Original Investigation

Medication Therapy Management Interventions in Outpatient Settings
A Systematic Review and Meta-analysis

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IMPORTANCE Medication therapy management (MTM) services (also called *clinical pharmacy services*) aim to reduce medication-related problems and their downstream outcomes.

OBJECTIVE To assess the effect of MTM interventions among outpatients with chronic illnesses.

DATA SOURCES MEDLINE, Cochrane Library, and International Pharmaceutical Abstracts through January 9, 2014.

STUDY SELECTION Two reviewers selected studies with comparators and eligible outcomes of ambulatory adults.

DATA EXTRACTION AND SYNTHESIS Dual review of titles, abstracts, full-text, extractions, risk of bias, and strength of evidence grading. We conducted meta-analyses using random-effects models.

MAIN OUTCOMES AND MEASURES Medication-related problems, morbidity, mortality, quality of life, health care use, costs, and harms.

RESULTS Forty-four studies met the inclusion criteria. The evidence was insufficient to determine the effect of MTM interventions on most evaluated outcomes (eg, drug therapy problems, adverse drug events, disease-specific morbidity, disease-specific or all-cause mortality, and harms). The interventions improved a few measures of medication-related problems and health care use and costs (low strength of evidence) when compared with usual care. Specifically, MTM interventions improved medication appropriateness (4.9 vs 0.9 points on the medication appropriateness index, $P < .001$), adherence (approximately 4.6%), and percentage of patients achieving a threshold adherence level (odds ratios [ORs] ranged from 0.99 to 5.98) and reduced medication dosing (mean difference, −2.2 doses; 95% CI, −3.738 to −0.662). Medication therapy management interventions reduced health plan expenditures on medication costs, although the studies reported wide CIs. For patients with diabetes mellitus or heart failure, MTM interventions lowered the odds of hospitalization (diabetes: OR, 0.91 to 0.93 based on type of insurance; adjusted hazard rate for heart failure: 0.55; 95% CI, 0.39 to 0.77) and hospitalization costs (mean differences ranged from −$363.45 to −$398.98). The interventions conferred no benefit for patient satisfaction and most measures of health-related quality of life (low strength).

CONCLUSIONS AND RELEVANCE We graded the evidence as insufficient for most outcomes because of inconsistency and imprecision that stem in part from underlying heterogeneity in populations and interventions. Medication therapy management interventions may reduce the frequency of some medication-related problems, including nonadherence, and lower some health care use and costs, but the evidence is insufficient with respect to improvement in health outcomes.

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Used appropriately, medications can alleviate distressing symptoms, prevent many acute and chronic illnesses, and improve patients' health. However, medications often are used inappropriately.[1-3] In the United States, adverse drug events led to an estimated 4.5 million ambulatory care visits per year during 2005 to 2007.[4] In addition to problems involving adverse drug events, many patients experience drug therapy problems related to appropriateness (eg, unwarranted polypharmacy, suboptimal regimens), effectiveness (eg, subtherapeutic doses, therapeutic response not achieved at an adequate dose), safety (eg, adverse drug effects, drug-drug interactions, and supratherapeutic doses), and adherence.[5]

Medication therapy management (MTM) is a strategy for delivering a variety of nondispensing clinical pharmacy services to patients and their clinicians; it is a structure for providing what pharmacists referred to in the early 1990s as *pharmaceutical care*.[6] Medication therapy management services aim to optimize therapeutic outcomes by identifying and resolving drug therapy problems.[7] The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173)[8] expanded access to MTM services for patients with certain chronic conditions through Medicare Part D prescription drug benefits. In 2005, 11 national pharmacy organizations established a consensus definition for MTM[9]; in 2008, a subset of these organizations established 5 core elements for an MTM service model.[10] These elements include a medication therapy review, a personal medication record, a medication action plan, intervention and/or referral for drug therapy problems, and documentation and follow-up.[7] Also by 2008, *Current Procedural Terminology* for MTM services (codes 99605, 99606, and 99607) became available and further defined MTM service-level expectations to include an assessment of drug-related needs, identification of drug therapy problems, and care planning and follow-up.[11-13]

Medication therapy management can be viewed as a professionally delivered service with common core features and goals; specific intervention components may vary based on the scope and setting of each MTM program. Recent widespread implementation of MTM services, stemming from perceived clinical need and access to billing codes, drives an urgent need for actionable, evidence-based information on its effectiveness and harms. Our study assessed the effectiveness and harms of outpatient-based MTM compared with usual care; we focus on the effect of MTM on drug-therapy problems and their sequelae, including biomarkers of morbidity, health outcomes, mortality, patient-centered functioning, quality of life, satisfaction, and health care use and costs. This article is based on a systematic evidence report commissioned by the US Agency for Healthcare Research and Quality (AHRQ) to determine the effectiveness of outpatient MTM.[14]

Methods

We developed a protocol for this review.[15] A trained librarian, in consultation with investigators, used numerous terms to identify MTM-related studies in MEDLINE, the Cochrane Library, and the International Pharmaceutical Abstracts database (inception through January 9, 2014) (eTable 1 in the Supplement). We limited searches to English-language and human-only studies. We manually searched the reference lists of landmark and background articles for additional relevant citations. We also searched numerous sources for unpublished literature described in eTable 1 in the Supplement. Finally, the AHRQ placed a request for unpublished studies in the *Federal Register*.

Study Selection

We prespecified required intervention characteristics to reduce underlying heterogeneity. We required MTM interventions to include a comprehensive (rather than condition-specific) medication review, patient-directed education, care coordination, and opportunity for follow-up. When articles included insufficient detail for us to decide on inclusion or exclusion, we contacted the authors for additional information. We limited our review to ambulatory settings. We anticipated modest randomized clinical trial (RCT) evidence and therefore also included nonrandomized clinical trials (NRCTs), cohort studies, and case-control studies. We excluded studies of MTM services provided within inpatient settings or shortly after hospital discharge; the goals of therapy and severity of illness are likely to differ markedly between outpatients and patients experiencing or recovering from an acute hospital stay.

