Effect of Electronic Prescribing Compared to Paper-Based (Handwritten) Prescribing on Primary Medication Adherence in an Outpatient Setting: A Systematic Review

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Abstract

Background Electronic prescriptions are often created and delivered electronically to the pharmacy while paper-based/handwritten prescriptions may be delivered to the pharmacy by the patients. These differences in the mode of creation and transmission of the two types of prescription could influence the rate at which outpatients fill new prescriptions of previously untried medications.

Objectives This study aimed to evaluate literatures to determine the impact of electronic prescribing compared with paper-based/handwritten prescribing on primary medication adherence in an outpatient setting.

Methods The keywords and phrases "outpatients," "e-prescriptions," "paper-based prescriptions," and "primary medication adherence" were combined with their relevant synonyms and medical subject headings. A comprehensive literature search was conducted on EMBASE, CINAHL, and MEDLINE databases, and Google Scholar. The results of the search were screened and selected using predefined inclusion and exclusion criteria. The Critical Appraisal Skills Program (CASP) was used for quality appraisal of included studies. Data relevant to the objective of the review were extracted and analyzed through narrative synthesis.

Results A total of 10 original studies were included in the final review, including 1 prospective randomized study and 9 observational studies. Nine of the 10 studies were performed in the United States. Four of the studies indicated that electronic prescribing significantly increases initial medication adherence, while four of the studies suggested the opposite. The remaining two studies found no significant difference in primary medication adherence between the two methods of prescribing. The variations in the studies did not allow the homogeneity required for meta-analysis to be achieved.

Conclusion The conflicting findings relating to the efficacy of primary medication adherence across both systems demonstrate the need for a standardized measure of medication adherence. This would help further determine the respective benefits of both approaches. Future research should also be conducted in different countries to give a more accurate representation of adherence.

Keywords

- electronic prescribing
- electronic health records and systems
- paper-based prescriptions
- primary medication adherence
- ambulatory care/primary care

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Background and Significance

Nonadherence to prescribed medication is a significant concern to both public health[1] and health care systems by inhibiting the effectiveness of pharmacotherapy, and increasing the overall cost of disease management.[2] The scale of the problem is highlighted by Hubbard[3] who argue that interventions targeted at improving medication adherence alone would have more benefit than any improvement in specific disease treatment. Some of the risks attributed to nonadherence to medications include serious relapses, adverse drug events, drug resistance, longer hospitalizations and readmissions, increased costs of treatment, and drug toxicity.[2,4] Furthermore, nonadherence is found to be higher in patients with chronic disease[2] which has repercussions for the treatment and management of such conditions. Similarly higher nonadherence rates were exhibited among populations living in low- and middle-income countries when compared with those in high-income countries.[2] This is of concern in consideration of the already limited funding available to the respective health services of these countries.

Primary medication nonadherence occurs when a new prescription is written for a patient but the patient neither fills the prescription nor obtains a suitable alternative.[5] Nonadherence to medication can either be intentional or unintentional. Intentional nonadherence occurs when a patient actively decides not to use the medication or follow the treatment recommendations.[6] This is often a product of a rational decision-making process in which the patient weighs the risks and benefits of the medication.[7] The patient's belief and knowledge are important factors in this decision process,[7–10] and it could be vital for the health care provider to communicate with the patient to explore the subjective norms that can affect the patient decision not to adhere to the treatment regimen.[6] Unintentional nonadherence happens due to unplanned behavior such as forgetfulness and lack of understanding of the drug regimen.[7–10] It is a passive process that is associated with the complexity of the medication regimen (polypharmacy) and the memory of the patient.[6,9] Interventions aimed at addressing unintentional nonadherence should be targeted at simplifying the drug regimen, reminding patients to take their medications, and assisting patients to incorporate medication taking into their daily routine.[6]

Prescription errors resulting from illegible writing significantly contribute to the preventable errors, and it is suggested that electronic prescribing can assist in minimizing this.[11–15] Further benefits of electronic prescribing also include improvement in pharmacy efficiency, promotion of formulary compliance by prescribers, and decrease in adverse drug reactions.[14] Essentially, electronic prescriptions can enhance prescription quality and provide for better pharmacovigilance.[16] However, the electronic prescription systems themselves can introduce a new type of medication error as a result of issues associated with the initial adoption of the system, untrained users, overriding of alerts, and poor interface functionality.[17–19]

