Patient Preference and Adherence

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REVIEW

Primary nonadherence to chronic disease medications: a meta-analysis

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Background: Medication nonadherence is a global problem that requires urgent attention. Primary nonadherence occurs when a patient consults with a medical doctor, receives a referral for medical therapy but never fills the first dispensation for the prescription medication. Nonadherence to chronic disease medications costs the USA ~$290 billion (USD) every year in avoidable health care costs. In Canada, it is estimated that 5.4% of all hospitalizations are due to medication nonadherence.

Objectives: The objective of this study was to quantify the extent of primary nonadherence for four of the most common chronic disease medications. The second objective was to identify factors associated with primary nonadherence to chronic disease medications.

Materials and methods: We conducted an extensive systematic literature review of eight databases with a wide range of keywords. We identified relevant articles for primary nonadherence to antihypertensives, lipid-lowering agents, hypoglycemics, and antidepressants. After further screening and assessment of methodologic quality, relevant data were extracted and analyzed using a random-effects model.

Results: Twenty-four articles were included for our meta-analysis after full review and assessment for risk of bias. The pooled primary nonadherence rate for the four chronic disease medications was 14.6% (95% CI: 13.1%–16.2%). Primary medication nonadherence was higher for lipid-lowering medications among the four chronic disease medications assessed (20.8%; 95% CI: 16.0%–25.6%). The rates in North America (17.0%; 95% CI: 14.4%–19.5%) were twice those from Europe (8.5%; 95% CI: 7.1%–9.9%). The absence of social support (20%; 95% CI: 14.4%–26.6%) was the most common sociodemographic variable associated with chronic disease medication primary nonadherence.

Conclusion: Evidence suggests that a considerable percentage of patients do not initially fill their medications for treatable chronic diseases or conditions. This represents a major health care problem that can be successfully addressed. Efforts should be directed toward proper medication counseling, patient social support, and clinical follow-up, especially when the indications for the prescribed medication aim to provide primary prevention.

Keywords: primary nonadherence, chronic disease medication, initial nonadherence, prescribed medications, predictors of primary nonadherence

Introduction

The World Health Organization (WHO) reviewed the literature on secondary nonadherence to chronic disease prescription medications and concluded the following: 1) medications do not work if patients do not take them, 2) medication nonadherence is a worldwide problem that crosses all jurisdictions, 3) the prevalence of medication nonadherence is of striking magnitude, and 4) this complex issue should be an urgent priority for policy makers and health care providers.[1] The analysis from the WHO was restricted to secondary nonadherence (patient quits taking medications after starting medical therapy).

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Primary nonadherence occurs when a patient consults with a medical doctor, receives a referral for medical therapy, but never fills the first dispensation for the prescription medication.[2] There are few articles published in the medical literature on primary nonadherence to prescription medications.[1] For example, in the province of Saskatchewan, Canada, the Health Quality Council concluded that only 29% of patients fill prescriptions for statin medications within 90 days of being hospitalized for a heart attack.[3]

The impact of medication nonadherence is significant. A research article from Canada demonstrated that 5.4% of all hospitalizations were due to medication nonadherence and that the subsequent total annual cost burden is as high as $1.6 billion Canadian dollars.[4] Estimates from a study in the USA suggest that nonadherence to chronic disease medications cost the health care system $290 billion American dollars every year.[5,6] Besides the cost implications, the impact to human health and quality of life could be enormous. Medication nonadherence is of paramount concern as current evidence suggests that placing an emphasis on efforts to address this important issue could potentially save more lives than discovering new medical innovations to tackle the conditions for which these medications are prescribed.[7,8]

Global improvements in care and prolonged life expectancy have led not only to an increase in the burden of chronic diseases but also a consequent rise in the number of medication prescriptions and increased budgetary spending on chronic diseases.[9] Chronic conditions such as hypertension, diabetes, and hyperlipidemia are among the predominant chronic conditions, and these ailments contribute directly and indirectly to 68% of all deaths worldwide.[10] Though not commonly categorized as a chronic condition, depression is the most disabling condition worldwide, contributing significantly to disease and medication prescription burden.[11]

Clearly, addressing the issues concerning medication nonadherence can have far-reaching implications toward improving the health and well-being of individuals and entire populations. The amount of research work published on primary medication nonadherence (PMNA) is varied with wide-ranging estimates of the effect size.[3,12–17] As such, this study seeks to obtain a pooled estimate of the impact of primary nonadherence to chronic disease medications and identify factors that might be contributing to this important issue.

Materials and methods

Data sources and study selection

This study sought to determine the PMNA rate to four common chronic disease medications. The four medication categories considered were antihypertensives, lipid-lowering agents, hypoglycemics, and antidepressants.

