The effects of clinical decision support system for prescribing medication on patient outcomes and physician practice performance: a systematic review and meta-analysis

Sharare Taheri Moghadam
Iran University of Medical Sciences
Farahnaz Sadoughi (sadoughi.f@iums.ac.ir)
Iran University of Medical Sciences https://orcid.org/0000-0002-7452-0864
Farnia Velayati
Iran University of Medical Sciences
Seyedjafar Ehsanzadeh
Iran University of Medical Sciences
Shayan Poursharif
Shaheed Beheshti University of Medical Sciences

Research article

Keywords: computerized clinical decision support systems, Medication prescription, Systematic review.

Posted Date: September 30th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-18677/v3

Version of Record: A version of this preprint was published on March 10th, 2021. See the published version at https://doi.org/10.1186/s12911-020-01376-8.

Abstract

Background: The clinical decision support systems (CDSSs) for prescribing is one of the technologies aimed at improving physician practice performance and patient outcomes by reducing medication prescription errors. This study, thus, was conducted to investigate the effect of various CDSSs on physician practice performance and patient outcomes.

Methods: This systematic review was conducted by searching in PubMed, EMBASE, Web of Science, Scopus, and Cochrane Library from 2005 to 2019. Two researchers independently evaluated the studies. Any discrepancies over the eligibility of the studies between the two researchers were then resolved by consulting a third researcher. Finally, we extracted data from the articles. Then, we conducted a meta-analysis based on medication subgroups, CDSS type subgroups, and outcome categories. Also, we presented a narrative form of the findings. In the meantime, we applied random-effects model to estimate the effects of CDSS on patient outcomes and physician practice performance with 95% confidence interval. Q statistics and I^2 were then used to measure heterogeneity.

Results: Based on the inclusion criteria, 45 studies were considered eligible for the analysis in this review. The CDSS for prescribing medications/COPE were used for various diseases such as cardiovascular diseases, hypertension, diabetes, gastrointestinal and respiratory diseases, AIDS, appendicitis, kidney disease, malaria, high blood potassium, and mental diseases. Meanwhile, other cases such as the concurrent prescription of multiple drugs for patients and its effects on the above-mentioned outcomes were evaluated. The analysis shows that in some cases the application of CDSS provides positive effects on patient outcomes and physician practice performance (std diff in means = 0.114, 95% CI: 0.090 to 0.138). Also, it was statistically significant for outcome groups such as those showing improved outcomes on physician practice performance and patient outcome or both. However, no significant difference was observed between some other cases and conventional methods. We think that this could be due to the disease type, the quantity, and the type of CDSS requirements that influenced the comparison. Overall, all types of CDSSs have positive effects on outcomes including combinational types and other types that only cause messages when appropriate and necessary.

Conclusions: Our findings suggest that positive effects of the CDSS can be attributed to factors such as user-friendliness, compliance with clinical guidelines, patient and physician cooperation, integration of electronic health records, CDSS and pharmaceutical systems, consideration of the views of physicians in assessing the importance of CDSS alerts, and the real-time alerts in the prescription.

Background

The health care industry is influenced by factors that raise costs and reduce health services quality [1]. One of such factors is prescribing errors and drug interactions that are common among medical errors; thus, no need to mention that eliminating such errors is of utmost importance in order to prevent the side effects of drugs and other associated implications [2]. One of the most important medical errors that can result in morbidity, mortality, and extended hospital stay is an inappropriate prescription medication [3]. Due to a lack of accurate documentation of medical records as well as a lack of data recording and reporting systems, we think that the main reason for most prescribing errors is a lack of adequate information about patients or their medication [4]. Thus, Clinical Decision Support System (CDSS) technology is widely used in the field to reduce prescribing errors. CDSS provides reminders and alerts that result in a reduction in prescribing errors; meanwhile, it improves physician performance and patient outcome [5]. Based on patient conditions, CDSS is used to manage complex activities from initiation to supervision and completion of medical treatment as well as providing suggestions to physicians [6].

Different types of CDSS systems based on clinical guidelines, alerts, reminders, instructions and recommendations are listed in this study. For instance, the alert-based type of CDSS uses the reminders and drug interaction alerts [7]. The advantages of CDSS include reducing and prevention of prescribing errors through using alerts and immediate reminders, automatic dosage error checking, and drug interaction. Also, E-prescribing systems with clinical decision support have the potential for reducing errors and improving clinical practice [8]. Assessing the effects of all computerized health care interventions is critical because they influence the care process and the patient outcome [9]. Over the past years, several systematic reviews have been conducted with the aim of exploring the effects of the CDSSs on prescribing errors or CPOEs on patient safety, process of care, or physician performance. In 2003, a systematic review through analyzing two main databases showed a decrease in medication errors by the use of CDSS; however, the outcome details were not released [10]. Another systematic review was also conducted in 2008 by focusing on the effects of CPOEs on medication errors. The results of this study showed a decrease in the risk failure error in 23 out of 25 included studies. This study demonstrated the efficacy of CPOEs, however, it did not explain patient outcome in the study [11]. Along the same line, another systematic review examined the effect of CDSS on prescribing errors in 2010. While this study excluded the RCT studies, its results demonstrated a little improvement on patient outcome. However, a significant improvement was seen on the process of care outcome [3]. In another study in 2015, a review on systematic reviews was conducted to examine the CDSS quality reports on patient safety. Results of this study showed improvement on outcomes. However, authors claimed that they need to include more studies with larger sample data in order to be able to further confirm the CDSSs effect on outcomes [12]. In this review on systematic reviews, the most recent sample was conducted in 2014 on a limited medication laboratory domain for some specific diseases [13]. Also, another systematic review was carried out in 2017 to discuss the effects of different kinds of alerts on patient safety and physician outcomes. surprisingly, the results of the study revealed no significant difference between different kinds of alerts except for several interrupting alerts that did not lead to any improvement in the outcomes [14]. In another systematic review, CPOE was used with pediatrics. The aim of this study was to find the errors, and the results demonstrated the usefulness of the system [15].

To this end and given the literature we reviewed so far, most studies have shown an upward trend with respect to the effectiveness of CDSSs compared to traditional clinical practices. Related literature on CDSS have also shown improvement in physician performance, however, the impact of these systems on patient outcomes is yet unknown [3, 16-18]. Due to the fact that CDSSs have been confirmed as effective tools in minimizing prescribing errors, we thus considered all types of prescription CDSSs since 2005 for all diseases and patients in accordance with the inclusion criteria in our study. Given the significance of CDSSs, we in the present study examine the effects of CDSSs on physician prescription performance and patient outcomes.

Methods

In this study, we used a systematic review and meta-analysis. The method section is divided into some subsections, namely Search strategy, Inclusion/exclusion criteria, Screening and data extraction, Quality assessment, data synthesis, and statistical analysis. Each subsection is described in more details, as follows.

Search strategy

The initial search was conducted in PubMed in order to identify the keywords. We used Medical Subject Headings (MeSH) in PubMed, Emtree in EMBASE and other words/phrases used in similar articles as the basis of search strategy. Then, we conducted the search in PubMed, EMBASE, Web of science, Scopus and Cochrane Library. We conducted the search in 2018 and used the approach designed for each database without language restrictions. Alerts have been used to access published articles after the search date and all the databases alerts were reviewed until July 2019. Also, reference tracking and citation search were used to augment the retrieval of eligible studies. An example of the full search strategy is given below:

(("clinical decision support system*" OR "clinical Decision Support*" OR "computerized decision support tool*" OR "Information System*" OR "computerized physician order entry*" OR "hospital information system*" OR "computerized medical record system*" OR "point-of-care system*" OR "medical order entry system*" OR "computer-assisted decision making" OR "computerized medical record system*" OR "reminder system*" OR "computer-assisted diagnosis" OR "clinical informatic*")) AND ("medical mistake*" OR "medical error*" OR "therapeutic error*" OR "diagnostic error*" OR "drug interaction*" OR "drug dose-response relationship" OR "drug administration schedule" OR "drug monitoring").

Registration number on PROSPERO is CRD42018079936 [19].

Inclusion/exclusion criteria

We used the PICO criteria to conduct the search strategy: Participants (P) were randomized clinical trial (RCT) articles; Intervention (I) was any type of CDSS/CPOE systems that contributed toward prescribing process; Comparator (C) was those papers that used other systems or used no system; Outcome (O) was any patient outcomes and physician performance outcomes. In this review, we included randomized CDSS clinical trial articles such as alert-based, recommendation, instruction, and reminder-based systems to evaluate their effects on the behavior of patients and providers. In selecting an article for this study, we first prepared a list of questions whose answers form the main inclusion criteria. Here are the questions:

- Does the study focus on evaluating the CDSS for prescribing / CPOE based on any category of patient outcomes and physician performance outcomes?
- Has the study been a randomized clinical trial in which patient care has been compared with and without a CDSS for prescribing/ CPOE ?
- Have the CDSS for prescribing/ CPOE been used by experts such as physicians, specialists, and residents in these studies?
- Does the decision support system/ CPOE evaluate patient-specific information in the form of management or probability options or recommendations for physicians?
- Has practice performance been described as a measure of the improved care process, or the outcome of patients with any improvement in the study?

Cohort or Non-experimental studies were excluded. Also, we excluded studies in which the system was used solely by students not experts, or "no" was the answer to the five key questions.

Screening and data extraction

The papers were screened in three different stages based on title, abstract, and full text. Meanwhile, we used PRISMA checklist as a reporting guideline in our study. PRISMA checklist is a known standard checklist for systematic review reports [20]. Evaluation was conducted by two authors of this study, (S.T) and (F.V). All phases of selection, screening of the articles, and extraction of data were independently conducted in order to avoid bias. Any discrepancies between researchers were resolved by consulting an expert in this field, (F.S). The extracted data items from included studies are: first author, year of publication, country, type of disease, design of study, intervention, type of intervention, number of centers/ providers/ patients, patient outcomes, provider outcomes, outcome impact, and statistical output.

Quality assessment

We assessed quality of studies by Jadad scale, the Oxford research methods scoring system for bias in clinical trials [21, 22]. We also determined the quality score by adding total scores of each sample by considering zero and one for the presence of items such as randomization, blindness, removal, dropouts, inclusion criteria, assessment of findings, and explanation of statistical analysis

Data synthesis and statistical analysis

We extracted the data from eligible articles through using a structured data extraction process. The results of studies were then presented in a descriptive-narrative form. In the meantime, we conducted a meta-analysis with Comprehensive Meta-Analysis (CMA) statistical software [23]. For all the analyzed outcomes, measures of both CDSS and control groups were summarized as mean standard deviation for each study and as comparisons of pooled estimates within the intervention group versus the control group. An effect size of std diff in the means of change in outcomes between groups was presented as standard error and 95% CI. An effect size with a lower limit greater than 0 indicates that the intervention group has a positive effect on the outcome. CDSS group has no impact on the outcome compared with the control group when lower limit is slower than 0. Also, when std diff in means equals 0, it indicates that the change in outcomes was similar between the CDSS and control groups. The meta-analysis by using a random-effects model was conducted to estimate the physician practice behaviour and patient outcome. We used Q statistics and I^2 to calculate heterogeneity (I^2 greater than 50% is considered heterogeneous). Sensitivity analysis was also conducted to define and reduce the sources of heterogeneity. In the next step, the funnel plot was used to assess publication bias. Funnel plot is a useful tool for assessing possible visual publication bias[24].

Results

Based on the inclusion criteria, 45 studies were considered eligible for the analysis in this review (Fig.1). The evaluation of the reviewed studies provided us with enlightening information with respect to the aims of the research, types of electronic prescribing systems, types of diseases, and patients. Table 1 shows that the results of the quality assessment for trials were acceptable.