There are generally two types of electronic prescription systems used in an outpatient setting; the standalone systems can be used only for prescribing and integrated systems which are part of the electronic health record systems.[20] These electronic prescribing systems can contain various support systems such as clinical decision support, formulary, and safety alert. Integrated systems were found to provide better incremental benefits than standalone systems with regard to both drug safety and efficiency.[20] Electronic prescription systems containing clinical decision support can significantly reduce prescription drug cost due to a shift in prescribing practice away from high cost therapies and brand name medications.[21] The integration of generic substitution decision support with electronic prescribing systems could lead to a significant and sustained increase in outpatient generic (lower price) against brand names (high price) e-prescribing across different specialties.[22] Generic prescribing was found to reduce the patient's copayment which in turn enhances adherence to prescribed medications.[23,24] This would mean considerable financial savings for both the patient and insurer as more prescriptions are written electronically. Enhanced connectivity and integration in the health system through electronic prescribing and electronic medical records (EMR) might improve the rate of primary medication adherence.[25]

The majority of published secondary studies comparing the effects of electronic and paper-based prescriptions focus on parameters such as prescribing and medication errors,[19] time spent prescribing, drug safety,[26,27] and the cost of prescription and compliance to formulary by prescribers.[28] There is no secondary study, to our knowledge, that compares the two methods of prescribing based on their impact on primary medication adherence. This systematic review aims to determine the effectiveness of electronic versus paper-based prescribing on primary medication adherence among outpatients.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[29] and Synthesis without Meta-analysis (SWiM)[30] reporting guidelines, and the Critical Appraisal Skills Program (CASP)[31] risk of bias assessments. It was also registered at the PROSPERO (CRD42020186776). The focused question for this review was "what is the impact of electronic prescribing (I) compared with paper-based prescribing (C) on the primary medication adherence (O) of outpatients (P)?" The keywords and phrases identified from the population, intervention, comparator, and outcome (PICO) components of the question, along with relevant synonyms and Medical Subject Headings (MeSH), were combined using appropriate Boolean operators and advanced search techniques (see ►Supplementary Appendices A–D, available in the online version). A detailed and comprehensive search was conducted on EMBASE, MEDLINE, and CINAHL databases, and Google Scholar from inception through March 4, 2021. The search strategy also included the reading of reference lists, searching of gray literature, and contacting of key authors of published studies. D.A. and N.K. formulated the search strategy and conducted the search.

Table 1 Inclusion and exclusion criteria

Components	Inclusion criteria	Exclusion criteria
Population	Outpatients, primary care, or ambulatory care patients	Studies on animals and inpatients (i.e., patients on admission)
Intervention	Electronic prescribing or computerized physician order entry (CPOE)	–
Comparator	Handwritten or paper-based prescribing	–
Outcome	Primary medication adherence of any measure	Secondary medication adherence and persistence
Study design	Quantitative primary studies (experimental and observational)	Qualitative studies, master's thesis, conference abstracts and press release (non–peer reviewed)
Time of study	No limit on the time of study	–
Language	No limit on the language of publication	–
Location	No limit on the country where the study was conducted	–

Inclusion and Exclusion Criteria

The complete inclusion and exclusion criteria are given in ►Table 1. This systematic review considered both experimental and observational quantitative primary studies on outpatients. Primary studies using qualitative methods and publications, such as master's thesis, press release, and conference abstracts, were excluded. Mixed methods papers would be included, providing they report statistical evidence related to medication adherence, as per the aims of the review. The main outcome of this review was primary medication adherence/compliance. Due to the lack of a standard approach to measuring medication adherence, all measures of primary medication adherence were included in the review. However, studies on secondary medication adherence and persistence were excluded. There was no limitation on the language, time of publication, or the geographical location where the study was conducted.

