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The Impact of Medication Adherence on Workplace Productivity Outcomes

A review of the scientific evidence and example for calculating savings from improved adherence

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August, 2018

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Abstract

Background

Medication nonadherence undermines the efficacy of treatments with known clinical value. Recent interventions to improve adherence have shown promising results, but the implications for how improved adherence will impact patients' lost work time is not well known. This potentially undervalues adherence interventions to employers and other societal stakeholders.

Study objective

The objective of this study is to perform a systematic review of the published literature linking adherence to productivity outcomes for different diseases, medications and types of lost work time—specifically, incidental sick-day absences (absenteeism) and disability leaves from work.

Results

A review of 13 peer-reviewed articles focused on 12 conditions finds mixed evidence that adherence-related improvements in health can reduce illness-related lost productivity in the short term. The most consistent evidence was for a relationship between adherence and improved short-term disability (STD) outcomes—particularly among patients with diabetes. To facilitate discussions about the economic value of interventions to improve adherence, we describe an approach for calculating the productivity value of adherence to employers using diabetes as a focal case. By our estimation method, for a population of 1,000 employees with diabetes and an average adherence of 61%, improving adherence by 10% would reduce STD and absence lost work time by 441 days, with net financial savings of about $94,000. Applications of the approach to healthcare utilization costs related to improved adherence are also discussed.

Conclusion

Improved medication adherence among populations of employees with some chronic conditions may generate productivity savings alongside healthcare utilization savings—the economic value of which may bolster the business case for effective interventions. Future studies may consider longitudinal assessments of adherence and productivity, paying particular attention to symptoms that precipitate intermittent absences rather than relatively longer-term disability episodes. The findings should be interpreted as reflective of the predominant adherence measure used in the reviewed studies' medication possession ratio (MPR) ≥ 80%. Other approaches that measure adherence more directly or that implement

medication monitoring technologies may increase confidence in the association with productivity outcomes.

Introduction

Medication nonadherence—a situation in which a patient's use of prescribed pharmaceuticals for a given condition does not meet established guidelines or provider recommendations (1)—undermines the efficacy of treatments with known clinical value (2). Typical patterns of nonadherence (sometimes referred to as *noncompliance*) include failure to fill prescriptions or to take medications in accordance with the recommended timing or dosage or ceasing long-term medications altogether. Studies have linked nonadherence to increased risk of adverse health outcomes, hospitalizations, mortality and increased costs of healthcare (3-9).

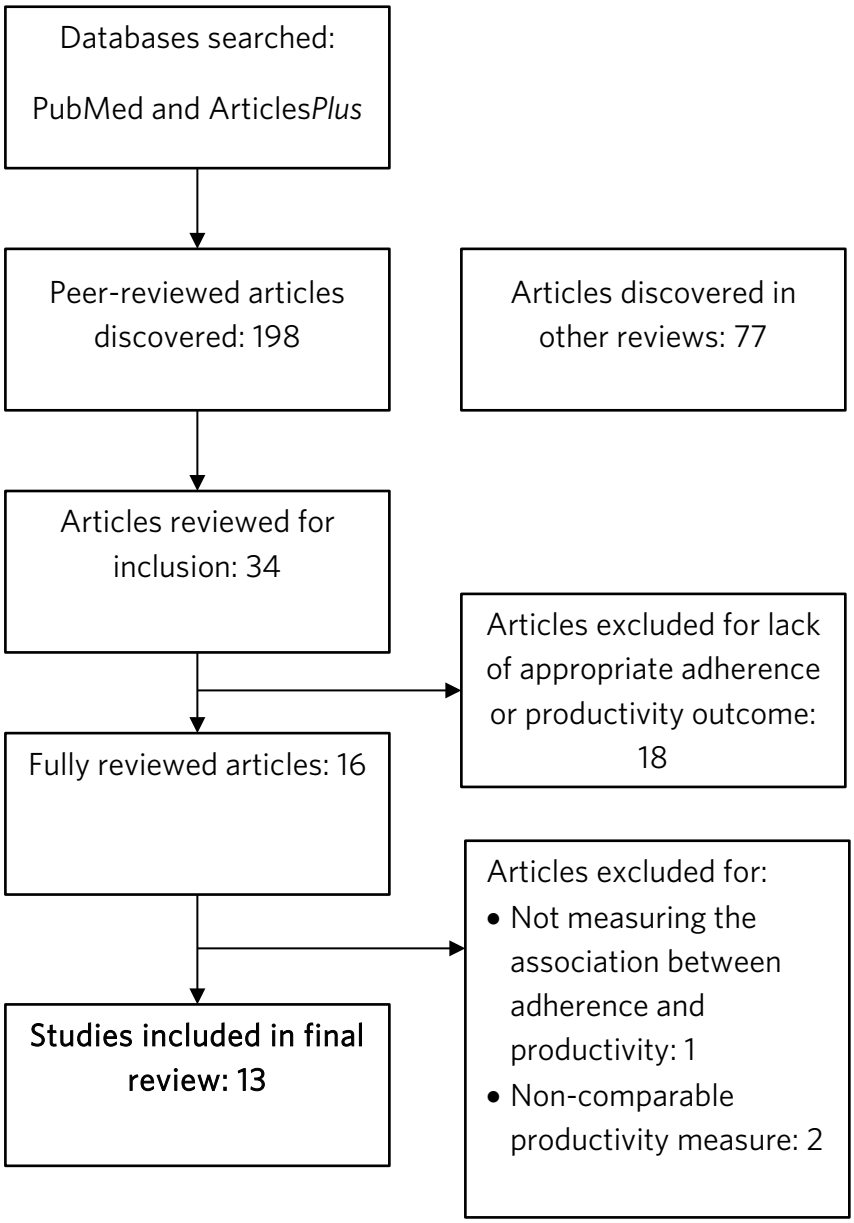
Several studies estimate that average adherence rates for long-term medications are about 50% (2). While a Cochrane review of randomized controlled trials through 2014 found little evidence in favor of interventions to improve adherence and clinical outcomes (2), more-recent innovations have shown promising results. These include appointment-based medication synchronization (ABMS) that allows patients to pick up all of their medications at once at prearranged appointments with pharmacists, simplifying the refill process. A recent study showed that patients with multiple chronic conditions who had medications synchronized by pharmacists were more adherent and had fewer crisis events such as hospitalizations and emergency department visits (10). A cost/benefit analysis of ABMS in community pharmacies found that for patients taking medication for hyperlipidemia, hypertension and diabetes, increased medication costs due to higher adherence were offset by reductions in disease-specific treatment costs (11).

