

Improving Adherence to Therapy and Clinical Outcomes While Containing Costs: Opportunities From the Greater Use of Generic Medications: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians

Niteesh K. Choudhry, MD, PhD; Thomas D. Denberg, MD, PhD; and Amir Qaseem, MD, PhD, MHA, for the Clinical Guidelines Committee of the American College of Physicians

Description: The discrepancy between health care spending and achieved outcomes in the United States has fueled efforts to identify and address situations where unnecessarily expensive therapies are used when less costly, equally effective options are available. The underuse of generic medications is an important example.

Methods: A literature review was conducted to answer 5 questions about generic medications: 1) How commonly are brand-name medications used when a generic version is available? 2) How does the use of generic medications influence adherence? 3) What is the evidence that brand-name and generic medications have similar clinical effects? 4) What are the barriers to in-

creasing the use of generic medications? 5) What strategies can be used to promote cost savings through greater generic medication use? This article was reviewed and approved by the American College of Physicians Clinical Guidelines Committee.

Best Practice Advice: Clinicians should prescribe generic medications, if possible, rather than more expensive brand-name medications.

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For author affiliations, see end of text.

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Per capita spending in the United States is higher than in any other country without correspondingly high performance on many measures of health care quality (1). Efforts to maximize the value of our health care dollars have focused on situations where expensive therapies are used when less costly, equally effective options are available. The underuse of generic medications is an important example. Prescription drugs now account for more than \$325 billion in annual spending in the United States (2) and play a central role in the management of chronic disease, yet physicians and other providers frequently treat patients with more expensive brand-name products even when equally effective, well-proven, and less expensive generic therapies are available (3).

The purpose of this article is to help guide inter-nists and other clinicians in making high-value, cost-conscious decisions about the use of generic drugs. This review sought to address 5 questions: 1) How commonly are brand-name medications used when a generic version is available? 2) How does the use of generic medications influence adherence? 3) What is the evidence that brand-name and generic medications have similar clinical effects? 4) What are the barriers to increasing the use of generic medications? 5) What strategies can be used to promote cost savings through greater generic medication use?

METHODS

The research presented was identified with a Google Scholar literature search conducted in 2015. For each of the 5 questions, 5 “key articles” that provided high-quality, relevant data (see the **Appendix Table**, available at www.annals.org) were identified with input from 3 other investigators who had conducted research on generic medications (see the Acknowledgment). For each key article, 100 “related articles” were identified by using this functionality in Google Scholar, resulting in a total of 2500 potentially relevant citations that were reviewed. From these, articles were included if they provided original empirical data that were directly relevant to the key question; in addition, the reference lists of the selected articles were reviewed for other potentially relevant studies. Studies that did not provide empirical data or that reported only pharmacokinetic or pharmacodynamic differences between agents without any clinical outcome data were excluded. In addition, the follow-on versions of biologic drugs (“biosimilars”) were excluded from this review because of their clinical and regulatory complexity and

See also:

Summary for Patients I-28

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the relatively limited evidence about their use. As such, this article is intended to provide practical advice based on the best available evidence about traditional “small-molecule” pharmaceuticals.

The target audience for this article is all clinicians, and the target patient population is all adults. This article was reviewed and approved by the American College of Physicians (ACP) Clinical Guidelines Committee.

HOW COMMONLY ARE BRAND-NAME MEDICATIONS USED WHEN A GENERIC VERSION IS AVAILABLE?

Although the use of generic drugs has increased over time (4), health care providers frequently prescribe brand-name medications when generic versions are available. For example, more than 40% of Medicare beneficiaries with cardiovascular disease in 2001 used brand-name angiotensin-converting enzyme inhibitors and calcium-channel blockers instead of molecularly identical generics (5). More recently, Gellad and colleagues (6) studied Medicare beneficiaries with diabetes in 2008 and found that the use of “multisource” brand-name drugs (brand-name products for which identical generic versions are available) accounted for 23% to 45% of their prescriptions, depending on the class. This rate was substantially higher than that observed among patients with diabetes receiving care in the Veterans Affairs (VA) system, which has a centrally managed formulary that promotes greater use of generics.