PMNA was determined in one of two ways: 1) the proportion of participants who failed to pick up a medication prescribed by their health professional (patient level of measurement) or 2) the proportion of all prescriptions that were not picked up within a specified time (prescription level of measurement).[18] Measurements made at the patient level can over- or underestimate the true PMNA, which is typically much closer to measurements made at the prescription level.[19]

We conducted an extensive systematic search of the following electronic databases: Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane central, Embase, MEDLINE, ProQuest, PsycINFO, PubMed, and Scopus. Our search was conducted using a combination of several keywords outlined in the search strategy for each database searched (Supplementary materials).

In determining the articles to be included in this study, the authors first eliminated duplicates using the EndNote reference management software. The remaining articles were then screened by their titles and abstracts for relevance. Afterward, two of the authors (CN and ML) reviewed the full-text articles independently for relevance and agreement with the predetermined inclusion criteria (Supplementary materials) to obtain the final articles to be included for the analysis. Methodologic quality and the risk of bias were also independently assessed by two reviewers (CN and ML) by using an adaptation of the Cochrane risk-of-bias tool[20] and a modified version of the Newcastle-Ottawa scale.[21] Any disagreements between the reviewing authors (CN and ML) were further discussed and deliberated upon for a possible resolution, and when an agreement was still not possible, a tie-breaking vote was cast by the final author (JM).

Data extraction

PMNA rates alongside the total number of participants (n) in each study were extracted from each of the included studies. Other relevant information extracted from each study included the type of medication prescribed, the duration of follow-up or observation, the study design, whether the data were from large administrative databases or smaller hospital databases, the average age of study participants, the study location, and the presence or absence of social support (which was defined as some form of routine contact between the health care professional and the participants either through regular follow-ups, text messages, or calls; with the principal aim of improving medication adherence).

Data analysis

The 95% CI of the included studies was determined using the extracted proportions and the sample size (n). The pooled estimate was obtained using a random-effects model to account for clinical heterogeneity. Heterogeneity was statistically assessed using Higgins I-squared[22] and further explored with the aid of a subgroup analysis based on categorizations determined a priori. An influence analysis using Tobias' method[23] was carried out to ascertain the robustness and effect each individual study had on the overall pooled estimate. This involved re-estimating the pooled effect with each study omitted in turn and then assessing whether the overall estimate was skewed significantly. Publication bias was assessed statistically using Begg's test.[24] All analyses used the "metaprop_one" command and were performed with STATA version 13.1.

Results

Study selection

A total of 1,492 articles were obtained from the initial search and this was narrowed to 959 articles after deduplication by use of the reference management software. Of the remaining studies, 894 were found to be unrelated to our study and, therefore, removed after careful screening by their titles and abstracts. Guided by the inclusion and exclusion criteria determined a priori, complete copies of the 65 remaining articles were obtained and further screened for relevance. After reviewing the full articles, 24 studies[3,12,14–16,19,25–42] were deemed appropriate for inclusion and underwent risk-of-bias assessment and further analysis (Figure 1). A detailed description of the studies included is provided in Table 1.

Risk-of-bias assessment

Of the selected final 24 articles, 13 were determined to have a low risk of bias, eight were unclear, and three had a high risk of bias. The main methodology concerns among the included experimental studies were centered on performance bias (besides the intervention of interest, researchers acted or treated participants in control or treatment group differently) and detection bias (systematic differences in the measurement of the outcome across both groups). The strengths among the experimental studies included adequate outcome data at follow-up and proper concealment of participant allocation. For the observational studies included for analysis,