These findings notwithstanding, cost/benefit analyses that focus only on healthcare spending may underestimate the overall economic value of adherence. Lost work productivity due to illness—particularly resulting from absence and disability leaves—imposes cost on patients, their employers and society at large (12). Many studies of overall disease costs include lost productivity (13-19), and several examine the productivity impact of specific treatments relative to alternatives (20, 21). Less is known about the productivity impact of adherence across a variety of conditions, however. The objective of this study is to perform a systematic review of the published literature linking adherence to productivity outcomes for different diseases, medications and types of lost work time—specifically, incidental sick-day absences (absenteeism) and disability leaves from work. Where possible, the results are used to assess the economic impact of adherence by applying daily wage values to marginal lost work time.

Method

A search for peer-reviewed journal articles was conducted using PubMed and the University of Michigan's Articles*Plus* database. Articles*Plus* is a search engine that includes more than 6,800 publishers, as well as databases such as Web of Science. Articles were extracted from Articles*Plus* if their titles, abstracts or keywords contained combinations of the following terms: *pharmaceutical* or *drug* or *medication* or *medicine*; *treatment* or *therapy* or *therapeutic*; *adherent* or *adherence*; and *productivity* or *absenteeism* or *disability* or *work loss.* The PubMed search combined the words *medication, medicine, drug* or *treatment* in the title/abstract with the MeSH terms *patient compliance* or *patient adherence,* and the MeSH terms *absenteeism* or *sick leave* or *productivity* or *work loss* in the title and abstract. The PubMed search language is shown in Appendix Table 1.

Figure 1: Flow chart of search results



Our criteria for inclusion in the final review were (a) English-language publications; (b) prospective or retrospective studies of pharmaceuticals; (c) including drugs with known guidelines for adherence or a pseudo-guideline (e.g., medication possession ratio); (d) comparing an adherent population to a nonadherent population or comparing periods of adherence to nonadherence; and (e) an outcome is absence from work measured in units of time (e.g., days or hours) or in the likelihood of having an absence from work.

Figure 1 summarizes the search process. The search

returned 198 peer-reviewed articles. Of these, 34 included outcome measures deemed by the authors to be of interest to the study and were further examined for inclusion. Of these, 16 were selected for a full review based on their assessment of both outcome and adherence measures. One reviewed study included both medication adherence and productivity as distinct outcome measures, without assessing their association (22). This study was excluded from the final review. A second study that allowed an indirect assessment of productivity outcomes based on the identification of patients as members of a successful adherence intervention was reviewed (23). Two additional studies (24, 25)—both on migraine—were excluded given their qualitative measure of on-the-job productivity loss or resumption of normal functioning rather lost work time, or for use of a response time indicator rather than an adherence measure (25).

The initial search also returned 12 systematic literature reviews (20, 21, 26-35). These were examined by two of the authors for cited articles that focused on work productivity outcomes. This process produced 77 additional articles for further examination. None, however, included medication adherence measures as required for inclusion in the review. The final number of studies included in the review was 13.

The diversity of outcomes, operationalizations of adherence, statistical methods and details of analytic findings (for example, not all studies reported variance information) precluded a meta-analytic approach to assessing the relationship between adherence and lost work time. Nonetheless, the discussion section includes a synthesis of the comparable findings for the purposes of describing a feasible approach to the cost implications of nonadherence.

Results

Overview of included studies

Table 1 describes the relevant characteristics of the studies included in the review, as well as a brief summary of the findings.

Table 1: Articles included in this review

Study	Authors	Date	Study type	Disease	Population	Included productivity outcome(s)	Medication	Adherence measure	Summary results
(36)	Joshi et al.	2006	Cross-sectional survey	Asthma	State employees receiving healthcare benefits from a state health insurance agency	Days missed from work; days experienced asthma while at work	Controller medications (such as inhaled corticosteroids, cromolyn sodium and nedocromil, long-acting β2-agonists, methylxanthines and leukotriene modifiers) and quick-relief medications	Self-reported on Morisky adherence scale	Low-adherence patients had the fewest missed workdays; difference was not statistically significant
(37)	Carls et al.	2012	Retrospective claims analysis	Asthma/COPD	Employees age 18 to 64 from 16 medium-sized to large companies covered for medical and pharmacy benefits	Days missed from work (payroll systems); STD leaves; days missed from work on STD leave	Formulations intended for long-term (daily) use of inhaled corticosteroids and steroids, leukotriene modifiers, mast cell stabilizers, methylxanthines, anti-cholinergic agents, long-acting β2-agonists, systemic corticosteroids or immunomodulators	MPR ≥ 80%	Adherent employees had significantly fewer absence days, STD leaves and STD days