Study Screening and Selection

The first stage of the process involved reading the titles and abstracts of the search results. The studies were then classified into excluded, included, and undecided based on eligibility on the exclusion and inclusion criteria. Studies that fell under included and undecided were taken forward to the second stage of screening and selection which involved obtaining and reading the full texts and applied the exclusion and inclusion criteria again to further screen the papers to be included in the final review. Two researchers (D.A. and P.R.) independently performed the screening and selection and differences between reviewers on eligible studies were resolved by common agreement in accordance with the specified inclusion/exclusion criteria. The specificity of these ensured that there were no disparities between reviewers.

Data Extraction and Quality Assessment

The data extraction and quality appraisal were performed by D.A. and E.A.O., and discrepancies were resolved through discussion to achieve consensus. Data relevant to the PICO components of the review question were extracted using a bespoke data extraction form pilot-tested beforehand (see ►Supplementary Appendix E [available in the online version] for a sample data extraction form). The included studies were then appraised for methodological quality and risk of bias using the CASP quality assessment framework (*https://casp-uk.net/casp-tools-checklists/*).[31] The critical appraisal process examined parameters such as selection bias, randomization, accounting for potential confounding factors, choice of statistical tests, follow-up, treatment effect, measurement, recall and classification biases. The intervention of interest in this review was electronic prescription or computerized physician order entry (CPOE), while the comparator group comprised of paper-based/handwritten prescription.

Data Synthesis

The results of the included studies vary significantly in the PICO measure, thereby limiting the ability to perform a meta-analysis due to clinical dissimilarities in the research designs.[32,33] To address for such observed heterogeneity/dissimilarities in included studies, narrative synthesis was employed in synthesis of data. Narrative synthesis, an alternative approach, has been criticized as a subjective process that could lead to bias in the data synthesis which may decrease transparency.[34–36] Despite the low recognition of narrative synthesis as a discrete method of data synthesis similar to meta-analysis, narrative synthesis can allow different study designs, participants, interventions, or outcome measures (heterogeneity) to be incorporated in a systematic review.[36] The SWiM[30] reporting guideline, an extension of the PRISMA,[29] was utilized to improve the rigor of this systematic review, since it examined the quantitative effect of two interventions for which meta-analysis of effect estimates could not be applied.[37] The narrative synthesis is the summary of the current state of knowledge and it attempts to answer the focused question of the review.[38]