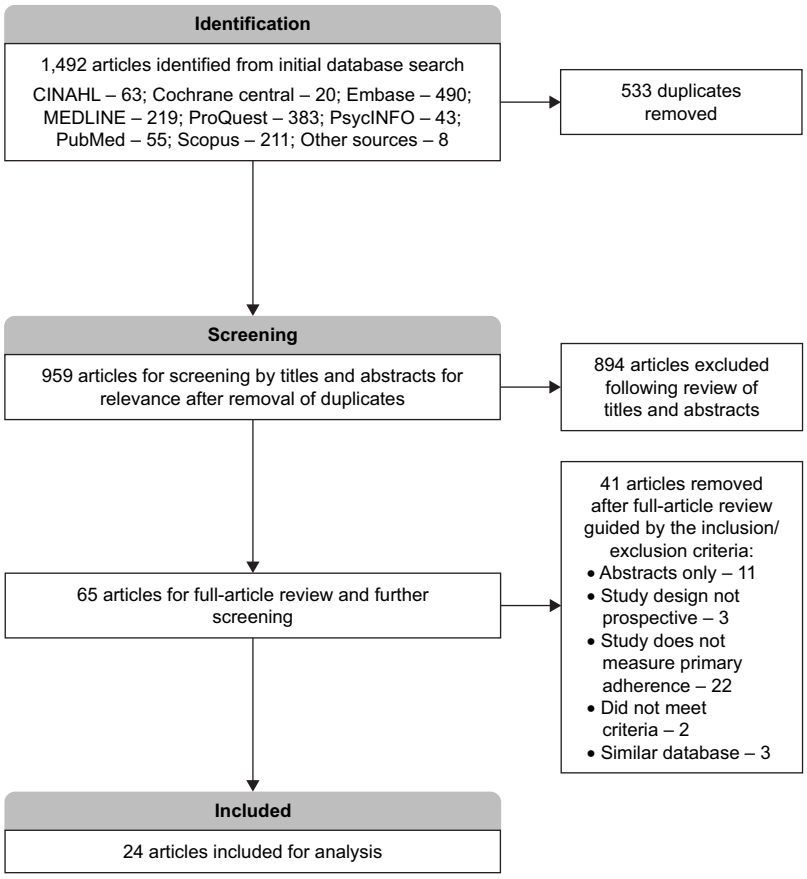

Figure 1 Prisma flow diagram for included studies.

Table 1 Description of included studies

Study and study location	Prescribed medication class	Duration of follow-up	Study design	Average/ median age (years)	Database	Level of measurement	Predictors of primary nonadherence
Aznar-Lou et al;[26] 2017, Spain	Hypoglycemics Antihypertensives Lipid-lowering Antidepressants	1 month	R.cohort	52.4	Administrative	Prescription	No comorbidities, diseases other than diabetes, young female prescribing GP, GP in training
Bauer et al;[15] 2014, USA	Antidepressants	2 months	R.cohort	58	Administrative	Patient	Lack of involvement in decision making
Casebeer et al;[27] 2009, USA	Lipid-lowering	4 months	CT	58	Hospital	Patient	No social support: absence of educational programs
Chan et al;[3] 2004, Canada	Antihypertensives Lipid-lowering	60 months	R.cohort	70	Hospital	Patient	–
Cheetham et al;[28] 2013, USA	Lipid-lowering	3 months	R.cohort	57[a]	Administrative	Patient	Black race, polymedication
Derose et al;[29] 2013, USA	Lipid-lowering	3 months	RCT	56.1	Administrative	Patient	No social support: absence of text reminder, no drug coverage
Ewen et al;[30] 2015, Germany	Antihypertensives	6 months	P.cohort	62.7	Hospital	Patient	–
Fischer et al;[31] 2015, USA	Hypoglycemics Antihypertensives Lipid-lowering	0.5 months	RCT	53.2	Hospital	Patient	–
Fischer et al;[12] 2010, USA	Hypoglycemics Antihypertensives Lipid-lowering Antidepressants	12 months	R.cohort	44.3	Administrative	Prescription	New prescriptions
Freccero et al;[32] 2016, Sweden	Antidepressants	1 month	R.cohort	48.2	Administrative	Patient	Country of origin, young age, marital status (divorce)
van Geffen et al;[33] 2009, the Netherland	Antidepressants	1 month	R.cohort	48.5	Hospital	Patient	New prescriptions
Jackevicius et al;[34] 2008, Canada	Hypoglycemics Antihypertensives Lipid-lowering Antidepressants	1 month	R.cohort	76.3	Administrative	Prescription	Older age, higher income, more medications
Karter et al;[35] 2009, USA	Hypoglycemics Antihypertensives Lipid-lowering	2 months	R.cohort	61.2	Administrative	Patient	–
Kerner et al;[36] 2017, USA	Antihypertensives	1 month	P.cohort	63.9	Hospital	Patient	No social support: absence of messages and calls
Linnet et al;[19] 2012, Iceland	Hypoglycemics Antihypertensives Antidepressants	1 month	R.cohort	–	Administrative	Prescription	Cost
O'Connor et al;[37] 2014, USA	Hypoglycemics	2 months	RCT	61.7	Administrative	Patient	No social support: absence of telephone support
Raebel et al;[25] 2012, USA	Hypoglycemics Antihypertensives Lipid-lowering	1 month	R.cohort	59.2	Administrative	Patient	Race, smoking, less care contacts, comorbidities, cost
Shah et al;[38] 2008, USA	Hypoglycemics	1 month	R.cohort	49	Administrative	Patient	Cost, good health
Shah et al;[39] 2009, USA	Antihypertensives	1 month	R.cohort	47	Administrative	Patient	Female, comorbidities, older age, less severe disease

(*Continued*)

Table 1 (*Continued*)