Study	Authors	Date	Study type	Disease	Population	Included productivity outcome(s)	Medication	Adherence measure	Summary results
(38)	Bagalman et al.	2010	Retrospective claims analysis	Bipolar disorder	Employees age 18 to 64; companies covered for medical and pharmacy benefits	PTO, STD and WC experiences and costs	Mood stabilizers or atypical antipsychotics	MPR ≥ 80%	Adherent patients had less absence, but differences were not statistically significant
(37)	Carls et al.	2012	Retrospective claims analysis	Congestive heart failure	Employees age 18 to 64 from 16 medium-sized to large companies covered for medical and pharmacy benefits	Days missed from work (payroll systems); STD leaves; days missed from work on STD leave	Hydralazine nitrates, diuretics, beta blockers, angiotensin receptor blockers, cardiac glycoside, angiotensin-converting enzyme inhibitors or calcium channel blockers	MPR ≥ 80%	Adherent employees had significantly fewer STD leaves, resulting in fewer overall STD days
(39)	Loeppke et al.	2011	Retrospective analysis of claims- and patient-reported outcomes	Coronary artery disease	Employees age 18 to 64 from five companies covered for medical and pharmacy benefits	Difference in employer-expected and actual hours worked in the prior four weeks	Statins, beta blockers, ACE or ARB, anti-platelet or anti-coagulant	MPR ≥ 80%	Employees adherent with statins had significantly fewer hours of absence; no significant association for other CAD medications

Study	Authors	Date	Study type	Disease	Population	Included productivity outcome(s)	Medication	Adherence measure	Summary results
(40)	Burton et al.	2007	Retrospective claims analysis	Depression	Employees at a financial services firm who participated in the company's pharmacy benefit plan	STD leave incidence and duration (days)	Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors	Adherence to HEDIS guidelines in acute and continuation treatment phases	Adherent employees had significantly fewer STD leaves; there were no significant differences in STD days missed from work
(41)	Birnbaum et al.	2010	Retrospective analysis of claims- and patient-reported outcomes	Depression	Survey respondents from two companies covered for medical and pharmacy benefits	Absence costs based on self-reported survey information	Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitor, bupropion or modified cyclic prescriptions	MPR ≥ 95% compared with MPR ≤ 26%	Highly compliant employees had significantly lower absenteeism costs
(39)	Loeppke et al.	2011	Retrospective claims analysis	Depression	Employees age 18 to 64 from five companies covered for medical and pharmacy benefits	Difference in employer-expected and actual hours worked in the prior four weeks	Antidepressant	MPR ≥ 0%	No significant association between adherence and lost work time

Study	Authors	Date	Study type	Disease	Population	Included productivity outcome(s)	Medication	Adherence measure	Summary results
(37)	Carls et al.	2012	Retrospective claims analysis	Diabetes	Employees age 18 to 64 from 16 medium-sized to large companies covered for medical and pharmacy benefits	Days missed from work (payroll systems); STD leaves; days missed from work on STD leave	Oral anti-diabetic medications (sulfonylureas, meglitinides, biguanides, thiazolidinediones and α-glucosidase inhibitors) or insulins	MPR $\geq$ 80%	Adherent employees had significantly fewer absence days and STD leaves; the latter resulted in fewer overall STD days
(42)	Hagen et al.	2014	Retrospective claims analysis	Diabetes	Ford Motor Company employees prescribed oral hypoglycemic medications	STD leave incidence and duration (weeks)	Oral hypoglycemic agents (metformin, sulfonylureas, meglitinides, thiazolidinediones and combinations thereof)	MPR $\geq$ 80%	Adherent patients had significantly fewer STD leaves, which contributed to significantly less STD lost work time
(43)	Gibson et al.	2010	Retrospective claims analysis	Type 2 diabetes	Employees from companies covered for medical and pharmacy benefits and for sick-day and STD benefits	Days missed from work (payroll systems); days missed from work on STD leave	Oral anti-diabetic medications (sulfonylureas, meglitinides, biguanides, thiazolidinediones and α-glucosidase inhibitors)	MPR $\geq$ 80%	Adherent patients had significantly fewer STD days; no significant association between adherence and absence

Study	Authors	Date	Study type	Disease	Population	Included productivity outcome(s)	Medication	Adherence measure	Summary results
(39)	Loeppke et al.	2011	Retrospective analysis of claims- and patient-reported outcomes	Type 2 diabetes	Employees age 18 to 64 from five companies covered for medical and pharmacy benefits	Difference in employer-expected and actual hours worked in the prior four weeks	Statins, ACE or ARB, insulin, or oral hypoglycemic or metformin	MPR ≥ 80%	No significant association between adherence and lost work time
(37)	Carls et al.	2012	Retrospective claims analysis	Dyslipidemia	Employees age 18 to 64 from 16 medium-sized to large companies covered for medical and pharmacy benefits	Days missed from work (payroll systems); STD leaves; days missed from work on STD leave	Statins, selective cholesterol absorption inhibitors, bile acid sequestrants, fibrates or prescription-strength niacin	MPR ≥ 80%	Adherent employees had significantly fewer absence days, STD leaves and STD days
(39)	Loeppke et al.	2011	Retrospective analysis of claims- and patient-reported outcomes	Hypertension	Employees age 18 to 64 from five companies covered for medical and pharmacy benefits	Difference in employer-expected and actual hours worked in the prior four weeks	Anti-hypertensives (ACE inhibitors, angiotensin receptor blockers, diuretics, calcium channel blockers, beta blockers and vasodilators)	MPR ≥ 80%	No significant association between adherence and lost work time

