Maine Legislature
Committee On Appropriation and Financial Affairs
Committee On Health and Human Services
2/28/2025

RE: LD210

Esteemed Members of the Committees:
Appropriation and Financial Affairs & Health and Human Services

Considering the proposed state budget for FY26 and FY27, Bedard Pharmacy would like to bring to your attention a few changes that can help to reduce the overall healthcare costs here in Maine instead of adding taxes.

Bedard Pharmacy & Medical Supplies has been servicing Maine communities for over 125 years and remains a locally owned business based in Auburn. Innovation and adapting to change have brought us this far. We feel it is time for the state to do the same.

Allow Generics Instead of Mandating Brands

MaineCare currently mandates that brands be dispensed even when a generic or biosimilar substitute is available. We request that this requirement be changed so pharmacies may dispense a generic or biosimilar substitute when available, based on the FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

These are similar topics being brought up in the context of PBM regulation and opportunities for savings within the federal government.

Several articles discussing these issues can be found in Appendix A.

The state ends up spending more money to, unnecessarily, fill brand-name prescriptions. While it might seem that pharmacies benefit from higher-cost medications, that is not always the case.

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The Average Wholesale Price (AWP), minus some small percentage, represents the standard cost of a medication that a wholesaler charges to a pharmacy. However, pharmacies are reimbursed by insurers or programs like MaineCare based on the Wholesale Acquisition Cost (WAC), plus a small percentage, which is typically lower than the AWP. This discrepancy means that pharmacies might have to pay more up front for medications (at AWP) but are reimbursed at a lower rate (WAC and dispensing fee). This can lead to financial strain as the pharmacy bears the cost difference, reducing their overall profit margins.

The margins are so slim that there is little financial benefit for a pharmacy to dispense an expensive brand versus a lower-cost generic. Furthermore, stocking these expensive medications ties up our credit lines and carries higher financial risks from expired medications or accidental loss of high-cost pills.

Rate Increase for Compliance Packaging to Increase Medication Adherence

One mechanism for reducing overall healthcare costs in Maine is by increasing medication adherence. A proven method for that is through compliance packaging.

Compliance packaging is important for medications because it helps ensure that patients, particularly older adults who may have complex medication regimens, take their medications correctly and consistently. This type of packaging can help reduce medication errors, improve health outcomes, and minimize waste by making it easier for patients to know when and how to take their medications. It also supports better medication management by caregivers and healthcare providers, ultimately enhancing adherence to prescribed treatments and potentially reducing healthcare costs associated with non-compliance. All of this leads to fewer hospitalizations due to non-adherence.

Various formats of compliance packaging are available, including single medication blister cards, multi-medication blister cards, hard packs, and strip packaging.

This type of packaging is particularly beneficial for patients on a polypharmacy plan, meaning they are taking five or more different medications regularly.

Appendix B includes a paper on medication adherence through the use of compliance packaging.

We ask that dispensing fees be increased to a suitable level when compliance packaging is utilized so that Maine pharmacies can be properly paid for the services they provide. The current dispensing fee does not provide any incentive for pharmacies to expand the use of compliance packaging.

Allow Shorter Duration Fills for Compliance Packaging

For compliance packaging to be an effective cost reduction mechanism, its increased use needs to be coupled with the ability to fill on a 28 or 30-day cycle, instead of the current 90-day requirement.

Compliance packaging is typically used for older adults, which are more likely to switch medications. Allowing 28 or 30-day fills means that less medication will go to waste, that the state already paid for, due to patients switching medications before they consume a 90-day supply.

This would result in more dispensing fees being paid by the state, due to the shorter filling cycle, but less medication given out unnecessarily and thrown away.

Thank you for the opportunity to submit written testimony in support of lowering the financial burden of healthcare in Maine.

Respectfully,

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Bedard Pharmacy & Medical Supplies
Director of Medical Supplies

Ben Nadeau
Bedard Pharmacy & Medical Supplies
CEO & Owner

About Bedard:

Since 1898, Bedard Pharmacy & Medical Supplies has been providing old-fashioned customer service while remaining at the forefront of advancements in pharmacy and medical supplies. As a local, family-owned business, we serve the health needs of Maine residents from our headquarters in Auburn, as well as ship supplies all over the country.

Appendix A - Several articles discussing the issues surrounding Brands vs Generics and access to Biosimilars.

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November 22, 2024

RESEARCH REPORT | Center for a Healthy America

Middlemen Favor Unaffordable Prescription Drugs

Charlie Katebi

TOPLINE POINTS

- Over the past 10 years, Americans have spent increasingly more on expensive brand-name prescription drugs.
- A major reason drugs are becoming more expensive for families is that drug manufacturers compensate pharmacy benefit managers for favoring high-cost brand-name drugs at the expense of more affordable generic drugs. In addition, the Affordable Care Act incentivized insurers to merge with PBMs and spend more on prescription drugs.
- Policymakers can make prescription drugs more affordable by increasing transparency, requiring PBMs to operate with a fiduciary responsibility, and ending perverse incentives that encourage PBMs to spend more on prescription drugs.

Overview

Americans rely on commercial and government health plans and payers to manage their drug benefits responsibly, ensuring that they receive the highest quality drugs at the lowest possible cost. These plans, often sponsored by employers or unions, contract with companies known as pharmacy benefit managers (PBMs) to design drug benefits for their members. However, PBMs often exploit their position as middlemen to enrich themselves at the financial expense of health plans and, ultimately, patients.

Patients need PBMs to work on their financial and clinical behalf. Lawmakers should implement reforms ensuring PBMs deliver value to patients and health plans. These reforms should include increasing transparency between PBMs and their clients, designating PBMs as fiduciaries when they work for health plans, and ending perverse incentives that encourage PBM consolidation.

Drugs Are Increasingly Unaffordable

Over the past several years, America's patients, taxpayers, and employers have been spending significantly more on prescription drugs, especially brand-name drugs. Between 2011 and 2021, America's annual spending on retail prescription drugs increased from $256.3 billion to $374.5 billion (CMS, 2022). In fact, the Assistant Secretary for Planning and Evaluation's (ASPE) most recent report concluded that the increase across all drug spending was driven by "increases in spending per prescription, and less so by increases in the number of prescriptions" (ASPE, 2022). In 2021, spending on brand-name drugs accounted for 80 percent of spending on both retail and non-retail prescription drugs.

Prescription drugs account for 22 percent of the cost of commercial health insurance premiums (AHIP, 2022). Due to the cost of drugs, Americans are struggling to afford the medicine they need. Last year, one in 10 Medicare beneficiaries indicated they did not fill a physician's prescription because they could not afford it (Dusetzina et al., 2023).

Over the next several years, Americans are expected to pay even more for retail prescription drugs. The Centers for Medicare and Medicaid Services (CMS) estimates that the total cost of retail drugs in the U.S. will grow from $388 billion in 2020 to $609 billion by 2030, a 57 percent increase (Roehig & Turner, 2022).

What Are PBMs?

When an individual enrolls in commercial health insurance, the health insurer administers the individual's benefits by managing networks of hospitals and clinics, processing claims, and negotiating with providers to determine the prices of health care services. However, health plans contract with other companies, known as PBMs, to manage the prescription drug benefits within each health plan. These services include creating pharmacy networks, processing pharmacy claims, and negotiating the price of prescription drugs with drug manufacturers.

PBM negotiations determine how much the health plan will pay for a drug and how much the plan's members will pay for the drug through copays and coinsurance. PBMs do this, in part, by using formularies. The formulary, as set by the PBM and the health plan, directs the plan's members to purchase some drugs and avoid others. When the PBM places a drug at the top of its formulary, patients will often pay lower cost-sharing for that drug, and the plan will pay a greater share. When the PBM places drugs lower on their formulary, patients will often pay higher cost-sharing for the drug and can also often face utilization management hurdles, such as prior authorization and step therapy, because it is not the preferred drug of the health plan.

PBMs manage formularies for thousands of employer health plans and negotiate with hundreds of drug manufacturers about where they place their drugs on employers' formularies. When PBMs negotiate with drug manufacturers, the manufacturers will offer the PBM a payment, known as a rebate, in exchange for meeting certain terms of the rebate contract. For example, to receive the rebate, the PBM must ensure that the beneficiaries of an employer's health plan purchase a certain amount of the drug being negotiated. This is often accomplished by the PBM placing the drug on a high tier of its

formulary, which will lower the patient cost-sharing for the drug and, in turn, encourage the plan's members to purchase it over other drugs. Rebates can also encourage PBMs to restrict access to drugs that compete with the drug manufacturer offering the rebate because the rebate is tied to plan beneficiaries using a certain volume of the preferred drug.

PBMs generate a significant amount of revenue from rebates. Contractual agreements between PBMs and health plans are often structured so that PBMs retain a percentage of the rebates they receive from drug manufacturers. This incentivizes PBMs to seek greater rebates on behalf of the health plan but can also incentivize PBMs to keep a larger percentage of the rebate. Separate analyses by the Pew Charitable Trusts (Pew Trusts, 2019) and the Government Accountability Office (GAO) (GAO, 2019) found that PBMs passed more than 90 percent of rebates back to health plans in 2016. However, recent investigations have found that the three largest PBMs use complex arrangements with their group purchasing organizations (GPOs) to retain rebate revenue not disclosed to the health plan (FTC, 2024).

PBM Incentives Harm Patients

The perverse incentives in the PBM industry contribute to the reasons Americans spend increasingly more on prescription drugs. Employers and health plans pay PBMs to design drug benefits so members can access high-quality drugs at the lowest possible cost. However, PBMs are incentivized to demand larger rebates from drug manufacturers to maximize their earnings. In return, pharmaceutical manufacturers are incentivized to increase the rebate provided on a drug as they bargain with PBMs for preferred formulary placement. This negotiation process often encourages manufacturers to artificially increase list prices to generate greater rebates as they negotiate with PBMs. One analysis of 13 manufacturers found that their net revenue[1] grew each year by an average of 2.9 percent. Rebates and other payments to PBMs, however, increased each year by an average of 13.5 percent. This means the growth in the gross revenue was primarily due to the growth in rebate payments, not an increase in net revenue.

In addition, the analysis found that 40 percent of the list price of drugs was devoted to payments to PBMs in 2019, meaning patients paid higher prices largely because rebates grew. This perverse incentive hurts patients. If a patient has not met a deductible and must pay the full list cost of the drug, this means the patient is paying 40 percent of the cost of the drug to the PBM (Weinstein & Schulman, 2020).

Rebates also increase costs for patients because they come with legal agreements that require PBMs to steer patients to more expensive medications. A 2023 report by the GAO found that brand-name drug manufacturers established legal agreements with PBMs that manage Medicare's drug benefit program, Part D, to ensure that the PBM favored their drug at the expense of cheaper generic versions (GAO, 2023). In fact, for some highly rebated drugs, the health plan paid less for the drug than the patient did.

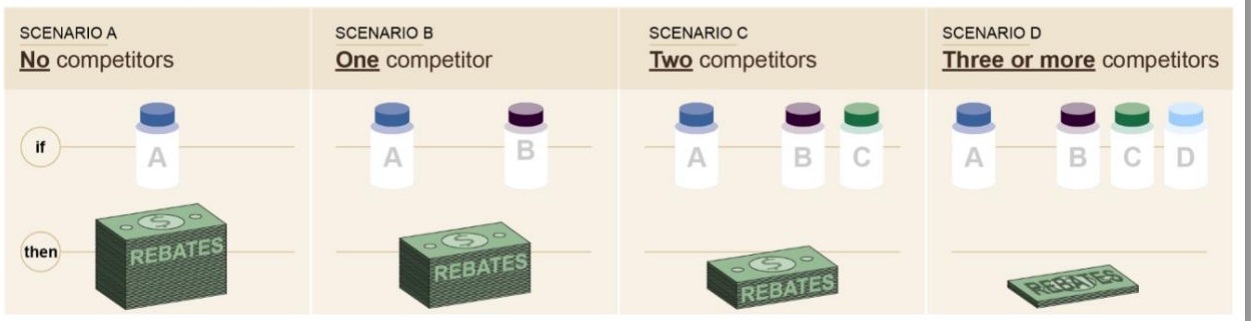
First, the GAO found drug manufacturers paid PBMs higher rebates if the manufacturer's drug was placed in a more favorable formulary tier than their competitor's drug. Second, they paid higher rebates if

[1] Net revenue is the amount of money a drug manufacturer makes after subtracting rebates and other discounts they give to PBMs and health plans.

the PBM placed fewer competing drugs on the same tier as the manufacturer's brand-name drug. Third, they paid higher rebates if the PBM did not impose utilization controls, such as prior authorization and step therapy, on the manufacturer's brand-name drug. And fourth, they paid higher rebates if the PBM imposed more utilization restrictions on their generic competitors.

Figure 5: Illustrative Examples of Rebate Offerings Based on the Number of Competitors on the Preferred Formulary Tier

The following scenarios describe manufacturer rebate offerings based on the number of competitor drugs covered by a plan sponsor's formulary on the preferred brand tier.