Two trained members of the research team (M.V., L.C.K., C.E.G., S.J.B, E.C.-S., and R.P. performed all functions discussed) independently reviewed each of the titles, abstracts, and articles against the inclusion/exclusion criteria (eTable 2 in the Supplement). Studies marked for possible inclusion by either reviewer underwent dual, independent full-text review.

Data Extraction and Risk of Bias Assessment

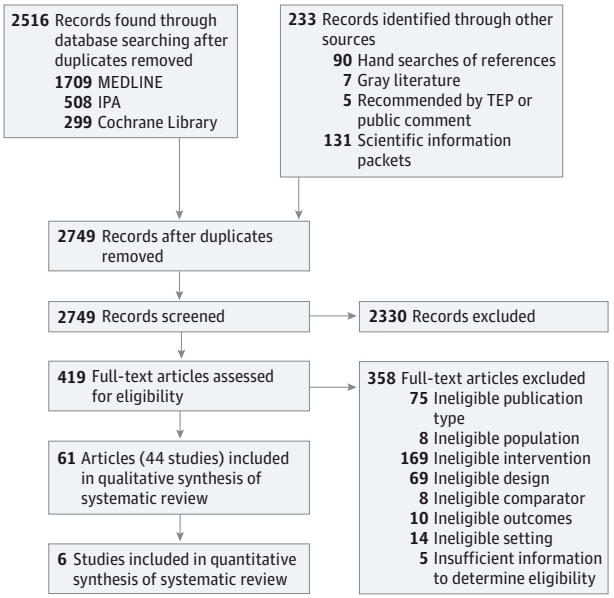
A trained reviewer abstracted information from eligible studies into structured evidence tables; a second team member reviewed all data abstractions for completeness and accuracy. Reviewers rated the risk of bias independently against prespecified criteria.[16] For RCTs, we relied on the risk-of-bias tool developed by the Cochrane Collaboration.[17] We assessed the risk of bias of NRCTs using an item bank developed by RTI International.[18]

We evaluated RCTs on the adequacy of randomization, allocation concealment, similarity of groups at baseline, blinding of outcome assessment, attrition, use of intention-to-treat analysis, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity. For NRCTs, we assessed for confounding rather than adequacy of randomization and allocation concealment. We also evaluated RCTs for confounding attributable to randomization failure through biased selection or attrition. We rated the studies as low, medium, high, or unclear risk of bias.[16] Two independent reviewers assessed the risk of bias for each study and resolved disagreements by consensus or by consulting a third member of the team.

Data Synthesis and Analysis

We excluded studies that we deemed at high risk of bias from our main data analyses, but we included them in sensitivity

Figure 1. Article Flowchart



IPA indicates International Pharmaceutical Abstracts; TEP, technical expert panel.

analyses. When we had no other evidence, we included high risk-of-bias studies in the main analyses.

We conducted meta-analysis when appropriate (≥3 studies with similar populations, interventions, comparators, outcomes, and design) using Comprehensive Meta-Analysis software (Biostat Inc). For all pooled analyses, we used random-effects models. To determine whether quantitative analyses were appropriate, we assessed the clinical and methodologic heterogeneity of the studies under consideration.[19] For all quantitative syntheses, we assessed statistical heterogeneity in effects between studies by calculating the χ^2 statistic and the I^2 statistic (the percentage of total variation across studies attributable to heterogeneity rather than chance).[20] When relevant, we examined potential sources of heterogeneity from the risk of bias using sensitivity analysis.

When quantitative analyses were inappropriate, we synthesized the data qualitatively, considering issues of consistency, precision, directness, and risk of bias. Whenever possible, we computed 95% CIs for outcomes reported in single studies, but numerous articles did not provide sufficient information for such computations.

Two reviewers assessed strength of evidence domains for each outcome and resolved differences by consensus or referral to a third senior member of the team. We based our grades on low or medium risk-of-bias RCTs or observational studies (unless none was available) based on guidance established by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[21-23] We considered one of the following grades for each outcome: (1) high (high confidence that the evidence reflects the true effect), (2) moderate (moderate confidence that the evidence reflects the true effect; future research may change the estimate), (3) low (low confidence that the evidence reflects the true effect; further research is likely to change the estimate), or (4) insufficient evidence.[24]

Results

We identified 61 articles (representing 44 studies) that met the inclusion criteria (**Figure 1**). The evidence base consisted of 21 RCTs, 4 NRCTs, and 19 cohort studies. Most studies compared an MTM intervention with usual care (no MTM intervention).

Methodologic problems in numerous studies led us to rate them as having a medium or high risk of bias. Of the 44 studies, we rated 16 as high risk of bias overall; in these studies, concerns about randomization failure, confounding, or overall attrition increased the risk of bias for all outcomes. In a few instances, we rated studies that were otherwise of low or medium risk of bias as high risk for individual outcomes chiefly because of measurement or detection biases related to the specific outcome. Because of the underlying heterogeneity of the populations, settings, and outcomes and the limited number of studies on any single outcome, we could use only 4 low or medium risk-of-bias studies in the meta-analysis [25-30] (**Figure 2** and **Figure 3** and eFigures 1-8 in the Supplement)[25-33] and 2 additional high risk-of-bias studies for sensitivity analysis (eTable 5).[34-36]

Characteristics of included studies are provided in eTable 3 and eTable 4 in the Supplement. The numbers of participants analyzed in each study ranged from 10 to 200 722. All studies used pharmacists to deliver MTM services, specifically medication review, patient-directed education, care coordination, and opportunity for follow-up. Despite these 4 common features, MTM interventions differed considerably across the studies. Of the 44 included studies, 34 were broadly focused (ie, included a patient population not defined by any specific clinical condition), and 10 were relatively narrowly focused on specific patient populations (eg, chronic heart failure, hypertension, diabetes mellitus, human immunodeficiency virus, glucocorticoid-induced osteoporosis, or hemodialysis) who then received comprehensive medication review. Services were provided face to face in half of the included studies. Included studies provided interventions in a variety of settings including community pharmacies, centralized pharmacies or pharmacy call centers, outpatient medical clinics, and patients' homes.