Study	Authors	Date	Study type	Disease	Population	Included productivity outcome(s)	Medication	Adherence measure	Summary results
(37)	Carls et al.	2012	Retrospective claims analysis	Hypertension	Employees age 18 to 64 from 16 medium-sized to large companies covered for medical and pharmacy benefits	Days missed from work (payroll systems); STD leaves; days missed from work on STD leave	Angiotensin-converting enzyme inhibitors, aldosterone receptor blockers, α1-blockers, central α2-agonists, angiotensin receptor blockers, beta blockers, calcium channel blockers, diuretics or vasodilators	MPR $\geq$ 80%	Adherent employees had significantly fewer absence days, STD leaves and STD days
(44)	Ivanova et al.	2012	Retrospective claims analysis	Multiple sclerosis	Employees at 23 companies covered for medical, pharmacy and STD benefits	STD and illness-related absenteeism costs; reporting method permits extrapolation of lost workdays	Glatiramer acetate, intramuscular interferon, beta-1a, subcutaneous interferon beta-1a, interferon beta-1b, or natalizumab	MPR $\geq$ 80%	Adherent employees had significantly fewer STD days, as extrapolated from results showing significantly different costs for lost work time

Study	Authors	Date	Study type	Disease	Population	Included productivity outcome(s)	Medication	Adherence measure	Summary results
(45)	Wade et al.	2011	Prospective cohort analysis of patient-reported outcomes	Osteoporosis	Postmenopausal women who reported using pharmacological osteoporosis agents	Number of days lost from work in the prior six months	Alendronate, risedronate, ibandronate, calcitonin, raloxifene or teriparatide	Treatment duration from study entry to date of self-reported medication discontinuation	Lost workdays for employees who persisted in their medication were not significantly different from those who discontinued or switched medication
(46)	Kleinman et al.	2014	Retrospective claims analysis	Overactive bladder and urinary incontinence	Employees from 27 companies covered for medical and pharmacy benefits and for sick-day, STD, LTD or WC benefits	Number of sick-day absences, STD, LTD or WC days missed from work	Urinary anti-spasmodics (fesoterodine, tolterodine, oxybutynin, solifenacin, darifenacin, trospium, flavoxate, imipramine and hyoscyamine)	MPR ≥ 80%	No significant associations between adherence and sick-day, STD, LTD or WC lost work time

Study	Authors	Date	Study type	Disease	Population	Included productivity outcome(s)	Medication	Adherence measure	Summary results
(23)	Stockl et al.	2010	Prospective cohort analysis of claims- and patient-reported outcomes	Rheumatoid arthritis	Patients receiving specialty pharmacy services through a national pharmacy benefits management company	Work time missed in past seven days (absenteeism)	Etanercept, infliximab, adalimumab, anakinra, abatacept, rituximab, certolizumab or golimumab	Proportion of days covered for medication	Employees who completed a disease therapy management program (DTM) had improved medication adherence rates; DTM participation was not significantly associated with absence days
(47)	Jinnett and Parry	2012	Retrospective claims analysis	Rheumatoid arthritis	Employees at 10 companies covered for medical, pharmacy and STD benefits	STD leave incidence	DMARDs such as anti-tumor necrosis factor agents, biologic response modifiers (biologics), select anti-malarials used as DMARDs and other drugs that act as DMARDs	MPR quartiles	Employees with at least 75% MPR had the lowest rate of leave use in one of the years analyzed; in the other year, MPR was not significantly associated with leave use

The reviewed studies examined adherence to medications for 12 diseases. Two studies (37, 39) examined the relationship between adherence and productivity for multiple conditions.

Study types

Two studies (36, 45) administered surveys to patients identified as having the focal disease. The remaining studies examined medical and pharmacy treatment claims as the indicators of disease states, prescription drug use and adherence (in some cases referred to as *compliance* or *persistence*). Lost-work-time information typically came from disability benefits claims for non-occupational short- or long-term disability (STD and LTD, respectively) or from workers' compensation (WC). Absence information came primarily from payroll systems or other administrative records but was usually treated by the researchers in a manner similar to disability claims. Two studies (39, 41) combined claims analyses with self-reported information on lost-time outcomes.

Nine studies explicitly identified their populations as employees in the United States. The remaining three studies were also likely U.S.-based given their use of the Thomson Reuters MarketScan data sets (37, 38), the identification of Ford Motor Company in combination with the University of Michigan (42) or given terms such as *national pharmacy benefits management company* (23).

Adherence measures

Ten studies used medication possession ratio or a similar measure to indicate adherence. MPR is typically calculated as the percentage of days for which a patient was supplied with an index medication, counting from the first prescription to a set number of days or to the date at which the prescription was discontinued. Other methods included self-reported adherence (36), duration from entry to self-reported adherence (45) and adherence to guidelines (40).

Overview of findings

Table 2 summarizes the substantive quantitative findings with regard to reductions in lost work time associated with adherence. Conditions are listed in the table and discussed in the text based on the number of studies reviewed. All values are annualized. Because not all studies provided the standard errors and coefficients necessary to estimate lower and upper bound estimates, we present point estimates only. Non-significant differences between adherent and nonadherent populations are represented by gray cells. Blank values indicate that a lost-work-time outcome was not included in a given analysis.