Efforts to increase rates of “generic substitution” are believed to result in substantial cost savings (7). A study examining all prescriptions filled by a nationally representative sample of patients between 1997 and 2000 estimated that using identical generic versions of brand-name prescription drugs could reduce drug spending by \$5.9 billion, although this analysis was based on average wholesale prices and did not account for discounts that manufacturers provide to payers, which would reduce the potential cost savings (8). A non-peer-reviewed analysis of 2009 Medicaid drug expenditures highlighted substantial use of brand-name multisource prescription medications, leading to excess costs of \$329 million annually in just 20 therapeutic classes (9).

The opportunity for therapeutic interchange (the substitution of a similarly effective but less expensive chemical entity to treat the same condition) may represent an even greater potential for cost savings.

For the management of common chronic conditions, physicians often choose medications that are newer and relatively expensive even when clinical practice guidelines recommend otherwise (10, 11). For example, Fischer and Avorn (11) assessed antihypertensive prescribing in a state pharmacy assistance program and estimated that physicians prescribed newer brand-name medications instead of thiazides (which were recommended by the then-current antihypertensive guidelines from the Seventh Report of the

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) approximately 40% of the time; guideline-consistent prescribing was estimated to save more than \$1.2 billion annually. Similarly, Desai and associates' study of commercially insured patients with diabetes (12) found that 35% of patients initiating therapy with an oral hypoglycemic drug did not receive recommended initial therapy with metformin and that almost 10% of patients received a dipeptidyl peptidase-4 inhibitor, such as sitagliptin (Januvia [Merck]), as initial monotherapy. These patterns of care were estimated to result in more than \$1100 of potentially avoidable health spending per patient per year. Of note, contraindications or other clinical factors may not have been adequately captured in the administrative claims data that were used in these studies; thus, they may have overestimated the actual financial implications of changing practice patterns.

Nevertheless, these results are consistent with Gellad and colleagues' estimate that Medicare could save \$1.4 billion for patients with diabetes alone if drug prescribing mirrored that in the VA system through an approach combining generic substitution and therapeutic interchange (6). A 2005 analysis of commercially insured persons in the United States produced by a large pharmacy benefits manager estimated the potential cost savings of therapeutic interchange to lower-cost, guideline-adherent therapies in just 8 medication classes to be more than \$20 billion annually (13). To put this into context, \$20 billion could provide Medicaid coverage for more than 3.6 million presently uninsured persons, under the assumption that Medicaid expansion under the Patient Protection and Affordable Care Act costs an average of \$5440 per person per year (14).

In situations where neither generic substitution nor therapeutic interchange is possible, the use of brand-name agents may be clinically appropriate. For example, until recently there was no molecularly identical nor therapeutically equivalent generic version of clopidogrel (Plavix [Bristol-Myers Squibb and Sanofi]), and although the use of ipratropium may be appropriate for some patients with chronic obstructive pulmonary disease, there is no long-acting generic alternative for tiotropium (Spiriva [Boehringer Ingelheim]). Some patients may idiosyncratically achieve less therapeutic response or have greater adverse effects from a generic agent, justifying a switch to the brand-name counterpart.

HOW DOES THE USE OF GENERIC MEDICATIONS INFLUENCE ADHERENCE?

Higher out-of-pocket costs for patients have consistently been associated with lower rates of long-term medication adherence (15). For example, prescriptions for brand-name medications are almost twice as likely as those for generic therapies to be “abandoned” (that is, never picked up after being filled) (16). Thus, greater use of generic drugs could result in better long-term adherence to essential therapies. Because higher adherence is associated with lower downstream health

care costs for chronic conditions, greater use of generic therapies could reduce overall health care costs by this mechanism in addition to its direct effects on drug costs (17-19).