Drug-Related Problems and Biomarkers of Morbidity

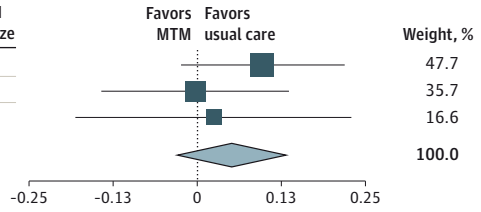
Thirty-two studies reported on 1 or more intermediate outcomes (**Table 1**). We were unable to pool the results because too few studies within each design stratum (ie, RCT or cohort) were of low or medium risk of bias.

Medication therapy management interventions significantly improved medication appropriateness (measured with a reliable and valid 10-item index of medication appropriateness measuring improved prescribing quality[53]; 4.9 vs 0.9 points, $P < .001$).[32] For some medications, MTM improved adherence as the percentage of prescribed doses taken (mean improvement, approximately 4.6%)[41] or percentage of patients

Figure 2. Effect of Medication Therapy Management (MTM) on Mean Number of Outpatient Visits

Source	Outcome	Time Point	Difference in Means (95% CI)	MTM Sample Size	No MTM Sample Size	Weight, %
IMPROVE[26,28-30]	Clinic visits	12 mo	0.10 (-0.02 to 0.22)	523	531	47.7
Sellors et al,[27] 2003	Clinic visits	5 mo	0.00 (-0.14 to 0.14)	379	409	35.7
Touchette et al,[25] 2012	Physician visits	3-6 mo	0.02 (-0.18 to 0.23)	183	183	16.6
Total			**0.05 (-0.03 to 0.13)**	**1085**	**1123**	**100.0**

Heterogeneity: $\tau^2 = 0$; $\chi^2_2 = 1.18$; $P = .56$, $I^2 = 0$
Test for overall effect: $Z = 1.16$; $P = .25$

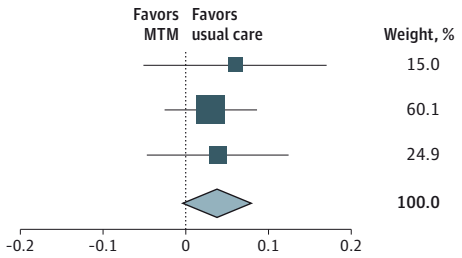


Three low or medium risk-of-bias randomized clinical trials of MTM versus control groups without MTM using the basic arm of the Touchette et al[25] study. Our meta-analysis found no significant difference in the number of outpatient visits between patients receiving MTM interventions and those receiving usual care (standardized mean difference, 0.05; 95% CI, −0.03 to 0.13; $P = .25$). IMPROVE indicates Impact of Managed Pharmaceutical care on Resource utilization and Outcomes in Veterans Affairs Medical Center.

Figure 3. Effect of Medication Therapy Management (MTM) on Mean Number of Hospitalizations

Source	Outcome	Time Point	Difference in Means (95% CI)	MTM Sample Size	No MTM Sample Size	Weight, %
IMPROVE[26,28-30]	Change in hospitalizations	12 mo	0.06 (-0.05 to 0.17)	523	531	15.0
Sellors et al,[27] 2003	Overall No. of hospitalizations	5 mo	0.03 (-0.03 to 0.09)	379	409	60.1
Touchette et al,[25] 2012	Overall No. of hospitalizations	3-6 mo	0.04 (-0.05 to 0.13)	183	183	24.9
Total			**0.04 (-0.01 to 0.08)**	**1085**	**1123**	**100.0**

Heterogeneity: $\tau^2 = 0$; $\chi^2_2 = 0.23$; $P = .89$, $I^2 = 0$
Test for overall effect: $Z = 1.68$; $P = .09$



Three low or medium risk-of-bias randomized clinical trials of MTM versus control groups without MTM, using the basic arm of the Touchette et al[25] study. Our meta-analysis found no significant difference in the number of hospitalizations between patients receiving MTM and those receiving usual care (WMD, 0.04; 95% CI, −0.01 to 0.08; $P = .09$). IMPROVE indicates Impact of Managed Pharmaceutical care on Resource utilization and Outcomes in Veterans Affairs Medical Center; WMD, weighted mean difference.

achieving a threshold adherence level (odds ratio [ORs], 0.99 to 5.98)[41] and reduced medication dosing (mean difference, −2.2 doses; 95% CI, −3.738 to −0.662)[48] (Table 1). We had enough consistency and precision across the body of evidence to assign a low strength-of-evidence grade for these outcomes. Evidence was insufficient to draw any conclusions about effectiveness for the number of drug therapy problems identified and resolved.

Evidence was insufficient to draw any conclusions about effectiveness for other intermediate outcomes, including the effect on anticoagulation, blood pressure, hemoglobin A_{1c}, and low-density lipoprotein cholesterol. We identified no studies that addressed the effect of MTM on meeting the goals of therapy.

Morbidity, Mortality, and Other Patient-Centered Outcomes

Twenty-one studies reported 1 or more patient-centered outcomes; we were able to synthesize some outcomes quantitatively. Specifically, MTM interventions did not improve measures of health-related quality of life[26,31,32] (**Table 2** and eTable 5 and eFigures 1-8 in the Supplement), yielding low strength of evidence for no benefit. For general health-related quality of life outcomes, meta-analyses of 7 of 8 domains and the 2 component scores (physical health and mental health) showed no significant benefit from MTM interventions. However, the vitality domain of the SF-36 showed benefit in meta-analysis estimates that did not adjust for multiple comparisons. We graded this outcome as imprecise after correcting for multiple comparisons and the evidence on vitality as insufficient (eFigure 5 in the Supplement). The various patient satisfaction outcomes used by studies[26,28-30,32,44,58] also showed no effect from MTM programs (low strength of evidence for no benefit), although we were unable to pool results because of the heterogeneity of measures. Evidence was insufficient to draw conclusions about the effect of MTM on adverse drug events, gastrointestinal bleeding, mortality, and cognitive and affective function. No studies evaluated the effect of MTM on activities of daily living, work or school absenteeism, or patient and caregiver participation in medical care and decision making.

