years of age if they were taking more than 1 drug and therefore at risk for drug interactions	15 months
Matsuyama JR, (1993) France	Medication-event monitoring system (MEMS III)	The microprocessor in the cap records each opening as a presumptive dose, storing the date and time for later retrieval by a microcomputer.	patients	Ambulatory care	at risk	Patients with poor to fair metabolic control of diabetes mellitus were enrolled.	11 months

Supplementary materials 3: Results of quality assessment.

Author(year)	1	2	3	4	5	6	7	9	10	11	12	13	14	Overall
Berner ES, 2006	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Bhardwaja B, 2011	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	G
Chrischilles, 2014	Y	N	NR	NR	NR	Y	N	N	NR	Y	N	Y	Y	P
Clyne, B, 2015	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	F
Fried TR, 2017	Y	Y	Y	NR	N	Y	N	N	NR	Y	N	Y	NR	P
Gurwitz JH, 2008	Y	Y	Y	NR	NR	Y	Y	N	N	NR	N	NR	NR	P
Holt TA, 2017	Y	Y	Y	NR	Y	Y	NR	Y	NR	Y	Y	Y	Y	F
Lopez-Picazo JJ, 2011	Y	Y	Y	N	Y	Y	NR	NR	NR	Y	N	Y	Y	F
Matsuyama JR, 1993	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	G
Muth C, 2018	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Rieckert A, 2020	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	G
Tamblyn R, 2008	Y	Y	N	N	NR	Y	Y	N	Y	N	Y	Y	NR	P
Tamblyn R, 2012	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	G
Tamblyn R, 2019	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	F

Abbreviations: Y, yes; N, no; NR, not reported; G, good quality; F, fair quality, P, poor quality.

Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs)

Signalling questions:

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?
3. Was the treatment allocation concealed (so that assignments could not be predicted)?
4. Were study participants and providers blinded to treatment group assignment?
5. Were the people assessing the outcomes blinded to the participants' group assignments?
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?
9. Was there high adherence to the intervention protocols for each treatment group?
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?

13. *Were outcomes reported or subgroups analysed prespecified (i.e., identified before analyses were conducted)?*

14. *Were all randomized participants analysed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?*