The combinations of diseases, medications and types of lost work time examined produced 38 analyses. Fourteen analyses indicated that adherent patients had significantly less lost

work time than nonadherent employees. Six of the 22 absenteeism analyses (27%) found a significant association between adherence and lost time, compared with eight of the 13 STD analyses (62%). The three analyses that examined LTD or WC produced no significant findings.

Table 2: Summary of quantitative findings

					Annualized reduction in lost workdays if adherent			
Disease	Study		Subjects	% adherent	Absence	STD	LTD	WC
Diabetes	(37)		7,817	58.7%	5.5			
			22,404	59.8%		2.8		
	(43)	[h]	1,753	72.7%	n.s.	4.0		
		[i]	3,027	72.7%	sig.	9.0		
	(39)	[a]	774	53.0%	1.1			
		[b]	790	63.3%	-3.0			
		[c]	1,312	58.4%	-2.7			
	(42)		4,978	57.0%		4.5		
Depression	(39)		2,120	63.1%	-1.36			
	(40)		2,112	61.6%		1.7		
	(41)		1,224	26.0%	sig.			
Asthma/chronic obstructive pulmonary disease	(36)		385	39.0%	1.4			
	(37)		5,417	22.5%	7.1			
			20,985	23.1%		3.7		
Hypertension	(37)		33,245	65.2%	5.2			
			91,129	65.5%		3.5		
	(39)		5,459	65.6%	-0.02			
Rheumatoid arthritis	(23)		828	73.7%	n.s.			
	(47)	[f]	447	52.1%		sig.		
		[g]	594	17.8%		n.s.		
Bipolar disorder	(38)		516	35.3%	4.77			
			791			2.84		
			667					4.54
Congestive heart failure	(37)		1,170	72.7%	3.1			
			4,567	75.0%		4.7		
Coronary artery disease	(39)	[a]	666	63.1%	14.6			
		[d]	478	65.3%	-4.6			
		[b]	543	65.4%	9.5			
		[e]	303	63.4%	14.8			

Disease	Study		Subjects	% adherent	Annualized reduction in lost workdays if adherent: Absence	STD	LTD	WC
High cholesterol	(37)		29,761	51.4%	6.3			
			106,676	53.6%		2.5		
Multiple sclerosis	(44)		648	69.0%	0.65	4.05		
Osteoporosis	(45)		2,528	72.0%	n.s			
Overactive bladder	(46)		813	12.8%	0.33			
			1,711			0.71		
			1,890				-0.09	
			2,443					-0.01

Values shown in gray are not statically significant < 0.05.

a Statins
b ACE or ARB
c Insulin, hypoglycemics or metformin
d Beta blockers
e Anti-platelet or anti-coagulant
f Year 1
g Year 2
h Oral anti-diabetics only
I Oral anti-diabetics and insulin
n.s. Authors cite non-significance without providing estimate
sig. Authors cite significant impact on costs or leave use that cannot be translated into days

RESULTS FOR SPECIFIC DISEASES

Diabetes

Four studies examined diabetes for a total of eight analyses. Five analyses examined absences, and three examined disability lost work time. Medications included oral anti-diabetic (OAD) medications and insulin (37, 43) and statins and ACE inhibitors or angiotensin receptor blockers (ARBs). All studies considered an MPR of at least 80% as adherent, with one study (43) evaluating adherence over two years. Adherence ranged from 53% for statins to 73% for OAD medications. Using instrumental variables (IV) regressions (with pharmacy benefits plan design elements included as instruments for adherence in the first stage, and lost-work-time experience as a function of the first-stage residual in the second stage), one

analysis (37) found that patients who were adherent with OAD medications and insulin had 5.5 fewer absence days per year on average ($p < 0.05$); another found a significant association with adherence among patients taking OAD medications and insulin. Three analyses found no significant relationship between adherence and absences, using both IV and ordinary least squares (OLS) regression approaches. Findings for disability lost work time were more consistent. All three analyses found significantly few STD days among adherent populations, with estimates ranging from 2.8 to 9 days per year. For one analysis (42), significantly lower STD incidence rates accounted for the difference in durations (16% compared with 22% for adherent and nonadherent employees, respectively; $p < 0.0001$). Contingent on any STD leave, adherence was not significantly associated with leave duration.

Depression

Three studies evaluated adherence with antidepressant medications. One study (39) measured adherence as 365-day MPR of at least 80%. Another (41) compared categories of nonadherent patients (114-day MPR of less than 26%; highly adherent patients had an MPR ≥ 95%; intermediate adherent patients had an MPR ≥ 26% and less than 95%). A third study (40) defined adherence by HEDIS treatment guidelines specifying an MPR of at least 74% during a 114-day acute treatment period and an MPR of 77% during a 231-day continuation period. Average adherence ranged from 26% (for "highly adherent") to 63%.

Only one study (41) found a significant association between adherence and lost work time; however, while days of absences provided the foundation of the lost-work-time outcome, the authors of the study reported results converted into dollar values based on unreported salary information. The lack of information about underlying lost work time limits the interpretation of findings to the direction and significance of findings. The study found that on average, compared with the nonadherent group, patients in the highly adherent group had significantly lower absenteeism costs ($p < 0.05$). In another study (40), during both the acute and continuation phases, adherent employees were significantly less likely to have an STD leave ($p < 0.05$). Using multiple regression and logistic approaches, however, there were no significant differences in the total number of STD days, neither for the entire study population nor for leave takers. The remaining study found no significant association between adherence and absence using OLS regression (39).