Health Care Use Outcomes

Thirty-three studies reported 1 or more outcomes related to the use of health care, such as the number of emergency department visits, number of hospitalizations, costs of laboratory tests, and total expenditures on medications. In addition to qualitative syntheses on all outcomes, we were able to pool the results on the number of outpatient and hospital visits.

Medication therapy management improved health plan expenditures on medications, but studies had wide

Table 1. Summary of Findings and Strength of Evidence for MTM Interventions on Drug-Related Problems and Biomarkers of Morbidity

Outcome	Study Design: No. of Studies (No. of Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Drug-Related Problems				
Drug therapy problems identified[a]	Cohort: 1 (582)[37]	Insufficient	High study limitations, consistency unknown, indirect, imprecise	Risk difference: 6.1%, *P* = .06
No. of drug therapy problems resolved	Cohort: 1 (120)[38-40]	Insufficient	High study limitations, consistency unknown, indirect, imprecise	Mean difference (95% CI), −1.00 (1.967 to −0.033), *P* = .04
Medication adherence measured as proportion of patients adherent to a threshold amount of pills taken	RCT: 1 (69)[31]	Insufficient	Medium study limitations, consistency unknown, direct, precise	100% of Intervention patients and 88.9% of controls were adherent (took ≥80% of medicine), *P* = .12
	Cohort: 2 (range, 224-200 722)[41,42]	Low for benefit	High study limitations, inconsistent, direct, precise	Two studies with findings in opposite direction; larger study showing range of ORs for medication-specific adherence depending on medication; for comparison of PDP vs controls, ORs ranged from 0.99 (95% CI, 0.90 to 1.08) to 1.43 (95% CI, 1.26 to 1.62); for comparison of MA-PD vs controls, ORs ranged from 1.10 (95% CI, 0.83 to 1.24) to 1.40 (95% CI, 1.29 to 1.52); for clinic-based MTM vs usual care for adherence to aspirin, ORs of adherence ranged from 5.981 (95% CI, 0.284 to 126.030; *P* = .25) during the intervention to 1.17 determined 1 y after the intervention (95% CI, 0.072 to 18.903; *P* = .91)
Medication adherence measured as percentage of prescribed doses taken	Cohort: 2 (range: 120-4500)[38,43]	Low for benefit for adherence to treatment for hypertension and dyslipidemia; insufficient for treatment of patients with diabetes mellitus, depression, and asthma	High study limitations, inconsistent, direct, imprecise	Mean difference from small study, −0.040 (95% CI, −0.101 to 0.021; *P* = .20); larger study found a small but statistically significant effect of MTM on adherence to medications for 2 of 5 conditions (4.6% difference for hypertension [95% CI, 3.211 to 5.989]; 4.7% for dyslipidemia [95% CI, 2.747 to 6.673]), but no statistically significant effect for the other conditions (asthma, depression, and diabetes)
Medication adherence using self-report measures (Morisky scale)	RCT: 1 (292)[44]	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Mean difference, 0.090 (95% CI, −0.076 to 0.256; *P* = .29
Medication adherence, miscellaneous measures	RCT: 2 (365)[32,45]	Insufficient	Medium study limitations, inconsistent, direct, imprecise	One study showed lesser (but nonsignificant) improvement in medication-taking risk scores among the intervention group (−3.47 vs −4.38, *P* = .52); second study's OR was nonsignificant for better adherence among intervention group: OR, 1.076 (95% CI, 0.527 to 2.197)
Medication appropriateness General Index Scores (range, 0-18; lower scores are better)	RCT: 1 (208)[32]	Low for benefit	Low study limitations, consistency unknown, direct, precise	Improvement in MTM group from score of 17.7 to 13.4 and to 12.8 at 3 and 12 mo, respectively, whereas in controls these values were 17.6, 16.5, and 16.7, respectively (*P* < .001 for 3- and 12-mo differences)
Medication-specific appropriateness	RCT: 2 (261)[46,47]	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Significant improvement in appropriateness in the MTM group for some medications: calcium supplements (percentage of intervention patients taking it increased from 39% to 56% at 9 mo vs controls, who decreased from 38% to 31%) but not bisphosphonate or estrogen therapy
Medication dosing	RCT: 1 (56)[48]	Low for benefit	Medium study limitations, consistency unknown, indirect, precise	Mean difference in doses, −2.2 (95% CI, −3.738 to −0.662)
Goals of therapy	0	NA	NA	NA

(continued)

CIs.[27,48,59] The MTM interventions also reduced the risk of hospitalization (2 studies): the adjusted OR for diabetes ranged from 0.91 (95% CI, 0.87 to 0.95) to 0.93 (95% CI, 0.88 to 0.98),[41] and the adjusted hazard rate for heart failure was 0.55 (95% CI, 0.39 to 0.77).[60] Medication therapy management also reduced the costs of diabetes-specific hospitalization (1 study[41]) (mean difference, −$363.45 [95% CI, −$562.00 to −$164.91]) (**Table 3**). These results are imprecise or come from cohort studies with inherent limitations, leading to a judgment of low strength of evidence.