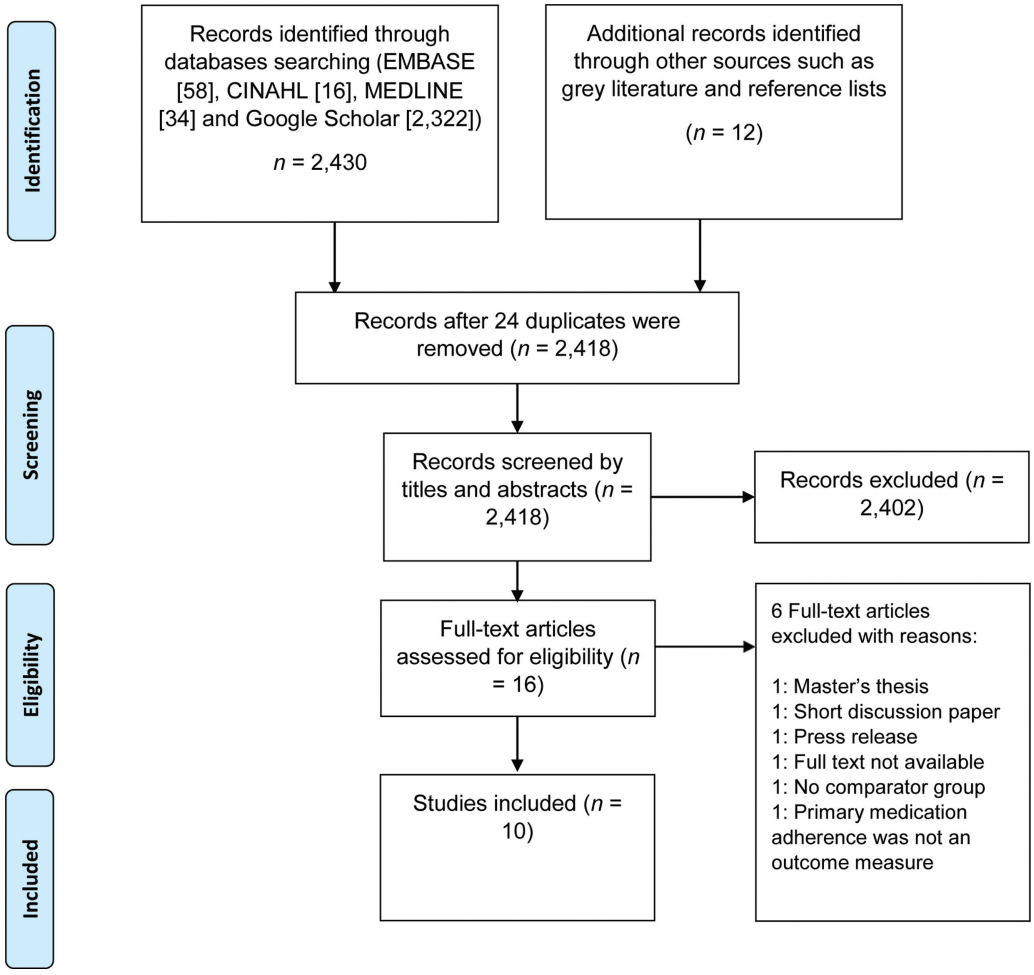

Fig. 1 PRISMA flow diagram. PRISMA, preferred reporting items for systematic reviews and meta-analysis

Results

Selection of Studies

The screening and selection process is illustrated by the PRISMA flow diagram (►Fig. 1). A total of 2,430 articles were retrieved from the databases searched (EMBASE [58], CINAHL [16], MEDLINE [34], and Google Scholar [2,322]). An additional 12 articles were recovered through other sources including the searching of gray literature and reading of reference lists. The total sum of retrieved articles was reduced to 2,418 following the removal of 24 duplicates. A further 2,402 articles were removed after the reading of the titles and abstracts. The full text could not be accessed for 1 of the 16 remaining articles after several efforts, including contacting the authors.[39] The full texts of the 15 articles were retrieved and screened using the inclusion and exclusion criteria (second stage of the screening). Five full text articles were then excluded (a short discussion paper,[40] a press release,[41] a master's thesis,[42] one study had no comparator group,[1] and the other study did not use primary medication adherence as an outcome measure[43]). The final review included the remaining 10 studies.[25,44–52]

Characteristics of Studies

All 10 included studies were published journal articles (►Table 2). Nine of the 10 articles were observational research designs (cohort, cross-sectional, and case-control studies)[25,44–46,48–52] and the last one was a prospective randomized study (experimental).[47] Even though the studies were conducted in different settings, only one of the studies used a population outside the United States.[45] The included studies reported population sample sizes ranging from 143 patients[50] to 10 million index prescriptions.[46]

Results of Studies Included

The summary of the findings of the 10 studies included in the review is presented in ►Table 3. All of the studies used electronic prescribing/prescription as the intervention and, paper and/or other prescriptions such as telephone, telefax, and pharmacy order as the comparator group. The included studies reported using electronic prescribing existing either as a standalone systems or integrated with EMR. Furthermore, the included studies made use of different measures of medication adherence such as self-report, pharmacy records, claim data, and patient interview. The results of four of the studies showed a statistically significant ($p < 0.05$) increase