Table 1. Quality assessment for trials.

nor (year of lication)	Was research described as randomized?	Was approach of randomization appropriate?	Was research described as blinding?	Was approach of blinding appropriate?	Was there a presentation of withdrawal and dropouts?	Was there a presentation of the inclusion / exclusion criteria?	Was approach used to assess outcome?	Was the approach of statistical analysis described?	Total
ler et 2014) [25]	1	0	0	0	1	0	1	1	4
nan et 2016) [26]	1	1	0	0	1	1	1	1	6
et 2018) [27]	1	1	1	1	1	1	1	1	8
sson et 2018) [28]	1	1	1	1	1	1	1	1	8
zaglia et 2016) [29]	1	1	1	1	1	0	1	1	7
sen et 2017) [30]	1	1	1	1	1	1	1	1	8
l et al. 18) [31]	1	1	0	0	1	1	1	1	6
u-zaheya et)17) [32]	1	1	0	0	0	1	1	1	5
nsari et al.)15) [33]	1	1	0	0	0	0	1	1	4
stensen et)10) [34]	1	1	1	1	1	1	1	1	8
jes et al . .8) [35]	1	1	1	1	0	1	1	1	7
se et al. .8) [36]	1	1	0	0	1	0	1	1	5
stelo- ez et 2016) [37]	1	1	0	0	1	1	1	1	6
nz et 2012) [38]	1	1	1	1	1	1	1	1	8
rloet et 2014) [39]	1	1	1	1	0	0	1	1	6
rloet et 2012) [40]	1	1	1	1	0	1	1	1	7
rts et al. .7) [41]	1	1	0	0	1	0	1	1	5
et al. 11) [42]	1	1	0	0	1	1	1	1	6
rsen et al. 17) [43]	1	1	1	1	1	1	1	1	8
rgeois et	1	1	1	1	1	1	1	1	8

2010) [44]									
czyk et 2017) [45]	1	1	1	1	1	0	1	1	7
ermott et 2014) [46]	1	1	1	1	1	1	1	1	8
inn et 2013) [47]	1	1	0	0	1	1	1	1	6
ammed et 2016)[48]	1	1	1	1	0	1	1	1	7
erman et 2013) [49]	1	1	0	0	1	0	1	1	5
eleches et 2011) [50]	1	1	0	0	1	1	1	1	6
nsino et 2012) [51]	1	1	1	1	1	0	1	1	7
ishu et al. 6) [52]	1	1	1	1	1	1	1	1	8
r et al. 2) [53]	1	1	1	1	1	1	1	1	8
et al. 11) [54]	1	1	0	0	1	0	1	1	5
h et al. 8) [55]	1	1	1	1	1	1	1	1	8
m et al. 0) [56]	1	1	0	0	1	1	1	1	6
m et 2010) [57]	1	1	1	1	1	1	1	1	8
tt et al. 7) [58]	1	1	1	1	0	0	1	1	6
voort et 2014) [59]	1	1	1	1	0	1	1	1	7
ler et al. 9) [60]	1	1	1	1	1	1	1	1	8
e et 2013) [61]	1	1	1	1	1	1	1	1	8
mann et 2015) [62]	1	1	1	1	1	0	1	1	7
ain et al. 1) [5]	1	1	0	0	1	1	1	1	6
chin et 2011) [6]	1	1	0	0	1	1	1	1	6
fey et al. 2) [63]	1	1	0	0	1	1	1	1	6
rs et 2011) [64]	1	1	1	1	1	1	1	1	8

hout et al. .8) [65]	1	1	1	1	1	1	1	1	8
is et 2013) [66]	1	1	1	1	0	1	1	1	7
blyn et 2012) [67]	1	1	1	1	0	1	1	1	7
Total point earned Quality Score									303 82.34

1 stands for the answer “yes”, and 0 stands for the answer “no”.

The findings also showed that the effect of CDSS was evaluated in several diseases such as cardiovascular disease, high blood pressure, and diabetes, or cases such as simultaneous prescription of drugs. Findings from the analyzed studies are presented in Table 2 in which * stands for p values and indicates a statistically significant difference.

The number of studies based on multiple evaluation results and types of studies are also shown in Fig. 2 and Fig. 3, respectively. Table 2 shows the variety of outcomes for different medication scopes (for example, the outcome "Increasing the ratio of prescribing prophylaxis" is specific for cardiovascular domain, or the outcome "Reducing blood pressure" is related to hypertension disorders). Also, Table 2 shows various kinds of CDSSs for prescribing that are classified according to alerts, reminders, recommendations, instruction, and combination of these types.

Table 2. Data extracted for CDSS trials

uthor (year of ublication)	Disease type	No. of hospitals/physicians/patients	Type of computer system	Outcome	P value
eeler et . (2014) [25]	cardiovascular	-/-/15736	Computerized system equipped with reminder to prevent intravenous thromboembolism	Increasing the ratio of prescribing prophylaxis 6-24 hours after admission/transfer	<0/0001 P value * *0/03
ckman et . (2016)[26]	cardiovascular	15 /-/1493	CDSS providing treatment recommendation	Reducing disagreement among physicians	*0/02
u et . (2018) [27]	cardiovascular	58/-/patients	CDSS in mobile devices	Increasing secondary preventive prescriptions after 15 months in the intervention group	From 73/7 to 86/8 percent
arlsson et . (2018) [28]	cardiovascular	43 /-/14134	CDSS equipped with alerts for patients with atrial fibrillation	Increasing the prescription of anticoagulation after 12 months	*0/01
lazzaglia et . (2016) [29]	cardiovascular	-/197 /-	Alert-based CDSS for patients using cardiovascular drugs	Increasing prescription of anti-blocking drugs	*P value<0/001
ielsen et . (2017) [30]	cardiovascular	-/-/191	CDSS to regulate the rate of warfarin use	Increasing the time outcome in the scope of treatment	0/67 Percent
atel et al. 2018) [31]	cardiovascular	23 /178/-	Framework for the UK Medical Research Council (MRC)	Increasing the number of anti-inflammatory/lipid-lowering drugs	*P value <0/001
khu-zaheya et . (2017) [32]	cardiovascular	-/-/160	Short message reminder system in adherence to a healthy nutritional diet, drugs, cessation of smoking	Increasing prescriptions in the short message group	*0/001
honsari et al. (2015) [33]	cardiovascular	-/-/62	Web-based software equipped with text reminders for patients with chronic coronary syndrome	Increasing adherence to drug usage	*P value<0/01
hristensen et . (2010) [34]	hypertension	-/-/398	Reminder in patient admission and blood pressure control	Reducing blood pressure after 12 months	0/06
uitjes et al . 018 [35]	hypertension	16/-/532 at pre implementation phase,-/-/1762 at post implementation phase	Innovative strategy including decision support system, audit and feedback	For the control group, reducing the secondary outcome of infant morbidity after implementation	*P <0/0001 value
uhse et al. 018) [36]	diabetes	22/-/363	ISDM-P program composed of CDSS and sessions	Reduction in faulty knowledge causing risk	*P value <0/001
erestelo-érez et . (2016) [37]	diabetes	14/29/168	The CDSS selects statin with an estimate of cardiovascular disease risk	Increasing satisfaction of decision making	*0/009

áenz et .. (2012) [38]	diabetes	66/-/697	The CDSS including patient data, glucose profile and recommendation for physician	Increasing long-term blood sugar using between group differences	*0/01
ervloet et .. (2014) [39]	diabetes	-/-/161	Real-time monitoring system for drug use by applying short message for diabetic patients	Increasing adherence in the group receiving short messages	*P value <0/001
ervloet et .. (2012) [40]	diabetes	-/-/104	Real-time medication monitoring system equipped with short message reminder for patients with type two diabetes	Increasing the drug dosage in one hour during a six month period	*0/003
eurts et al. 2017) [41]	digestive diseases	-/-/222	Recommendation decision support system	Increasing the standard use of oral rehydration solution	*P value <0/05
ill et al. 2011) [42]	digestive diseases	27/119/5234	CDSS equipped with alert functionality and integrated with electronic health record and clinical guidelines	Increasing the receiving care on the basis of instructions for patients with low-dose aspirin use (25%)	1/30
etersen et al. 2017) [43]	digestive diseases	General physicians	CDSS equipped with risk notification service	Increasing the drug prescription in patients with risk above 5 percent	*0/01
ourgeois et .. (2010) [44]	pulmonary diseases	-/112/-	Chronic obstructive pulmonary disease pattern in electronic health records	Reduced antibiotic prescriptions in visits by using templates	*0/02
uszczyk et .. (2017) [45]	pulmonary diseases	-/79/-	Electronic health records combined with databases of Electronic medical records such as links to clinical practice research data	Reducing unnecessary prescription of antibiotics	*0/04
lcdermott et .. (2014) [46]	pulmonary diseases	-/103/-	DSS and electronic learning	Increasing physicians self-efficacy	*0/02
lcginn et .. (2013) [47]	pulmonary diseases	-/-/984	A real time and unified CDSS during care combined with integrated clinical prediction rules	Reduced antibiotic prescription	*0/008
lohammed et .. (2016) [48]	pulmonary diseases	-/-/2207	Short message as a two-way reminder	Inability to be effective in treatment success rate	0/76
ckerman et .. (2013) [49]	pulmonary diseases	-/29/33	CDSS in Electronic Health Records	Reducing excess prescription of antibiotics	*0/003
op-eleches et .. (2011) [50]	AIDS	-/-/428	Short-message reminder systems	Reducing the number of treatment interruptions	*0/02

			(daily and weekly) in the antivirus treatment process	in both groups receiving weekly messages	
vansino et . (2012) [51]	appendicitis	-/7/-	Systematically developed order set for using the decision support system	Increasing the follow-up clinical guidelines for systematic prescriptions compared to case prescriptions	*0/003
wdishu et al. :016) [52]	kidney diseases	-/514/1278	DSS Warning	An increase in not taking medication or changing dose of inadequate drugs	P* value<0/0001
rler et al. :012) [53]	kidney diseases	-/44/404	Software including a database in coronary resection	Reduction in the amount of medication received in the intervention group in excess of the prescribed dose	*0/04
ox et al. 2011) [54]	taking multiple medications	-/-/216	The CDSS with medication order entry in order to determine the initial drug dosage	An increase in the number of prescriptions for initial drug use	*P value <0/0001
				An increase in the conformity of prescribed medication percentage with the suggested medication	*P value <0/00001
luth et al. :018) [55]	taking multiple medications	-/71/465	Reminder-based CDSS	Ineffectiveness of drug prescriptions after 6 and 9 months	0/31, 0/18
crom et al. :010) [56]	taking multiple medications	-/1981/-	Computerized drug prescribing systems equipped with hard-alerted CDSSs	Increasing the percentage of appropriate alerts that have been responded to by physicians in the intervention group compared to the control group	57/2 vs. 13/5
crom et . (2010) [57]	taking multiple medications	-/1963/-	Computerized medication order entry system equipped with various alerts	Reduction in the appropriate response of physicians to alerts during 17 months	*0/007
lliott et al. :017) [58]	taking multiple medications	-/-/110	Prescribing CDSS for creating drug treatment recommendations such as drug-drug and drug-gene interaction	Reducing the average number of days re-hospitalized 60 days after discharge	*0/007
				Reducing the combination of re-hospitalizations, emergency ward visits and morbidity 60 days after discharge	*0/005
ruxvoort et . (2014) [59]	Malaria	82/-/-	Text message reminders for Malaria treatment	Physicians' knowledge in using Lumefantrine orthometer	*P value <0/0001
eeler et al.	increasing	29/-/4861	Three types of CDSSs	An increase in the	*P value

:019) [60]	blood potassium		including reminder, high potassium and calcium alerts	average monitoring time of potassium level	<0/001
uke et . (2013) [61]	increasing blood potassium	-/1029/-	Drug-drug interaction alerts for patients in danger of high potassium level	A decrease in the conformity rate in normal risk patients for increased potassium	*P value <0/01
schmann et . (2015) [62]	increasing blood potassium	15/-/37000	Electronic health records equipped with alerts and reminders systems	A decrease in the reaction time of reminders for physicians monitoring alerts of potassium level	*0/04
urtain et al. :011) [5]	medication prescription for the patient	185/-/-	CDSS for drug distribution in treatment with proton pump	Reduction in the approved percentage of inhibitor intervention proton pump which is registered by the pharmacologist	*P value <0/001
urchin et . (2011) [6]	medication prescription for the patient	-/3703/-	Hard alert systems to facilitate medication services	Increasing overall efficiency of system functionalities prior to admission	*P value <0/0001
riffey et al. :012) [63]	medication prescription for the patient	-/-/1407	CDSS for recommending drug dosage	Increasing the number of prescriptions by recommending the determined system dose	*P value <0/0001
[yers et . (2011) [64]	medication prescription for the patient	-/59/-	Computerized alerts for manual or automatic correction of medical abbreviation	Reducing the significant number of inappropriate abbreviations	*0/02
an :iphout et al. :018) [65]	medication prescription for the patient	2/115/1094	CDSS integrated with training session	More efficient medical summary	*0/03
Villis et . (2013) [66]	medication prescription for the patient	-/-/2219	CDSS alerts for the primary care clinic	A lack of difference in the rate of patient adherence to treatment, drug treatment significance, economic and clinical outcomes in three groups	*0/01
amblyn et . (2012) [67]	mental disorders	-/81/5628	DSS equipped with three types of alerts	Reduction in dose of drugs after one year for antipsychotics	*0/02

The effect of CDSS on cardiovascular diseases

For patients admitted to the hospital, the level of venous thromboembolism prophylaxis and the proportion of prescribed prophylaxis increased during 6-24 hours after admission [25]. In another study, discrepancies among physicians over the thromboprophylaxis treatment decreased with the help of CDSS by providing treatment recommendation (p value = 0.02) [26]. In other studies, alert-based CDSSs have positive effects on physician performance and treatment improvement in anti-inflammatory and lipid-lowering drugs [28, 29, 31]. By following medical recommendations in another study, physicians in the intervention group were able to improve the prescribing level of secondary preventive medication with the help of a regular CDSS [30]. Also, in other trials, the short messages of the program had a positive effect on patient adherence to medication, diet, and the cardiovascular diseases (p value<0.01) [32, 33].