Source: GAO analysis of selected rebate contracts between manufacturers and Medicare Part D plan sponsors; GAO (illustrations). | GAO-23-105270

As a result of these rebate agreements, PBMs have placed brand-name drugs on a more favorable tier of their formularies at the expense of generics. A 2019 analysis of Part D plans found that 72 percent of PBM formularies placed at least one brand-name drug in a lower cost-sharing tier than its cheaper generic counterparts (Socal, Bai, & Anderson, 2019). This analysis also found that 30 percent of Part D formularies imposed utilization controls less frequently on at least one brand-name drug when compared to its generic version.

Over time, the formularies of many PBMs have become less favorable to more affordable generics. In 2010, PBMs for Part D plans placed 73 percent of generic versions of brand-name drugs on the lowest cost-sharing tier of their formularies (Feldman, 2021). However, by 2017, PBMs reduced the share of generics in their lowest cost-sharing tier to 28 percent. This increased the average copay for a generic prescription in Part D plans from $11 to $33, tripling the average cost in just seven years.

The rebate agreements that drug manufacturers establish with PBMs incentivize these companies to administer drug benefits in a fashion that increases spending on prescription drugs, which can lead to higher premiums and greater cost-sharing for patients. A 2022 analysis by the Congressional Budget Office found that the net price, after accounting for rebates, of the average brand-name drug prescription in Part D increased from $149 to $353 between 2009 and 2018, a 136 percent increase (CBO, 2022).

To address the perverse incentives of rebates, the Trump Administration finalized a new regulation in 2020 to require PBMs that operate in the Part D program to pass along manufacturer rebates directly to the patient (42 C.F.R. 1001, 2020). Debate on the effects of the proposal centered around whether seniors' premiums in Part D would increase: Some actuarial projections

indicated premiums would rise, while the secretary of the Department of Health and Human Services (HHS) publicly confirmed that the policy would not result in increased beneficiary premiums, out-of-pocket costs for patients, or federal spending (Sachs, 2020). In 2022, Democrats rescinded this policy through the Inflation Reduction Act (Cubanski, Neuman, & Freed, 2023).

Spread Pricing Increases Drug Spending

Another PBM practice that increases drug costs is known as spread pricing. When a patient fills a prescription at a pharmacy, the patient's health plan, including Medicare Part D and Medicaid, pays the PBM the cost of the drug so that the PBM can reimburse the pharmacy for the prescription. However, PBMs will often reimburse the pharmacy that dispenses a drug just a fraction of the amount the plan paid them. The PBM keeps the difference, the "spread," as profit. This practice encourages PBMs to charge health plans a higher price than they actually paid to the pharmacy. A report by Ohio's state auditor found that PBMs retained nearly $225 million in profits from the state's Medicaid Managed Care Organization (MCO) program from spread pricing in 2017 (Ohio, 2018). Another report found that PBMs managing Kentucky's Medicaid MCOs charged taxpayers $123 million in spread pricing in 2018 (Kentucky, 2019).

Spread pricing can also hurt patients. If a patient has not yet met a deductible, the patient is often required to pay the list price of the drug, which includes the spread amount. For this reason, several states have acted to address spread pricing and its effect on patients. As of 2019, 11 states have instituted some prohibitions on spread pricing in MCO contracts (KFF, 2019). Other states allow pharmacists to inform the patient of the lowest cost of the drug purchased with cash, which excludes the spread cost (GAO, 2024).

PBMs Need Transparency

One reason that PBMs can operate against the interests of patients, employers, and federal payers is that employers and payers often lack the information they need to hold the PBM accountable. In general, PBMs do not disclose to employers and payers an itemized receipt of claims data, rebate amounts for drugs on their formulary, an explanation of why they included certain drugs in their formulary but excluded less expensive alternatives, or other relevant information (Barlas, 2015). To obtain this information, employers must pay between $15,000 and $200,000 to audit the PBM (Barlas, 2015). This lack of transparency makes it impossible for employers to compare their PBM's performance to the performance of alternative PBMs or to shop around for more competitively priced options. Employers and unions are trusted to make the best decisions on behalf of their employees, and without detailed pricing and claims data, they are left to blindly trust that the PBM is working in their best interest.

Greater transparency would help employers determine if their PBM was designing their drug benefit in their best interests—namely, to obtain the highest-quality drug at the lowest possible price for their employees. These measures would also give employers actionable information to demand that their PBM change their drug benefit program to serve their employees better. After a health plan within the Federal Employees Health Benefits Program instituted transparency measures for their pharmacy spending, they learned that their PBM, Express Scripts, overcharged them by $45

million for the costs of prescription drugs (OPM, 2024).

President Trump signed into law several proposals that empower the federal government to require PBMs to provide greater transparency to employers and patients through the Consolidated Appropriations Act (CAA) of 2021 (2020). The law prohibits gag clauses in contracts between PBMs, insurers, and employers, which had kept employers from accessing their medical and pharmacy claims data. The law also requires PBMs and other service providers to make standard disclosures to the employer, such as the description of the services they anticipate providing to the employer or any indirect compensation that might present a conflict of interest. Yet neither HHS nor the Department of Labor (DOL) have meaningfully enforced these provisions of the CAA.

Other federal laws on the books could also be used to increase transparency. The Trump Administration used authority from the Patient Protection and Affordable Care Act (ACA) to promulgate the "Transparency in Coverage" rule, which requires health plans and payers to provide extensive price and cost-sharing information to patients. The rule also requires information on medical and drug claim payment policies and practices to be made public, as well as other information as determined appropriate by the secretaries. HHS, DOL, and the Treasury could further build on these reforms by requiring health plans and payers to make public the claims-level drug pricing and discount data (i.e., rebate or spread amounts) they receive from the PBMs. However, the Biden-Harris Administration delayed implementing parts of the rule and has not updated the rule to include the required prescription drug pricing data (HHS, 2023).

Currently, Congress is considering more transparency measures to require PBMs to disclose their pricing and formulary decisions to employers and health plans. These proposals include the Lower Costs, More Transparency Act (2023), the Modernizing and Ensuring PBM Accountability Act (2023), and the Pharmacy Benefit Manager Reform Act (2023).

PBMs Have No Legal Obligation to Work on Behalf of the Health Plan or Patients

Another reason PBMs engage in anti-patient behavior is that PBMs have no legal responsibility to act in the best fiscal interests of the plan for which they work. Under the Employee Retirement Income Security Act of 1974 (ERISA), employers that sponsor health insurance for their workers must delegate an individual, committee, or company to be a "fiduciary" to administer the plan (29 U.S. Code §1104, 1974). The law defines a fiduciary as an individual who exercises "discretionary authority or discretionary control" over the health plan (29 U.S. Code § 1002, 1974). The fiduciary must administer the plan "solely in the interest of the participants" and "for the exclusive purpose of providing benefits to participants." In 1998, DOL issued an information letter outlining that fiduciaries must consider both the "quality of services" and the "reasonableness of the fees" that an insurer would charge the employer and its workers for providing health insurance (DOL, 1998). Roughly 139 million individuals receive health insurance through a health plan governed by ERISA (DOL, 2022).

Since employers often lack the expertise or resources to administer a health plan, they will often delegate these tasks to a health insurer acting as a third-party administrator (TPA). The

companies then perform plan administration duties such as collecting premiums, adjudicating claims, and contracting with a PBM to manage the employer's drug benefit.

However, the courts have repeatedly reiterated that TPAs and PBMs do not have a fiduciary responsibility to act exclusively in the interest of the plan. In 2007, the U.S. Court of Appeals for the Seventh Circuit found that Caremark, the PBM, was not the fiduciary because the PBM did not exercise "discretionary authority" or control over an ERISA-regulated union plan (*Chicago v. Caremark*, 2007). In a lower court, the U.S. District Court for the District of New Jersey found that plan design and administration were not significant enough to impose a fiduciary duty on the PBM (*Mulder v. PCS Health Systems, Inc.*, 2006).

To change this, policymakers should expand the fiduciary duty under ERISA to include certain services that PBMs provide to employer health plans. Under an extension of fiduciary duty, PBMs would have a legal obligation similar to other entities that contract with employee welfare benefit plans (*e.g.*, retirement plans). For example, under a fiduciary duty, PBMs could have a legal obligation to design drug benefits solely in the interest of the participants.

Lawmakers could amend ERISA to officially designate PBMs as fiduciaries when they design drug benefits for self-funded group health plans. In lieu of a statutory change, DOL could also issue guidance that clarifies that PBMs are fiduciaries, providing evidence that some of the functions they provide exercise discretionary authority over the management of drug benefits of ERISA-regulated health plans.

As policymakers contemplate expanding the fiduciary duty to PBMs, they should ensure that the fiduciary duty PBMs owe to employer health plans is appropriately balanced with PBMs' financial relationships with drug manufacturers. Policymakers should also consider designing appropriate guardrails against administrative overreach, especially as the Biden-Harris Administration has grossly misinterpreted "fiduciary duty" within the financial services sector.

Extending fiduciary duty to PBMs could further equip companies and employees with powerful legal recourses to ensure that these companies are designing benefits that are in their best interests. In fact, employees have leveraged fiduciary duty to hold employers accountable if they believe their health benefits have been mismanaged. In February 2024, employees at Johnson & Johnson sued the company for allegedly breaching its fiduciary responsibility (*Lewandowski v. Johnson and Johnson et al.*, 2024). According to the lawsuit, Johnson & Johnson paid its PBM to design its drug benefit plan so that workers pay dramatically more for generic drugs under the plan than if they simply purchased the drugs with cash. For example, a 90-day supply of the generic drug teriflunomide could be purchased for as little as $40.55 with cash. But if an employee paid for the drugs with a drug benefit, it would cost the employee and the company a total of $10,239.69.

The ACA Promotes PBM-Health Plan Monopolies

Policymakers should also remove harmful government interventions that financially reward health insurers when PBMs inflate the cost of prescription drugs. A major provision of the ACA, known as the medical loss ratio (MLR), prohibits large health insurers from spending

more than 15 cents of every dollar they collect in insurance premiums on profits and administrative expenses (42 U.S.C. 300gg-18, 2010). In the individual market, insurers cannot spend more than 20 cents of every premium dollar on profits and administrative expenses. The remaining 80–85 cents must be spent on health care claims. The architects of the law assumed the MLR would prevent insurers from skimming higher profits from their members and, therefore, encourage insurers to reduce premiums.

As well-intentioned as it might have been, this policy has inadvertently increased the cost of prescription drugs for patients. Because insurers cannot retain more than 15–20 cents in profits and administrative expenses for every 80–85 cents they disperse in claims, insurers can generate higher profits when their PBM manages their drug benefit in a way that increases spending on prescription drugs (CBO, 2022).

For example, a health insurer in the individual market charges members $100 million in premiums, spends $80 million on health care claims, including $20 million in drug claims, and retains the remaining $20 million for administrative expenses and profits in one year. This insurer would have an MLR of 80 percent. To generate greater profits the next year and comply with the MLR rule, the insurer could encourage the PBM with which they contract to raise spending on prescription drugs from $20 million to $40 million, leading to $100 million in total health claims. This would allow the insurer to raise premiums to $125 million. As a result, the insurer could increase the money it directs to profits and administrative expenses by $5 million and remain in compliance with the ACA's MLR.

	No MLR Incentive	**MLR Incentive**
Initial Spending on Medical Costs	$60 million	$60 million
Initial Spending on Drug Costs	$20 million	$40 million
Profit and Administration	$20 million	$25 million
Premium Charges	$100 million	$125 million
Medical Loss Ratio	80%	80%

The MLR also incentivized insurers to merge with PBMs (Frank & Milhaupt, 2023). Within Medicare Advantage, where insurers must maintain an 85 percent MLR, evidence shows that after an insurer merges with a PBM, the insurer can use creative accounting for gaming the MLR. For instance, the insurer can direct premium dollars to their own PBM to pay prescription drug claims. The profit that the PBM generates from these transactions does not count against their MLR limits. Therefore, the insurer can spend more on prescription drugs and generate higher profits through a PBM while still complying with MLR's profit cap.

With these incentives, insurers and PBMs began merging to use the MLR better. Since the ACA took effect, Cigna has purchased Express Scripts (Humer, 2018), CVS Caremark has bought Aetna (Richman, 2018), and United Healthcare has bought Catamaran (Eastwood, 2015) and established OptumRx (Business Wire, 2011). Between 2010 and 2018, the share of Part D beneficiaries enrolled in a plan integrated with a PBM increased from 30 percent to 80 percent (Gray, Alpert, & Sood, 2023). Nationwide, 80 percent of all prescription claims are negotiated by three PBMs integrated with

an insurer: Caremark, Express Scripts, and OptumRx (Fein, 2023).