Table 2 Study and participants characteristics

Study (year)	Publication type	Study design	Country	Setting	Population/sample size	Duration of study
Craghead and Wartski (1989)[44]	Journal	Cross-sectional study	The United States	Ireland Army Community Hospital (IACH), Fort Knox Kentucky	295,932 handwritten prescriptions and 15,945 e-prescriptions	January 1987–March 1988
Ekedahl and Mansson (2004)[45]	Journal	Cross-sectional study	Sweden	Three health care districts served by 22 pharmacies	240,000 inhabitants	March 2000–October 2000
Shrank et al (2010)[46]	Journal	Cross-sectional cohort study	The United States	Data from CVS Pharmacy chain and Caremark Pharmacy Benefit Manager company	10,349,139 index prescriptions filled by 5,249,380 patients	January 2008–December 2008
Fischer et al (2011)[25]	Journal	Case control	The United States	Outpatients in Multiple States	423,616 prescriptions	July 2007–June 2009
Fernando et al (2012)[47]	Journal	Prospective randomized control study	The United States	Ronald Reagan University of California Los Angeles Medical Center Emergency Department, California	224 discharged patients	1 year (7–31 days follow-up duration and 52.4% successful follow-up rate)
Bergeron et al (2013)[48]	Journal	Cross-sectional evaluation	The United States	One academic general internal medicine ambulatory care clinic	344 adult patients	2 years (2009–2011)
Pevnick et al (2014)[49]	Journal	Case control	The United States	Outpatients of primary care physicians in New Jersey	12,389 initial claims	June 2003–July 2006
Anderson et al (2015)[50]	Journal	Case control	The United States	Outpatient university dermatology clinic, Wake Forest Baptist Medical Center, North Carolina	143 patients (40 males and 103 females)	3 months
Forestal et al (2016)[51]	Journal	Cross-sectional	The United States	Noninstitutionalized elderly patients (65 years and over) in Pennsylvania	148,325 prescription claims	September 2014
Adamson et al (2017)[52]	Journal	Case control	The United States	Outpatient dermatological clinic at Parkland Memorial Hospital in Dallas, Texas	2,496 patients and 4,318 prescriptions	January 2011–December 2013

Table 3 Summary of study findings

Study	Intervention (I)	Comparator (C)	Primary adherence measure	Adherence results (*p*-values and 95% CI)	Adherence result information
Craghead and Wartski (1989)[44]	Electronic prescription (from EP integrated with EMR)	Handwritten prescription	Prescription claim data	I (981.6 per 1,000 prescriptions) C (998.8 per 1,000 prescriptions)	Increased adherence with handwritten prescriptions
Ekedahl and Mansson (2004)[45]	Electronic prescription (from EP integrated with EMR)	All other prescriptions including telephone, telefax, and paper	Pharmacy record of prescription claim data	I = 97.63% C = 99.89% $p < 0.05$	Increased adherence with paper-based prescriptions
Shrank et al (2010)[46]	Electronic prescription	All other types of prescription	Pharmacy data and insurance claim	I = 97.7% (RR =1.64) C = 98.3% (RR =1.00) $p < 0.001$	Increased adherence with paper-based prescriptions
Fischer et al (2011)[25]	Electronic prescribing (from standalone EPS)	Paper/printed prescription	Insurance claim	I: OR =1.00 C: OR = 0.54; 95% CI: 0.52–0.57 $p < 0.001$	Increased adherence with e-prescribing system
Fernando et al (2012)[47]	Electronically delivered prescription (from EP integrated with EMR)	Standard written prescription	Self-report (telephone interview)	I = 86.3% C = 88.8% $p = 0.578$	No significant difference
Bergeron et al (2013)[48]	Electronic prescribing (from EP integrated with EMR)	Paper prescribing	Patient interview	I = 89.4% at 6 months I = 97.5% at 12–18 months) C = 93.1%) $p = 0.07$	No significant difference
Pevnick et al (2014)[49]	Electronic prescribing (from standalone EPS)	Traditional paper-based and other methods of delivering prescriptions.	Claim data	Electronic prescribing led to about a 3.6% increase in primary medication adherence ($p = 0.04$)	E-prescribing increases adherence
Anderson et al (2015)[50]	Electronic prescription (from EP integrated with EMR)	Paper prescription	Self-report	I = 94%) C = 67%) $p < 0.001$	E-prescription increases adherence
Forestal et al (2016)[51]	Electronic prescription	All other prescriptions including written, telephone, fax, and pharmacy	Prescription claim data	Electronic prescriptions (I) were more likely to be reversed at day 0 (I = 50%, any other [AO] = 49%, $p < 0.05$) and after day 0 (E = 58%, AO = 42%, $p < 0.05$)	Increased adherence with paper-based prescriptions
Adamson et al (2017)[52]	Electronic prescription (from EP integrated with EMR)	Paper prescription	Prescription fill and pick up (pharmacy record)	I = 84.8%) C = 68.5%) $p < 0.01$	E-prescription increases adherence