Study and study location	Prescribed medication class	Duration of follow-up	Study design	Average/ median age (years)	Database	Level of measurement	Predictors of primary nonadherence
Shin et al;[16] 2012, USA	Hypoglycemics Antihypertensives Lipid-lowering Antidepressants	3 months	R.cohort	46.5	Administrative	Prescription	Minority race, lower income, greater number of prescriptions on the index date
Tamblyn et al;[40] 2014, Canada	Hypoglycemics Antihypertensives Lipid-lowering	9 months	P.cohort	61.6	Hospital	Prescription	New prescriptions, young age, cost, lower health visits
Thengilsdóttir et al;[14] 2015, Iceland	Lipid-lowering Antidepressants	12 months	R.cohort	58.7 45.4	Administrative	Prescription	Female gender, cost
Trinacty et al;[41] 2009, USA	Hypoglycemics	1 month	R.cohort	51	Administrative	Patient	–
Xing et al;[42] 2011, USA	Antidepressants	24 months	R.cohort	51.5	Administrative	Prescription	New prescriptions, young age

Notes: Database: the data source, that is, administrative (from large admin databases), hospital (from clinic or hospital records). Level of measurement: primary nonadherence could have been measured as the proportion of participants (patient level of measurement) failing to fill their prescription or the proportion of prescriptions not filled (prescription level of measurement). [a]The age obtained from this particular study was a median value (unlike the others which were means).
Abbreviations: CT, controlled trial; GP, General Practitioner; PMNA, primary medication nonadherence; P.cohort, prospective cohort; R.cohort, retrospective cohort; RCT, randomized controlled trial.

selection of the cohort of interest was adequate and there was minimal bias noted with the comparability of the cohorts and assessment of the outcome (Figure 2A and B).

Characteristics of the pool

A total of 550,485 prescriptions were pooled from the 24 included studies, with 64,892 of those prescriptions not being redeemed within the defined period (Table 2). Seventeen of the included studies assessed PMNA by following up 467,483 prescriptions for a 3-month duration or less,[15,16,19,25,26,28,29,31–39,41] while seven studies assessed PMNA among 83,002 prescriptions over an extended time-frame (ie, >3 months).[3,12,14,27,30,40,42] Eight studies determined PMNA at the level of the prescription.[12,14,16,19,26,34,40,42] The highest number of chronic disease medication prescriptions identified in this study were for antihypertensives (190,658), followed closely by antidepressants (164,542), lipid-lowering medications (149,714), and hypoglycemics (45,571). A majority (16) of the studies were retrospective cohort studies,[3,12,14–16,19,25,26,28,32–35,38,39,41,42] while seven studies were either prospective cohorts or clinical trials.[27,29–31,36,37,40] Six of the included studies were conducted in Europe,[14,19,26,30,32,33] while the rest were in either the United States or Canada.[3,12,15,16,25,27–29,31,34–36,37–42] All but seven of the studies utilized data from large administrative databases[9,14–16,19,25,26,28,29,32,34,35,37–39,41,42] (Table 3).

Pooled analyses

Overall, the pooled estimates showed that the incidence of PMNA for the four most common chronic diseases was 14.6% (95% CI: 13.1%–16.2%) (Table 1; Figure 3). These estimates were unlikely to be influenced by bias, as PMNA did not differ significantly in the studies with a low risk of bias when compared to those with an unclear or high risk of bias (Table 3). Variation between the studies was addressed using a random-effects model and a subgroup analysis was carried out to further explore the potential reasons for between-study variations.

The following findings were of interest. The only sociodemographic variable with a consistent association with PMNA was lack of social support. Those without social support had higher rates of PMNA (20%; 95% CI: 14.4%–26.6%) than those with social support (13.1%; 95% CI: 11.4%–14.8%). Other variables, like age, demonstrated inconsistent associations. PMNA for lipid-lowering medications like statins (20.8%; 95% CI: 16.0%–25.6%) was higher than the PMNA rates for antihypertensives (12.4%; 95% CI: 9.5%–15.3%), hypoglycemics (13.2%; 95% CI: 9.6%–16.8%), and antidepressants (10.8%; 95% CI: 8.2%–13.4%). The extent of PMNA for North America (17.0%; 95% CI: 14.4%–19.5%) was twice the rate estimated for Europe (8.5%; 95% CI: 7.1%–9.9%). Another significant finding was that studies with prescription follow-up lasting >3 months (25.3%; 95% CI: 19.7%–30.9%) had more than twice the PMNA, compared to those where the studies follow patients for 3 months or less (10.0%; 95% CI: 8.7%–11.4%). Where prospective cohort study designs or clinical trials were used, PMNA was higher, but not significant, compared to