Asthma

Two studies (36, 37) examined asthma or asthma with chronic obstructive pulmonary disease (COPD) for a total of three analyses. One study (36) surveyed asthma patients about their medication adherence (as high, medium or low on the Morisky adherence scale (48)), their days missed from work and other productivity, cost and quality-of-life factors. Thirty-nine

percent of respondents reported "high" adherence. Adherence was not a significant predictor of lost-productivity costs in multivariate regression models. The other study (37) evaluated formulations intended for long-term daily use. Adherence measured as 365-day MPR of at least 80% was about 23%. On average, adherence with asthma/COPD medications was associated with 7.1 fewer days of absence and 3.7 fewer STD days (both significant < 0.05). For STD, adherence with asthma/COPD medications was associated with both a reduced use of STD leaves and reduced STD durations, contingent on any use.

Hypertension

Two studies (37, 39) evaluated a variety of anti-hypertension medications for a total of three analyses. Both studies measured adherence as 365-day MPR of at least 80%. Average adherence was about 65%. Using the IV regression approach described in the diabetes section, one study (37) found that, on average, adherence with hypertensive medications was associated with 5.2 fewer days of absence and 3.5 fewer STD days ($p < 0.05$ for both). For STD, adherence with hypertensive medications was associated with both a reduced use of STD leaves and reduced STD durations, contingent on any use. The other study (39) found that using an OLS approach, adherence with anti-hypertensive drugs was not significantly associated with absences.

Rheumatoid arthritis

Two studies examined rheumatoid arthritis (RA) for a total of three analyses (23, 47). One study (23) compared absenteeism among cohorts of participants in a disease therapy management (DTM) program for patients using injectable RA medications. The DTM cohorts included patients with a fill of an injectable RA medication at a specialty pharmacy who (a) did not opt into the DTM program, (b) opted into the DTM program (an intent to treat, or ITT, group), or (c) opted into and completed the program (a subset of the ITT cohort). An additional cohort of patients who filled an injectable RA medication at a community pharmacy but had no fills at a specialty pharmacy was also included. Adherence as measured by 240-day MPR was 73.7%. Compared with the cohort of patients who used only community pharmacies, patients using specialty pharmacies for their injectable medications had consistently and significantly higher rates of days covered. The average proportion of covered days for the ITT group did not differ significantly from the average proportion of days among the cohort of specialty pharmacy patients who were not enrolled in a DTM program. Patients who completed DTM, however, had better adherence than the specialty cohort (0.89 compared with 0.81, $p < 0.001$), which is consistent with a successful intervention. Nonetheless, DTM patients experienced no significant change in the number of absence days from the first administration of a validated health and productivity survey to the second survey six months later.

A second study (47) compared STD leave use among employees treated with disease-modifying anti-rheumatic drugs (DMARDs). Adherence was measured in quartiles of 365-day MPR. Hierarchical models were used to estimate STD leaves for two years separately. In the analysis of the first year, 54% of patients had at least 75% MPR. In the second-year analysis, 18% of patients had an MPR of at least 75%. On average, in the first-year analysis patients with at least 75% MPR had significantly lower odds of an STD leave than patients with < 25% MPR (odds ratio [OR] = 0.35, $p < 0.05$). In the second year, adherence was not significantly associated with leave use.

Bipolar disorder

One study (38) compared rates of paid-time-off (PTO) absences, short-term disability and workers' compensation among employees with bipolar disorder who were treated with mood stabilizers or atypical antipsychotics. Adherence was measured as 365-day MPR and averaged about 35%. Compared with nonadherent employees, adherent employees generally had lower absence incidence rates and used fewer PTO days, if any. With the exception of the percentage of patients using WC, however, differences were not statistically significant across the groups in bivariate analyses. Odds ratios from logistic regression models of any absences reported confidence intervals that bracketed 1.0, also suggesting statistical insignificance. Confidence intervals of coefficients from models predicting the costs of all absences were not provided, precluding assessment of association between adherence and total lost work time.

Congestive heart failure

One study (37) evaluated a variety of medications, including hydralazine and nitrates, beta blockers, diuretics, ACE inhibitors, ARBs and others. Adherence ranged from 73% to 75%. On average, adherence with congestive heart failure (CHF) medications reduced the predicted odds of an STD leave to 0.61 ($p < 0.05$) times the odds for nonadherent employees. Otherwise, adherence had no significant association with lost workdays.

Coronary artery disease

One study (39) separately evaluated adherence with statins, beta blockers, and ACE inhibitors or ARBs for employees with coronary artery disease (CAD). Adherence ranged from 63.1% for statins to 65.4% for ACE inhibitors or ARBs. On average, adherence with statins was associated with nine fewer hours of absence over a 28-day period ($p < 0.05$), which converts to almost five days over a year. Adherence was not significantly associated with absence for any other CAD medication.

High cholesterol

One study (37) evaluated a variety of cholesterol management medications, evaluating the association with both absences and STD days. Adherence ranged from 51% to 54%. On average, adherence with cholesterol management medications was associated with 6.3 fewer days of absence and 2.5 fewer STD days ($p < 0.05$ for both). For STD, adherence with hypertensive medications was associated with both a reduced use of STD leaves and reduced STD durations, contingent on any use.