Abbreviations: C, comparator; CI, confidence interval; EP, electronic prescribing; EPS, electronic prescription system; EMR, electronic medical record; I, intervention; OR, odd ratio; RR, relative risk.

in primary medication adherence following the adoption of electronic prescribing,[25,49,50,52] while four of the studies indicated significantly higher primary medication adherence in paper-based prescriptions compared with electronic prescriptions.[44–46,51] The remaining two studies suggested no significant ($p > 0.05$) difference in primary medication compliance between electronic and paper-based prescriptions.[47,48]

Risk of Bias Assessment

In this assessment, the percentage of positive answers to the questions gave the final score of the study (►Table 4). Studies scoring 50% and below of positive answers were classified as having high risk of bias, while studies that scored 51 to 74% were classified as moderate risk of bias. Studies that scored 75% and above were classified as low risk of bias. Four studies were appraised as having high risk of bias[45,48,50,51] and another four studies as moderate risk of bias.[44,47,49,52] The remaining two studies were assessed as low risk of bias.[25,46] The main weaknesses were pertaining to sample recruitment/selection,[45,46,50–52] method used to measure adherence,[47–50] identifying and accounting for potential cofounding factors,[44,45,47,48,51] and applicability of findings.[44,45,47–52] Moreover, some of the studies collected their data at the early stage of implementation of electronic prescription systems and there could be differences in the characteristics of both the prescribers and patients who utilized and did not utilize electronic prescribing systems at this early stage.[44,45,49] The prescribers could also be given the choice to use or not to use the electronic prescription system at this stage of adoption, thereby creating an opportunity for selection bias in the studies.

Discussion

This systematic review was aimed at determining the impact of electronic prescribing compared with paper-based/handwritten prescribing on primary medication adherence among outpatients. The lack of randomized control studies minimizes firm conclusions.[31] All four studies that indicated an increase in primary medication adherence following the introduction of an electronic prescribing system were of retrospective case-control design.[25,49,50,52] Only one of the studies which was appraised with high risk of bias lasted for a duration fewer than 2 years, recruited a convenient sample of 143, and applied a subjective measure of primary medication adherence (self-report).[50] The use of subjective measures of medication adherence is widely criticized due to the associated social desirability and recall biases which could lead to artificial inflation in adherence value.[53] All four studies made use of electronic prescribing as the intervention and paper prescription as the comparator. Two of the studies reported using data from a standalone electronic prescribing system[25,49] while the other two studies reported obtaining data retrospectively from an EMR (integrated) system.[50,52]

On the other hand, all four studies that reported an increase in initial medication adherence with paper-based prescriptions were of cross-sectional design.[44–46,51]

Table 4 Risk of bias assessed by the critical appraisal skills program (CASP) quality tools

Authors	Study design	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	%yes/risk of bias
Craghead and Wartski (1989)[44]	Cross-sectional	Y	Y	Y	Y	–	U	U	–	–	U	Y	N	Y	60%/moderate
Ekedahl and Mansson (2004)[45]	Cross-sectional	Y	Y	Y	U	–	Y	N	–	–	N	Y	N	N	50%/high
Shrank et al (2010)[46]	Cross-sectional cohort	Y	Y	U	U	–	Y	Y	Y	Y	Y	Y	U	Y	75%/low
Fischer et al (2011)[25]	Case control	Y	Y	Y	Y	–	Y	U	–	–	Y	Y	U	Y	80%/low
Fernando et al (2012)[47]	Randomized control study	Y	Y	Y	Y	Y	N	Y	N	N	N	N	N	Y	54%/moderate
Bergeron et al (2013)[48]	Cross-sectional	Y	Y	Y	Y	–	N	U	–	–	N	N	N	Y	50%/high
Pevnick et al (2014)[49]	Case control	Y	Y	Y	Y	–	N	U	–	–	Y	Y	N	Y	70%/moderate
Anderson et al (2015)[50]	Case control	Y	Y	N	Y	–	N	U	–	–	Y	N	N	Y	50%/high
Forestal et al (2016)[51]	Cross-sectional	Y	Y	N	U	–	Y	U	–	–	N	N	N	Y	40%/high
Adamson et al (2017)[52]	Case control	Y	Y	U	Y	–	Y	U	–	–	U	Y	N	Y	60%/moderate