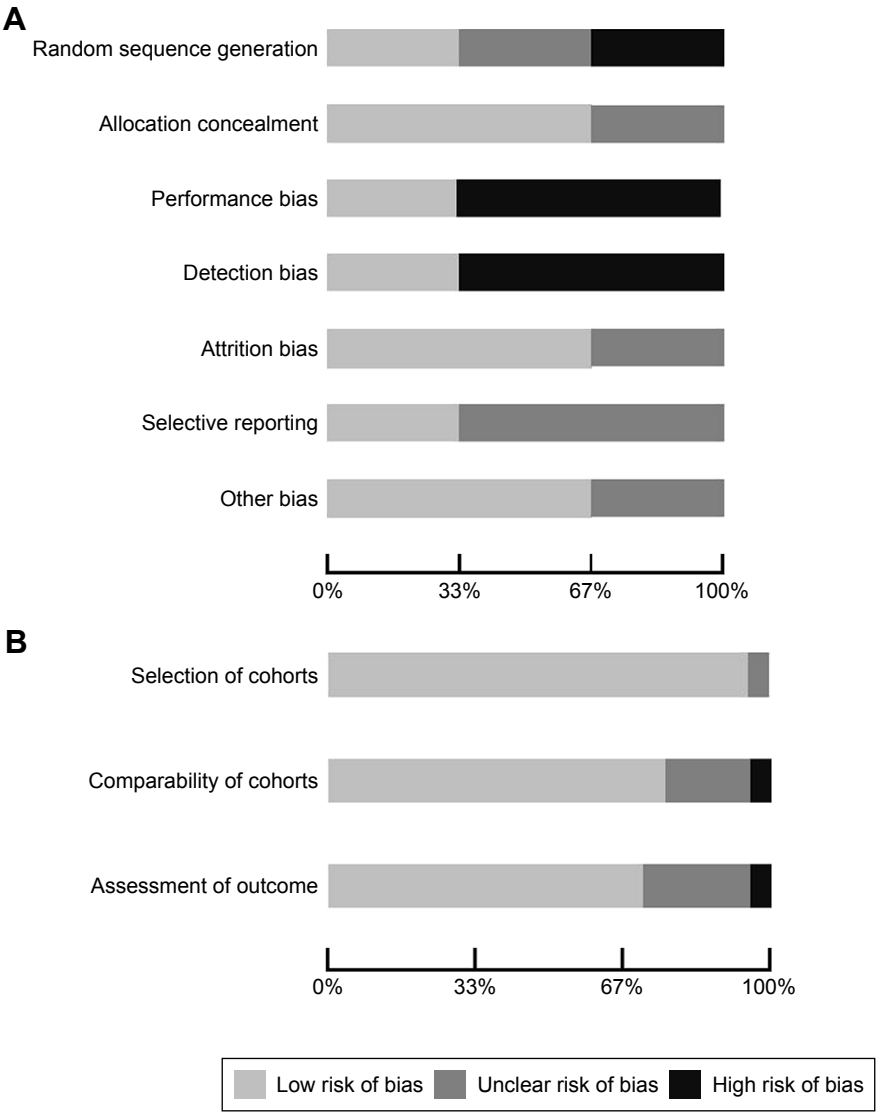

Figure 2 (**A**) Risk-of-bias plot – experimental studies. (**B**) Risk-of-bias plot – observational studies.

retrospective cohort studies. Similarly, PMNA was higher for studies obtained from hospital databases compared to those from large administrative databases but the association was not significant (Table 3).

Influential analyses carried out following Tobias' method showed that the pooled estimates did not vary significantly with the exclusion of any one study. This suggests that none of the studies had a significant influential effect on the overall estimates (Supplementary materials). Publication bias was assessed statistically using Begg's test. The test was not statistically significant (adjusted Kendall's score=208, P=0.066), suggesting that publication bias was unlikely.

Discussion

The WHO has identified the issue of medication nonadherence as a global concern and one that requires urgent intervention.[1] In our meta-analysis, we found that on average 15 of every 100 medications prescribed for chronic diseases or conditions are not initially filled by patients. Cost barriers play a key role in promoting medication non-adherence.[43]

For secondary nonadherence to chronic disease medications, two meta-analyses reviewed nonadherence to statins (49.0%; 95% CI: 48.9%–49.2%) and antihypertensive medications (48.5%; 95% CI: 47.7%–49.2%) in real-world settings.[2,44] If we put together the findings from these two meta-analyses on secondary nonadherence, along with the findings from our meta-analysis that showed primary nonadherence of 14.6%, we can extrapolate that ~41.8% of patients are adherent to chronic disease or chronic condition medications (49% of 85.4% equals 41.8%). Placing these figures alongside the cost estimates from the New England Health Institute, one can preliminarily ascertain that if steps