A harmful effect of this trend is that large insurers have started to use their PBMs to raise premiums on patients enrolled in plans with competing insurers. As the largest insurers have merged with the three largest PBMs, smaller stand-alone insurers have had little choice but to contract with PBMs that are integrated with their competitors. A 2023 study in the National Bureau of Economic Research found that the premiums for Part D plans that contracted with a competitor's PBM were 65 percent higher than the premiums of insurers that were integrated with a PBM in 2018 (Gray, Alpert, & Sood, 2023). This suggests that the largest PBM-insurer conglomerates are designing formularies for their competitors to raise their premiums and disadvantage them in the marketplace.

The ACA Promotes PBM-Pharmacy Monopolies

The ACA's MLR requirements have also driven the consolidation of PBMs and pharmacies. As the largest PBMs merged with insurers, they acquired or established their own pharmacies and inserted language in contracts to steer members to their pharmacies rather than to independent ones. Between 2015 and 2021, the share of Part D prescriptions that were dispensed by a pharmacy owned by their PBM-integrated insurance plan increased from one-quarter to one-third, according to a 2023 report from the Medicare Payment Advisory Commission (MedPAC) (MedPAC, 2023). Nationwide, pharmacies operated by the three largest PBMs, Caremark, OptumRx, and Express Scripts, generated 57 percent of all specialty pharmacy revenue in 2018 (Fein, 2019).

The MLR contributed to PBM-integrated insurers consolidating the pharmacy industry and raising consumer costs. A 2024 report by the Federal Trade Commission (FTC) details how the MLR encourages PBMs to pay higher reimbursements to their in-house pharmacies: "For example, if an affiliated insurer pays an inflated price for a specialty generic to its affiliated pharmacy, the higher payment is credited as spending on clinical care and helps the affiliated insurer satisfy its MLR obligations" (FTC, 2024).

Because of these incentives, evidence is sufficient to show that patients and taxpayers spend more on prescription drugs when patients fill their prescriptions at pharmacies owned by the PBM that manages their drug benefits. A case study by the FTC found that the three largest PBM-integrated insurers paid pharmacies they own more than they paid unaffiliated pharmacies for two generic drugs. In the commercial market, PBM-integrated insurers paid affiliated pharmacies 80–90 percent more than they paid unaffiliated pharmacies. In Part D, PBM-integrated insurers paid affiliated pharmacies more than 30 percent more than they paid unaffiliated pharmacies. In other words, PBMs are vertically integrating to raise prices for patients and taxpayers alike.

Policy Recommendations

Policymakers should enact reforms that directly address the perverse incentives in the PBM industry to lower premiums and out-of-pocket costs for patients. America First policies would give PBMs the flexibility to design benefits for the unique needs of patients and employers while ensuring

that PBMs also work in the best interests of the health plan, the patient, and the taxpayer.

Require Transparency from PBMs: Lawmakers should require PBMs to provide a report to employers and Part D plans that details their rebate and claims data, their formulary decisions, the net cost of the drugs on their formularies, affiliate pharmacies, and other relevant information needed for health plans to make cost decisions. Policymakers should also enforce provisions of the CAA and the ACA that require greater transparency between the health plan and the PBMs.

End Perverse Incentives that Favor PBM-Insurer Monopolies: Lawmakers should reform the MLR to prevent this policy from increasing the cost of care for families. Policymakers should also explore regulatory reforms to prevent health insurers from gaming the MLR by consolidating with PBMs and health care providers. In 2023, Senators Mike Braun (R-IN) and Elizabeth Warren (D-MA) issued a letter to HHS, urging the agency to determine if PBM insurers were charging higher prices at their in-house pharmacies because of the MLR (Warren & Braun, 2023).

Expanding Fiduciary Duty: Lawmakers could amend ERISA to officially designate PBMs as fiduciaries when they design drug benefits for self-funded group health plans. DOL could also issue guidance that clarifies that PBMs are fiduciaries, providing evidence that some of the functions they provide exercise discretionary authority over the management of drug benefits of ERISA-regulated health plans. In 2023, Senators Mike Braun and Roger Marshall (R-KS) offered and withdrew an amendment to the Pharmacy Benefit Manager Reform Act that would have enacted this reform (Proposed Amendment, 2023). Braun and Marshall successfully offered an amendment requiring the DOL to study the impact of imposing fiduciary responsibility on PBMs (Braun & Marshall, 2023).

Ban Spread Pricing in Government Programs: Policymakers should prohibit spread pricing in contracts between a PBM and public health programs, such as Medicare and Medicaid. The Modernizing and Ensuring PBM Accountability Act (2023) and the Lower Costs, More Transparency Act (2023) would enact a spread pricing ban in Medicaid.

Strengthen Antitrust Enforcement: Policymakers should direct the FTC to investigate and penalize PBM practices that raise prescription drug spending and curtail competition. In 2021, the FTC issued a report that indicated many common rebate arrangements that drug manufacturers and PBMs establish in commercial and Part D plans potentially violate the Sherman Act (FTC, 2021). In addition, the FTC found that the PBMs' vertically integrated and concentrated market structure has allowed them to profit at the expense of patients and independent pharmacists (FTC, 2024).

Conclusion

PBMs have enormous potential to negotiate lower prices because of the substantial number of patients they represent, but they operate in a system with perverse incentives. The current system has encouraged PBMs to favor high-cost brand-name drugs over more affordable options, including generic drugs. It has inadvertently raised list prices, which has hurt patients, who must pay more for their drugs. Furthermore, the ACA has incentivized insurers to merge with PBMs and

pharmacies, which has encouraged these companies to benefit from higher spending on prescription drugs.

Policymakers should remove these perverse incentives in the PBM industry to ensure that PBMs negotiate lower prices for families. In addition, lawmakers should require PBMs to manage drug benefits in the best interest of the employers for whom they work. Furthermore, PBMs should provide employers with more transparency in how they design their drug formularies and detailed claim information that employers need to make decisions for their employees. High drug costs are a top concern for Americans, and solutions that address the misaligned incentives of PBMs could make meaningful progress toward putting patients back in charge of their health care.

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ISSUE BRIEF | Center for a Healthy America

Federal Barriers Make Biologic Drugs Unaffordable

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TOPLINE POINTS

- ★ Over the past 10 years, the cost of important prescription drugs known as biologics has skyrocketed.
- ★ A major reason brand-name biologics are so expensive is that they face little competition from generic versions known as biosimilar drugs. The Food and Drug Administration (FDA) imposes an expensive and burdensome approval process on biosimilars that blocks new ones from entering the market and competing with brand-name biologics.
- ★ Policymakers should introduce more competition and make biologics more affordable by reforming the FDA's approval process for biosimilar drugs.

Background

Since the 1860s, scientists and physicians have developed most medicines by synthesizing relatively simple chemical ingredients. Examples of these simple drugs, known as small-molecule drugs, include aspirin, penicillin, Ibuprofen, and antihistamines. Today, 90 percent of all medicines approved in the United States are small-molecule drugs (Coherent Market Insights, 2022).

Starting in the 1970s, scientists began to develop more complex drugs, known as biologics (Lybecker, 2020). Biologics are produced from components of living organisms, including human, plant, and animal cells, and microorganisms such as bacteria or yeast. Examples of biologics include Humira, Remicade, Herceptin, and Avastin. These biologics treat a range of diseases, including cancer, psoriasis, rheumatoid arthritis, and Crohn's disease.

Biologics are Unaffordable

During the past 10 years, the cost of biologics has increased dramatically. Between 2013 and 2021, patient and taxpayer spending on biologics increased from $100 billion

(IQVIA, 2018) to $260 billion (adjusted for inflation), a 160 percent increase (IQVIA, 2023). By 2018, biologic drugs accounted for only 0.4 percent of all prescriptions but represented 46 percent of all drug spending in the United States. For the average patient who is prescribed a biologic, these drugs cost $10,000 to $30,000 every year (Chen, 2018).

The high cost of biologics has contributed to growing numbers of Americans struggling to afford the medicine they need. One 2022 survey found that one in nine Medicare beneficiaries did not fill a physician's prescription because they could not afford to pay for it (Dusetzina, 2023).

Affording biologics is even harder for patients with expensive medical conditions. High-priced oncology drugs now make up 50 percent to 60 percent of a cancer patient's total costs to treat the illness (Loria, 2022). Once individuals are diagnosed with cancer, more than 40 percent of them spend their entire life's assets to treat their cancer within two years of their diagnosis (Gilligan, 2018).

Over the next several years, the cost of medication is expected to increase even more. One analysis of national health expenditure data from the Centers for Medicare and Medicaid Services (CMS) estimates the total annual cost of drugs in the United States will grow from $564 billion in 2020 to $917 billion by 2030, a 62 percent increase (Roehrig & Turner, 2022).

The FDA Stifles Biosimilar Competition

Patients urgently need solutions to make prescription drugs affordable. The most proven method to lower the cost of prescription drugs is to introduce more generic choices at much lower prices into the prescription drug market. Data from the Food and Drug Administration (FDA) show that introducing a single generic competitor on average reduces drug prices by 39 percent. Two competitors lower prices by 54 percent. Four competitors lower prices by 79 percent. And six competitors lower prices by 95 percent (Conrad, 2019).

Unfortunately, the FDA imposes a burdensome approval process that significantly delays high-quality biosimilars, the generic equivalent of biologics, from entering the market. The FDA regulates biosimilars based on standards established under the Biologics Price Competition and Innovation Act (BPCIA), a provision of the Affordable Care Act (42 USC 262, 2010).

Under this law, when the FDA approves a brand-name biologic to enter the market, it prohibits other drug manufacturers from selling competing biosimilars for 12 years. During this period, the FDA requires that drug companies wishing to sell a competing biosimilar perform lengthy comparative efficacy trials to demonstrate that their drug has

"no clinically meaningful difference" from the brand-name biologic.

After the FDA approves the biosimilar to enter the market, the drug must meet additional requirements for pharmacists to dispense it. The BPCIA requires biosimilars that are intended to be "interchangeable" with biologics to be subject to additional studies to show that patients would not face increased health risks if they switched between the biosimilar and original biologic drug.

This expensive process requires biosimilar makers to spend $100 million to $300 million, from start to finish, to receive FDA approval (Fontanillo, 2022). Unfortunately, growing scientific evidence shows the BPCIA's financially burdensome requirements do not increase the safety or effectiveness of biosimilar drugs (Kirsch-Stefan, 2023). Instead, they raise the cost of developing biosimilars, curtail competition, and raise the price of these important drugs for patients.

The Need for Clinical Efficacy Trials Should Be Revisited

The FDA's most burdensome requirement is the agency's mandate that biosimilar makers perform comparative efficacy trials on their drugs in order to sell them. These clinical trials account for 65 percent of the financial cost of bringing a biosimilar to market (Fontanillo, 2022).

When a drug developer submits an application to the FDA to sell a biosimilar, the agency requires data proving that the drug is highly similar to the original biologic based on "a clinical [efficacy] study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency"(42 USC 262, 2010). Clinical efficacy trials require assembling hundreds of patients with the same medical condition, purchasing large quantities of the original brand-name biologic, and administering the biologic and biosimilar head-to-head to evaluate whether the biosimilar treats the condition as effectively as the brand-name drug (Bielsky, 2020).

However, biosimilar makers already provide the FDA with the information it needs to verify their drug's efficacy before they perform a clinical trial. When a drug maker builds a biosimilar, it purchases large quantities of the original biologic and performs tests known as analytical studies to determine the drug's structure (FDA, n.d.). With this information, the drug maker can rebuild the biologic from scratch.

After drug makers build their own biosimilars, they perform additional tests known as pharmacokinetic (PK) studies. These tests directly evaluate how a person's body responds to a drug—specifically, how the drug is absorbed, distributed, metabolized, and excreted. Through these tests, drug makers can determine if there are any meaningful differences between how patients interact with a biosimilar drug and how patients interact

with its biologic counterpart (Cohen, 2023).

Because these tests can already confirm whether a biosimilar performs as effectively as its biologic counterpart, numerous real-world studies have concluded that comparative efficacy studies are superfluous and unnecessary. One review of clinical trials for 38 biosimilar drugs found that 95 percent of these studies delivered "no value to the scientific review process" to determine if biosimilar drugs performed as effectively as the biologic (Schiestl, 2020). Another review of clinical trials for 20 biosimilar drugs approved in the EU found these studies "did not identify any instance where efficacy trials added crucial information" (Bielsky, 2020).

PK tests are also significantly less expensive to perform, accounting for just 10 percent of the cost of developing a biosimilar (Fontanillo, 2022). PK tests cost less than efficacy studies because they require fewer participants, can be completed with healthy volunteers, and can be completed in less time.

Because PK tests can effectively confirm biosimilarity, the FDA regularly approves drugs based on data gathered from these tests and ignores results from clinical efficacy studies. A 2019 review of biosimilar applications found that the FDA has never rejected a single biosimilar application that passed a PK test but failed its clinical efficacy study (Webster, 2019).

In recent years, the FDA has recognized the superiority of PK tests and has exempted several biosimilars from its requirement to conduct efficacy studies. Since 2020, the agency has waived efficacy study requirements for biosimilar versions of insulin, filgrastim, and pegfilgrastim (Cohen, 2023).