Most, but not all (20), studies evaluating the use of a generic rather than a brand-name drug for the treatment of chronic disease show significantly higher long-term adherence after treatment initiation (21-23). For example, Shrank and colleagues (21) evaluated commercially insured patients initiating therapy in 6 classes of long-term medications and found that those who began therapy with a generic medication had adherence rates that were 5 to 7 percentage points higher than among comparable patients initiating therapy with a brand-name drug. The observational nature of this study and the relatively limited adjustment for patient comorbidity make it possible that the results were at least partially attributable to unmeasured confounding.

The most recent evidence came from Gagne and associates (24), who studied a cohort of more than 90 000 Medicare beneficiaries initiating a statin and compared adherence and outcomes between patients initiating a generic statin and those who initiated a brand-name version of the same statin. Patients in the former group were 6% more adherent than those in the latter group. Although this study used propensity score matching to adjust for baseline differences in a large number of patient characteristics and compared patients initiating generic statins with those initiating brand-name versions of the same drug, it is still subject to the limitations of observational studies. No randomized studies comparing the effect of generic medication use on adherence have been reported or are likely to be conducted.

Of note, large increases in the prices of some generic drugs have been reported in the popular press and have been attributed, in part, to recent drug shortages (25). Although prices of generic drugs seem unchanged overall (26), sustained increases could undermine adherence to and the clinical outcome benefits of generics. No peer-reviewed reports systematically examining this issue have been published.

WHAT IS THE EVIDENCE THAT BRAND-NAME AND GENERIC MEDICATIONS HAVE SIMILAR CLINICAL EFFECTS?

To be approved for use by the U.S. Food and Drug Administration, generic drugs must demonstrate bioequivalence to their brand-name counterparts, which is defined as the absence of a significant difference in the availability of the active ingredient at the site of drug action (27). Bioequivalence can be established on the basis of the maximum serum concentration of the drug, the time until the maximum concentration is reached, or the area under the curve based on serum concentration as a function of time (28).

Because generic drugs are not required to be therapeutically (as opposed to biologically) equivalent to brand-name agents, some physicians and patients have

expressed concern that generic medications are less effective or more dangerous than their brand-name counterparts. For example, some professional societies of physicians have expressed concern about the clinical equivalence of brand-name and generic thyroid hormone (29). Similarly, after the loss of patent protection for bupropion (Wellbutrin [GlaxoSmithKline]), many spontaneous reports were submitted to the U.S. Food and Drug Administration describing a loss of antidepressant effect or new or worsening adverse effects among patients who had switched from the brand-name to the generic version of this agent (30). Subsequently, several generic versions of bupropion were found not to be bioequivalent to the brand-name version (31).

In contrast, most of the peer-reviewed evidence has found that generic drugs are as effective as their brand-name counterparts with regard to clinical outcomes. For example, a meta-analysis of 47 studies compared the effectiveness of generic and brand-name drugs in 9 classes of cardiovascular medications and found no evidence of superiority of brand-name medication, including among anticoagulants and antiarrhythmics with narrow therapeutic windows (28). Most of the included studies were randomized, controlled trials, although few of these explicitly evaluated noninferiority.

A 2011 systematic review focused specifically on warfarin and included 11 randomized and observational studies (32). In the 5 randomized, controlled crossover trials included in this review, there was no significant difference in international normalized ratio or in the magnitude or number of dosage changes between patients who switched to brand-name or generic warfarin.

In other therapeutic areas, comparative effectiveness studies of proton-pump inhibitors indicate no meaningful difference in clinical effectiveness between any of the available formulations (33). For example, based on head-to-head trials, absolute differences in the rate of healing of erosive esophagitis 4 weeks after initiation of treatment for patients treated with omeprazole and equipotent doses of other proton-pump inhibitors ranged from -6% to 2%, with none of these differences being statistically significant (34). Eight weeks after the start of treatment, there was a trend toward better esophagitis healing with esomeprazole compared with omeprazole (risk difference, 3% [95% CI, 0% to 6%]), but the clinical significance of this difference is unclear. Further, there were no differences between agents for the healing of duodenal or gastric ulcers (34).