Table 2 Pooled estimates

Study and study location	Prescribed medication class	Number of study prescriptions	Primary nonadherence rate (%)	95% CI
Aznar-Lou et al;[26] 2017, Spain	Hypoglycemics	8,270	13.2	12.5–14.0
	Antihypertensives	74,346	7.5	7.3–7.7
	Lipid-lowering	69,602	8.8	8.6–9.0
	Antidepressants	97,635	11.5	11.3–11.7
Bauer et al;[15] 2014, USA	Antidepressants	1,523	4.3	3.3–5.4
Casebeer et al;[27] 2009, USA	Lipid-lowering	913	43.2	39.9–46.4
Chan et al;[3] 2004, Canada	Antihypertensives	1,700	33.5	31.3–35.8
	Lipid-lowering	1,700	71.0	68.8–73.1
Cheetham et al;[28] 2013, USA	Lipid-lowering	19,826	15.4	14.9–15.9
Derose et al;[29] 2013, USA	Lipid-lowering	5,216	18.4	17.4–19.5
Ewen et al;[30] 2015, Germany	Antihypertensives	100	2.0	0.2–7.0
Fischer et al;[31] 2015, USA	Hypoglycemics	346	6.4	4.0–9.5
	Antihypertensives	2,065	3.3	2.6–4.2
	Lipid-lowering	528	6.4	4.5–8.9
Fischer et al;[12] 2010, USA	Hypoglycemics	5,525	21.9	20.8–23.0
	Antihypertensives	30,211	19.5	19.0–19.9
	Lipid-lowering	12,963	19.9	19.2–20.6
	Antidepressants	11,767	21.4	20.6–22.1
Freccero et al;[32] 2016, Sweden	Antidepressants	11,624	14.9	14.3–15.6
van Geffen et al;[33] 2009, the Netherland	Antidepressants	965	4.3	3.1–5.7
Jackevicius et al;[34] 2008, Canada	Hypoglycemics	146	13.7	8.6–20.4
	Antihypertensives	5,337	6.4	5.8–7.1
	Lipid-lowering	758	5.2	3.7–7.0
	Antidepressants	43	32.6	19.1–48.5
Karter et al;[35] 2009, USA	Hypoglycemics	8,191	4.0	3.6–4.5
	Antihypertensives	12,712	3.2	2.9–3.5
	Lipid-lowering	6,426	8.5	7.8–9.2
Kerner et al;[36] 2017, USA	Antihypertensives	9	22.2	2.8–60.0
Linnet et al;[19] 2012, Iceland	Hypoglycemics	760	8.7	6.8–10.9
	Antihypertensives	4,127	8.6	7.7–9.5
	Antidepressants	4,492	6.6	5.9–7.4
O'Connor et al;[37] 2014, USA	Hypoglycemics	2,378	13.3	11.9–14.7
Raebel et al;[25] 2012, USA	Hypoglycemics	1,521	11.3	9.8–13.0
	Antihypertensives	4,721	7.0	6.3–7.8
	Lipid-lowering	4,607	12.6	11.6–13.6
Shah et al;[38] 2008, USA	Hypoglycemics	1,132	15	13.0–17.2
Shah et al;[39] 2009, USA	Antihypertensives	3,240	17.1	15.8–18.5
Shin et al;[16] 2012, USA	Hypoglycemics	14,417	12.6	12.0–13.1
	Antihypertensives	48,982	7.8	7.5–8.0
	Lipid-lowering	22,249	22.3	21.8–22.9
	Antidepressants	27,383	7.7	7.4–8.0
Tamblyn et al;[40] 2014, Canada	Hypoglycemics	979	29.1	26.3–32.1
	Antihypertensives	3,108	32.2	30.5–33.8
	Lipid-lowering	2,794	33.6	31.9–35.4
Thengilsdóttir et al;[14] 2015, Iceland	Lipid-lowering	2,132	6.2	5.2–7.3
	Antidepressants	8,553	8.0	7.4–8.6
Trinacty et al;[41] 2009, USA	Hypoglycemics	1,906	10.0	8.7–11.5
Xing et al;[42] 2011, USA	Antidepressants	557	13.1	10.4–16.2
Pooled random estimate		550,485	14.6	13.1–16.2