International and global health institutions have also recognized that clinical trials are unnecessary for approving biosimilars. In 2022, the United Kingdom's Department of Health and Social Care issued guidance removing the requirement for comparative efficacy studies (Medicines & Healthcare Products Regulatory Agency, 2022). That same year, the World Health Organization issued guidance stating "pharmacokinetic and pharmacodynamic studies are sufficient to demonstrate biosimilarity" and "large confirmatory efficacy and safety studies are generally not needed" (Kurki, 2022).

Policymakers and the FDA should recognize this growing scientific consensus and base the approval of biosimilars on whether these drugs can pass a PK test. These tests can verify that biosimilars effectively treat patients at a significantly lower cost than clinical trials. Removing the need for clinical efficacy trials for all biosimiliars would dramatically reduce development costs and empower drugmakers to provide these medications at an affordable price.

Longer Exclusivity Delays Biosimilar Competition

Once the FDA determines a biosimilar to be safe and effective, the agency prohibits the drug from entering the market until the original biologic's 12-year exclusivity period expires. The exclusivity period is the duration of time the FDA allows brand-name drugs to compete without generic competition. The FDA enforces exclusivity periods to ensure brand-name drug makers can earn enough profits to recoup the money they invest to invent new drugs.

In contrast, the agency enforces a far shorter five-year exclusivity period for brand-name, small-molecule drugs. When Congress enacted the BPCIA in 2010, the bill's architects believed biologic drugs took longer to develop and required greater financial risks than simpler small-molecule drugs. So in order to encourage drug makers to develop biologics and recoup their research and development investments, they assumed they needed a longer exclusivity period on the market without biosimilar competition.

However, biologic drugs do not require more time to develop than small-molecule drugs. In 2019, a study in *Nature* found biologic and small-molecule drugs take the same amount of time to develop (Beale, 2019). The study's authors evaluated the development time of biologics and small-molecule drugs approved by the FDA between 2007 and 2016. They found both types of drugs take a median of 12.4 years to develop.

Drug makers also do not suffer greater financial risks when they develop biologics rather than small-molecule drugs. On average, biologics have an 18 percent rate of successfully passing the FDA's clinical trials. By comparison, small-molecule drugs have a success rate of just nine percent (Smietana, 2016).

As a result of the BPCIA's mistaken assumptions, the United States now has the longest exclusivity period among industrialized countries for these essential drugs. In Australia and New Zealand, biosimilars can compete with biologics after five years. And in Canada, they can compete after eight years (Beale, 2019).

Allowing biosimilars to compete sooner would save consumers billions of dollars. An analysis by the Blue Cross Blue Shield Association estimates that shortening exclusivity from 12 years to seven years would save Americans $101 billion over a decade, including $23 billion in out-of-pocket costs (Ellis, 2023).

The FDA's Interchangeability Standard Limits Biosimilar Substitution

After the FDA approves a biosimilar to enter the market, the agency imposes additional barriers that limit access to the drug and raise costs. Following approval of a biosimilar, physicians are free to prescribe it, but the FDA imposes severe limits on pharmacists who seek to dispense the drug. While pharmacists may dispense cheaper generic drugs when patients seek to fill a prescription for a non-biologic brand-name drug, the FDA prohibits

pharmacists from dispensing most biosimilars when a patient arrives with a prescription for a biologic (Sacks, 2020).

Under the BPCIA, a pharmacist may substitute a biologic with a biosimilar only if the FDA designates the biosimilar as "interchangeable." For a biosimilar to be considered interchangeable, the BCPIA requires biosimilar makers to prove that patients would not face increased "risk in terms of safety or diminished efficacy" if they alternated between the original biologic and the biosimilar drug during their treatment plan (42 USC 262, 2010). To deliver this evidence, the FDA requires biosimilar makers to perform additional clinical tests known as "switching studies" (FDA, 2019).

The architects of the BPCIA feared that patients would suffer from an immunogenic reaction if they switched between a biologic and a biosimilar. An immunogenic reaction occurs when a person's immune system interprets a medicine's contents to be a foreign substance. In response, the patient's immune system creates antibodies that neutralize the drug's effects. To safeguard against this risk, the BPCIA requires biosimilar makers to conduct switching studies to demonstrate that their drug won't create an immunogenic reaction.

During the switching study, some patients take the original biologic for the entirety of their treatment plans. The rest alternate between the original biologic and the biosimilar. Once it is confirmed that switching between the two medications delivers the same clinical result as taking the original biologic, the FDA approves the biosimilar as interchangeable.

Despite the worries of the BPCIA's authors, patients face virtually zero risks when they alternate between a biologic and biosimilar drug. Since 2006, the European Union has authorized member countries to allow biosimilars to be interchangeable with their biologic counterparts without a switching study. In 2020, European researchers reviewed 178 studies measuring the safety and efficacy of European patients that switched between biosimilars and biologics. Their study found zero evidence that "switching from a reference biological to a biosimilar is related to any major efficacy, safety, or immunogenicity issues" (Barbier, 2020).

As a result of the growing evidence, global health institutions now endorse empowering pharmacists to dispense biosimilars without switching studies. In 2022, the World Health Organization officially recommended that all countries authorize biosimilars to be interchangeable with their biologic counterparts (World Health Organization, 2022). That same year, the European Medicines Agency (EMA) also recommended its member countries allow biosimilars to be interchangeable (European Medicines Agency, 2022).

FDA Hurdles Reduce Competition and Raise Prices

Due to the FDA's costly and unnecessary hurdles, the agency has failed to approve enough biosimilars for these drugs to compete meaningfully with brand-name biologics. As of April 2023, the FDA had approved 671 brand-name biologic drugs (FDA, 2023). However, as of October 2023, the FDA has granted approval to only 43 biosimilar drugs (FDA, 2023). And no biosimilars are in development for 47 percent of biologics that currently lack competition (IQVIA, 2023). Also, the FDA's interchangeability requirements have inhibited the ability of pharmacists to dispense biosimilars. While the FDA has approved 43 biosimilars, it has granted interchangeability to only five (Stewart, 2023).

Expanding the number of biosimilar competitors holds the promise of making biologics significantly more affordable. When biosimilars enter the market, they cost 18 to 50 percent less than brand-name biologic drugs (IQVIA, 2023). In response, biologic makers are compelled to lower their prices or risk losing customers.

Over time, greater biosimilar competition would generate billions of dollars in savings for families, employers, and taxpayers. According to the health company IQVIA, biosimilars are expected to save Americans $125 billion to $237 billion between 2023 and 2027 (IQVIA, 2023). The report noted that how much savings biosimilars actually generate will depend on how many can enter the market and gain greater market share against more expensive brand-name biologics.

Patients who rely on biologic drugs would experience enormous financial relief from these expected savings. Under IQVIA's estimates, the average patient who is prescribed a biologic could save as much as $1,800 to $5,500 every year from greater biosimilar competition. These savings would ensure that many more Americans could afford the medications they need to survive.

Policy Recommendations

Modernizing the FDA's outdated and expensive approval process for biosimilars would bring affordable drugs to the market faster, enhance healthcare access, and improve outcomes for patients. Policymakers should implement the following reforms to ensure patients can purchase low-cost biosimilar drugs without unnecessary delays:

- **Reform clinical efficacy trial requirements:** Lawmakers should remove the requirement that biosimilar makers perform comparative efficacy studies to prove their drug is safe and effective. Instead, the FDA should approve biosimilars based on the results of PK studies and analytical studies.

- **Decrease the exclusivity period for biologics:** Lawmakers should reduce the exclusivity period for biologic drugs instituted by the Biologics Price Competition

and Innovation Act (BPCIA), a provision of the Affordable Care Act. The Fair Care Act (2020) would reduce the exclusivity period for biologics from 12 years to five years. The Trump Administration once proposed decreasing the exclusivity period for biologics from 12 years to ten years as part of the United States-Mexico-Canada Agreement negotiations, and the Obama Administration once proposed a reduction to seven years (Zalewski, et al., 2019).

- **Let pharmacists substitute biologics for biosimilars:** Congress should allow pharmacists to substitute biologics for biosimilars without the need for switching studies. The Biosimilar Red Tape Elimination Act (2023) and the Primary Care and Health Workforce Expansion Act (2023) would empower pharmacists to dispense these important medications.

Conclusion: End Barriers That Stifle Biosimilar Competition

After years of rising prices, it is clear the FDA has failed to approve enough biosimilars to provide robust competition against brand-name biologics. Decades of research show the BPCIA's standards for approving biosimilars do not protect the health and safety of America's patients. Instead, they have worsened the health of families by making biologics increasingly unaffordable and out of financial reach for patients in need.

Patients urgently need solutions from Congress and the executive branch to modernize the FDA's biosimilar approval process. Lawmakers should introduce scientifically sound reforms that maintain high levels of drug safety and efficacy, while also introducing greater biosimilar drug choices. More biosimilar options would increase competition, lower prices, and ensure more families could afford to treat their medical conditions.

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HEALTHCAREDIVE

DIVE BRIEF

PBM practices are keeping consumers from generics savings, white paper finds

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Flickr; Images Money

Dive Brief:

- Generic prescriptions aren't saving U.S. consumers much money, largely due to the practices of pharmacy benefit managers and industry middlemen between drug manufacturers and health plans, according to a new white paper.
- Consumers are overpaying for generic drug prescriptions by as much as 20%, research from the USC Leonard D. Schaeffer Center for Health Policy and Economics found, citing an analysis of Medicare claims. PBM strategies increasing the cost of generics may also be contributing to quality issues and care fragmentation, according to researchers.
- Strategies include copay clawbacks, when copayments paid by commercially insured patients exceed a drug's cost; and spread pricing, when a PBM charges a health insurer a higher price for a drug than what it reimburses a pharmacy. In both cases, PBMs pocket the difference. In addition, formularies often advantage branded drugs over generics, as the branded medicine comes with manufacturer rebates.

Dive Insight:

PBMs say they save money by negotiating down steep pharmaceutical prices. But the middlemen are often fingered as a driver of increasing healthcare spending and are facing increasing scrutiny for their practices from both legislators in Congress and regulators in the Federal Trade Commission.

The new report adds to a growing body of evidence showing that consumers overpay for generics, as "pharmacy benefit managers game opaque and arcane pricing practices to pad profits," the white paper said.

Generics make up more than 90% of prescriptions in the U.S. but just 18% of drug spending. By one estimate, the use of generic and biosimilar drugs in place of their branded equivalents saved the healthcare system $338 billion in 2020 alone.

However, despite generics driving down prices relative to branded drugs, consumers are not benefiting from savings, the white paper said.

"Generics are overlooked when we talk about drug pricing issues in this country," said Erin Trish, co-director of the USC Schaeffer Center, in a statement. "But the same lack of transparency that is causing outrage over high and rising spending on branded drugs is also creating issues in the generic drug space."

Researchers highlighted consolidation as a key issue likely driving the profit-focused practices outlined in the white paper.

The three largest PBMs — which process almost 80% of all retail prescription claims — are all owned by large insurers: CVS Caremark by CVS Health, which owns Aetna; Express Scripts by Cigna; and OptumRx by UnitedHealth Group, which operates the largest private payer in the U.S., UnitedHealthcare.

The white paper estimates that practices like spread pricing and copay clawbacks add up to billions in overpayment. One recent study, also conducted by Trish, found Medicare Part D standalone plans paid $2.6 billion more in 2018 for 184 common generics compared to the cash prices paid by Costco members.

Researchers suggested several policy solutions to deter the practices, including restricting rebate contracting which incentivizes PBMs to prefer brands over generics, and using fixed fees per transaction, rather than fees determined as a share of a drug's price.

Researchers also highlighted the need for increased competition and improved price transparency in the generics industry.

There has been some recent action on the Hill to curb PBM practices, as the FTC reviews industry comments solicited earlier this year on how such strategies effect patients and payers.

Last week, a bipartisan duo of senators introduced legislation that would stop PBMs from clawing back fees or overcharging pharmacies and require PBMs to report more financial data, among other measures.

Appendix B - Paper on medication adherence through the use of compliance packaging.

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Packaging interventions to increase medication adherence: systematic review and meta-analysis

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Abstract

Objective—Inadequate medication adherence is a widespread problem that contributes to increase chronic disease complications and health care expenditures. Packaging interventions using pill boxes and blister packs have been widely recommended to address the medication adherence issue. This meta-analysis review determined the overall effect of packaging interventions on medication adherence and health outcomes. In addition, we tested whether effects vary depending on intervention, sample, and design characteristics.

Research design and methods—Extensive literature search strategies included examination of 13 computerized databases and 19 research registries, hand searches of 57 journal, and author and ancestry searches. Eligible studies included either pill-boxes or blister packaging interventions to increase medication adherence. Primary study characteristics and outcomes were reliably coded. Random-effects analyses were used to calculate overall effect sizes and conduct moderator analyses.