Although several brand-name antidepressants are top-selling medications in the United States, on the basis of comparative effectiveness evidence, clinical practice guidelines do not recommend their use unless lower-cost generic therapies have been unsuccessful (35-37). Similarly, although the observational studies in a meta-analysis of studies comparing the effectiveness of brand-name and generic antiepileptics suggested worse seizure control among users of generics, the

odds of uncontrolled seizure did not differ between patients receiving generic and brand-name medications in the 7 randomized trials included in this meta-analysis (odds ratio for poor seizure control among generic compared with brand-name agents, 1.1 [CI, 0.9 to 1.2]) (38).

In Gagne and associates' study, the rate of the primary composite clinical outcome of acute coronary syndrome, stroke, and all-cause death was 8% lower among patients initiating treatment with a generic compared with a brand-name agent (24). The magnitude of this effect is consistent with the observed improvements in adherence from other studies (39), but as noted earlier, although this study was rigorously conducted, it may still have been subject to the effects of unmeasured confounding.

Most recently, Berkowitz and colleagues (40) studied whether the class of oral hypoglycemic medication with which patients with diabetes initiated therapy influenced their likelihood of requiring treatment intensification with a second agent or insulin. This analysis found that patients initiating metformin therapy were significantly less likely to require treatment intensification than those initiating therapy with thiazolidinediones or dipeptidyl peptidase-4 inhibitors (which are only available as brand-name medications) as well as sulfonylureas, without differences in rates of adverse clinical events. Although this analysis evaluated only patients receiving therapeutically effective doses of oral hypoglycemic monotherapy, as with other nonrandomized studies, the possibility of unmeasured confounding remains. Further, although the need for treatment intensification is highly relevant to patients because it seems to reduce quality of life by the same amount as diabetes complications (41, 42), its relationship with other clinically relevant diabetes outcomes has not been established.

In contrast to the data for other therapeutic classes, some published evidence suggests a lack of equivalence of brand-name and generic ophthalmic agents (43). For example, a small open-label crossover study comparing brand-name and generic latanoprost for patients with glaucoma in India found greater reductions in intraocular pressure with the brand-name version (44). In contrast, several other small studies found no difference in intraocular pressure between the generic and brand-name versions of this agent (45, 46). The largest study to date was a double-blind randomized trial involving 184 patients in Italy, which found that the generic version of latanoprost was noninferior to the brand-name version (47).

WHAT ARE THE BARRIERS TO INCREASING THE USE OF GENERIC MEDICATIONS?

Some of the underuse of generic medications is likely a result of patient and physician perceptions about the safety and efficacy of the lower-cost options (48-50). A national survey found that most patients believe generics are less expensive and offer greater

value than brand-name medications and that most patients believe more Americans "should" use generic medications; however, only 36% prefer to use generics themselves (49). Patient concerns about the safety of generics and a perceived lack of efficacy are probably central contributors (51). Patients may also associate the lower price of generics with lower levels of effectiveness (52). Differences in the physical appearance of molecularly identical generics and between generics and their brand-name counterparts could also influence patient perceptions of efficacy or safety; such variations in pill appearance have been associated with higher rates of nonadherence (53, 54).

About 25% of physicians express concerns about the safety and efficacy of generics and prefer not to use them themselves or for their family (50). This may stem in part from a lack of awareness of the regulatory standards for approval of generic drugs (55), especially in the context of media reports of problems with the manufacturing of generics (56), even though manufacturing issues also commonly affect brand-name manufacturers (57) and 5 of the top 10 manufacturers of generics are actually brand-name pharmaceutical companies (58). In addition, most physicians refer to drugs by their original brand name even when molecularly identical generic versions are available, which may result in inadvertent dispensing of brand-name drugs, especially in states where automatic generic substitution is prohibited (59). This may be especially true for particular classes of drugs and for subspecialist physicians, for whom the odds of requesting that a brand-name prescription be dispensed as written are 78.5% greater than for generalists ($P < 0.001$) (60).