Multiple sclerosis

One study (44) examined STD and illness-related absenteeism costs among adherent and nonadherent employees treated for multiple sclerosis (MS) with glatiramer acetate, intramuscular interferon, beta-1a, subcutaneous interferon beta-1a, interferon beta-1b, or natalizumab. Patients with 730-day MPR of at least 80% were considered adherent. The adherence rate was 69%. Predicted values from regression models of indirect costs associated with STD and illness-related absenteeism were extrapolated from tables that included unadjusted days and costs over the two-year period. Average costs per lost workday are assumed to be $139 for adherent employees and $135 for nonadherent employees based on the weighted averages of STD and absenteeism days. On average, indirect costs for adherent employees were $1,164 lower than for nonadherent employees ($p < 0.05$). Assuming that the ratios of STD and absenteeism days reported in the unadjusted tables are applicable to the regression-adjusted costs results, this implies that adherent employees had 0.6 fewer absenteeism days and 4 fewer STD days per year.

Osteoporosis

One study (45) examined health-related lost workdays among a panel of postmenopausal women who were persistent with a pharmacological osteoporosis therapy compared with women who discontinued therapy or who switched from one therapy to another. Persistence was measured as the duration of care between the beginning of the study until therapy was discontinued or switched and the reporting date of the survey response (whichever was sooner). Persistence ranged from 70.7% to 72%. At the end of the first year of follow-up, there were no statistically significant differences in lost workdays among the three groups.

Overactive bladder

One study (46) examined absence, STD, LTD and WC days among adherent and nonadherent employees treated with urinary anti-spasmodic medications. Patients with 365-day MPR of at least 80% were considered adherent. The analyses included two-stage regression models, predicting any absence in the first stage and number of days in the second stage. Overall,

12.8% of patients were adherent. Adherence was not significantly associated with absences for any model.

Discussion and example for calculating savings

This review sought to evaluate the evidence that adherence with medications for chronic conditions can reduce lost work time, ostensibly by improving patients' health status and functioning. The findings provide mixed evidence that adherence improves outcomes in the short term (usually one year). The strongest evidence is that adherence with diabetes medications can reduce the number of workdays lost to STD leaves. This association was demonstrated by three separate studies using uniform measures of adherence and similar underlying measures of STD duration, with a mix of IV and OLS approaches and two separate data sources. Unfortunately, even with these underlying similarities, the studies lack the information necessary for a meta-analysis to determine the "true" association between adherence and disability lost work time.

For example, risk ratios and odds ratios with confidence intervals are provided in one study (37), but the lost-workdays estimate is limited to the subset of employees with any disability leave, rather than assuming zero leave days for the remaining employees. Another study provides estimated durations for adherent and nonadherent patients without providing standard errors. This complicates efforts to develop comparable variance estimates—although, as described below, weighted averages of overall effects may still be useful for the purposes of applying economic values to a particular set of results.

While almost all the analyses of STD outcomes had statistically significant findings, these come from single studies for most of the conditions in this review. Further analyses, including newer specialty pharmaceuticals where possible, are warranted. Research in this area could be advanced considerably with the inclusion of reliably collected disability leave information as real-world data in follow-up analyses to clinical trials (49-51).

The evidence that adherence to medications can reduce intermittent sick-day absences is weaker. There were considerably more non-significant than significant findings, with underlying differences in the methods and measures precluding meta-analytic comparisons across different conditions.

EXAMPLE FOR CALCULATING SAVINGS

The general findings of each study lend themselves to estimates of changes in outcomes at a given level of adherence, relative to the baseline level of adherence. This can facilitate discussions of the economic value of interventions designed to improve adherence by focusing on the productivity gains. For example, in Table 2 the Carls et al. (37) study of

asthma/COPD finds that 22% of the population is adherent, and this group had an average 7.1 fewer days of absence than the nonadherent population. Thus, for this population adherence resulted in 8,654 fewer absences than would have been observed otherwise $(5{,}417 \times 22.5\% \times 7.1)$. If adherence increased to 25%, we would expect a net savings of about 962 days $[(5{,}417 \times 25\% \times 7.1) - 8{,}654]$. The financial value of savings can be calculated by applying average daily wages for the U.S. workforce ($196), the disability wage replacement rate (62%) and the average daily employee benefits costs ($91).[1] The value of increasing adherence to 25% in this example is $204,444 $\left[962 \times [(\$196 \times 62\%) + \$91]\right]$.

Because the sample sizes in the studies contribute to the confidence intervals around the estimated effects, weighting the results by the number of participants in each analysis provides one means of generalizing findings for demonstration purposes. Strictly speaking, this approach is limited to calculating a point estimate, the confidence in which is uncertain.

From Table 2, we can weight the marginal lost work time from four analyses on adherence and STD days and from four analyses of absences that provide numeric findings expressed as days. Table 3 shows that for a population of 1,000 employees with diabetes and an average adherence of 61%, improving adherence by 10% would reduce STD and absence lost work time by 441 days, with net financial savings of about $94,000.

[1] Wage and benefits information comes from the U.S. Bureau of Labor Statistics (BLS), "Employer Costs for Employee Compensation – December 2017," USDL-18-0451, March 20, 2018, <https://www.bls.gov/news.release/ecec.nr0.htm>. Benefits costs include paid leave, supplemental pay, insurance, retirement and savings, and legally required contributions such as Social Security, Medicare and workers' compensation. Wage replacement rates come from the BLS "Employee Benefits Survey," March 2017, <https://www.bls.gov/ncs/ebs/>.