The effect of CDSS on hypertension

In one study, the electronic monitoring and recall program had no effect on blood pressure reduction and the admission of patients [34]. However, in another study, the patient outcome improved after the implementation of the CDSS [35].

The effect of CDSS on diabetes

In some studies, the Real Time Medication Monitoring (RTMM) system, equipped with a short message reminder, improved precision of patients' compliance and taking forgotten dosages [36, 37, 39, 40]. In another study, HbA1c and group differences were greater in the intervention group using recommendation CDSS than that of the control group [38]. The use of statins (p value = 0.03) and the problem areas in diabetes (PAID) (p value=0.01) improved in another study for intervention group that used CDSS [37].

The effect of CDSS on digestive diseases

In all studies, the CDSS had an effect on prescribing non-steroidal anti-inflammatory drugs, proton pump inhibitors, and increasing the standard use of oral rehydration solution without any difference in other results [41-43]. Also, alert-based CDSS improved the quality of patient care in another study [42].

The effect of CDSS on pulmonary diseases

In some trials, the use of CDSS which was integrated with electronic health record or prediction rules resulted in a decrease in the prescription of antibiotics and macrolides; therefore, it helped minimize the inappropriate use of antibiotics (p value = 0.0005), lower the resistance to antibiotics (p value = 0.04), and enhance primary care [44-47, 49]. The patients adhered to the reminder message in another study; however, the messages did not affect therapy success [48].

The effect of CDSS on AIDS

In the reviewed study, it was shown that the reminder system for short text messages had a positive effect on the treatment process. Also, the length of the messages had no significant effect on patients' compliance rates (p value = 0.12) [50].

The effect of CDSS on appendicitis

This study showed that the system's systematically developed order set, which used clinical guidelines, improved the system usability (p value=0.05) and reduced system-related problems with respect to unfamiliarity with the system (p value=0.05). This is a result of Computerized Provider Order Entry (CPOE) which improved efficiency, quality, and safety [51].

The effect of CDSS on kidney diseases

One study showed the positive effect of multipurpose intervention on creatinine value estimation and dose adjustment to reduce the insufficient dosage of primary care drugs [53]. In the other study, the appropriate prescription rate for kidney problems was rather low, contrary to the results of the former study. Furthermore, the effectiveness of the CDSS with physician guidelines has been increased, especially for new versions [52].

The effect of CDSS on taking multiple medications

In one study, 194 hard-alerted CDSSs resulted in delayed drug treatment for four patients who required immediate treatment. This suggests that adverse events of these systems need to be evaluated and monitored [56]. In another study, the CDSS improved the primary dose of medication, time intervals for drug use, and drug concentration which is to be injected intravenously compared to standard doses [54]. Also in another study, the average number of readmission days for each patient and the combination of re-hospitalization and emergency ward visits in the 30 days after hospital discharge was not different between the intervention group using recommendation CDSS and control groups [58]. In some trials, there was no discrepancy between the outcomes of the dosage rate and the Modified Medication Appropriateness Index (MMAI). Meanwhile, no discrepancy was seen among improper medication prescribing (p value = 0.48), the Medication Regimen Complexity Index, and the mean pain outcome difference after 6 months (p value = 0.13) and 9 months (p value = 0.78) between the intervention group using alert or reminder CDSS and the control group [55, 57].

The effect of CDSS on Malaria

The use of text messages in the study did not affect the behavior of patients in completing the course of medication for the full duration of treatment. However, when the side effects were low (p value = 0.02), it had effects on the continuous use of the medication. In addition, text messages had an effect on the physicians' knowledge in using medication with fatty foods (p value<0.0001) [59].

The effect of CDSS on increasing the level of blood potassium

In one study, there is no statistical difference in terms of following alerts and patients' compliance rate between the control and intervention groups. However, the physicians' compliance rate improved at the medium potassium level from 3 to 3.9 (mili-equivalents/liter) (p value<0.01) [61]. Due to the rapid response of physicians to program alerts for high potassium levels in the intervention group, the positive effect of the system on physician performance was evident in another study (p value = 0.01) and a high level of potassium (p value = 0.05). Thus, patient safety could be increased [62]. However, in another study in this section, the time lapse in hyperkalemia monitoring (p value = 0.20) and the incidence rate of hyperkalemia (p value = 0.22) did not differ significantly even with the use of three different kinds of reminder and alert-based CDSSs [60].

The effect of CDSS on medication prescription for patients

Based on the results of some studies, the regular or alert based CDSSs resulted in better drug prescriptions for the proton pump inhibitor and a reduction in abbreviation prescriptions [5, 64]. Also, in the other studies, the overall utilization of system functionalities, system utilization between two time laps (p value<0.0001), number of users (p value<0.0001), and physicians' compliance regarding drug recommendations given by the CDSS improved medication prescriptions which eventually resulted in reduced side effects (p value = 0.02) and harm to patients due to the lower number of errors regarding the alert-based CDSS [6, 63]. In one study, there was no difference in medication prescription among physicians (p value=0.14); however, the percentage of skilled questions answered for the intervention group equipped with training CDSS (p value = 0.01) improved [65]. In another study, alert-based CDSSs have been effective in identifying evidence-based pharmacotherapies (EBP). Meanwhile, the compliance with treatment by health care managers have had no effect on patient outcome [66].

The effect of CDSS on mental disorders

CDSS alerts resulted in reduced risk of injury and reduced dose of antipsychotics and anticoagulants (p value = 0.03) during an interval of one year. Therefore, CDSS reduced the risk of injury (p value = 0.02) [67].

Statistical and sensitivity analysis

The pooled std diff in means of p values showed a significant difference between the CDSS and the control group (std diff in means = 0.091, 95% CI: 0.072 to 0.109, standard error = 0.010). 95% CI for the effectiveness was drawn for each study in the horizontal line format (Q = 209.2, df = 45, p value = 0.0002, I^2 = 78.492, Tau^2: 0.004) (Fig. 4). Due to the high heterogeneity of results, sensitivity analysis was performed. In doing so, we excluded these studies: khonsari et al [33]; Ackerman et al. [49]; Avansino et al. [51], and Bruxvoort et al. [59]. Because of the limited number of patients in these trials, we decided to exclude them from our meta-analysis. In Tables 2 and 3, the characteristic of these studies are extracted in narrative results. The findings indicate that heterogeneity improved considerably after sensitivity analysis (Fig. 5). (Q = 164.8, df = 41, p value = 0.0001, I^2 = 75.136, Tau^2: 0.003). After this change, the overall effects of CDSS for prescribing medication on patient outcomes and physician practice performance based on the random effect model was statistically significant (std diff in means = 0.84, 95% CI: 0.067 to 0.102).

Subgroup analysis for medication scope

Fig. 5 shows the meta-analysis results for each subgroup of medication scope and the total analysis. Subgroup analysis is performed on different medication groups because there were common outcomes in related similar medication scope studies. The subgroup analysis showed a significant difference between CDSS and control groups for medication scopes namely as hypertension: (std diff in means = 0.187, 95% CI: 0.102 to 0.272); increasing blood potassium: (std diff in means = 0.036, 95% CI: 0.006 to 0.066), multiple medications: (std diff in means = 0.208, 95% CI:0.084 to 0.332), AIDs: (std diff in means = 0.241, 95% CI:0.038 to 0.444), kidney disorders: (std diff in means = 0.133, 95% CI:0.073 to 0.193), diabetes: (std diff in means = 0.381, 95% CI:-0.223 to 0.539), cardiac: (std diff in means = 0.073, 95% CI:0.035 to 0.111), mental disease: (std diff in means = 0.062, 95% CI:0.010 to 0.114), medication prescription for patients: (std diff in means = 0.157, 95% CI:0.094 to 0.219), and pulmonary disease: (std diff in means = 0.079, 95% CI:0.014 to 0.144). However, there was no significant difference between the intervention and control group for digestive diseases: (std diff in means = 0.182, 95% CI: -0.072 to 0.437). Fig. 5 shows the forest plot for subgroup meta-analysis. We, however, eliminated malaria and appendicitis diseases due to the decrease of heterogeneity among studies. We then described malaria and appendicitis diseases in narrative results. Also, Fig. 6 and Fig. 7 show the number of studies associated with each country and type of CDSS.

Categorization of Outcomes

Physician practice performance and patient outcome are presented in Table 3 as primary outcome and are categorized based on the summary of the outcome concept and the impact of CDSS as outcome category. Improvement or neutrality in outcomes are shown by plus or zero in Table 3. Outcome categorization of outcomes was conducted because similar outcomes may have different impacts on various diseases. For instance, the outcome "decrease prescribing" may have positive effect on some diseases and no effect on other medication domains.

Table 3. Outcome classification for trials

Author (year of publication)	Primary Outcome	Outcome summarization	Outcome impact	Outcome Category
Beeler et al. (2014) [25]	Increasing the ratio of prescribing prophylaxis 6-24 hours after admission/transfer	Increasing prescribing	+	physician practice performance improved
Eckman et al. (2016) [26]	Reducing disagreement among physicians	Reducing disagreement among physicians	+	
Du et al. (2018) [27]	Increasing secondary preventive prescriptions after 15 months in the intervention group	Increasing prescribing	+	
Karlsson et al. (2018) [28]	Increasing the prescription of anticoagulation after 12 months	Increasing prescribing	+	
Mazzaglia et al. (2016) [29]	Increasing prescription of anti-blocking drugs	Increasing prescribing	+	
Patel et al. (2018) [31]	Increasing the number of anti-inflammatory/lipid-lowering drugs	Increasing prescribing	+	
Perestelo-pérez et al. (2016) [37]	Increasing satisfaction of decision making	Increasing satisfaction of decision making	+	
Sáenz et al. (2012) [38]	Increasing long-term blood sugar using between group differences	Increasing prescribing	+	
Geurts et al. (2017) [41]	Increase in standard use of oral rehydration solution	Increasing prescribing	+	
Petersen et al. (2017) [43]	Increase in drug prescription in patients with risk above 5 percent	Increasing prescribing	+	
Bourgeois et al. (2010) [44]	Reduced antibiotic prescriptions in visits by using templates	Reducing prescribing	+	
Juszczyk et al. (2017) [45]	Reducing unnecessary prescription of antibiotics	Reducing prescribing	+	
Mcdermott et al. (2014) [46]	Increasing physicians self-efficacy	Increasing physicians efficacy	+	
Mcginn et al. (2013) [47]	Reduced antibiotic prescription	Reducing prescribing	+	
Avansino et al. (2012) [51]	Increase in following clinical guidelines for systematic prescriptions compared to case prescriptions	Increase in following clinical guidelines	+	
Awdishu et al. (2016) [52]	Increase in not taking medication or changing dose of inadequate drugs	Reducing prescribing	+	
Erler et al. (2012) [53]	Reduction in the amount of medication received in the intervention group in excess of the prescribed dose	Reducing prescribing	+	
Cox et al. (2011) [54]	Increase in the number of prescriptions for initial drug use	Increasing prescribing	+	
Strom et al. (2010) [56]	Increasing the percentage of appropriate alerts that have been responded to by physicians in the intervention group compared to the control group	Increasing the percentage of appropriate alerts	+	
Beeler et al. (2019) [60]	Increase in the average monitoring time of potassium level	Increase in the average monitoring time of potassium level	+	
Eschmann et al. (2015) [62]	Decrease in the reaction time to reminders in physicians for monitoring alerts for potassium level	Decrease in the reaction time to reminders	+	
Curtain et al. (2011) [5]	Reduction in the approved percentage of inhibitor intervention proton pump which is registered by the pharmacologist	Reduction in the approved percentage of inhibitor intervention proton pump which is registered by the pharmacologist	+	
Turchin et al. (2011) [6]	Increasing overall efficiency of system functionalities prior to admission	Increasing overall efficiency of system functionalities	0	