Results—Data were synthesized across 22,858 subjects from 52 reports. The overall mean weighted standardized difference effect size for two-group comparisons was 0.593 (favoring treatment over control), which is consistent with the mean of 71% adherence for treatment subjects compared to 63% among control subjects. We found using moderator analyses that

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interventions were most effective when they used blister packs and were delivered in pharmacies, while interventions were less effective when studies included older subjects and those with cognitive impairment. Methodological moderator analyses revealed significantly larger effect sizes in studies reporting continuous data outcomes instead of dichotomous results and in studies using pharmacy refill medication adherence measures as compared to studies with self-report measures.

Conclusions—Overall, meta-analysis findings support the use of packaging interventions to effectively increase medication adherence. Limitations of the study include the exclusion of packaging interventions other than pill boxes and blister packs, evidence of publication bias, and primary study sparse reporting of health outcomes and potentially interesting moderating variables such as the number of prescribed medications.

Keywords

medication adherence; meta-analysis; intervention; medication compliance

Introduction

Inadequate medication adherence (MA) is a pervasive global hidden epidemic with devastating health and economic consequences[1, 2]. The cost of nonadherence has been estimated at over €25 billion in the European Union and $100 billion yearly in the United States[3–5]. Overall, MA is suboptimal, estimated at around 50%[1, 6–8]. Between 20% and 25% of prescriptions are never filled, and another 20% of prescriptions are filled, but are not consumed due to patient-initiated drug holidays[9]. Rates of MA have not improved over the decades[10, 11]. Considering these findings, it is not surprising that the World Health Organization (WHO) calls poor adherence a “worldwide problem of striking magnitude”[1].

The consistent evidence of widespread inadequate MA, as well as the importance of the issue, has led to considerable research testing diverse interventions to remedy the problem. Packaging interventions have long been recommended[12–17], and several trials have tested various packaging types with inconclusive results. A few small reviews of six to twelve primary studies have attempted to summarize the effectiveness of packaging interventions[12–16, 18]. Very limited meta-analyses have been reported across two, three, and six primary studies[15, 16, 18]. These reviews have been hampered by narrow searches and very small numbers of primary studies. Moderator analysis, which examines the associations between study characteristics and MA behavior outcomes, is a strength of meta-analytic work. Previous reviews have retrieved too few studies to conduct moderator analyses to determine sample, design, and intervention characteristics linked to better MA outcomes.

Primary studies testing packaging interventions have not been adequately synthesized, which seriously impedes research progress and effective practice. This project aimed to provide the most comprehensive integration of scientific knowledge about packaging interventions to increase MA. This meta-analysis addressed the following research questions: 1) What are the overall effects of packaging interventions on MA? 2) Do the effects of packaging interventions on MA outcomes vary depending on intervention characteristics? 3) Do the effects of packaging interventions on MA outcomes vary

depending on study design or sample characteristics? 4) What are the overall effects of packaging interventions on health outcomes?

Methods

We used standard meta-analysis review methods to identify and secure potential studies, assess eligibility, code data from primary study reports, meta-analyze results across studies, and interpret findings[19].

Search Strategies

Multiple search strategies were employed to ensure a comprehensive search, move beyond previous narrow reviews, and limit the bias associated with limited searches[20, 21]. An experienced health sciences reference librarian performed searches in PubMED, MEDLINE, PsychINFO, EBSCO, CINAHL, PQDT, Cochrane Central Trials Register, Cochrane Database of Systematic Reviews, ERIC, IndMed, International Pharmaceutical Abstracts, EBM Reviews - Database of Abstracts of Reviews of Effects, and Communication and Mass Media. Broad search terms were used. For example, the primary MeSH terms upon which searches were constructed were *Patient Compliance* and *Medication Adherence. Patient Compliance* was used to locate studies published prior to 2009 because the term 'medication adherence' was not in MeSH usage until that year. *Medication adherence* (MeSH term) was used to locate studies published after 2008. Other MeSH terms used in constructing search strategies were: *pharmaceutical preparations, dosage forms, drugs, generic, or prescription drugs*. Keywords used in searches were: *medication(s), regimen(s), prescription(s), prescribed, drug(s), pill(s), tablet(s), agent(s), compliant, compliance, adherent, adherence, noncompliant, noncompliance, nonadherent, nonadherence, improve, promote, enhance, encourage, foster, advocate, influence, incentive, ensure, remind, optimize, increase, impact, prevent, address, decrease.* Other potential MA search terms, such as persistence, were not used because they are not MeSH terms and *medication adherence* and *patient compliance* are broader terms. Nineteen research registers were searched (e.g., Research Portfolio Online Reporting Tool). Hand searches were conducted in 57 journals where multiple eligible studies in the parent project were published. Author searches were conducted for authors of more than one eligible primary study in the parent project. Ancestry searches were conducted on all eligible studies and review papers. We retrieved abstracts from forty-eight conferences that contained, or led to, includable reports. Final searching was completed in 2013.

Inclusion Criteria

We included reports of packaging interventions to increase MA among adult subjects. MA refers to the extent to which patient medication-taking behavior is consistent with health care provider recommendations[1, 6].

Packaging interventions provide a physical assembly of medications into an object that indicates the day and/or time medications should be administered[16]. Examples of packaging interventions include professionally prepared single-use sealed containers of medications, which are called blister packs, unit-packaging, unit-of-use systems, unit-of-dose packaging,

and monitored dosage systems in the literature[14–16]. Blister packs provide correct medications in containers because they are filled by professionals. Pill boxes, reusable multi-compartment containers with designated spaces for medications to be consumed at a particular time, are another common type of packaging[16]. Unlike blister packs, pill boxes do not require professional action: they may be filled by patients, informal caregivers, or health care providers. While this may reduce costs, pill boxes may contain incorrect medications because they may be filled by patients or informal caregivers. Both blister packs and pill boxes may be recommended for aging adults with multiple chronic diseases. Possible cognitive limitations in this population could increase the incidence of incorrect medications in pill boxes. Other types of medication container changes such as replacing child-resistant caps, placing medications in envelopes instead of bottles, changing labels on medication containers, or instituting individual electronic medication containers caps which display the last medication administration time, were excluded from this review because they were functionally dissimilar to pill boxes and blister packs.

Studies of incarcerated or institutionalized persons were excluded because of institutional control over medication administration. Subjects with psychiatric (e.g., schizophrenia, major clinical depression) or substance abuse problems (e.g., nicotine, alcohol) were excluded because patients often deliberately decide to omit or cease medications. Contraceptive and sexual dysfunction medications were excluded because they are voluntary medications were patient decisions about consuming medications are expected. Although packaging interventions might be beneficial for these patients, the reasons for poor MA may differ significantly from the typical reasons for inadequate MA among persons with acute and chronic physical diseases. Nutraceuticals were excluded because they are food-focused instead of medication-focused.

Since only studies with adequate data to calculate an effect size (ES) were included, strategies to ensure adequate data were used. For reports without adequate data, author searches were completed to locate other reports about the same sample which might include the necessary information such as a measure of variability. Corresponding authors were contacted to secure ES data when such data were not provided in reports nor found in companion papers. Procedures that meta-analysts use for missing ESs are to exclude the study from the analysis, set the ES to 0 for studies reporting lack of statistically significant effect, estimate possible ESs from studies with sample size and direction of effect information, or estimate the ES magnitude derived from other studies with nonsignificant or significant findings. Using 0 may result in underestimating the ESs and distorting estimates of heterogeneity, if the treatment is effective but the primary study exhibited low statistical power. Imputing values from other studies requires assumptions that may not be justified. We excluded from the meta-analysis studies without sufficient ES information.

Both unpublished and published studies were included to reduce potential publication bias[22, 23]. Small-sample and pre-experimental studies were included[19]. Non-English studies were included if research specialists or investigators were fluent in that language. Studies distributed from 1960 until 2013 were eligible for inclusion. The flow of potential primary studies through the project is displayed in Figure 1.

Data Coding and Evaluation

A coding frame was developed from elements in previous related meta-analyses by this research team, suggestions from MA and meta-analysis experts, and a preview of 50 studies with diverse MA interventions. The coding frame includes source, participant, methodology, and intervention characteristics as well as MA outcome data. Extensive pilot testing was used to fine-tune the coding frame. The year of distribution, dissemination medium (e.g. journal article, dissertation), and presence of funding were recorded as source information. Participant characteristics included gender, age, ethnicity, chronic diseases, cognitive impairment, number of prescribed medications, and whether the subjects were selected because of poor MA.

Intervention characteristics coded included whether the intervention was a pill box or blister pack. For pill boxes, we coded whether the device was given to subjects or if subjects were told to obtain a pill box on their own. We also coded other packaging intervention details including cycle (i.e., duration in days that the current packaging lasts before subjects must obtain additional packages or refill the device) and the number of compartments. We recorded other intervention characteristics, such as information about MA intervention components in addition to the packaging, location of intervention delivery, and the professional background of the interventionist.

We coded a wide variety of aspects of how researchers conducted their studies. Of primary interest were MA data necessary for calculating effect sizes: baseline and outcome means, measures of variability, success rates, and sample sizes. If studies reported multiple MA outcome data, we preferentially selected the data from the most distal time point with the largest number of subjects using the most valid MA measure (e.g., coded pharmacy refill data when self-report data were also available). We noted the type of MA measure as an additional indicator of methodological quality in MA research. In addition, methodological features we coded included sample size, attrition rates, random vs. nonrandom assignment of participants to groups, allocation concealment, data collector masking, intention-to-treat analyses, and days between receiving the intervention and MA outcome measurement. Each attribute was analyzed as a potential moderator variable. This sensitivity analysis was used to determine if findings were robust to variations in methodological quality.

All data were independently coded by two extensively trained coders. Every variable was compared between coders to achieve 100% agreement[24, 25]. A doctorally-prepared coder further verified effect size data. To obtain sample independence, author lists on every study were cross checked with author lists of all other studies to identify and resolve any potentially overlapping samples. Senior authors were contacted when necessary to clarify the uniqueness of samples in their research. When multiple reports about the same sample were located, we kept these ancillary reports and used them to enhance the detail of coding.

Statistical Analysis

Analyses were conducted using Comprehensive Meta Analysis software. The main analyses in this project compared treatment and control groups after interventions. Supplementary analyses examined treatment group pre- versus post-intervention scores. A similar single-

group analysis was conducted for control subjects. Unless otherwise stated, all analyses and results in the report address the treatment versus control post-intervention comparisons.

Data calculations were handled by meta-analytic standardized mean difference (*d*) ES[26]. For treatment versus control comparisons, a standardized mean difference is the difference between treatment group versus control group post-intervention means divided by the pooled standard deviation. For single group ES, the *d* represents the outcome scores minus the baseline scores divided by the baseline standard deviation. A positive *d* reflects more favorable outcomes for treatment groups or following interventions. The ESs were weighted by the inverse of variance to give larger sample studies more influence and adjust for bias[27]. To acknowledge that ESs vary both from subject-level sampling error and other sources of study-level error such as participant or method variations, random-effect models were used to calculate ESs[26]. ES confidence intervals were constructed. Homogeneity was assessed using a conventional heterogeneity statistic (*Q*) and computing the I^2 index of heterogeneity beyond within-study sampling error[26]. Since clinical and statistical heterogeneity is common in behavior change research[28], the expected heterogeneity was managed in four ways. Random-effects models were used for analyses because they take into account heterogeneity beyond that explained by moderator analyses. Potential heterogeneity was explored with moderator analyses. Heterogeneity was quantified, along with the location parameter. Finally, the interpretation of findings considered the context of discovered heterogeneity.

Potential outliers were detected by examining the externally standardized residuals of ESs. Potential publication bias was explored using funnel plots of ES against sampling variance[26]. Larger samples typically yield less sampling error in observed ESs. Observed ESs should be symmetrical around the overall average ES regardless of sample size in the absence of publication bias. Begg's and Egger's tests were used to assess publication bias.

We conducted exploratory moderator analyses to examine the association between study characteristics and ESs[26]. Continuous moderator analyses consisted of testing effects through an unstandardized regression slope, which is a meta-analytic analogue of regression. Dichotomous moderators were examined by testing effects of between-group heterogeneity statistics ($Q_{between}$), which is a meta-analytic analogue of ANOVA.

Results

We identified 52 eligible primary study reports with a total of 22,858 subjects[29–80]. Eight additional articles reported on the same studies and were used as companion papers for additional coding information[81–88]. One Spanish language study was included[58]. One study was included by using ESs data obtained directly from the author because the published article lacked sufficient ES data[47]. These reports yielded ES data for 51 comparisons for treatment vs. control at outcome, 19 treatment pre- vs. post-intervention, and 7 control baseline vs. outcome comparisons.