Abbreviations: (–), not applicable; N, no; Q1, Did the study address a clearly focused issue?; Q2, Did the authors use an appropriate method to answer their question?; Q3, Were the cases/cohort recruited in an acceptable way?; Q4, Were the controls selected in an acceptable way?; Q5, Was the assignment of patients to treatments randomized/blinded?; Q6, Was the outcome accurately measured to minimize bias?; Q7, Aside from the experimental intervention, were the groups treated equally?; Q8, Was the follow-up of patients complete enough?; Q9, Was the follow up of subjects long enough?; Q10, Have the authors taken account of the potential confounding factors in the design and/or in their analysis?; Q11, Do you believe the results?; Q12, Can the results be applied to the local population?; Q13, Do the results of this study fit with other available evidence?; U, unclear; Y, yes.

Although the studies recruited large sample sizes, this study design is often placed below case-control design in the hierarchy of evidence since they are quick and easy to undertake and may not permit distinction of cause and effect.[54,55] Furthermore, the utilization of a heterogeneous comparator group by the three of the four studies that included other types of prescriptions in addition to paper prescription, such as telephone, telefax, and pharmacy order, may perhaps impact the first-fill adherence of paper prescription.[45,46,51] This may be responsible for the observed decrease in medication adherence after the implementation of the electronic prescription system as reported by the studies. Additionally, these four studies made use of claim-based measures of medication adherence which may not contain information to determine whether the prescriptions were retrieved.[51] Insurance claim measure of adherence gives only information about prescriptions that have been filled. Even though only new prescriptions were considered in the research, misclassification can happen when new prescriptions are paid by the patients themselves thereby not reflecting in the insurance claim database.[51] It is also possible for a subset of the population to have other sources of insurance coverage that may not be captured by the claim database.[25] Also, the study by Forestal et al[51] analyzed claim data for September 2014 only. A sample with a prolonged duration may give a more accurate outcome measure of medication adherence across the methods of prescribing. Some experts have cautioned against the use of a claim-based measure of initial medication adherence.[56,57] Only two of the studies gave information about using an electronic prescription system integrated with EMR.[44,45]

Among the two primary studies that found no significant difference in primary medication adherence between the two methods of prescribing were a prospective randomized control[47] and cross-sectional studies.[48] Both studies recruited small sample sizes of 224 and 344 patients, respectively, measured medication adherence through patient interviews and made use of electronic prescription integrated with EMR. Moreover, the use of a short follow-up duration (7–31 days) and a low successful follow-up rate (52.4%) by Fernando et al[47] could affect the adherence measure since continuity of care with enhanced follow-up has been found to increase the patient adherence to medication.[58]

The difficulty observed in comparing studies on adherence was because of these variations in follow-up durations, population demographics, and the reliability of the different methods of measuring medication adherence. Higher incomes may be associated with increased adherence and the factors affecting medication adherence across different countries include the availability of medicines, prevalence of disease conditions, and variations in health insurance systems.[59] The copayment to be paid by the patient could be the strongest predictor of primary medication nonadherence and there might be a significant relationship between the income levels of the patients and the rate of adherence.[46] Lower socioeconomic status has been found to discourage adherence to prescribed medications.[60,61]