Griffey et al.(2012) [63]	Increasing the number of prescriptions by recommending the determined system dose	Increasing prescribing	+	
Myers et al. (2011) [64]	Reducing the significant number of inappropriate abbreviations	Reducing prescribing	+	
Van Stiphout et al. (2018) [65]	More efficient medical summary	More efficient medical summary	+	
Akhu-zaheya et al. (2017) [32]	Increasing prescriptions in the short message group	Increasing prescribing	+	patient outcome improved
Khonsari et al. (2015) [33]	Increasing adherence to drug usage	Increasing adherence	+	
Vervloet et al. (2014) [39]	Increasing adherence in the group receiving short messages	Increasing adherence	+	
ervloet et al. (2012) [40]	Increasing the drug dosage in one hour during a six month period	Increasing prescribing	+	
Elliott et al.(2017) [58]	Reducing the average number of days re-hospitalized 60 days after discharge	Reducing the average number of days re-hospitalized	+	
Bruxvoort et al. (2014) [59]	Knowledge of the physician in using Lumefantrine or thometer	increased Knowledge of the physician	+	
Tamblyn et al. (2012) [67]	Reduction in dose of drugs after one year for antipsychotics	Reducing prescribing	+	
Luitjes et al. (2018) [35]	For the control group, reducing the secondary outcome of infant morbidity after implementation	reducing morbidity	+	physician practice performance and patient outcome improved
Ackerman et al. (2013) [49]	Reducing excess prescription of antibiotics	Reducing prescribing	+	
Pop-eleches et al. (2011) [50]	Reducing the number of treatment interruptions in both groups receiving weekly messages	effective in process of care	+	
Christensen et al.(2010)[34]	Reducing blood pressure after 12 months	Reducing morbidity	0	physician practice performance not improved
Nielsen et al. (2017) [30]	Increasing the time outcome in the scope of treatment	Increasing the time outcome	0	
Buhse et al. (2018) [36]	Reduction in faulty knowledge causing risk	Reducing risk	0	
Gill et al. (2011) [42]	Increase in receiving care on the basis of instructions for patients with low-dose aspirin use (25%)	Increase in receiving care	0	
Muth et al. (2018) [55]	Ineffectiveness of drug prescriptions after 6 and 9 months	ineffectiveness in process of care	0	
Strom et al. (2010) [57]	Reduction in the appropriate response of physicians to alerts during 17 months	Reduction in the appropriate response of physicians to alerts	0	
Duke et al. (2013) [61]	Decrease in the conformity rate in normal risk patients for increased potassium	Decrease in the conformity rate in normal risk patients	0	
Willis et al. (2013) [66]	Lack of difference in the rate of patient adherence to treatment, drug treatment significance, economic and clinical outcomes in three groups	no difference in process of care outcomes	+	patient outcome not improved
Mohammed et al. (2016) [48]	Inability to be effective in treatment success rate	ineffectiveness in process of care	0	

Evaluation for publication bias

We conducted funnel plot and Egger's regression to evaluate the publication bias regarding the effect of CDSS on patient outcomes and physician performance [68, 69]. There was no significant difference with respect to publication bias (std diff in means = 0.054, CI 95%: 2.116 to 2.941, p value:0.000001). Fig. 8 shows that the X-axis shows std diff in mean in the funnel diagram, and the Y-axis reflects standard error.

Discussion

The aim of this systematic review is to establish the effect of CDSS on patient outcomes and physician performance. The effect of CDSS was measured using different methods in included studies. In most cases, the effect of these programs on physician performance and patient outcomes was positive. In others, however, no significant effect was observed.

The results show that the use of CDSSs in cardiovascular patients has positive effects on physician performance through increasing the prescription of anticoagulants, anti-inflammatory drugs, anti-thrombotic drugs, lipid-lowering drugs, blood pressure drugs, cardiovascular drugs recommended for the reduction of cardiovascular diseases in patients with diabetes, observing clinical guidelines, and improving the quality of patients [25, 27-29]. The results of the current study are consistent with the results of Duke et al. and Brokel et al. in reducing inadequate prescriptions and enhancing the process of observing clinical guidelines in the positive effect of CDSS [61, 70]. The system's user-friendliness environment and low running cost resulted in its efficiency in the care delivery process [25, 27-29].

However, the results of our study showed that using CDSSs for cardiac patients did not affect the physician performance in a number of outcomes such as physician conduct in prescribing drugs, the warfarin treatment system, minimizing dissatisfaction with guidelines for antithrombotic diagnosis, and job satisfaction [26, 29-31]. The results of this study are also consistent with Byrnes and Lazaro studies in that clinical factors and treatment issues were the reasons for physicians' disagreement with system recommendations [71, 72]. The main reason that no change was found in medical guidance disputes was the difficulty of clinical conditions which could increase the risk of patient injury and hinder the decision-making process [26, 29-31].

Also, the results of this study indicate that the use of CDSSs in cardiovascular patients has a positive effect on a number of outcomes such as adherence to drug use by patients and following a nutrition-based diet in the Mediterranean [32, 33]. Similarly, according to clinical guidelines and reminders, the Schedlbauer et al.'s study reported the positive effect of CDSS on cardiovascular patient outcome [73]. The reason for low Mediterranean diet adherence was the delivery of a short message outlining the advantages of the Mediterranean diet which resulted in an improved conformity level [32, 33].

The study also showed that the use of CDSS in cardiovascular patients did not affect patient outcomes such as readmission rate, mortality, and smoking cessation [32, 33]. Similarly, the findings of Simpson et al.'s study indicate that accurate compliance with the Short Message System (SMS) reduces mortality risk and improves health outcomes [74]. One of the reasons for the negligible reduction in mortality is the short duration of the study, small sample size, and inability to identify causes of mortality [32, 33]. Also, study results show that using CDSS in patients with hypertension in adherence to clinical guidelines and laboratory tests has a positive effect on physician performance [35]. Zwart et al.'s study, which is consistent with the results of our study, assessed the impact of CDSS on adherence to clinical guidelines. The study reported effective results about the treatment for pregnant women with hypertensive disorders [75]. In addition, physicians' awareness about special care during pregnancy for hypertension resulted in more patient care and adherence to CDSS [35].

Based on the results of this research, the use of CDSS in diabetic patients has a positive effect on physician performance in a number of outcomes such as adjusting the form of insulin and improving the quality of decision-making about statin prescription [36-38]. The findings of Den Ouden et al.'s and Mann et al.'s studies are also consistent with the results of our review which suggest physicians' strong adherence to CDSS, enhanced statin prescribing, and improved quality of care [76, 77]. In fact, the CDSS can dynamically recommend the insulin dose based on the rounds of previous days, the type of insulin injected, and the glucose level of the patient on the day before [36-38].

The results of this study indicate that the use of CDSS in diabetic patients has a positive effect on a variety of patient outcomes such as adherence to the nutritional diet of patients with diabetes type two and taking the missed dose of medication [39, 40]. Meanwhile, the results of this study are consistent with Vervloet et al.'s and Krishna et al.'s systematic review on the positive effect of CDSS with alerts on patients with diabetes [78, 79]. The main reason for the effect of CDSS on improving patient adherence seems to be due to the fact that it raises patients' awareness about taking medication [39, 40].

Also, the results of this study show that the use of CDSS in digestive disorders has a positive effect on the physician performance in a variety of outcomes such as the standard use of oral rehydration solution, the prescription of non-steroidal anti-inflammatory drugs and proton pump inhibitors in normal and high-risk patients, and the provision of care services in line with the guidelines for primary care [41-43]. The results of this study are also consistent with the findings of Nicastro's study that claim the positive effects of the system on the physicians performance such as adherence to clinical guidelines and prescription of drugs [80]. The reason for the positive effect of CDSS on the prescription of non-steroidal anti-inflammatory drugs and proton pump inhibitors in high-risk patients and the use of oral rehydration solution was the systems' recommendations about the above-mentioned drugs [41-43].

Also, the results of this study showed that the use of CDSS in respiratory patients has a positive effect on physician performance and reduced antibiotic prescription [44-47, 49]. The results of this study are thus consistent with the findings of Mcdermott et al.'s and Butler et al.'s results on the positive effect of CDSS on the self-efficacy of physicians in managing chronic respiratory patients and reducing prescription of antibiotics [81, 82]. We think that the reason for the system's positive effect on the self-efficacy of physicians was their tendency to cooperate on decision-making and not to receive mandatory CDSS recommendations [44-47, 49].

With respect to respiratory patients, the results of this study show that the use of CDSS has a positive effect on some patient outcomes such as reduced antibiotic resistance and a reduction in antibiotic prescription [48, 49]. Similarly, Hebert et al.'s and Steinman et al.'s studies show reduced antibiotic resistance [83, 84]. We think that the reason for the positive effect of CDSS on reducing irrational prescription of antibiotics and reducing resistance was the patient-physicist collaboration with the aid of CDSS guideline which played a significant role in the medication prescription [48, 49].

With respect to appendicitis, the results of our review indicate that the use of CDSS has a positive effect on physician performance in certain outcomes such as performance, quality, and safety with the aid of physicians' computerized order entry [51]. The results of this review are in line with Holden's report which explores how physicians who use the order entry system get more up-to-date information and boost the system's ability [85]. Although prescriptions are not strong in terms of content, errors are reduced as CPOE makes physicians to think about the cases [51].

Also, the results show that the use of CDSS in kidney patients has a positive effect on physicians performance in some outcomes such as reduced dosage of inadequately prescribed drugs and improved rate of adequate prescription [52, 53]. Such findings are consistent with Bates et al.'s and Chertow et al.'s studies which show the positive effect of CDSS alerts on modifying insufficient prescriptions and increasing the recommended level of inadequate dosage [86, 87]. Timeline of CDSS alerts was the main reasons for the success of CDSS in prescribing adequate drugs and correct dosage [52, 53].

Based on the results of our review, the use of CDSS in patients with a high level of blood potassium has a positive effect on physicians performance in some outcomes such as the faster physicians' response in the intervention group to system alerts and reminders [62]. Our study are also consistent with Helmous et al.'s and Paterno et al.'s reports which show that physicians' adherence to alerts improved by 19 percent [88, 89]. A main reason for the positive effect of CDSS on the physician performance was uninterrupted alerts and reminders [62].

Results of the study showed that the use of CDSS in prescribing drugs for patients has a positive effect on physician performance in certain outcomes such as drug prescription for proton pump inhibitors, CDSS productivity and usability, reducing side effects of drugs, and improving the learning rate and skills of physicians [5, 6, 63-65]. The results of this study are in line with the results of Curtis and Shah et al.'s study indicating that relevant CDSS, while providing users with performance-related information, reduces patients' harms and errors, and increases physicians' knowledge and skills [90, 91]. One of the main reasons for the proton pump's enhanced medication performance was the monitoring of physicians' prescribed drug dose as well as equipping pharmacies with CDSS with hard alerts which reduce costs and improve usability [5, 6, 63-65].

Results show that the use of CDSS in prescribing a number of drugs has a positive effect on physician performance in some outcomes such as the number of emergency ward visits, the number of re-hospitalizations, and determination and supervision of the amount of drugs including the initial dose [54, 58]. The results are consistent with Vincent and Cordero's research which demonstrates that combining the computerized order entry process with an alert system saves time in prescribing and optimizing the dosage of drugs [92, 93]. The reason for CDSS' positive effect on the number of re-hospitalizations, emergency ward visits, and reduced morbidity rate was due to the fact that CDSS had knowledge base in pharmacogenetics and was equipped with drug interaction alerts [54, 58].

Analysis of the results of the reviewed studies shows that the use of CDSS in prescribing a number of drugs has no effect on the physician performance in outcomes such as drug prescription rates with drug suitability index, average functional status outcome, and drug complexity index [55-57]. Results of our study are consistent with Olsson's study which suggest that CDSS for elderly people, who use multiple types of medicines, has no effect on important outcomes [94]. We think that the unexpected findings of our review could be attributed to the lack of information for patients with serious infections who require immediate care and the lack of an efficient checklist for the patients' drug problems [55-57].