Primary Study Characteristics

Most comparisons were disseminated as journal articles (*k*=50); two dissertation comparisons were included (*s*=number of reports, *k*=number of comparisons). The numbers

of studies that have examined packaging interventions have increased in recent years. Nine reports were disseminated before 1990, and 31 were disseminated in 2000 or after. Table 1 shows descriptive statistics across the all primary studies. Most studies (*k*=32) received funding. The median of mean sample size was 104.5 subjects. Attrition was modest and similar between treatment (median=3.45%) and control (2.74%) groups. The mean length of follow-up was 12 weeks, with a range from 1 to 52 weeks. The median value for mean age was 54.4 years. Among the studies that reported gender distribution (*s*=33), almost half the subjects were women. Ethnicity was very poorly reported; only four comparisons provided this information. Among the seven studies that reported the mean number of medications prescribed to subjects, the median of mean value was 5.94 medications. Length of follow-up was poorly reported, it ranged from one week to one year.

Tables 2 and 3 contain information about individual treatment vs. control comparisons which were included in the meta-analysis. Among the two-group comparisons, 28 were conducted in North America, 9 in Europe, 5 in Asia, 4 in Africa, and 2 in Australia. No studies conducted in South America were retrieved. Eleven studies included samples with diverse chronic diseases. Twenty studies focused on infectious diseases, including eight studies with HIV subjects. Six of the nine studies focused on cardiovascular populations recruited samples with hypertension.

Most interventions targeted MA behavior exclusively, ten interventions focused on multiple health behaviors. Packaging interventions were combined with other MA intervention components in 33 comparisons.

Risk of bias was poorly reported in many primary studies. For example, 36 comparisons did not report whether allocation was concealed. Data collector masking is a common risk of bias measure which could be difficult to implement in this research, 38 studies did not report masking data collectors. Most studies randomly assigned subjects to treatment and control conditions, 14 did not.

Overall Effects of Packaging Interventions on Medication Adherence Outcomes

Overall MA ESs are presented in Table 4. We calculated ESs for 48 treatment-vs.-control-group outcome comparisons of 21,944 subjects. The overall standardized mean difference ES was 0.593. For two-group comparisons, three ESs were excluded as outliers (the ES with outliers included was 0.757). The positive ES documents that treatment subjects had significantly better MA outcomes than were reported for control subjects. The 0.593 ES is consistent with the finding of 71% adherence rate among treatment subjects compared to 63% adherence rate among control subjects. The forest plot in Figure 2 includes ES for individual studies which compared treatment and control groups.

Subgroup analyses were conducted for primary studies that reported continuous outcome data and those that reported dichotomous outcome data[16]. The overall ES for continuous data was 1.160. The overall ES for dichotomous data studies was significantly smaller at 0.535.

We calculated ESs for 19 treatment group pre-post comparisons of 1,757 subjects and for 7 control pre-post comparisons with 844 subjects. No outliers were found for treatment or control group pre-post comparisons. For treatment baseline vs. outcome comparisons, the overall ES was 0.540. In contrast to treatment subjects, control group subjects did not have improved MA outcomes from participating in studies, the overall ES was 0.002, which was not significantly different from zero.

Treatment vs. control and treatment pre- vs. post-intervention comparisons were significantly heterogeneous (based on Q statistics) with I^2 from 79 to 92. The funnel plots of ES vs. sampling variance suggested possible evidence of publication bias among treatment vs. control group comparisons which was confirmed with Begg's test ($p = .021$) but not by the Egger's test ($p = .324$). The funnel plot for treatment group pre-post comparisons displayed evidence of publication bias which was confirmed by the Begg's test ($p = .010$) but not by the Egger's test ($p = .235$). No publication bias was evident for the control group pre-post comparisons as confirmed by both the Begg's ($p = .368$) and Egger's ($p = .529$) tests. (Funnel plots are available from the corresponding author.)

Moderator Analyses

Tables 5 and 6 display dichotomous and continuous moderator analyses. Many additional potential moderators could not be analyzed because they occurred too infrequently or were poorly reported (e.g., ethnicity). Moderator analyses are exploratory and should be interpreted with caution given the small number of studies in some analyses.

Intervention Moderators—Studies that used blister packs reported significantly larger ESs (0.802) than studies that used pill boxes (0.384). There was no difference in ESs between studies that gave pill boxes to subjects and studies where interventionists merely recommended that subjects acquire a pill box. Medication refill cycle was recorded as the number of days before participants would be required to refill pill boxes or obtain new blister packs. Studies with longer cycles reported slightly lower MA ES than studies with shorter cycles ($\hat{\beta_1} = -0.006$).

Packaging was the sole intervention in 15 studies while other researchers ($k = 33$) combined packaging with other MA interventions. The ESs did not differ between trials with exclusively packaging interventions and studies with packaging as one component of multiple MA interventions. None of the studies combined packaging with telemedicine interventions.

ESs were significantly smaller for studies with physician intervention delivery (0.269) as compared to interventions not delivered by physicians (0.641). The same pattern was present for nurse delivered interventions; studies with nurse interventionists had significantly smaller ESs (0.295) than studies with interventions not delivered by nurses (0.661). While the trend for interventions to be more effective when delivered by pharmacists (0.782) as compared to interventions without pharmacists (0.475) did not achieve statistical significance, interventions delivered in pharmacies reported significantly larger ESs (0.945) than interventions administered elsewhere (0.485). Interventions were less effective when delivered while patients were hospitalized (0.194) than when not delivered in an inpatient

setting (0.704). ESs were also smaller for interventions delivered in ambulatory care settings (0.334) than for interventions delivered elsewhere such as subjects' homes or pharmacies (0.710).

Report and Sample Moderators—The ESs did not differ between published and unpublished studies. Studies completed more recently reported slightly larger ESs than studies distributed earlier ($\hat{\beta_1}$ =0.018). The ESs did not differ between studies conducted in North America and studies conducted in Asia, Australia, Africa or Europe. Neither the presence of funding for the research nor the source of funding (for-profit vs. not-for-profit) was a significant moderator.

Studies with younger subjects reported larger ESs than studies with older samples ($\hat{\beta_1}$ = −0.022). The reported socio-economic status of participants was unrelated to ESs. Studies with more female subjects reported slightly larger ESs than studies with fewer female participants ($\hat{\beta_1}$ = 0.006). Interventions were much less effective in samples with cognitive impairment (0.074) as compared to samples without reported cognitive impairment (0.649). The ES difference between samples recruited because of medication nonadherence (0.835) and studies that did not target nonadherent subjects (0.568) was not statistically significant. The number of chronic illnesses and prescribed medications were too infrequently reported for moderator analyses.

Potential Sources of Bias: Design and Methods Moderators—Studies with larger sample sizes reported slightly larger ESs than studies with smaller samples. Allocation of subjects to treatment groups, individually randomized vs. some other allocation, was not related to ESs. The difference between ESs of studies with allocation concealment (0.276) and studies without concealment (0.636) did not achieve statistical significance. Studies with masked data collectors reported significantly smaller ESs (0.289) than studies that did not report masking (0.625). There was no difference in ESs between studies that reported intention-to-treat analyses and those that did not report such analyses.

Studies with lower attrition rates reported significantly higher MA ESs ($\hat{\beta_1}$ = −0.795). Studies with longer follow-up, days between completion of the intervention and MA outcome measurement, reported slightly higher MA ES ($\hat{\beta_1}$ = 0.004).

Primary studies reported either continuous data (e.g., means and measures of variability) or dichotomous data such as success rates. Studies that reported continuous data outcomes had significantly larger ESs (1.160) than studies that reported dichotomous outcomes (0.535). The largest ESs were reported among studies that measured MA with pharmacy refills (1.044) as compared to studies with pill counts (0.628), drug metabolites (0.418), and self-report (0.247). No studies used electronic monitoring to assess MA.

Overall Effects of Packaging Interventions on Health Outcomes

Health outcomes findings should be considered exploratory and interpreted with caution given the small number of comparisons for each health outcome (see Table 4). ESs ranged from 0.102 to 0.591: quality of life (ES=0.226), diastolic blood pressure (ES=0.318), systolic blood pressure (ES=0.416), knowledge (ES=0.456), mood (ES=0.591), and HIV

viral load (ES=0.102). ESs were significantly heterogeneous for quality of life and both systolic and diastolic blood pressure.

Discussion

The completed meta-analyses of 48 comparisons between treatment groups receiving packaging interventions and control groups without packaging interventions provided valuable new information not available in the previous meta-analyses of two to six primary studies[15, 1618]. The moderate effect sizes that we found document that packaging interventions significantly improve MA.

There are several reasons packaging interventions may be effective at producing good MA. Packaging interventions provide a mechanism for patients to self-monitor medication consumption. Difficulty remembering whether a certain dose had been consumed may be an important aspect of forgetting medications: the most often patient-reported reason for nonadherence[14, 16]. Packaging interventions also allow third parties, such as informal and home-visiting formal caregivers, to monitor dose removal from the device[12].

Packaging interventions may be especially effective for medications that should be consumed at different times of day[16], because patients do not need to make decisions about which medications to consume at different times. The number of prescribed medications has been positively linked to lack of MA[16], and packaging interventions may be useful for this particular issue, because patients do not need to open multiple containers for each administration. Unfortunately, primary studies rarely reported the number of prescribed medications, so no moderator analyses could be conducted on this possibly relevant variable. Future research should examine possible interactions between the number of medications and effectiveness of packaging interventions.

Most MA interventions, such as pharmacist counseling, are time limited[16]. Pill boxes are a more persistent intervention than programs that are designed to last a discrete period of time[17]. The moderator analyses of this study documented improved MA over time using packaging interventions. This contrasts with MA behavior following most MA intervention with a reveal a pattern of diminished MA over time. Since persisting MA is important to achieve positive health outcomes, this is an important benefit of packaging interventions. Future research should continue follow-up months or years after interventions to determine long-term benefits from packaging interventions.

Another benefit of pill boxes is that they do not require much health care provider labor, unless they are filled by providers during home or clinic visits. In contrast, blister packs require pharmacist effort[17]. The low cost of pill box interventions make them especially attractive for widespread use.

Packaging interventions have limitations. Packaging interventions can be useful for non-intentional nonadherence, but not for intentional nonadherence[12, 16]. Some packaging may not be child resistant[17]. A further limitation is that pill boxes and blister packs do not provide feedback to tell patients the time when previous doses were consumed. Packaging

interventions may be less useful when patients make voluntary decisions about consuming medications, such as for some psychiatric and substance abuse medications.

The exploratory moderator analyses showed that blister pack interventions were significantly more effective than pill boxes. Because blister packs are prepared by pharmacists, they are more likely to contain the appropriate medications than pill boxes, which are often filled by patients or caregivers. We noted that the observed pattern of interventions being the most effective when delivered in pharmacies (as compared to in-patient or ambulatory care settings) by pharmacists (as compared to physicians and nurses) was not entirely due to pharmacists preparing blister packs; 12 of the comparisons with pharmacist interventionists did not involve blister packs and 8 of the pharmacist-delivered interventions were not located in pharmacies.

Although blister packs are more expensive than pill boxes, because they require pharmacist activity and special technology, the gains in MA may make such expenditure reasonable in light of reducing health care costs arising from disease complications. Unfortunately, none of the packaging primary studies provide data about cost-effectiveness. This is an important limitation in existing primary research. It is crucial that future research examine the cost-benefit of using these interventions. Without such cost-benefit information, policy changes will be difficult to secure.

The blister pack interventions included in this meta-analysis involved medications dispensed by pharmacists in blister packs, rather than medications sold in blister packs. Regulations vary by country regarding the approvals needed for pharmaceutical manufacturers to utilize blister packs, as opposed to other forms of medication packaging. In the U.S., manufacturers must have packaging methods approved by the Food and Drug Administration as part of new drug applications, or as an equivalent change to approved packaging methods[89, 90]. The European Union has guidelines for plastic packaging; blister packs are regulated separately by each country[91]. In the U.S., repackaged blister packs are used almost exclusively in long-term care settings, while in other countries such practices are more common.

We found two surprising results analyzing pill box interventions. Pill box interventions in which pill boxes were just suggested to the patient were as effective as interventions that actually provided them to patients. Other studies found that patients are receptive to using pill boxes as descriptive research has documented that 35% to 77% of surveyed adults use pill boxes[47, 9293]. Also, MA interventions that exclusively used packaging interventions were as effective as interventions that combined packaging with other MA interventions. The effectiveness and very low cost of recommending pill boxes to patients are sufficient rationale for health care providers to incorporate this minute step into their treatment programs.

We did find circumstances when packaging interventions were not effective. Packaging interventions did not help MA in in primary research studies among patients with documented cognitive impairments as much as in studies that reported samples without cognitive limitations. Perhaps packaging interventions do not provide stimulus to take medications for cognitively impaired adults. Cognitive impairment could also affect

accuracy in filling pill boxes. Older subjects also benefited less from packaging interventions than younger subjects. One possible explanation for this finding could be the increased number of medications among older adults and the additional burden that a heavy medication load imposes on MA. Unfortunately, too few studies reported the numbers of medications to explore this possibility through moderator analyses. It is also possible that opening blister packs may be an obstacle among older subjects with greater dexterity problems.