Table 3 Subgroup analysis

Subgroup	PMNA (95% CI)	N
Medication		
Hypoglycemics	13.2 (9.6–16.8)	45,571
Antihypertensives	12.4 (9.5–15.3)	190,658
Lipid-lowering	20.8 (16.0–25.6)	149,714
Antidepressants	10.8 (8.2–13.4)	164,542
Duration of follow-up		
≤3 months	10.0 (8.7–11.4)	467,483
>3 months	25.3 (19.7–30.9)	83,002
Study design		
R.cohort	13.5 (11.8–15.2)	532,049
P.cohort, CT, RCT	18.9 (11.0–26.8)	18,436
Average age, years		
50 or less	14.8 (11.4–18.2)	199,011
51–60	11.4 (9.8–12.9)	295,714
>60	20.4 (14.9–25.8)	46,381
Data source		
Administrative database	11.7 (10.2–13.3)	535,278
Hospital database	24.0 (12.0–35.9)	15,207
Level of measurement		
Prescription	14.5 (12.7–16.4)	457,136
Patient	14.8 (11.4–18.2)	93,349
Risk of bias		
Low risk	12.9 (11.2–14.5)	493,728
Unclear/high risk	17.3 (13.0–21.5)	56,757
Location		
North America	17.0 (14.4–19.5)	267,879
Europe	8.5 (7.1–9.9)	282,606
Absence of social support		
Yes	20.5 (14.4–26.6)	27,769
No	13.1 (11.4–14.8)	522,716

Abbreviations: CT, controlled trial; N, total number of prescriptions; PMNA, primary medication nonadherence; P.cohort, prospective cohort; RCT, randomized controlled trial; R.cohort, retrospective cohort.

were taken to reduce the PMNA rate for chronic disease medications by even 1% (on an absolute level – not relative) it can potentially save the US health care system ~$2.9 billion (USD) annually.[6]

Our subgroup analysis showed that lipid-lowering medications like statins had the highest rate of PMNA for the chronic disease medications (20.8%). A plausible explanation for the observed high PMNA rate is that these medications are often used for primary prevention and, therefore, patients may feel that there is no immediate threat to their health.[2,45] This was not the case with hypoglycemic or antidepressant medications, where the common indications for use have clear morbidity and mortality implications that can be easily recognized by patients.

Additionally, we found a difference between the PMNA rates for chronic disease medications when we stratified by the location of the study. Prescriptions for medications based out of Europe had a PMNA rate of 8.5%, while those from North America had PMNA rates of 17.0%. These differences may be related to the variations in the delivery of care and the cost of health care in these regions. In most cases, European nations have stronger social programs that include universal health care coverage with a greater percentage of public funding.[46,47] On the other hand, the North American studies were predominantly from the USA, where universal coverage is limited and there is greater dependence on private insurance systems.[47]

Our subgroup analysis by the duration of follow-up showed that PMNA rates for studies with a longer period of follow-up (3 months or more) were more than double the rates for those with shorter follow-up (3 months or less). This is expected, as the longer the study duration, the more likely nonadherence will be detected.[27] For example, in one study, it took patients an average of ~2 years to fill their first prescription for statin medications.[2]

The absence of social support was also noted to play a key role in negatively impacting the PMNA rates. These findings are not surprising, as studies in the past have shown a clear relationship between the absence of social support and patient nonadherence.[15,27,29,36,37,48,49] Given that social support from clinicians, family members, and friends is a modifiable factor, this variable represents an area of interest and further research.

The Cochrane Collaboration reviewed the literature on the impact of social support on medication nonadherence and concluded that more frequent interaction between doctors and patients was the most effective intervention.[50] A second meta-analysis from the Cochrane Collaboration reviewed interventions to specifically improve adherence to lipid-lowering medications. Overall, only one of four patients continued to take medications in the long term. In this review, patient reinforcement and regular reminders were the most promising interventions. The authors concluded that a combination of strategies including reminders, reinforcement, and emphasis on appreciating the patient's perspective might lead to the most effective strategy.[51] Similarly, the National Collaborating Centre for Primary Care performed a systematic review of the literature and advocated that health care professionals 1) adapt their consultation style to the needs of individual patients, 2) make information more accessible and easy to understand for their patients, 3) increase patient involvement in decision making, 4) be aware that patients may have concerns about their prescribed medicines, and 5) recognize that nonadherence is quite common and that they should routinely assess for it in a nonjudgmental way.[52]

In summary, our meta-analysis helps to provide a more clear and accurate picture of the burden of PMNA, while identifying a number of associated factors. Health care professionals and policy makers should place more emphasis