Positive effects of CDSSs for prescribing on outcome ascends by considering the reasons provided through the reviewed trials. The most important CDSS system factors for outcome improvement are: alignment of guideline knowledge with registered and EHR data to conduct decisions based on each patient [29, 31, 33]; the short massages, embedding only necessary alerts such as drug interaction alerts that are sent in the right time for prescribing and user friendly interface for saving physicians' time [18, 20, 44, 45, 47, 48]; Also, the alert systems should give the choice to users by allowing them to close the alert window and move through next steps or provide uninterrupted alerts [37-41, 56]; Physician and patients behavior could have positive effects on the outcomes in environments equipped by CDSSs through collaboration, following the guidelines, recommendations, alerts and reminders that system provides [37, 42]. Also, considering physician perception in defining the importance of alerts helps identify the interruption status of alerts [37-41].**Subgroup analysis for CDSS types**

The subgroup analysis for various CDSS types showed a significant difference between CDSS and control groups for alerts: (std diff in means = 0.134, 95% CI: 0.082 to 0.0187); combination types of CDSSs: (std diff in means = 0.197, 95% CI: 0.022 to 0.372); recommendation CDSSs: (std diff in means = 0.114, 95% CI:0.063 to 0.166); reminders: (std diff in means = 0.131, 95% CI:0.072 to 0.189); and instructional CDSSs: (std diff in means = 0.129, 95% CI: 0.081 to 0.178). Fig. 9 shows the forest plot for CDSS types categorization meta-analysis.

Outcome analysis

Fig. 10 shows the meta-analysis results for outcome categories and the total analysis. The pooled std diff in means of p values did not show a significant difference between CDSS and the control group (std diff in means = 0.0110, 95% CI: 0.086 to 0.138, standard error = 0.013). 95% CI for the effectiveness was drawn for each study in the horizontal line format (Q = 209.2, df = 45, p value= 0.0003, I^2 = 78.492, Tau^2: 0.004). The findings indicate that heterogeneity improved considerably after sensitivity analysis (Fig. 11). (Q = 164, df = 41, p value = 0.0002, I^2 = 75, Tau^2: 0.003). After this change, the overall effects of clinical decision support system for prescribing medication on patient outcomes and physician practice performance based on the random effect model was significantly different: (std diff in means = 0.114, 95% CI: 0.090 to 0.138).

The outcome analysis showed a significant difference between CDSS and control groups for the categorization of outcomes. Results showed that patient outcome improved: (std diff in means = 0.435, 95% CI: 0.122 to 0.747); physician practice performance improved: (std diff in means = 0.105, 95% CI: 0.78 to 0.133); physician practice performance and patient outcome improved: (std diff in means = 0.196, 95% CI: 0.111 to 0.281); physician practice performance didn't improve: (std diff in means = 0.131, 95% CI: 0.040 to 0.222). The outcome analysis did not confirm a significant difference between CDSS and control groups for the category of patient outcome: (std diff in means = 0.064, 95% CI: -0.038 to 0.165).

The CDSS types that improved the outcome for patients or physician practice are as follows: alerts, recommendations, instructional CDSSs, reminders, and a combination of all of them. Patient outcomes and practice performance outcomes were improved by using the CDSSs for prescribing. In some trials, however, the CDSS was not directly related to patient outcomes and showed only a little improved impact on physician practice outcomes.

Limitations and implications for research

Although we conducted meta-analysis on the outcomes based on subgroup analysis, the heterogeneity among the studies included in our analysis prevented us from using sturdier mix methods. The effect we expected of the system as a whole was statistically significant. Since we used the main outcome data for meta-analysis of the trials, there could be other outcomes by selecting such secondary outcomes that are not quite different from our findings. Further outcomes can be obtained by extending the spectrum of all kinds of CDSSs in addition to CDSS for prescribing.

Conclusion

This systematic review study was conducted with the aim of identifying the effect of CDSS on patient outcomes and physician performance. The results show that the use of CDSS in some diseases has positive effects on the outcomes of patients and physician performance, while it has no significant effect on others. In addition, the type of outcomes and the effects of CDSS on the diseases are different. Using this technique in some cases yields positive results for patients and physician, while in some other cases it demonstrates no significant difference compared to those of conventional methods. The positive effect of CDSS seems to be due to factors such as user-friendliness of the system, the number of patients requiring treatment, the rate of observance of clinical guidelines, conformity of clinical guidelines and data registry, the rate of patients' accurate adherence to messages of the system, usefulness of short messages, the existence of algorithms with dynamic functioning based on patient data, existence of patient medical records, and the relationship between electronic health records with CDSS and timely alerts of the system in the prescribing process. In addition, the positive effect of CDSS depends on a number of other factors such as having an instruction section, not being confronted with mandatory recommendations, patient and physician cooperation with the help of CDSS guidelines, not lagging between alerts where the alert is of low importance, the identification of important alerts, equipping pharmacies with CDSS and system applicability, and considering the opinions of physicians when assessing the value of alerts and notifications for drug interaction.

Abbreviations

CDSS: Clinical Decision Support System; MeSH: Medical Subject Headings; CPOE: Computerized Physician Order Entry; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MRC: UK Medical Research Council; RTMM: Real Time Medication Monitoring system; PAID: Problem Areas in Diabetes; MMAI: Modified Medication Appropriateness Index; SMS: Short Message System; RCT: Randomized Control Trial

Declarations

Ethics approval and consent to participate

Before collecting the data for the present study, authors obtained the Code of Ethics from Ethics Committee for University Research, Iran University of Medical Sciences.

All stages of research were conducted by two independent researchers.

During the research project, all papers related to the accuracy of the method were identified and analyzed.

Consent to publish

There is not any individual person's data in any form in this research.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare that *there are no* financial and non-financial competing interests associated with this research.

Funding

This study is the result of a research which is funded by Iran University of Medical Science (IUMS) with the Number of: IUMS / SHMIS-96-04-136-32465 at the Iran University of Medical Science (IUMS).

Authors' contributions

TM and FV searched the literature, extracted the information, and discussed it. FS convinced the PRISMA result, reviewed the contradictions and organized the entire outcome. SP helped analyze the clinical outcomes. The statistical analysis and meta-analysis was performed by TM. SE assisted in the writing process and language editing. All authors read and approved the final manuscript.

Acknowledgment

This article is a research project entitled "The effects of clinical decision support system for prescribing medication on patient outcomes and physician practice performance: A systematic review and meta-analysis", approved by Iran University of Medical Science (IUMS), in March 2018 with the ethical code "IR.IUMS.REC 1396.32465". Also, we thank Professor Brian Haynes for his valuable comments.

References

1. Meidani Z, Sadoughi F, Maleki MR, Tofighi S, Marani AB. Organization's Quality Maturity as a Vehicle for EHR Success. J Med Syst. 2012;36(3):1229-34.
2. Leape L, Berwick D, Clancy C, Conway J, Gluck P, Guest J, et al. Transforming healthcare: a safety imperative. BMJ Qual Saf. 2009;18(6):424-8.
3. Hemens BJ, Holbrook A, Tonkin M, Mackay JA, Weise-Kelly L, Navarro T, et al. Computerized clinical decision support systems for drug prescribing and management: a decision-maker-researcher partnership systematic review. Implement Sci. 2011;6(1):89.
4. Moghaddasi H, Sheikhtaheri A, Hashemi N. Reducing medication errors: Role of computerized physician order entry system. Journal of Health Administration. 2007;10(27):57-67.
5. Curtain C, Peterson GM, Tenni P, Bindoff IK, Williams M. Outcomes of a decision support prompt in community pharmacy-dispensing software to promote step-down of proton pump inhibitor therapy. Br J Clin Pharmacol. 2011;71(5):780-4.
6. Turchin A, James OD, Godlewski ED, Shubina M, Coley CM, Gandhi TK, et al. Effectiveness of interruptive alerts in increasing application functionality utilization: A controlled trial. J Biomed Inform. 2011;44(3):463-8.
7. Moore M, Loper KA. An introduction to clinical decision support systems. J Electron Resour Med Libr. 2011;8(4):348-66.
8. Scott GPT, Shah P, Wyatt JC, Makubate B, Cross FW. Making electronic prescribing alerts more effective: Scenario-based experimental study in junior doctors. J Am Med Inform Assoc. 2011;18(6):789-98.

9. Haynes RB, Wilczynski NL, the Computerized Clinical Decision Support System Systematic Review T. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: Methods of a decision-maker-researcher partnership systematic review. Implement Sci. 2010 2010/02/05;5(1):12.
10. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med. 2003;163(12):1409-16.
11. Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. J Am Med Inform Assoc. 2008;15(5):585-600.
12. Jia P, Zhang L, Chen J, Zhao P, Zhang M. The effects of clinical decision support systems on medication safety: an overview. PloS one. 2016;11(12):e0167683.
13. Bayoumi I, Al Balas M, Handler SM, Dolovich L, Hutchison B, Holbrook A. The effectiveness of computerized drug-lab alerts: a systematic review and meta-analysis. Int J Med Inform. 2014;83(6):406-15.
14. Page N, Baysari MT, Westbrook JI. A systematic review of the effectiveness of interruptive medication prescribing alerts in hospital CPOE systems to change prescriber behavior and improve patient safety. Int J Med Inform. 2017;105:22-30.
15. Tolley CL, Forde NE, Coffey KL, Sittig DF, Ash JS, Husband AK, et al. Factors contributing to medication errors made when using computerized order entry in pediatrics: a systematic review. J Am Med Inform. 2018;25(5):575-84.
16. Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. J Am Med Inform . 2005;293(10):1223-38.
17. Holbrook A, Pullenayegum E, Thabane L, Troyan S, Foster G, Keshavjee K, et al. Shared electronic vascular risk decision support in primary care: Computerization of Medical Practices for the Enhancement of Therapeutic Effectiveness (COMPETE III) randomized trial. Arch Intern Med. 2011;171(19):1736-44.
18. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *BMJ* . 2005;330(7494):765.
19. Taheri Moghadam S, Sadoughi F, Haynes B. The effects of computerized decision support system for prescribing on provider behavior and patient outcomes: a systematic review. PROSPERO, International prospective register of systematic reviews. 2018; Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79936
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.
21. Chalmers TC, Smith Jr H, Blackburn B, Silverman B, Schroeder B, Reitman D, et al. A method for assessing the quality of a randomized control trial. Control Clin Trials. 1981;2(1):31-49.
22. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
23. Borenstein M, Hedges L, Higgins JPT, Rothstein HR. Comprehensive meta-analysis (Version 2.2.027) [Computer software]. 2005 01/01;11:188-91.
24. Gallin JI, Ognibene FP. Principles and practice of clinical research: Academic Press; 2012.
25. Beeler P, Eschmann E, Schumacher A, Studt J, Amann-Vesti B, Blaser J. Impact of electronic reminders on venous thromboprophylaxis after admissions and transfers. J Am Med Inform. 2014;21(e2):e297-e303.
26. Eckman MH, Lip GY, Wise RE, Speer B, Sullivan M, Walker N, et al. Impact of an atrial fibrillation decision support tool on thromboprophylaxis for atrial fibrillation. Am Heart J. 2016;176:17-27.
27. Du J, Rao C, Zheng Z, Group MC. P1701 Randomized cluster trial to improve guideline-adherence of secondary preventive drugs prescription after coronary artery bypass grafting in China. Eur Heart J. 2018;39(suppl_1):ehy565. P1701.
28. Karlsson LO, Nilsson S, Bång M, Nilsson L, Charitakis E, Janzon M. A clinical decision support tool for improving adherence to guidelines on anticoagulant therapy in patients with atrial fibrillation at risk of stroke: A cluster-randomized trial in a Swedish primary care setting (the CDS-AF study). PloS Med. 2018;15(3):e1002528.
29. Mazzaglia G, Piccinni C, Filippi A, Sini G, Lapi F, Sessa E, et al. Effects of a computerized decision support system in improving pharmacological management in high-risk cardiovascular patients: A cluster-randomized open-label controlled trial. Health Inform J. 2016 Jun;22(2):232-47. PubMed PMID: 25210009.
30. Nielsen PB, Lundbye-Christensen S, van der Male M, Larsen TB. Using a personalized decision support algorithm for dosing in warfarin treatment: A randomised controlled trial.
31. Patel B, Usherwood T, Harris M, Patel A, Panaretto K, Zwar N, et al. What drives adoption of a computerised, multifaceted quality improvement intervention for cardiovascular disease management in primary healthcare settings? A mixed methods analysis using normalisation process theory. Implement Sci. 2018;13(1):140.