Table 3: Example of productivity savings from improved adherence with diabetes medications

Assumptions	
Employees with diabetes	1,000
Average daily wages paid to each employee	$196
Average daily benefits	$91
Disability wage replacement rate	62%
Employees eligible for paid sick days	60%

	Weighted averages	Adherence increases by 10%	**Net savings**
Adherence rate	61%	67%	
Impact (reduction) on STD days	3.7	3.7	
Total days STD saved by adherence	2,250	2,475	**225**
Financial savings of adherence on STD days	$478,158	$525,974	**$47,816**
Impact (reduction) on absence days	3.6	3.6	
Total days STD saved by adherence	2,156	2,371	**216**
Financial savings of adherence on STD days	$458,129	$503,942	**$45,813**
Total impact (reduction)			
Days saved	**4,406**	**4,846**	**441**
Financial savings	**$936,288**	**$1,029,916**	**$93,629**

INCORPORATING SAVINGS ESTIMATES FROM OTHER SOURCES

This review began from a position that cost/benefit analyses focused only on healthcare spending may underestimate the overall economic value of adherence. The converse—narrowly focusing on productivity outcomes—is also true. While an inclusion of studies evaluating the impact of adherence on healthcare utilization and costs is beyond the scope of this work, newer demonstrations provide opportunities to develop approaches allowing comparisons to relevant productivity outcomes.

As an example, we incorporate findings from a recent evaluation of an ABMS approach to improving adherence rates for patients with diabetes, high cholesterol or hyperlipidemia (10). In addition to showing a significant association between ABMS and adherence, the authors' presentation of findings permits estimates of average reductions in office, hospitalization and emergency department visits per adherent patient, as well as increased prescription drug costs that obtain from greater adherence. Table 4 shows how applying average costs for these types of services permits estimation of savings from the hypothetical increases in savings shown in Table 3. If each adherent patient translates to an average of 0.6 fewer

hospitalizations and emergency department visits at an average cost of $6,247, 5.9 fewer office visits at an average cost of $273 and 3.6% greater overall prescription costs ($681 per additional adherent), increasing adherence among diabetes patients from 61% to 67% would save about $277,000.[2] Including the productivity savings shown in Table 3, the combined savings from a 10% increase in adherence among 1,000 diabetes patients is almost $371,000.

Table 4: Example of utilization savings from improved adherence with diabetes medications

Findings from Krumme 2018, Exhibit 3 (10)

	Synchro-nized	Control	Difference	Annual difference per adherent patient	Cost per visit	Annual savings per adherent
Optimally adherent	63.7%	57.6%	6.1%			
Average monthly hospitalizations and emergency department visits	0.045	0.048	-0.003	-0.6	$6,247	$3,687
Average monthly office visits	0.77	0.80	-0.03	-5.9	$273	$1,611
Average monthly proportion of days covered for prescriptions	0.87	0.84	0.03			
Average annual prescription costs[c]	$1,205	$1,163	$41.54			-$681

Modeled costs for 1,000 patients

Adherence rate[a]	Targeted adherence[b]	Percentage point difference	Increase in number of adherent patients
61%	67%	6%	60

Savings from increased adherence: $277,013

[a] Weighted average from Table 3
[b] 10% increase from Table 3
[c] Assuming a direct relationship between costs and coverage

Conclusions

The research literature on medication adherence provides evidence that increasing rates of adherence can improve clinical outcomes cost-effectively. This review finds mixed evidence that adherence-related improvements in health can reduce illness-related lost productivity in the short term. The most consistent evidence was for a relationship between adherence and improved STD outcomes—particularly among patients with diabetes. Using diabetes as a focal case, the findings form the basis of a method for calculating the productivity and healthcare savings from improved adherence—the economic value of which may bolster the business case for effective interventions.

[2] Costs of services come from Center for Financing, Access and Cost Trends, Agency for Healthcare Research and Quality, Medical Expenditure Panel Survey, 2015, <https://meps.ahrq.gov/mepstrends/hc_use/>. The values reported are for adults age 18 to 64. The combined costs for hospitalization inpatient stays and emergency department visits reflect the relative frequencies of these events.

While several studies matched adherent patients to nonadherent controls, this technique cannot account for unobserved factors that may influence patterns of adherence (52). Future studies may consider approaches that assess changes in lost productivity over time among adherent and nonadherent patients, potentially by implementing "fixed effects" approaches such as first differencing. In light of the lack of consistent findings for sick-day absenteeism, future studies may also consider spelling out more clearly the disease symptoms that may be affected by appropriate medication use and how occurrences of these symptoms might precipitate intermittent absences rather than relatively longer-term disability episodes. This could help establish an appropriate analytic time frame that allows for improvement in disease states and functioning to manifest in more-consistent work attendance.

Finally, the findings should be interpreted as reflective of the adherence measures used in the reviewed studies. The predominant approach was to dichotomously assess MPR at or above 80%. The underlying MPR method, however, as well as other approaches that use time period as a denominator, may ignore medication discontinuation and therefore overestimate adherence (53). Direct approaches such as measurement of drugs in blood or urine, physical observation of patients' medication-taking or the use of electronic medication packaging devices may provide a more accurate gauge of adherence (54) and increase confidence in the association with productivity outcomes.

Appendix

APPENDIX TABLE 1: PUBMED SEARCH TERMS

((((medication[Title/Abstract] OR treatment[Title/Abstract] OR medicine[Title/Abstract] OR drug[Title/Abstract])) AND ("patient compliance"[MeSH Terms] or "medication adherence"[MeSH Terms]))) AND ("absenteeism"[MeSH Terms] OR absenteeism[Text Word] or "sick leave"[MeSH Terms] OR sick leave[Text Word] OR productivity[Title/Abstract] OR "work loss"[Title/Abstract])) AND Humans[Mesh] AND English[lang]

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This report was supported by funding from Pfizer, Inc. We thank Randy Vogenberg and Kim Jinnett for comments and suggestions on an earlier draft of the document.

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