Three RCTs did not reduce the number of hospitalizations,[25-30] although a single cohort study[43] found a lower mean number of inpatient visits for patients accepting MTM (compared with patients refusing MTM). Overall,

Table 1. Summary of Findings and Strength of Evidence for MTM Interventions on Drug-Related Problems and Biomarkers of Morbidity (continued)

Outcome	Study Design: No. of Studies (No. of Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Biomarkers of Morbidity				
Anticoagulation	RCT: 1 (10)[31]	Insufficient	Medium study limitations, consistency unknown (single study), direct, imprecise	Therapeutic INR achieved: 100% vs 16.7%; $P = .048$
HbA_{1c}	RCT: 2 (102)[31,49]	Insufficient	Medium study limitations, inconsistent, direct, imprecise	One trial with mean difference in HbA_{1c} at 6 mo of −0.20 (95% CI, −0.93 to 0.53), $P = .59$; 1 trial with OR, 56.5 (95% CI, 2.81 to 1133.91), $P = .008$ for percentage with HbA_{1c} <7.5 at 12 mo
	Cohort: 2 (2688)[42,50-52]	Insufficient	High study limitations, inconsistent, direct, imprecise	One study with adjusted difference-in-difference coefficient, 2.44 (95% CI, 1.22 to 4.86), $P = .01$, at 12 mo for percentage with HbA_{1c} <7%, but findings not maintained at 24 mo; 1 study with change in mean HbA_{1c} of −0.02; 95% CI, −0.10 to 0.06; $P = .63$; and OR, 1.14; 95% CI, 0.97 to 1.35; $P = .11$, for change in percentage with HbA_{1c} <7% at 6 mo
LDL-C	RCT: 1 (38)[31]	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	OR, 56.00 (95% CI, 5.583 to 561.753), for percentage of patients at LDL-C goal based on ATP III criteria at 12 mo
	Cohort: 2 (3062)[42,50-52]	Insufficient	High study limitations, inconsistent, direct, imprecise	One study with adjusted difference-in-difference coefficient, 1.95 (95% CI, 0.81 to 4.84), $P = .13$ for percentage with LDL-C <100 mg/dL at 12 mo; 1 study with OR, 1.39 (95% CI, 1.160 to 1.670), $P < .001$ for achieving LDL-C <100 mg/dL and mean difference in LDL-C, −4.1 (95% CI, −6.02 to −2.18), $P < .001$ at 6 mo
Blood pressure	RCT: 1 (53)[31]	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	OR, 28.88 (95% CI, 5.49 to 151.99), $P < .001$, for percentage of patients with SBP and DBP at goal at 12 mo
	Cohort: 2 (2507)[42,50-52]	Insufficient	High study limitations, consistent within design but inconsistent with RCT, direct, imprecise	One study with adjusted difference-in-difference coefficient, 0.73 (95% CI, 0.32 to 1.65, $P = .45$) for percentage achieving BP <130/80 mm Hg at 12 mo; 1 study found OR, 0.95 (95% CI, 0.81 to 1.13, $P = .57$) for percentage with BP <130/80 mm Hg at 6 mo among patients with both diabetes mellitus and hypertension and OR, 0.90 (95% CI, 0.73 to 1.10, $P = .30$) among patients with hypertension but not diabetes mellitus

Abbreviations: ATP III, Adult Treatment Panel III; BP, blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c}; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; MA-PD, Medicare Advantage prescription drug plans; MTM, medication therapy management; NA, not applicable; OR, odds ratio; PDP, Prescription Drug Plans (stand-alone Part D plans); RCT, randomized clinical trial; SBP, systolic blood pressure.

SI conversion factor: To convert LDL-C to millimoles per liter, multiply by 0.0259.

[a] Drug therapy problems refer to a range of issues pertaining to drug-related appropriateness, effectiveness, safety, and adherence.

we judged the strength of evidence for mean number of hospitalizations to be insufficient because of the lack of consistency across studies.

Evidence was insufficient on the effect of MTM interventions on the use of generic medications; measures of medication costs other than health plan expenditures; number (Figure 2) and costs of outpatient visits; number and costs of laboratory tests; number and costs of emergency department visits; and the number (Figure 3), percentage, and costs of hospitalization for unspecified conditions, congestive heart failure, or chronic obstructive pulmonary disease. Frequently, the results were inconsistent for the same outcome; that is, MTM may have raised the use of health care services in one study and lowered it in another. We could not interpret these results as either benefits or harms because studies uniformly evaluated overall change in health care use rather than whether the increase or decrease in use met the goal of MTM for individual patients.

Harms of MTM Interventions

Only 1 cohort study (high risk of bias) reported harms, specifically on inconvenience resulting from monthly appointments.[66,67] The evidence was insufficient to judge the effect of MTM on inconvenience. We found no evidence on other prespecified harms including care fragmentation, patient decisional conflict, patient anxiety, increased adverse drug events, prescriber confusion, and prescriber dissatisfaction.

Effectiveness of MTM by Intervention Features

We found information from only 1 study for each of 5 intervention features: (1) access of pharmacists to patient records,[25]

Table 2. Summary of Findings and Strength of Evidence for Patient-Centered Outcomes of MTM Interventions