32. Akhu-Zaheya LM, Shiyab WY. The effect of short message system (SMS) reminder on adherence to a healthy diet, medication, and cessation of smoking among adult patients with cardiovascular diseases. Int J Med Inform. 2017;98:65-75.
33. Khonsari S, Subramanian P, Chinna K, Latif LA, Ling LW, Gholami O. Effect of a reminder system using an automated short message service on medication adherence following acute coronary syndrome. Eur J Cardiovasc Nurs. 2015;14(2):170-9.
34. Christensen A, Christrup LL, Fabricius PE, Chrostowska M, Wronka M, Narkiewicz K, et al. The impact of an electronic monitoring and reminder device on patient compliance with antihypertensive therapy: a randomized controlled trial. J Hypertens. 2010;28(1):194-200.
35. Luitjes SHE, Hermens R, de Wit L, Heymans MW, van Tulder MW, Wouters M. An innovative implementation strategy to improve the use of Dutch guidelines on hypertensive disorders in pregnancy: A randomized controlled trial. Pregnancy Hypertens. 2018 Oct;14:131-8. PubMed PMID: 30527100. Epub 2018/12/12. eng.
36. Buhse S, Kuniss N, Liethmann K, Müller UA, Lehmann T, Mühlhauser I. Informed shared decision-making programme for patients with type 2 diabetes in primary care: cluster randomised controlled trial. *BMJ open*. 2018;8(12):e024004
37. Perestelo-Pérez L, Rivero-Santana A, Boronat M, Sánchez-Afonso J, Pérez-Ramos J, Montori V, et al. Effect of the statin choice encounter decision aid in Spanish patients with type 2 diabetes: a randomized trial. Patient Educ Couns. 2016; 99(2):295-938. Sáenz A, Brito M, Morón I, Torralba A, García-Sanz E, Redondo J. Development and validation of a computer application to aid the physician's decision-making process at the start of and during treatment with insulin in type 2 diabetes: a randomized and controlled trial. J Diabetes Sci Technol. 2012;6(3):581-8.
38. 39**.** Vervloet M, van Dijk L, de Bakker DH, Souverein PC, Santen-Reestman J, van Vlijmen B, et al. Short- and long-term effects of real-time medication monitoring with short message service (SMS) reminders for missed doses on the refill adherence of people with Type 2 diabetes: Evidence from a randomized controlled trial. Diabet Med. 2014;31(7):821-8.
39. Vervloet M, van Dijk L, Santen-Reestman J, van Vlijmen B, van Wingerden P, Bouvy ML, et al. SMS reminders improve adherence to oral medication in type 2 diabetes patients who are real time electronically monitored. Int J Med Inform. 2012;81(9):594-604.
40. Geurts D, de Vos-Kerkhof E, Polinder S, Steyerberg E, van der Lei J, Moll H, et al. Implementation of clinical decision support in young children with acute gastroenteritis: a randomized controlled trial at the emergency department. Eur J Pediatr. 2017;176(2):173-81.
41. Gill JM, Mainous AG, Koopman RJ, Player MS, Everett CJ, Chen YX, et al. Impact of EHR-based clinical decision support on adherence to guidelines for patients on NSAIDs: a randomized controlled trial. Ann Fam Med. 2011;9(1):22-30.
42. Petersen J, Jarbol D, Hallas J, Munch M, Schaffalitzky DMO, Hansen J. Can the use of a computer decision support system prevent complicated ulcer among patients treated with NSAID or aspirin? a randomised controlled cluster trial in general practice. gastroenterology; 2017; 152(5): S222.
43. Bourgeois FC, Linder J, Johnson SA, Co JP, Fiskio J, Ferris TG. Impact of a computerized template on antibiotic prescribing for acute respiratory infections in children and adolescents. Clin Pediatr (Phila). 2010 Oct;49(10):976-83. PubMed PMID: 20724348.
44. Juszczyk D, Charlton J, Gulliford M. Incorporating electronic health records data into efficient trial interventions-cluster randomised trial to reduce antibiotic prescribing in primary care. Trials Conference: 4th international clinical trials methodology conference , ICTMC and the 38th annual meeting of the society for clinical trials United kingdom. 2017;18(Supplement 1): p. 278.
45. McDermott L, Yardley L, Little P, Van Staa T, Dregan A, McCann G, et al. Process evaluation of a point-of-care cluster randomised trial using a computer-delivered intervention to reduce antibiotic prescribing in primary care. BMC Health Serv Res. 2014;14(1):594.
46. McGinn TG, McCullagh L, Kannry J, Knaus M, Sofianou A, Wisnivesky JP, et al. Efficacy of an evidence-based clinical decision support in primary care practices: a randomized clinical trial. JAMA Intern Med. 2013;173(17):1584-91.
47. Mohammed S, Glennerster R, Khan AJ. Impact of a daily SMS medication reminder system on tuberculosis treatment outcomes: A randomized controlled trial. PLoS ONE. 2016;11(11).
48. Ackerman S, Gonzales R, Stahl M, Metlay J. One size does not fit all: evaluating an intervention to reduce antibiotic prescribing for acute bronchitis. BMC Health Serv Res [Internet]. 2013; 13:[462 p.].
49. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, De Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS (London, England). 2011;25(6):825.
50. Avansino J, Leu MG. Effects of CPOE on provider cognitive workload: A randomized crossover trial Pediatr. 2012;130(3):e547-e52.
51. Awdishu L, Coates CR, Lyddane A, Tran K, Daniels CE, Lee J, et al. The impact of real-time alerting on appropriate prescribing in kidney disease: A cluster randomized controlled trial. J Am Med Inform. 2016;23(3):609-16.
52. Erler A, Beyer M, Petersen JJ, Saal K, Rath T, Rochon J, et al. How to improve drug dosing for patients with renal impairment in primary care - A cluster-randomized controlled trial. BMC Fam Pract. 2012;13.
53. Cox ZL, Nelsen CL, Waitman LR, McCoy JA, Peterson JF. Effects of clinical decision support on initial dosing and monitoring of tobramycin and amikacin. Am J Health Syst Pharm 2011;68(7):624-32.
54. Muth C, Uhlmann L, Haefeli WE, Rochon J, van den Akker M, Perera R, et al. Effectiveness of a complex intervention on Prioritising Multimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster randomised controlled trial. *BMJ open*.

2018;8(2):e017740.

55. Strom BL, Schinnar R, Aberra F, Bilker W, Hennessy S, Leonard CE, et al. Unintended effects of a computerized physician order entry nearly hard-stop alert to prevent a drug interaction: A randomized controlled trial. Arch Intern Med. . 2010;170(17):1578-83.
56. Strom BL, Schinnar R, Bilker W, Hennessy S, Leonard CE, Pifer E. Randomized clinical trial of a customized electronic alert requiring an affirmative response compared to a control group receiving a commercial passive CPOE alert: NSAIDe-warfarin co-prescribing as a test case. J Am Med Inform. 2010;17(4):411-5.
57. E Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. PLoS One. 2017;12(2):e0170905.
58. Bruxvoort K, Festo C, Kalolella A, Cairns M, Lyaruu P, Kenani M, et al. Cluster randomized trial of text message reminders to retail staff in tanzanian drug shops dispensing artemether-lumefantrine: Effect on dispenser knowledge and patient adherence. Am J Trop Med Hyg. 2014;91(4):844-53.
59. Beeler PE, Eschmann E, Schneemann M, Blaser J. Negligible impact of highly patient-specific decision support for potassium-increasing drug-drug interactions–a cluster-randomised controlled trial. Swiss Med Wkly. 2019;149(1516).
60. Duke JD, Li X, Dexter P. Adherence to drug-drug interaction alerts in high-risk patients: a trial of context-enhanced alerting. J Am Med Inform. 2013;20(3):494-8.
61. Eschmann E, Beeler P, Blaser J. Impact of Specific Alerts in Potassium-Increasing Drug-Drug Interactions. Stud Health Technol Inform. 2015; 216:949.
62. Griffey RT, Lo HG, Burdick E, Keohane C, Bates DW. Guided medication dosing for elderly emergency patients using real-time, computerized decision support. J Am Med Inform. 2012;19(1):86-93.
63. Myers JS, Gojraty S, Yang W, Linsky A, Airan-Javia S, Polomano RC. A randomized-controlled trial of computerized alerts to reduce unapproved medication abbreviation use. J Am Med Inform. 2011;18(1):17-23.
64. Van Stiphout F, Zwart-van Rijkom J, Versmissen J, Koffijberg H, Aarts J, van der Sijs I, et al. Effects of training physicians in electronic prescribing in the outpatient setting on clinical, learning and behavioural outcomes: a cluster randomized trial. Br J Clin Pharmacol. 2018;84(6):1187-97.
65. Willis JM, Edwards R, Anstrom KJ, Johnson FS, Del Fiol G, Kawamoto K, et al. Decision support for evidence-based pharmacotherapy detects adherence problems but does not impact medication use. Stud Health Technol Inform. 2013;183:116-25.
66. Tamblyn R, Eguale T, Buckeridge DL, Huang A, Hanley J, Reidel K, et al. The effectiveness of a new generation of computerized drug alerts in reducing the risk of injury from drug side effects: A cluster randomized trial. J Am Med Inform. 2012;19(4):635-43.
67. E Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ(Clin Res Ed).1997; 315 (7109): 629–634.
68. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.
69. Brokel J. Randomised controlled trial: evidence-based clinical decision support improves the appropriate use of antibiotics and rapid strep testing. Evid Based Med. 2014; 19(3): 118
70. Byrnes PD. Why Haven't I Changed That?: Therapeutic Inertia in General Practice. Aust Fam Physician. 2011;40(1/2):24.
71. Lázaro P, Murga N, Aguilar D, Hernández-Presa MA, Investigators IS. Therapeutic inertia in the outpatient management of dyslipidemia in patients with ischemic heart disease. The inertia study. Rev Esp Cardiol (Engl Ed). 2010;63(12):1428-37.
72. Schedlbauer A, Schroeder K, Peters T, Fahey T. Interventions to improve adherence to lipid lowering medication. Cochrane Database Syst Rev. 2004 (4).
73. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15.
74. Zwart JJ, Richters A, Öry F, de Vries JI, Bloemenkamp KW, van Roosmalen J. Eclampsia in the Netherlands. Obstet Gynecol. 2008;112(4):820-7.
75. Den Ouden H, Vos RC, Rutten GE. Effectiveness of shared goal setting and decision making to achieve treatment targets in type 2 diabetes patients: A cluster-randomized trial (OPTIMAL). Health Expect. 2017;20(5):1172-80.
76. Mann DM, Ponieman D, Montori VM, Arciniega J, McGinn T. The Statin Choice decision aid in primary care: a randomized trial. Patient Educ Couns. 2010;80(1):138-40.
77. Vervloet M, Linn AJ, van Weert JC, De Bakker DH, Bouvy ML, Van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. J Am Med Inform. 2012;19(5):696-704.
78. Krishna S, Boren SA. Diabetes self-management care via cell phone: a systematic review. J Diabetes Sci Technol. 2008;2(3):509-17.