Provider behaviors with respect to generic drugs also seem to be influenced by patient requests. In a national survey of 3500 randomly sampled physicians in 7 specialties, approximately 4 of 10 physicians reported that they sometimes or often prescribe a brand-name drug to a patient when a generic version is available because the patient wants it (3). The likelihood of this behavior was significantly higher for physicians who also reported that they received industry-provided food and samples or who met with detailing representatives (3). These interactions have been shown to increase actual prescribing of brand-name agents even when generic versions are available (61).

All states have adopted laws permitting generic substitution, but they vary in the role that the patient or pharmacist may play. Some states have "mandatory" generic substitution requiring the pharmacist to substitute a generic for a brand-name multisource medication except when prescribers explicitly indicate "brand only"; others endorse "permissive" generic substitution, where pharmacists are permitted but not required to make the substitution. In addition, some states require the patient to provide consent before generic substitution, whereas others permit it without explicit discussion with the patient. After the patent for Zocor (Merck) expired, states that require patients to provide consent for generic substitution experienced a rate of simvasta-

tin dispensing that was 25% lower than among states that did not have this requirement (62).

WHAT STRATEGIES CAN BE USED TO PROMOTE COST SAVINGS THROUGH GREATER GENERIC MEDICATION USE?

With the implementation of Medicare Part D in 2006 and the expanded role of the federal government in the support of state Medicaid programs resulting from passage of the Affordable Care Act, efforts to encourage generic medication use when appropriate could have important effects on national health care spending. This is particularly true given that patents for a host of blockbuster medications, including clopidogrel, olanzapine, and atorvastatin, have recently expired (63).

Although several strategies to increase prescription of generic drugs seem promising, as a whole, the evidence base supporting many of these strategies is limited.

Provider Strategies

Greater adoption of electronic medical records could support generic medication use through notification of the formulary status of prescribed medications. For example, in a pre-post study with concurrent controls (64), Fischer and associates found that the introduction of an e-prescribing system by 2 large insurers in Massachusetts was associated with a 3% increase in the prescription of generics and medications in the lowest cost-sharing tier of the plans' incentive formularies. Further, an interrupted time-series analysis of a decision-support tool introduced by a large academic medical center into an e-prescribing system specifically to promote generic substitution found an absolute increase in generic drug use of more than 20% that was sustained for more than 2 years after the intervention went into effect (65).

Interactive forms of continuing medical education, such as academic detailing, are effective methods of changing physician behavior (66) and could therefore promote prescription of generic drugs. A randomized trial found that the addition of vouchers that patients could use when switching to or initiating a generic drug resulted in a statistically significant 2% increase in prescription of generics compared with academic detailing alone (67). Although the magnitude of this effect was small, it would nevertheless be expected to have important economic implications given the large cost differences between generic and brand-name medications (15).

Because receipt of brand-name drug samples seems to be associated with greater prescription of brand-name products (3), providing physicians with free samples of generic medications to provide to their patients could increase their use, but this approach has been incompletely evaluated (68, 69). Finally, the relationship between a physician accepting food from industry representatives and their greater likelihood of acquiescing to patient requests for brand-name medi-

cations suggests that "gift bans" and similar policies may have a role in promoting the use of generic medications (3), but this strategy has not been prospectively tested.

Patient Strategies

Targeting the underlying barriers to generic medications may also promote their use. Once patients have used a generic drug through generic substitution, they seem much more likely to accept one in the future (70). Accordingly, targeted education about generic medication standards and bioequivalence may stimulate more value-conscious decision making. However, population-based educational interventions to improve patient or physician perceptions about generics have, thus far, shown limited success and must be crafted carefully (71). Large-scale public awareness campaigns or advertising campaigns similar to those used for brand-name agents might help to alter patient perceptions about generics but have not been rigorously studied.