Outcome	Study Design: No. of Studies (No. of Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Adverse drug events[a]	RCT: 2 (806)[25,32]	Insufficient	Medium study limitations, inconsistent, direct, imprecise	One study with OR, 0.73 to 1.63 (P = NS) for percentage of patients with an adverse drug event and mean difference in number of ADEs ranging from −0.06 to 0.28 (all but 1 P value was NS) depending on study arm comparison (basic MTM or enhanced MTM) and timing of outcome measurement (3 or 6 mo); 1 study with OR, 0.65 (95% CI, 0.37 to 1.15), P = .14 for percentage of patients with an adverse drug event at 12 mo
Cognitive and physical function	RCT: 1 (133)[54]	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	No significant differences between study arms on 3 different tests of physical functioning (timed manual performance, physical performance test, and functional reach) and 3 different tests of cognitive functioning (WAIS digit span, WAIS digit symbol, and Randt memory test) at 6 wk
Affective function	RCT: 2 (181)[54,55]	Insufficient	Medium study limitations, inconsistent, direct, imprecise	One study with unadjusted mean difference in CES-D score, −1.10 (95% CI, −3.8 to 1.62), P = .43, and in self-rating anxiety score, −0.10 (95% CI, −2.39 to 2.19), P = .09, at 6 weeks; other study with significant differences in mean Beck depression and anxiety inventory scores, but OR, 2.41 (95% CI, 0.60 to 9.63), P = .22 for percentage of patients achieving depression remission as defined by Beck depression inventory score <11
Mortality	RCT: 1 (181)[32]	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	OR, 0.59 (95% CI, 0.12 to 2.49), P = .48
	Cohort: 2 (173 329)[37,56]	Insufficient	High study limitations, inconsistent (magnitude), direct, imprecise	One study with OR, 0.5 (95% CI, 0.3 to 0.9); 1 study with adjusted HR, 0.92 (95% CI, 0.87 to 0.96), P < .001
Gastrointestinal bleeding events	Cohort: 1 (unclear)[57]	Insufficient	High study limitations, consistency unknown, direct, imprecise	RRR, 60%; P = .001
General health-related quality-of-life domains other than vitality and emotional role functioning	RCT: 3 (1169)[26,31,32]	Low for no benefit	Medium study limitations, consistent, direct, precise	Variable mean difference with CIs consistently spanning the null effect (eTable 5 in the Supplement)
General health-related quality-of-life vitality and emotional role functioning domain	RCT: 3 (1169)[26,31,32]	Insufficient	Medium study limitations, consistent, direct, imprecise	Vitality: mean difference of 2.797 not corrected for multiple comparison (95% CI, 0.655 to 4.939), P = .01; emotional role functioning: mean difference, 5.386 (95% CI, −7.244 to 18.013); wide CIs
Condition-specific health-related quality of life (diabetes mellitus)	RCT: 1 (73)[49]	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Nonsignificant improvement of 0.1 point on a 5-point scale in the intervention group vs no change in the control group
Patient satisfaction	RCT: 3 (1463)[26,28-30,32,44,58]	Low for no benefit	Medium study limitations, consistent, direct, precise	No differences on 17 of 21 items of patient satisfaction; 4 statistically significant differences ranged in magnitude from −0.15 to −0.36, favoring MTM
Activities of daily living	0	NA	NA	NA
Work or school absenteeism	0	NA	NA	NA
Patient and caregiver participation in medical care and decision making	0	NA	NA	NA

Abbreviations: ADEs, adverse drug events; CES-D, Center for Epidemiologic Studies Depression Scale; HR, hazard ratio; MTM, medication therapy management; NA, not applicable; NS, not statistically significant; OR, odds ratio; RCT, randomized clinical trial; RRR, relative risk ratio; WAIS, Wechsler Adult Intelligence Scale.

[a] In contrast to drug therapy problem outcomes presented in Table 1, this outcome refers to actual drug-related adverse events experienced by patients.

(2) intensity of care coordination and follow-up after comprehensive medication review,[68] (3) community pharmacy vs call center,[69] (4) level of intensity of intervention,[70] and (5) type of payer (private vs Medicaid) (eTable 6 in the Supplement).[71] Evidence was insufficient for most outcomes for the first 2 intervention features, with 2 exceptions. First, MTM delivered by community pharmacists when compared with call center pharmacists increased the proportion of generics dispensed (low strength of evidence). Second, enhanced MTM with pharmacists' access to patient records reduced the mean number of adverse drug events; this finding suggested benefit when compared with basic MTM (low strength of evidence). Evidence was insufficient for all outcomes for the intensity of intervention and type of payer.

Table 3. Summary of Findings and Strength of Evidence for Health Care Use Outcomes of MTM Interventions