79. Nicastro E, Vecchio AL, Liguoro I, Chmielewska A, De Bruyn C, Dolinsek J, et al. The impact of e-learning on adherence to guidelines for acute gastroenteritis: a single-arm intervention study. PloS one. 2015;10(7):e0132213.
80. McDermott L, Yardley L, Little P, Ashworth M, Gulliford M. Developing a computer delivered, theory based intervention for guideline implementation in general practice. BMC Fam Pract. 2010;11(1):90.
81. Butler CC, Kinnersley P, Prout H, Rollnick S, Edwards A, Elwyn G. Antibiotics and shared decision-making in primary care. J Antimicrob Chemother. 2001;48(3):435-40.
82. Hebert C, Beaumont J, Schwartz G, Robicsek A. The influence of context on antimicrobial prescribing for febrile respiratory illness. A cohort study. Ann Intern Med. 2012;157:160-9.
83. Steinman MA, Landefeld CS, Gonzales R. Predictors of broad-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care. J Am Med Inform. 2003;289(6):719-25.
84. Holden RJ. Physicians' beliefs about using EMR and CPOE: in pursuit of a contextualized understanding of health IT use behavior. Int J Med Inform. 2010;79(2):71-80.
85. Bates DW, Kuperman GJ, Wang S, Gandhi T, Kittler A, Volk L, et al. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. J Am Med Inform. 2003;10(6):523-30.
86. Chertow GM, Lee J, Kuperman GJ, Burdick E, Horsky J, Seger DL, et al. Guided medication dosing for inpatients with renal insufficiency. J Am Med Inform.. 2001;286(22):2839-44.
87. Helmons PJ, Suijkerbuijk BO, Nannan Panday PV, Kosterink JG. Drug-drug interaction checking assisted by clinical decision support: a return on investment analysis. J Am Med Inform. 2015;22(4):764-72.
88. Paterno MD, Maviglia SM, Gorman PN, Seger DL, Yoshida E, Seger AC, et al. Tiering drug–drug interaction alerts by severity increases compliance rates. J Am Med Inform. 2009;16(1):40-6.
89. Curtis JR, Back AL, Ford DW, Downey L, Shannon SE, Doorenbos AZ, et al. Effect of communication skills training for residents and nurse practitioners on quality of communication with patients with serious illness: a randomized trial. J Am Med Inform.2013;310(21):2271-81.
90. Shah NR, Seger AC, Seger DL, Fiskio JM, Kuperman GJ, Blumenfeld B, et al. Improving acceptance of computerized prescribing alerts in ambulatory care. J Am Med Inform. 2006;13(1):5-11.
91. Cordero L, Kuehn L, Kumar RR, Mekhjian HS. Impact of computerized physician order entry on clinical practice in a newborn intensive care unit. J Perinatol. 2004;24(2):88.
92. Vincent WR, Martin CA, Winstead PS, Smith KM, Gatz J, Lewis DA. Effects of a pharmacist-to-dose computerized request on promptness of antimicrobial therapy. J Am Med Inform Assoc. 2009;16(1):47-53.
93. Olsson IN, Runnamo R, Engfeldt P. Drug treatment in the elderly: an intervention in primary care to enhance prescription quality and quality of life. Scand J Prim Health Care. 2012;30(1):3-9.

Figures

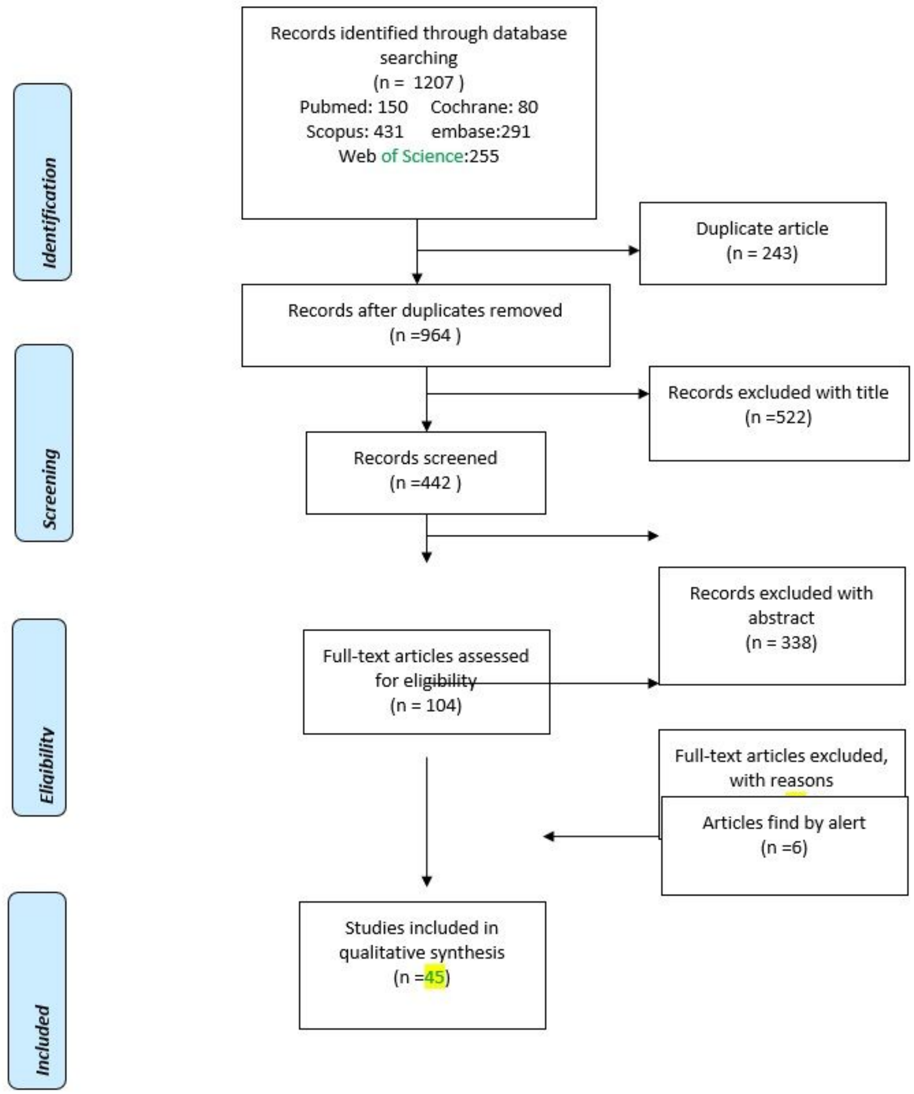

Figure 1

Algorithm of screening articles based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

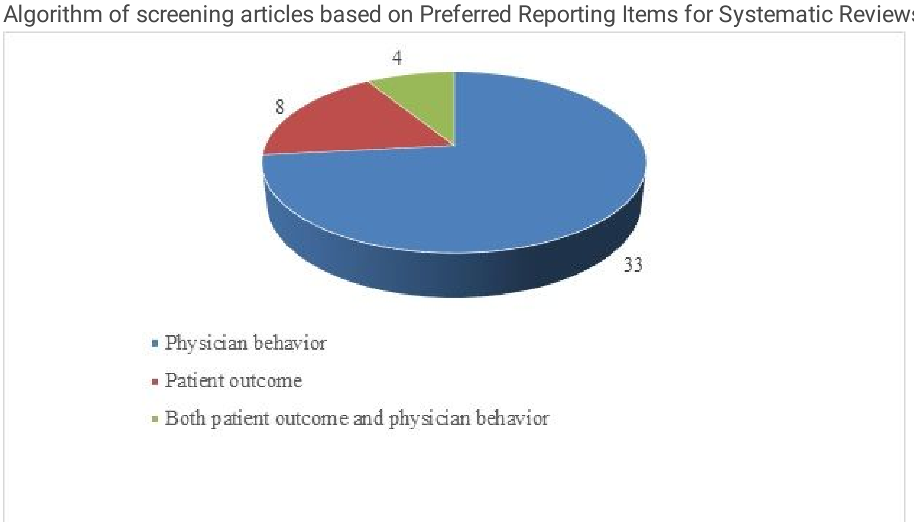

Figure 2

The number of studies based on several evaluating outcomes

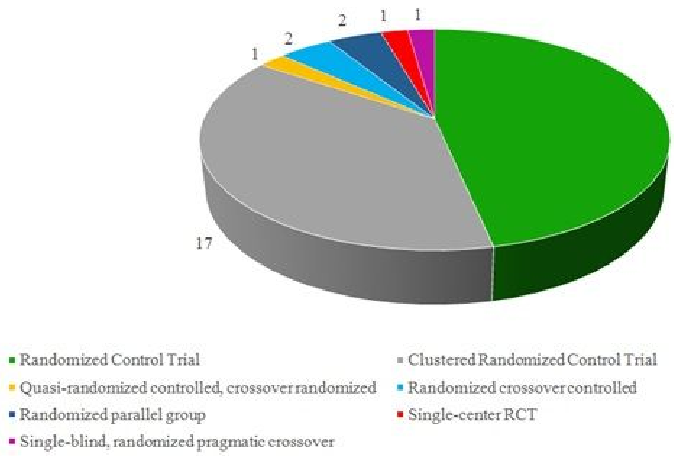

Figure 3

Type of included studies

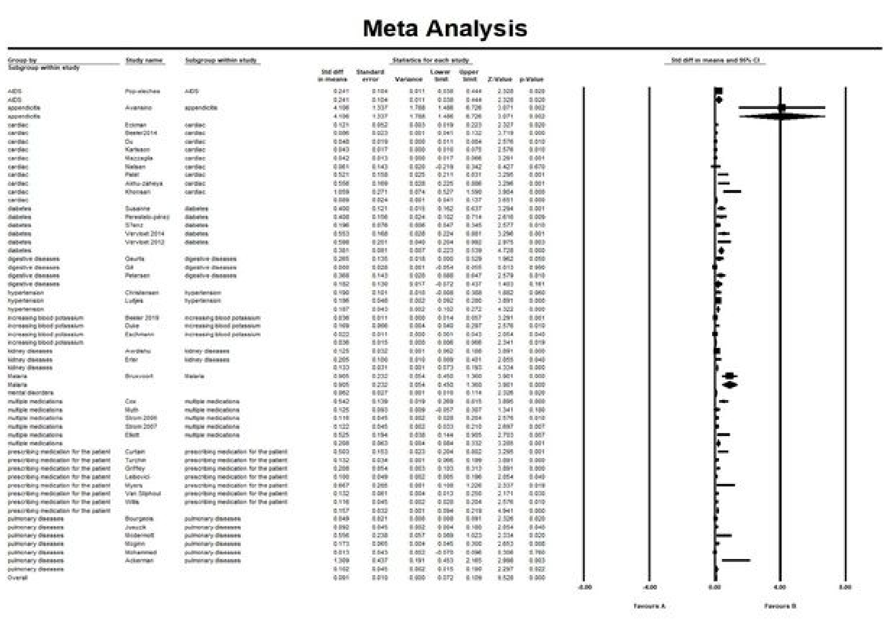

Figure 4

Forest plot of the overall effect of CDSS for prescribing on physician practice performance and patient outcome based on medication subgroup analysis. CI: confidence interval.

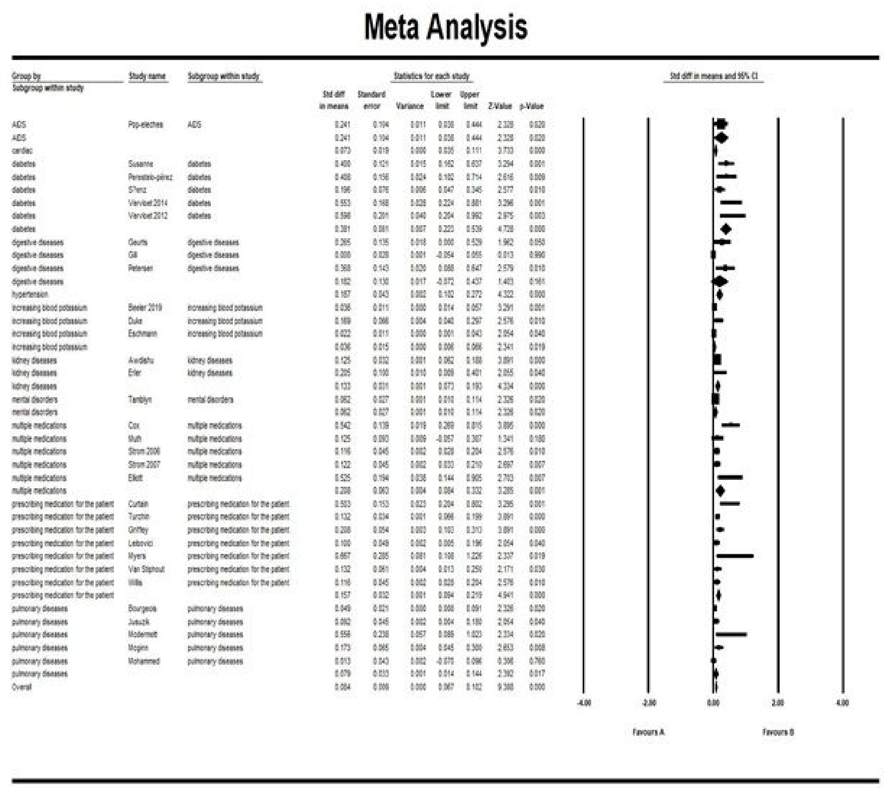

Figure 5

Forest plot of the overall effect of CDSS for prescribing on physician practice performance and patient outcome based on medication subgroup analysis. (excluded khonsari et al. [33]; Ackerman et al. [49]; Avansino et al. [51] and Bruxvoort et al. [59]