Payer and Insurance-Based Strategies

Payers and policymakers have long attempted to promote generic drug use. Financial penalties for using expensive brand-name medication in the form of tiered formularies and greater copayments are the most common application to address these concerns (72). Clear evidence shows that these benefit designs increase generic and lower-cost medication use (15, 73). Prior-authorization and step therapy requirements are also commonly implemented to encourage generic drug use and have been shown to substantially reduce unnecessarily expensive medication use (15, 74). The high rate of generic drug use in the VA system reflects the universal use of these policies.

Incentives to limit patient or physician "dispense as written" designations on prescriptions may enhance generic medication use (62). Policy solutions that limit the need for patient or pharmacist consent before generic substitution, which already exist in many states, may also promote generic medication use without jeopardizing the quality of care (62, 75-77).

The general movement to realign physician and hospital incentives to reward quality should also encourage physicians to prescribe in accordance with guidelines, which could lead to greater generic medication use. The Healthcare Effectiveness Data and Information Set and the Medicare star ratings now include assessments of adherence that may trigger the deployment of interventions that help to identify lower-cost therapies that will encourage appropriate medication use (78, 79). Pay-for-performance programs have achieved modest improvements in the quality of care and could, in principle, be linked to measures associated with the use of generic drugs (80-82). In accountable care organizations, providers are placed at risk for the cost of care that they provide; this could be a powerful incentive for physicians to be thoughtful about the cost of the medications they prescribe, although high-quality data evaluating this premise have yet to be published.

Figure. American College of Physicians best practice advice: improving adherence to therapy and clinical outcomes while containing costs: opportunities from the greater use of generic medications.



**SUMMARY OF THE AMERICAN COLLEGE OF PHYSICIANS BEST PRACTICE ADVICE:
IMPROVING ADHERENCE TO THERAPY AND CLINICAL OUTCOMES WHILE CONTAINING
COSTS: OPPORTUNITIES FROM THE GREATER USE OF GENERIC MEDICATIONS**

| | |
|---|--|
| Disease/Condition | All diseases or conditions requiring any kind of medication |
| Target Audience | All prescribing clinicians |
| Target Patient Population | All patients receiving any kind of medication |
| Interventions | Medication therapy |
| Evidence for Prescribing Generic vs. Brand-Name Medications | Brand-name medications show no superiority in effectiveness compared with molecularly identical generic medications. Using generic medications reduces out-of-pocket costs for patients and helps to encourage better adherence to therapy, especially in chronic diseases. |
| Barriers to Evidence-Based Practice | Physician perceptions about safety and efficacy of generic medications Patient expectations and preferences |
| Strategies to Increase the Use of Generic Medications | Adoption of electronic health records that notify prescribers about formulary status of medications and costs (including out-of-pocket costs) Tiered formulary copayment system Prior-authorization and step therapy requirements Patient education Physician education Physician performance measures |
| Talking Points for Clinicians When Discussing Medications With Patients | Newer brand-name medications are not necessarily more efficacious. The generic versions of a particular brand-name medication may come in different shapes, sizes, and colors but offer the same benefit. Dosage levels vary for different medications, including brand-name and generic alternatives that are used to treat the same condition, and similar dosages may not necessarily achieve the same outcome. Changing from brand-name to generic medication reduces patient costs. Changing from a generic medication to a brand-name medication is rarely indicated in patients with chronic diseases that are already well-controlled. |
| Best Practice Advice | <i>Clinicians should prescribe generic medications, if possible, rather than more expensive brand-name medications.</i> |

AREAS OF UNCERTAINTY AND DIRECTIONS FOR THE FUTURE

Although rates of generic drug use have increased steadily over the past decade, substantial opportunities remain to increase the use of these medications even further and, in so doing, to maintain or improve health care quality while also reducing cost (6). Given the large cost differences between generic and brand-name medications, even small incremental increases in the rate of generic dispensing are estimated to have important economic implications for both patients and payers (13). This is especially true given the recent loss of patent protection for many widely used medications.