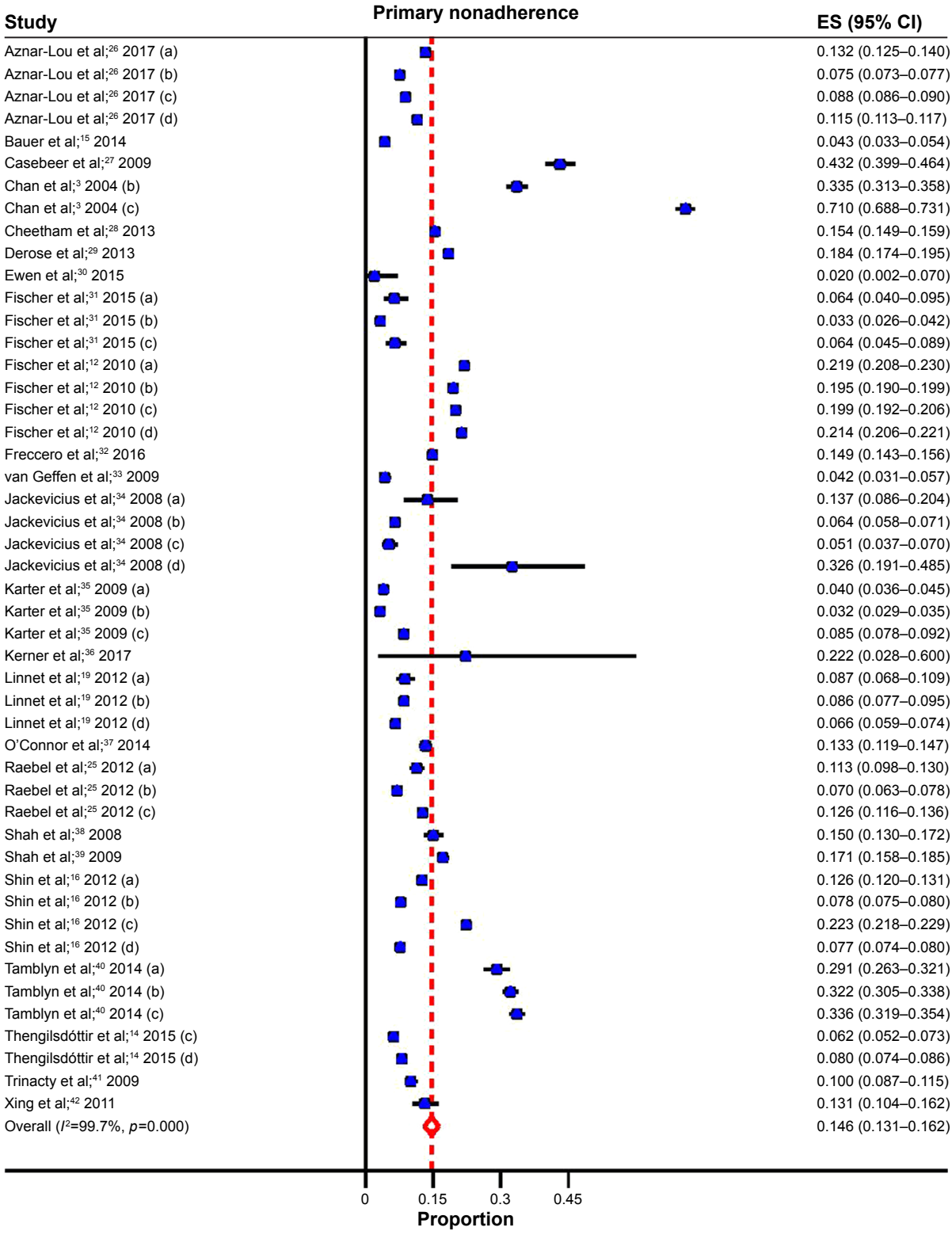

Figure 3 Forest plot for primary medication nonadherence.
Notes: (a) hypoglycemics; (b) anti-hypertensives; (c) lipid-lowering; (d) anti-depressants.
Abbreviation: ES, effect size.

on proper medication counseling, patient social support, and clinical follow-up to help reduce PMNA, especially where the indications for the prescribed medication aim to provide primary prevention.

Strengths and limitations

Our study has several strengths. There is a high level of congruence between our findings and those reported in the existing literature. However, our study provides a more

clear and accurate picture of the PMNA impact because its reported effect estimates are not influenced by any single study. Additionally, the increased sample size obtained from pooling the effects of the included studies provides statistical strength.

Despite its strengths, our study has a few limitations. Given the nature of our study and its reliance on secondary data, we experienced some challenges in handling the residual (unmeasured) confounding effects that may be present within each study (eg, some of the included studies had identified their inability to assess the attitudes and beliefs of patients toward the prescribed medication, when these factors could clearly affect PMNA). Also, some of the values from the included studies might be either under- or overestimated because there is no way to independently verify whether patients either filled or did not fill their prescriptions from other sources or locations (ie, filled in different pharmacies or different states or provinces). Finally, some of the included studies were carried out with populations that could not be entirely generalizable and, therefore, should be interpreted with some level of caution.

Disclosure

The authors report no conflicts of interest in this work.

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