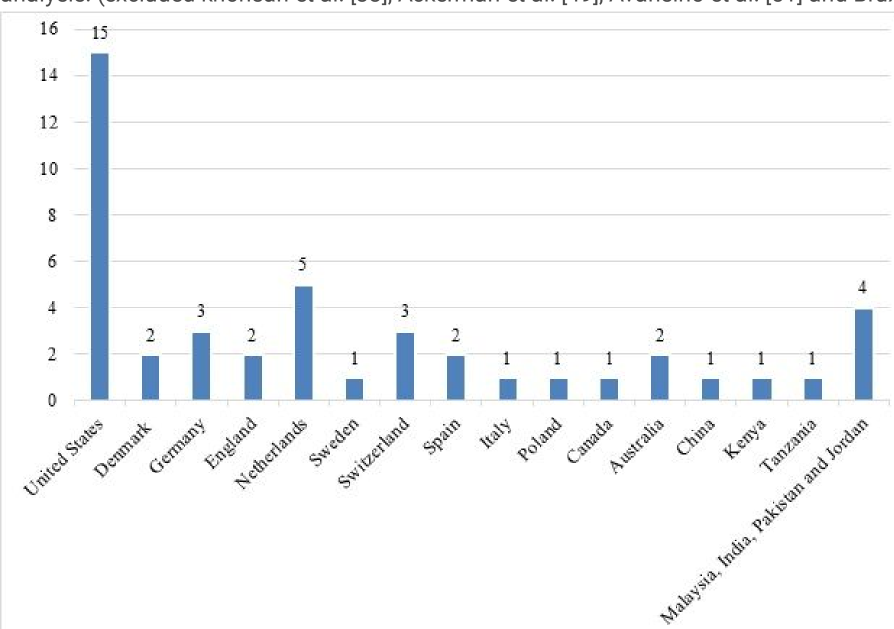

Figure 6

The number of studies associated with each country

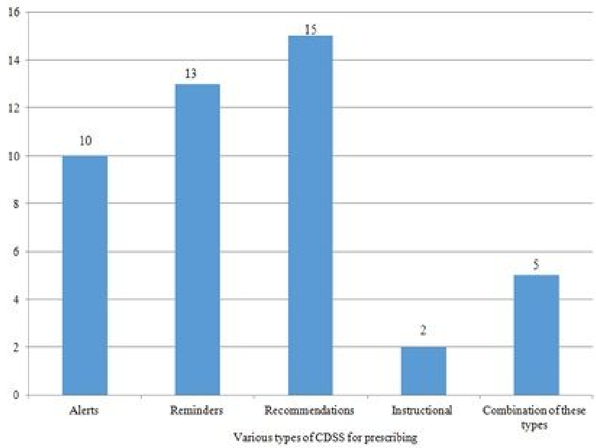

Figure 7

The number of studies associated with each CDSS type

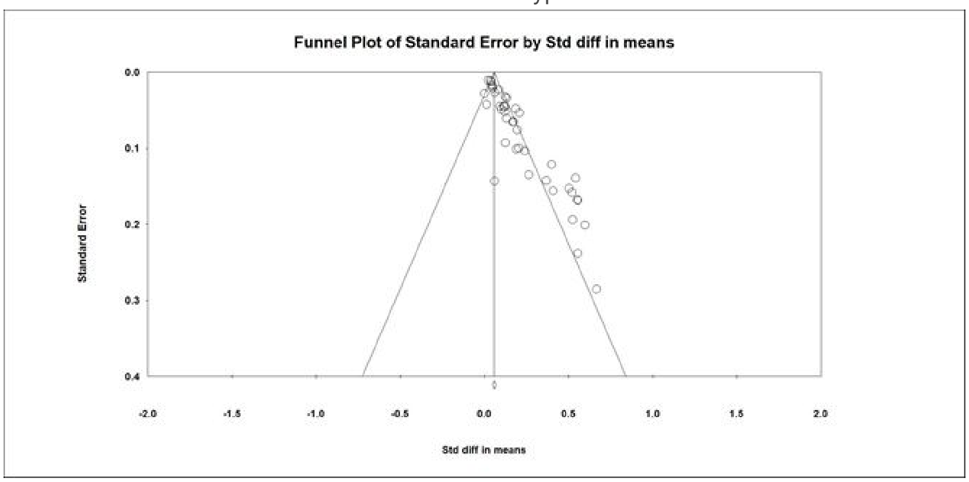

Figure 8

Funnel plot of standard error by std diff in means

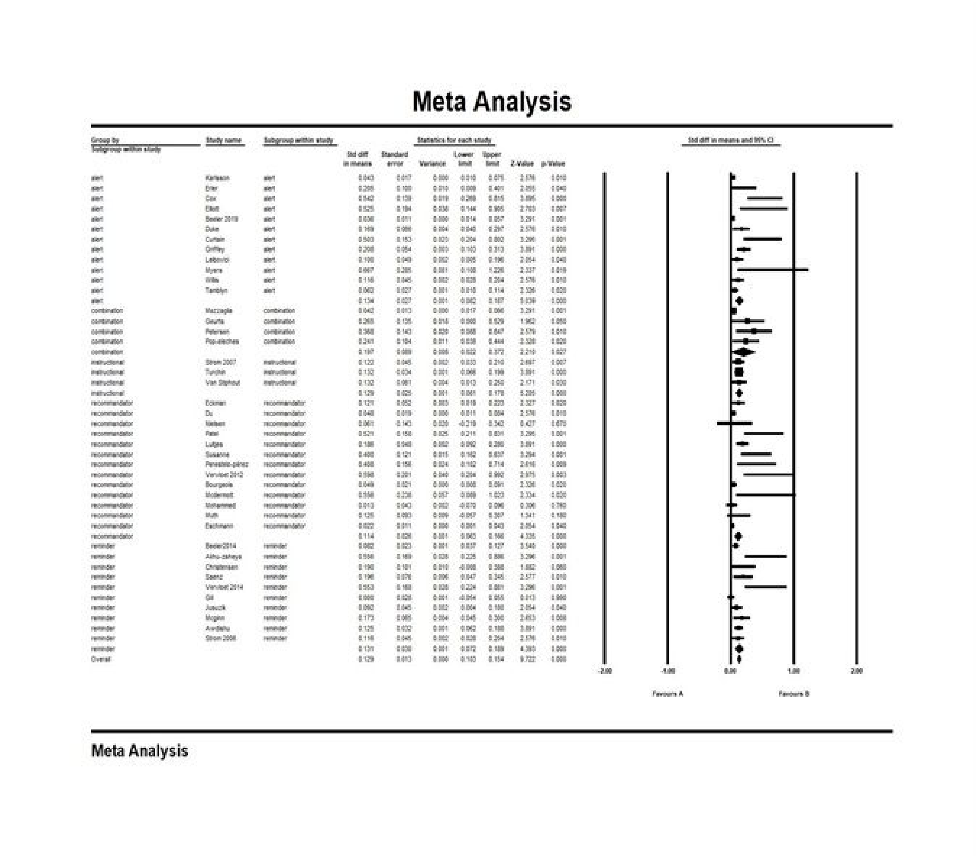

Figure 9

Forest plot of the effect of CDSS for prescribing on physician practice performance and patient outcome based on sub group analysis for CDSS types. (excluded khonsari et al. [33]; Ackerman et al. [49]; Avansino et al. [51] and Bruxvoort et al. [59] studies)

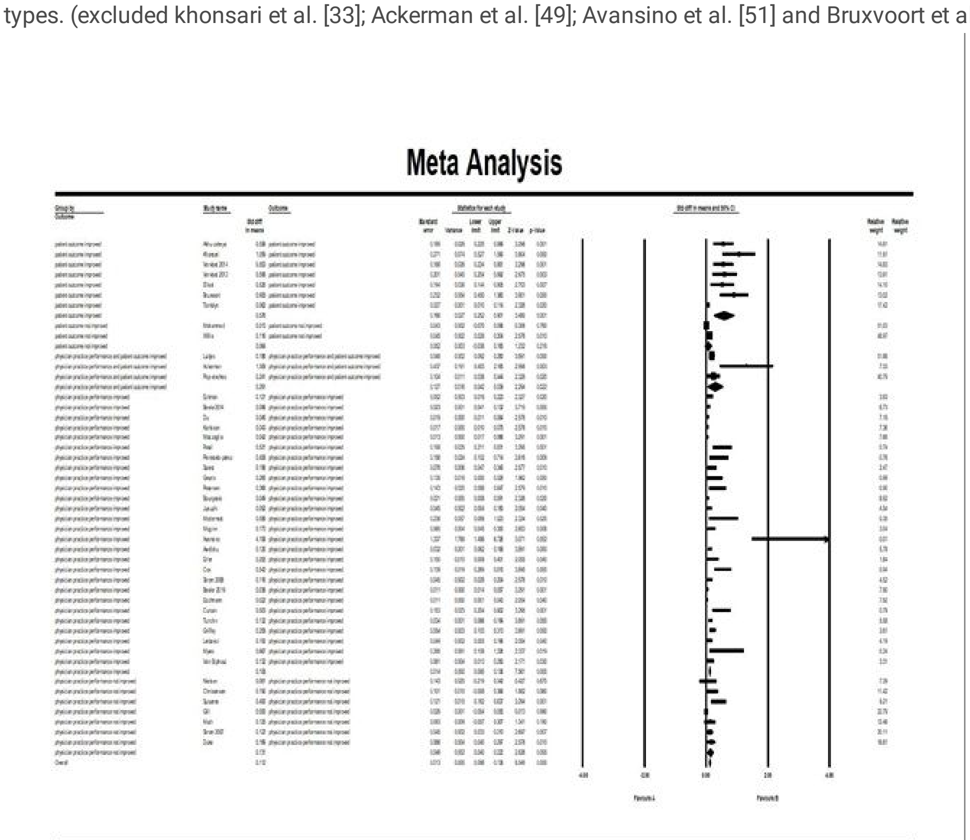

Figure 10

Forest plot of the overall effect of CDSS for prescribing on physician practice performance and patient outcome based on outcome categorization

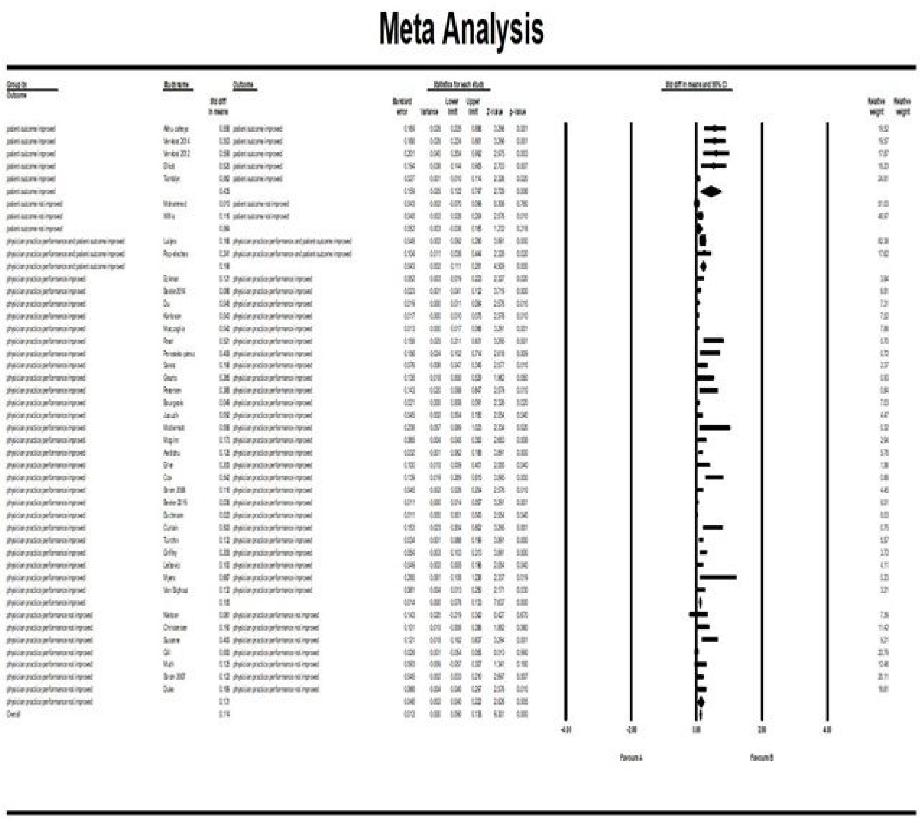

Figure 11

Forest plot of the overall effect of CDSS for prescribing on physician practice performance and patient outcome based on outcome categorization. (excluded khonsari et al. [33]; Ackerman et al. [49]; Avansino et al. [51] and Bruxvoort et al. [59]