Common methodological weaknesses in primary research on packaging interventions include the infrequent application of steps such as random allocation to groups, concealed allocation, masked data collectors, and intention-to-treat analyses. Poor reporting, such as baseline MA values, prevented analyses controlling for baseline values or determining if baseline MA differed between pill boxes and blister packs. The moderator analyses revealed some lower ESs among studies with stronger methodological features. MA outcome measurement using self-report is a significant methodological weakness associated with significantly lower ES outcomes, leading us to think that intervention effectiveness may be masked by imprecise measurement of MA. Overall, the largest ESs among these primary studies was for research using pharmacy refill data to assess MA. Because this study focused on packaging interventions, electronic medication cap monitoring device data were not available for measuring MA[94]. In the future, new packaging technology, such as devices that accept blister packs, use an audible cue for dose administration, record administration, and display when previous pills were administered, will provide alternative MA interventions and measures[95].

MA is not a unitary construct. Aspects of MA, such as initiation, implementation, and persistence, may be influenced by different MA adherence interventions. Lack of conceptual clarity may have contributed to the scant primary research which has evaluated different aspects of MA. The primary studies in this project examined implementation as the proportion of prescribed drugs which were consumed. As future primary research examines different dimensions of MA, meta-analyses may find variations in effectiveness for initiation, implementation, and persistence.

MA outcomes reported as a dichotomous variable (i.e., success rates of treatment and control groups) is another significant weakness in the MA primary research. In studies that reported dichotomous outcomes, continuous data about MA behavior were recorded and researchers categorized individual subjects as adherent or non-adherent. Significant information about the size of the effect is lost when these continuous data are transformed to dichotomous data. Furthermore, a criterion value for acceptable levels of MA has not been established for most medications, so establishing a cut-off point for success is somewhat arbitrary. Moderator analyses confirmed a larger ES for studies that reported continuous data as compared to those that reported dichotomous data. Future primary research should include continuous data MA outcomes.

This meta-analysis encountered a few factors that could have limited the robustness of the results. We were unable to assess potentially interesting variables that were poorly reported, such as the numbers of medications and chronic illnesses. Another limitation of the project

was the dearth of primary studies with health outcomes. Although all of the present health outcomes had overall positive ESs, the scant amount of primary study data limits confidence in these findings. Additional reporting of intermediate and clinical health outcomes in MA research would be very valuable[14]. Also, although extensive searching was completed, it is possible the investigators missed some potentially eligible studies. This study used a specific operational definition of packaging interventions consistent with extant research. Other aspects of interventions related to packaging, such as labeling, were not examined.

This meta-analysis is the most comprehensive quantitative synthesis of packaging interventions to improve MA to date. Interventions were moderately effective across most populations. Blister packs were more effective than pill boxes, although pill boxes remain an attractive intervention due to low cost. Future research should include pharmacy refill or other objective measures of MA over self-report data. Furthermore, studies should report outcomes as continuous data instead of converting continuous data to dichotomous outcomes. Finally, we recommend that more MA studies report health and health care cost outcomes to fully evaluate the importance of MA interventions.

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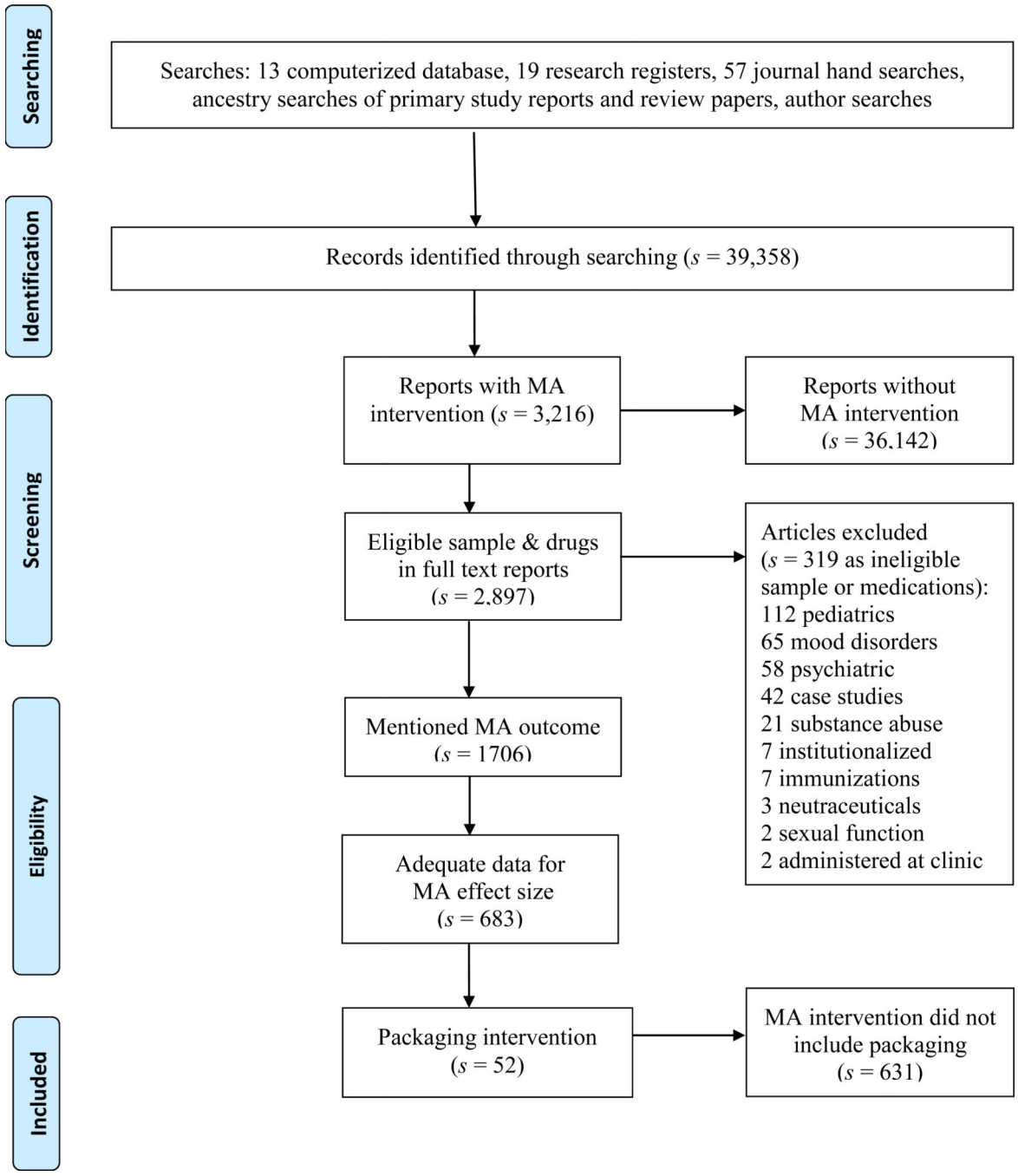

Figure 1.
Flow diagram

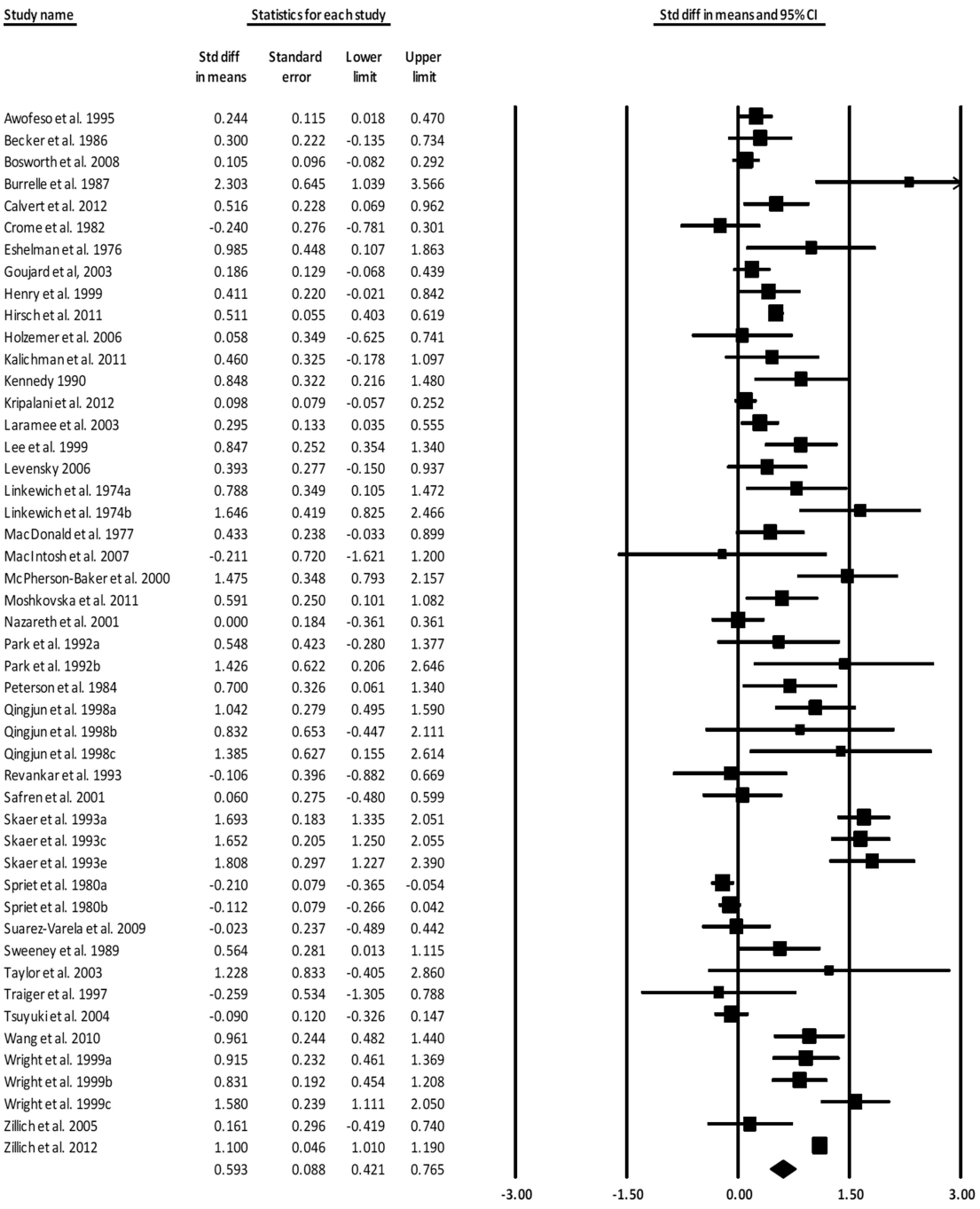

Figure 2.
Forest plot for treatment vs. control comparisons

Table 1

Characteristics of Primary Studies Included in Medication Adherence Meta-analyses

Characteristic	*s*	Min	Q_1	*Mdn*	Q_3	Max
Mean age (years)	31	26.8	43.5	54.4	69.85	85
Total post-test sample size per study	48	16	53	104.50	183.75	12969
Percentage attrition treatment group	32	0	0	3.45	20.10	81.36
Percentage attrition control group	32	0	0	2.74	24.31	68
Percentage female	36	0	27.28	43.5	64	92
Percentage ethnic minority	4	4.6	24.4	59.55	89.2	92.5
Mean number of prescribed medications	7	2.04	4.45	5.94	6.00	8.09

Note. Includes all studies that contributed to primary analyses at least one effect size for any type of comparison.

s=number of reports providing data on characteristic; Q_1=first quartile, Q_3=third quartile.

Table 2

Characteristics and Quality Indicators of Pill Box Intervention Primary Studies.