Use of Resources Outcomes	Study Design: No. of Studies (No. of Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Use of generic formulations	Cohort: 1 (range, 63 198-200 722)[41]	Insufficient	High study limitations, consistency unknown, direct, imprecise	OR, −0.01 (95% CI, −0.013 to −0.008) to 0.006 (95% CI, 0.003 to 0.009)
Medication costs: patient copayments	RCT: 1 (NR)[61]	Insufficient	Medium study limitations, consistency unknown, indirect, precision cannot be determined	Mean difference, −$64, variance not calculable
	Cohort: 1 (1606)[62]	Insufficient	High study limitations, consistency unknown, indirect, precise	Mean difference for MTM vs same country, control $80.40 (95% CI, $10.43 to $150.37), *P* = .024; mean difference for MTM vs different country control, $88.60 (95% CI, $24.61 to $152.59), *P* = .007
Medication costs: health plan expenditures	RCT: 3 (965)[27,48,59]	Low for benefit	Medium study limitations, consistent, indirect, imprecise	Mean difference varied from −CaD$34 (95% CI, −CaD$273.6 to CaD$205.2) to −$293 (95% CI, −501.5 to −84.5) during 6 mo
	NRCT and cohort: 5 (range, 120-200 722)[38-41,43,62,63]	Insufficient	High study limitations, inconsistent, indirect, imprecise	Mean difference varied from −$800 over 1 y (95% CI, NR or calculable) to $425 over 2 y (95% CI, $109.79 to $12 054.24)
Medication costs: total outlays	RCT: 6 (2636)[26-30,32,33,54,59,64]	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Mean difference varies from −$20.16 (95% CI, −$5.78 to −$34.54) to $5.25 (95% CI, −$0.42 to $10.92) per month
	Cohort: 2 (177 565)[52,56]	Insufficient	High study limitations, inconsistent, indirect, imprecise	Mean difference varied from −$563 (95% CI, −$735.33 to −$390.67) to $310 (95% CI, $271 to $350) annually
Medication costs: medication costs plus other expenditures	RCT: 2 (996)[27,32,33]	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences in mean costs ranging from −CaD$8.1 (95% CI, −CaD$386.72 to CaD$4350.52) to $1947 (95% CI, NR or calculable)
	NRCT and cohort: 3 (5300)[43,63,65]	Insufficient	High study limitations, inconsistent, indirect, imprecise	Differences in mean costs ranging from −$1039 (95% CI, −$2084.85 to $6.85) to $1100 (95% CI, NR or calculable)
No. of outpatient visits	RCT: 3 (2208)[25-30]	Insufficient	Medium study limitations, inconsistent, indirect, precise	Standardized mean difference, 0.049 (95% CI, −0.034 to 0.133); *P* = .25; I^2 = 0
	Cohort: 1 (4500)[43]	Insufficient	High study limitations, consistency unknown, indirect, imprecise	Mean difference, 2.48 (95% CI, 1.67 to 3.29), *P* < .001
Outpatient costs	RCT: 3 (2050)[26-30,32,33]	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Dissimilar measures varying from −$11.92/mo for costs of health care other than clinic visits to CaD$1.13 for physician visits/mo
No. of laboratory tests	RCT: 2 (1842)[26-30]	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences ranged from 0.15 (95% CI, −0.96 to 1.26) to −1.60 (95% CI, −2.55 to −0.65) tests
Costs of laboratory tests	RCT: 3 (2050)[26-30,32,33]	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences ranged from CaD$15 (95% CI, −CaD$46.34 to CaD$58.88) to −$140 (95% CI, NR or calculable)
No. of emergency department visits	RCT: 3 (1552)[25,27,32,33]	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Mean difference ranged from −0.7 (95% CI, NR or calculable, *P* value not significant) to −0.03 (95% CI, −0.113 to 0.053)
	Cohort: 3 (range, 795-200 722)[37,41,43]	Insufficient	High study limitations, inconsistent, direct, imprecise	Adjusted OR ranged from 0.89 (95% CI, 0.86 to 0.93) to 1.09 (95% CI, 1.04 to 1.15); mean difference (1 study), 0.04 (95% CI, −0.04 to 0.12), *P* = .35
Costs of emergency department visits	RCT: 2 (996)[27,32,33]	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Mean difference ranged from −$52 (95% CI, NR or not calculable) to −CaD$5.60 (95% CI, −CaD$23.06 to CaD$11.86)
	Cohort: 1 (range, 150 470-200 722)[41]	Insufficient	High study limitations, consistency unknown, direct, imprecise	Difference ranged from −$16.00 (95% CI, −$35.37 to $2.96) to −$12.80 (95% CI, −$0.14 to $25.76)
No. of hospitalizations	RCT: 3 (2208)[25-30]	Low for no benefit	Medium study limitations, consistent, direct, precise	Mean difference, 0.037 (95% CI, −0.006 to 0.080)
	Cohort: 1 (4500)[43]	Low for benefit	High study limitations, consistency unknown, direct, precise	Mean difference, −0.21 (95% CI, −0.26 to −0.16), *P* < .001
Hospitalization risk	RCT: 1 (556)[25]	Insufficient	Low study limitations, consistency unknown, direct, imprecise	OR for MTM basic vs usual care, 2.069 (95% CI, 1.104 to 3.878), *P* = .02; OR for MTM enhanced vs usual care, 1.345 (95% CI, −0. 693 to 2.609), *P* = .38
	Cohort: CHF, COPD, or unspecified: 3 (range, 795-200 722)[37,41,56]; diabetes: 1 (150 470)[41]	CHF, COPD, or unspecified: insufficient; diabetes: low for benefit	High study limitations, inconsistent, direct, imprecise; and high study limitations, consistency unknown, direct, precise	Adjusted OR for CHF, COPD, or unspecified ranged from 0.90 (95% CI, 0.87 to 0.94) to 1.4 (95% CI, 1.1 to 2.0); adjusted OR for diabetes ranged from 0.91 (95% CI, 0.87 to 0.95) to 0.93 (95% CI, 0.88 to 0.98)

(continued)

Table 3. Summary of Findings and Strength of Evidence for Health Care Use Outcomes of MTM Interventions (continued)

Use of Resources Outcomes	Study Design: No. of Studies (No. of Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Hospitalization rate (patients with heart failure and home medicine review)	Cohort: 1 (5717)[60]	Low for benefit	High study limitations, consistency unknown, direct, precise	Adjusted HR, 0.55 (95% CI, 0.39 to 0.77)
Costs of hospitalization	RCT: 3 (2050)[26-30,32,33]	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Inconsistent direction, consistent lack of effect: mean difference in costs for MTM vs usual care, $2402; *P* value reported as NS at .05 level in 1 study[32,33]; −$221.00 (95% CI, −$566.33 to $124.33) in second study[26,28-30]; mean difference in costs in third study: CaD$159.74 (95% CI, −CaD$281.99 to CaD$601.47)[27]
	Cohort, CHF: 1 (169 099)[41]	Insufficient	High study limitations, consistency unknown, direct, imprecise	Risk-adjusted costs of condition-specific hospitalization for CHF, −$222.08 (95% CI, −$525.99 to $81.82)
	Cohort, COPD: 1 (200 722)[41]	Insufficient	High study limitations, consistency unknown, direct, imprecise	Risk-adjusted costs of condition-specific hospitalization for COPD, $200.21 (95% CI, −$55.81 to $456.23)
	Cohort, diabetes: 1 (150 470)[41]	Low for benefit	High study limitations, consistency unknown, direct, precise	Risk-adjusted costs of condition-specific hospitalization for diabetes, −$363.45 (95% CI, −$562.00 to −$164.91); all hospitalization costs (risk-adjusted) for diabetes, −$398.98 (95% CI, −$651.21 to −$146.75)
Length of hospital stay	RCT: 1 (208)[32,33]	Insufficient	Low study limitations, consistency unknown, direct, imprecise	MTM reduced length of stay by 1.8 d (6.7 vs 4.9 mean hospital days for MTM vs usual care)

Abbreviations: CaD$, Canadian dollars; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MTM, medication therapy management; NR, not reported; NS, not significant; NRCT, nonrandomized clinical trial; OR, odds ratio; RCT, randomized clinical trial.