Electronic prescribing integrated with EMR can enable the health care provider to monitor the patient medication regimen and initiate targeted intervention when the need arises.[62] Additionally, prescriptions transmitted electronically to the pharmacy could be filled before the patients arrive to pick them up, thereby reducing the pharmacy wait time.[44] This in turn saves time and improves the quality of prescriptions delivered at the pharmacy for the patient. Furthermore, automated electronic reminders, such as text message notifications and phone calls, could remind patients to pick their prescriptions when transmitted electronically to the pharmacy. These are expected to reduce the number of unclaimed prescriptions and increase primary medication adherence. However, the decrease in medication adherence that could be associated with electronic prescriptions implementation may be caused by the lack of patient-initiated steps.[46] Electronic prescriptions are likely to be automatically delivered to the pharmacy for patients who do not intend to fill them, leading to intentional nonadherence.[51] The automatic transmission of electronic prescription can also increase the likelihood of forgetfulness by the patients leading to unintentional nonadherence but a printed copy of the prescription can serve as a physical reminder for the patients to pick their prescription at the pharmacy.[51,52] In addition, the early increase in nonadherence observed following the adoption of electronic prescription systems may be attributed to the adaptation by both the patients and prescribers to the change in practice.[48] A learning curve may exist in the implementation process that would later resolve at which the nonadherence rate falls below the baseline levels.[48] The education of the prescribers and patients about electronic prescribing/prescription would quicken this process of adaptation.

Limitations and Recommendations

The incomplete reporting of effect estimates and the significant variations in the characteristics of the included studies made it difficult to achieve the consistency required to conduct a meta-analysis.[37] The actual rate of medication adherence could be higher because nonadherent patients are prone to be underrepresented in clinical research.[63] Unlike electronic prescribing which transmits all prescriptions directly to the pharmacy, it is difficult to track and trace the filling of handwritten/paper prescriptions generally and in the included studies since they could be lost, forgotten, misplaced, or ignored.[44,51,64] This could make the measurement of initial medication adherence in handwritten/paper-based prescriptions challenging. Furthermore, some prescriptions may be printed and given to the patient at the pharmacy without actually being dispensed resulting in the overestimation of primary medication compliance. Future research comparing the effect of the two methods of prescribing on primary medication adherence should utilize a standardized objective measure of medication adherence with prolonged follow-up durations. This can allow the effect sizes to be combined through meta-analysis to ascertain the effect of electronic prescribing on primary medication adherence. Nine out of the ten included papers recruited their

study sample from the United States where the health system is primarily insurance-based. And there could be a relationship between the lack of medical insurance and nonadherence to prescribed medications.[65] These could limit the application of the findings of the studies in countries where the health system differs. Further studies should be performed in both varying settings and countries to give a more precise representation of adherence. The unavailability of full text for one study,[39] after several efforts including contacting the authors, can affect the thoroughness of this systematic review as the findings of this article might influence the review's methodology and conclusion.

Conclusion

This systematic review has reemphasized the need for standardization in methods to measure medication adherence. The wide variations in the characteristics of the included studies limited the opportunity to pool the effect estimates via meta-analysis and arrive at a definite conclusion. Medication adherence should be a shared responsibility between the health care provider, pharmacy, and patient, and an ideal method of prescribing must incorporate the advantages of both paper and electronic prescriptions to facilitate efficiency, minimize cost, and maximize the treatment outcome.

Clinical Relevance Statement

Evidence from the retrieved articles demonstrates the need for a standardized objective method for measuring medication adherence and the scarcity of high-quality studies of the randomized control type. This would permit for the meta-analysis of the effect estimates of electronic versus paper-based prescribing on initial medication adherence. Finally, it has highlighted the importance of further research in this area to be conducted in different countries to give a more accurate representation of primary medication adherence.

Multiple Choice Questions

1. Which of the following is a subjective method of measuring medication adherence?
   a. pharmacy record
   b. patient Interview
   c. insurance claim
   d. prescription refill

   Correct Answer: The correct answer is option b. The subjective methods involve the evaluation of adherence by the biases, for example, patient's self-reports and health care professional assessments. They are vulnerable to recall and social desirability biases.

2. Electronic prescription systems can exist either as standalone or integrated with …?
   a. internet
   b. text messages
   c. phone calls
   d. electronic health records

   Correct Answer: The correct answer is option d. Electronic prescription systems were introduced as standalone systems ab initio and were later integrated with electronic health records.

Protection of Human and Animal Subjects

This is a secondary study that synthesized the findings of original studies. No human or animal subjects were recruited.

Conflict of Interest

None declared.

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