Study & location	Sample	Random assignment	Allocation concealed	Bundled intervention	Behavior target	Masking	Attrition	Intention to treat	Adherence measure
Bosworth et al. (2008) North America	N = 636 hypertension	yes	NR	yes	MA +	NR	0%	yes	self-report
Burrelle et al. (1987) North America	N = 16 hypertension	yes	NR	yes	MA	NR	0%	no	pill counts
Calvert et al. (2012) North America	N = 143 cardiac diseases	yes	yes	yes	MA	yes	27%	no	pharmacy refills
Goujard et al. (2003) Europe	N = 367 HIV	no	NR	yes	MA	NR	35%	no	self-report
Henry et al. (1999) Australia	N = 119 infections	yes	NR	yes	MA	NR	2%	yes	combined measures
Holzemer et al. (2006) North America	N = 240 HIV	yes	NR	yes	MA +	no	25%	no	combined measures
Kalichman et al. (2011) North America	N = 40 HIV	yes	yes	yes	MA	yes	3%	yes	self-report
Kennedy (1990) North America	N = 65 chronic diseases	yes	NR	yes	MA	yes	34%	no	pill counts
Kripalani et al. (2012) North America	N = 862 chronic diseases	yes	no	yes	MA	yes	25%	yes	self-report
Laramee et al. (2003) North America	N = 287 heart failure	yes	NR	yes	MA +	NR	20%	no	self-report
Lee et al. (1999) North America	N = 125 infections	yes	yes	yes	MA	NR	0%	yes	pill counts
Levensky (2006) North America	N = 54 HIV	yes	NR	yes	MA +	NR	2%	yes	pill counts
MacDonald et al. (1977) Europe	N = 74 chronic diseases	no	NR	yes	MA	NR	0%	no	combined measures
MacIntosh et al. (2007) North America	N = 25 cancer	yes	NR	no	MA	NR	4%	no	pill counts
McPherson-Baker et al. (2000) North America	N = 42 HIV	no	NR	yes	MA	NR	0%	no	pharmacy refills
Moshkovska et al. (2011) Europe	N = 84 gastrointestinal	yes	yes	yes	MA	NR	0%	yes	drug level
Nazareth et al. (2001) Europe	N = 362 chronic diseases	yes	NR	yes	MA	yes	NR	no	self-report
Park et al. (1992) North America	N = 31 chronic diseases	yes	NR	no	MA	NR	0%	no	combined measures
Park et al. (1992) North America	N = 31 chronic diseases	yes	NR	no	MA	NR	0%	no	combined measures
Peterson et al. (1984) Australia	N = 27 epilepsy	yes	NR	yes	MA	NR	NR	no	drug level
Saafren et al. (2001) North America	N = 56 HIV	no	NR	yes	MA	NR	5%	no	self-report
Suarez-Varela et al. (2009) Europe	N = 182 chronic diseases	yes	NR	no	MA	NR	0%	no	self-report
Sweeney et al. (1989) Europe	N = 103 chronic diseases	no	no	yes	MA	no	34%	no	pill counts
Taylor et al. (2003) North America	N = 81 chronic diseases	yes	NR	yes	MA	NR	15%	no	self-report
Traiger et al. (1997) North America	N = 41 organ transplant	no	NR	yes	MA	NR	12%	no	self-report
Tsuyuki et al (2004) North America	N = 276 heart failure	yes	NR	yes	MA +	NR	0%	yes	pharmacy refills

Study & location	Sample	Random assignment	Allocation concealed	Bundled intervention	Behavior target	Masking	Attrition	Intention to treat	Adherence measure
Wang et al. (2010) Asia	N = 116 HIV	yes	NR	yes	MA +	NR	16%	no	self-report
Zillich et al. (2005) North America	N = 125 hypertension	no	NR	yes	MA +	NR	6%	no	self-report

NR: not reported

Some reports contained multiple comparisons of different treatment groups compared to control groups.
Bundled interventions include packaging plus other medication adherence enhancing interventions.
Behavioral target: MA studies focused exclusively on MA. MA + studies targeted MA and other health behaviors such as diet, exercise, etc.
Masking refers to masking of data collectors regarding group assignment.
Combined MA measure indicates primary studies that reported MA outcomes from combined measures. Conn et al. did not combine measures.

Table 3

Characteristics and Quality Indicators of Blister Pack Intervention Primary Studies included in Meta-Analysis.

Study & location	Sample	Random assignment	Allocation concealed	Bundled intervention	Behavior target	Masking	Attrition	Intention to treat	Adherence measure
Awofeso et al. (1995) Africa	N = 294 infections	no	NR	yes	MA	NR	0%	no	drug level
Becker et al. (1986) North America	N = 171 hypertension	yes	NR	no	MA	NR	8%	no	pill counts
Crome et al. (1982) Europe	N = 78 chronic diseases	yes	NR	no	MA	NR	NR	no	pill counts
Eshelman et al (1976) North America	N = 100 hypertension	yes	NR	no	MA	NR	35%	no	drug level
Hirsch et al. (2011) North America	N = 2234 HIV	no	NR	yes	MA	NR	0%	no	pharmacy refills
Linkewich et al. (1974) North America	N = 46 infections	yes	NR	yes	MA	NR	NR	no	pill counts
Linkewich et al. (1974) North America	N = 51 infections	yes	NR	yes	MA	NR	NR	no	pill counts
Qingjun et al. (1998) Asia	N = 342 malaria	yes	NR	no	MA	NR	0%	no	self-report
Qingjun et al. (1998) Asia	N = 59 malaria	yes	NR	no	MA	NR	0%	no	tracers
Qingjun et al. (1998) Asia	N = 65 malaria	yes	NR	no	MA	NR	0%	no	tracers
Revankar et al. (1993) Asia	N = 189 infections	no	NR	no	MA	NR	0%	no	drug level
Skaer et al. (1993) North America	N = 163 hypertension	yes	NR	yes	MA	NR	0%	no	pharmacy refills
Skaer et al. (1993) North America	N = 131 type 2 diabetes	yes	NR	yes	MA	NR	0%	no	pharmacy refills
Skaer et al. (1993) North America	N = 64 hypertension	yes	NR	yes	MA	NR	0%	no	pharmacy refills
Spriet et al. (1980) Europe	N = 842 neurological	yes	yes	no	MA	NR	0%	no	pill counts
Spriet et al. (1980) Europe	N = 833 neurological	yes	yes	yes	MA	NR	0%	no	pill counts
Wright et al. (1999) Africa	N = 143 STD	no	no	no	MA +	no	NR	no	pill counts
Wright et al. (1999) Africa	N = 162 STD	no	no	no	MA +	no	NR	no	pill counts
Wright et al. (1999) Africa	N = 142 STD	no	no	no	MA +	no	NR	no	pill counts
Zillich et al. (2012) North America	N = 12969 chronic diseases	no	NR	yes	MA	NR	0%	yes	pharmacy refills

NR: not reported

Some reports contained multiple comparisons of different treatment groups compared to control groups.
Bundled interventions include packaging plus other medication adherence enhancing interventions.
Behavioral target: MA studies focused exclusively on MA. MA + studies targeted MA and other health behaviors such as diet, exercise, etc.
Masking refers to masking of data collectors regarding group assignment.

Table 4

Random-Effects Medication Adherence and Health Outcome Estimates and Tests

	k	Effect size	p (ES)	95% Confidence interval	Standard error	I^2	*Q*	p (*Q*)
Medication Adherence Outcomes								
Treatment vs. control all studies[a]	48	0.593	<.001	0.421, 0.765	.088	91.940	583.090	<.001
Treatment vs. control continuous data studies	18	1.160	<.001	0.699, 1.621	.235	96.186	445.729	<.001
Treatment vs. control dichotomous data studies	33	0.535	<.001	0.327, 0.742	.106	92.052	402.636	<.001
Treatment subjects pre- vs. post-comparisons	19	0.540	<.001	0.374, 0.705	.084	79.338	87.117	<.001
Control subjects pre- vs. post-comparisons	7	0.002	.995	−0.181, 0.184	.093	49.981	11.995	.062
Health Outcomes[b]								
Quality of life	5	0.226	.168	−0.112, 0.645	.193	80.502	20.515	<.001
Diastolic blood pressure	5	0.318	.159	−0.125, 0.762	.226	86.951	30.653	<.001
Systolic blood pressure	4	0.416	.092	−0.068, 0.900	.247	86.335	21.954	<.001
Knowledge	3	0.456	.082	−0.058, 0.970	.262	72.843	7.364	.025
Mood	2	0.591	.011	0.135, 1.047	.233	46.093	1.855	.173
HIV viral load	2	0.102	.476	−0.178, 0.381	.143	15.921	1.189	.275

k denotes number of comparisons, *Q* is a conventional homogeneity statistic, I^2 is the percentage of total variation among studies' observed ES due to heterogeneity.

[a]Three comparisons were excluded as outliers. The overall effect size with inclusion of outliers was .757 (SE = .099, CI: .563, .952).

[b]Health outcomes were calculated for treatment vs. control comparisons.

Table 5

Dichotomous Moderator Results for Medication Adherence: Treatment vs. Control at Outcome

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Report Moderators					
Publication status				0.000	.996
Published articles	46	0.592	0.090		
Dissertations	2	0.591	0.225		
Location of primary research				2.493	.114
Europe, Asia, Africa, Australia	20	0.444	0.113		
North America	28	0.699	0.115		
Presence of funding for research				2.024	.155
Funded	32	0.655	0.101		
Unfunded	16	0.420	0.131		
Source of funding for research				1.672	.196
Funding from for-profit source	8	0.948	0.257		
Funding from not-for-profit source	22	0.583	0.117		
Research Methods Moderators					
Allocation to treatment groups				0.003	.958
Randomization of individual subjects	34	0.595	0.102		
Subjects not individually randomized	14	0.586	0.132		
Allocation concealment				3.807	.051
Allocation concealed	6	0.276	0.161		
Did not report allocation concealed	42	0.636	0.090		
Data collector masking				4.088	.043
Data collectors masked to group assignment	5	0.289	0.136		
Did not report data collectors masked to group assignment	43	0.625	0.096		

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Intention-to-treat approach				0.804	.370
Reported intention-to-treat approach	9	0.429	0.210		
Did not report intention-to-treat approach	39	0.636	0.097		
Outcome data					
Continuous outcome data in primary report	18	1.160	0.235		
Dichotomous outcome data in primary report	33	0.535	0.106		
Medication adherence measure: pharmacy refill				7.522	.006
Pharmacy refill data	8	1.044	0.201		
Study did not use pharmacy refill data	40	0.455	0.075		
Medication adherence measure: pill count				0.069	.792
Pill count data	15	0.628	0.167		
Study did not use pill counts to measure medication adherence	33	0.577	0.100		
Medication adherence measure: drug metabolite				1.167	.280
Drug metabolite data	5	0.418	0.149		
Study did not use drug metabolite data	43	0.609	0.095		
Medication adherence measure: self-report				11.692	.001
Self-report data	12	0.247	0.080		
Study did not use self-report to measure medication adherence	36	0.715	0.111		
Sample Characteristic Moderators					
Sample socio-economic status				0.388	.533
Reported low socio-economic status	6	0.737	0.245		
Did not report low socio-economic status	42	0.574	0.093		
Sample with cognitive impairment				15.682	<.001
Reported subjects had cognitive impairment	5	0.074	0.115		
Did not report cognitively impaired subjects	43	0.649	0.088		
Sample selected for poor medication adherence				0.719	0.396

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Reported sample selected for poor medication adherence	6	0.835	0.301		
Did not report targeting subjects with poor medication adherence	42	0.568	0.093		
Intervention Feature Moderators					
Pill boxes vs. blister packs				6.255	.012
Pill boxes	28	0.384	0.072		
Blister packs	20	0.802	0.151		
Packaging recommended to patients vs. given to patients				0.300	.584
Recommended to patients	6	0.379	0.153		
Given to patients	17	0.483	0.112		
Intervention exclusively packaging vs. other interventions				0.019	.890
Medication intervention exclusively packaging	15	0.573	0.192		
Intervention included packaging and other strategies	33	0.602	0.101		
Interventionist: physician				5.992	.014
Physician interventionist	9	0.269	0.121		
Study did not report physician interventionist	39	0.641	0.093		
Interventionist: pharmacist				3.126	.077
Pharmacist interventionist	18	0.782	0.146		
Study did not report pharmacist interventionist	30	0.475	0.095		
Interventionist: nurse				4.734	.030
Nurse interventionist	10	0.295	0.135		
Study did not report nurse interventionist	38	0.661	0.101		
Intervention location: inpatient				13.930	<.001
Intervention delivered while subjects was an inpatient	10	0.194	0.089		
Study did not report inpatient location	38	0.704	0.104		
Intervention location: ambulatory care clinic				6.838	.009
Intervention delivered in ambulatory care clinic	19	0.334	0.095		

Moderator	*k*	Effect size	Standard error	$Q_{between}$	*p* ($Q_{between}$)
Study did not report clinic as location for intervention	29	0.710	0.108		
Intervention location: pharmacy				4.326	0.038
Intervention delivered in pharmacy	11	0.945	0.103		
Study did not report intervention delivered in pharmacy	37	0.485	0.196		

k denotes number of comparisons, effect size is standardized mean difference, *Q* is a conventional homogeneity statistic.

Table 6

Continuous Moderator Results for Medication Adherence: Treatment vs. Control at Outcome

Moderator	*k*	Slope	Standard Error	Tau^2	Q_{model}	p (slope)
Report Moderator						
Year of publication	48	0.018	0.002	.253	100.976	<.001
Method Moderators						
Sample size	48	<.001	0.000	.209	217.352	<.001
Attrition proportion	32	−0.795	0.202	.237	15.466	<.001
Days between intervention completion and outcome measurement	24	0.004	0.000	.276	99.876	<.001
Sample Attribute Moderators						
Age	31	−0.022	0.002	.207	90.021	<.001
Percent women	36	0.006	0.001	.263	21.015	<.001
Intervention Feature Moderator						
Cycle (days when subjects must take action to refill/receive packaging)	28	−.0.006	0.003	.518	5.985	.014

k denotes number of comparisons, *Q* is a conventional homogeneity statistic, Tau^2 is the between-study variance.