Discussion

Evidence was insufficient to draw conclusions about the effect of MTM on most of the outcomes that we evaluated. We assigned grades of low strength of evidence for either a benefit (some measures of drug-therapy problems and health care use) or a lack of benefit (patient satisfaction and health-related quality of life) to few evaluation outcomes. The degree to which identifying and resolving drug therapy problems translate into consistent, detectable improvements in biomarkers of morbidity, health, patient experience, use, and costs cannot be determined from this body of evidence.

Although we tried to capture a range of contexts and settings and fill gaps by including observational studies, we did not find credible, consistent evidence that MTM improved outcomes globally regardless of study design. We included a very large retrospective cohort study of Medicare Part D MTM programs operating in 2010.[41] This evaluation focused on beneficiaries with congestive heart failure, chronic obstructive pulmonary disease, and diabetes. The authors reported that, although uptake of and adherence to evidence-based medication improved for patients with congestive heart failure or diabetes, these improvements did not consistently translate to fewer condition-specific hospitalizations and emergency department visits.[41]

Overall, we rated the MTM evidence base as insufficient, even though some studies evaluated important outcomes and had low or moderate risk of bias. Our assessment was often based on inconsistency in the magnitude or direction of effect. Inconsistent effects of the intervention, as well as poor measures, could explain inconsistent results.

For example, clinically effective MTM can either increase or decrease health care use and expenditures based on the needs of the patient. The goal of MTM overall is to optimize pharmacotherapy and reduce unnecessary health care use, but for patients who need more care, MTM could optimize pharmacotherapy while increasing necessary health care use.

Future studies will benefit from better outcome measures. In addition, analyses should take into account whether increases in health care use are appropriate and whether identified inappropriate use can be attributed to overuse or underuse. Studies often used nonstandardized measures for outcomes, such as adverse events, adherence, and expenditures or costs; this tendency limited our ability to meta-analyze results.

Included MTM studies were largely practice based; they varied substantially in usual-care comparators, specific intervention elements, and patient populations. Standard medical care usually involves varying degrees of MTM-like services from the patient's prescribing providers and health care teams. This reality is problematic for systematic reviews because MTM effectiveness in relationship to usual care can be adequately characterized only by controlling for the variation in the active intervention components that might also be present in the usual-care group.[72]

For MTM, this variation in practice likely reflects the evolution of the professional practice of pharmacy. Most studies were not designed to capitalize on variants in MTM program elements for a rigorous, prospective evaluation of outcomes by those variants. In addition, most studies did not report patient characteristics beyond age and sex, thus limiting our ability to address the underlying heterogeneity in our review. Finally, most studies did not measure fidelity to intended MTM intervention elements; thus, whether studies demonstrating

no effect of MTM were actually failures of implementation is difficult to determine.

Our findings emphasize several important needs for future efforts to review MTM programs systematically. The first is for researchers and program evaluators to specify and design MTM interventions based on existing definitions, taxonomies, and service models. The second is to use the appropriate consensus guidelines for study reporting based on design,[73-76] giving particular attention to reporting intervention features, usual care practices, and fidelity of intervention delivery.[77] Progress on these steps would enable systematic reviews of MTM services to better differentiate between various types of services, different levels of intervention fidelity, and heterogeneous comparison groups.

Medication therapy management is already in widespread practice, which presents both challenges and opportunities for researchers and policy makers. The MTM programs of the future may contribute to coordinated and improved care through delivery within accountable-care organizations or patient-centered medical homes. However, as MTM becomes more integrated into routine health care, the more difficult it is to attribute change to MTM alone. Furthermore, secular trends in related quality-improvement initiatives (eg, medication adherence interventions; practice-based, medication-related patient safety initiatives or requirements; and meaningful use requirements for electronic health records) might obscure the effects of MTM efforts. Positive deviance analyses[78] with rigorous measurement of implementation features or stepped wedge trial designs[79] may be useful, since they provide rigorous approaches to evaluating real-world implementation. Finally, the population effect of MTM may depend on higher rates of patient participation; future studies and evaluations should consider including measures of reach and examine alternative ways of enrolling patients and keeping them engaged.

Study Limitations

Because MTM services vary substantially, any constraints applied by a systematic review to establish scope necessarily limit the applicability of the review findings. Our review did not address MTM interventions conducted in inpatient settings or single-episode types of interventions (eg, medication reconciliation, which some view as a specific type of MTM service). Although we tried to distinguish MTM from disease or case management interventions, making this distinction was challenging. We allowed MTM interventions that targeted patients with a single condition, such as diabetes or hypertension, as long as the MTM services included a comprehensive review of all medications rather than just medications for the single condition. Despite these limitations, the range of included study designs enhanced the applicability of findings for real-world settings when evidence was sufficient.[24]

We included interventions labeled *pharmaceutical care* or *medicines management* to ensure that the evidence base included studies before the Medicare Part D MTM era and non-US studies. Although our approach made results more challenging to interpret because of the resultant heterogeneity, it ensured that we captured interventions that had MTM components but lacked the descriptor phrase *medication therapy management*. We attempted to stratify findings by whether the study was a Part D program, but we did not have enough studies that used the same outcomes to be able to draw conclusions.

Future Research

New research should be based on national priorities. Studies designed to identify causal relationships between MTM interventions and their outcomes (including cost-effectiveness analyses) must control for confounding, but they may offer limited information on the elements that explain program success or failure. Studies designed to explore the reasons for program success or failure using qualitative or single-arm designs may offer hypotheses-generating rather than hypotheses-confirming insights on MTM effectiveness. New research, regardless of specific focus, will likely continue to find inconsistent results until studies account for underlying sources of variability in populations, interventions, and outcome measures.

Conclusions

We found a low strength of evidence of benefit for a limited number of intermediate and health care use and cost outcomes. Evidence was insufficient for most outcomes because of inconsistency in direction and magnitude and also because of imprecision. Wide variations in populations and MTM interventions likely explain these inconsistencies.

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