This review highlights that patient and provider perceptions remain the major obstacle to increasing generic medication use. Despite a long-established regulatory approval process for generic drugs, increas-

ing their use will require the development of more robust data about their comparative safety and effectiveness relative to their brand-name counterparts. These data are especially urgent for widely used drug classes, such as antidepressants and thyroid hormone, for which beliefs about the differences between brand-name and generic drugs are strongly held (3, 29). Incentives for providers and insurers introduced by payment reform, new funding sources for comparative effectiveness research, and advances in the methods to conduct these types of analyses should facilitate the generation of this evidence.

Beyond the generation of better information, a pressing need also exists to identify and test strategies for translating this information into greater use of generic medications by patients and providers. For example, decision-support tools in electronic health records

seem promising, but the evidence base assessing their potential value is limited thus far (67). Efforts to more closely regulate interactions between pharmaceutical manufacturers and prescribers could also be effective (3). Patient-targeted educational campaigns or the use of such behavioral strategies as motivational interviewing (83), shared decision making (84), and commitment devices (85) have shown promise in other areas of medicine and may be effective for promoting generic drug use. Harmonization of the appearance of generic and brand-name products, formally called “trade dress,” could also increase uptake of generic drugs (53, 54). Finally, policy levers, such as tiered formularies, have been the most effective strategies for driving patients to adopt generics, but current copayment differentials between generic and brand-name medications may not be sufficient to motivate generic drug use by some patients (86); thus, a need for further research about these behavior change tools also remains.

ACP BEST PRACTICE ADVICE

Clinicians should prescribe generic medications, if possible, rather than more expensive brand-name medications.

The **Figure** summarizes the recommendation and clinical considerations.

From Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; Carilion Clinic, Roanoke, Virginia; and American College of Physicians, Philadelphia, Pennsylvania.

Note: Best practice advice papers are “guides” only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP best practice advice papers are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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Requests for Single Reprints: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Choudhry: Division of Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02120.

Dr. Denberg: Carilion Clinic, PO Box 13727, Roanoke, VA 24014.

Dr. Qaseem: American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.

Author Contributions: Conception and design: N.K. Choudhry, A. Qaseem.

Analysis and interpretation of the data: N.K. Choudhry, A. Qaseem.

Drafting of the article: N.K. Choudhry, T.D. Denberg, A. Qaseem.

Critical revision of the article for important intellectual content: N.K. Choudhry, T.D. Denberg, A. Qaseem.

Final approval of the article: N.K. Choudhry, T.D. Denberg, A. Qaseem.

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Administrative, technical, or logistic support: N.K. Choudhry, A. Qaseem.

Collection and assembly of data: N.K. Choudhry, A. Qaseem.

Appendix Table. Key Articles Used to Perform the Literature Searches

Question 1: How commonly are brand-name medications used when a generic version is available?

- Haas JS, Phillips KA, Gerstenberger EP, Seger AC. Potential savings from substituting generic drugs for brand-name drugs: Medical Expenditure Panel Survey, 1997–2000. *Ann Intern Med.* 2005;142:891-7. [PMID: 15941695] doi:10.7326/0003-4819-142-11-200506070-00006
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Question 2: How does the use of generic medications influence adherence?

- Shrank WH, Hoang T, Ettner SL, Glassman PA, Nair K, DeLapp D, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Arch Intern Med.* 2006;166:332-7. [PMID: 16476874]
- Taira DA, Wong KS, Frech-Tamas F, Chung RS. Copayment level and compliance with antihypertensive medication: analysis and policy implications for managed care. *Am J Manag Care.* 2006;12:678-83. [PMID: 17090224]
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- Gagne JJ, Choudhry NK, Kesselheim AS, Polinski JM, Hutchins D, Matlin OS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. *Ann Intern Med.* 2014;161:400-7. [PMID: 25222387] doi:10.7326/M13-2942
- Sedjo RL, Cox ER. Lowering copayments: impact of simvastatin patent expiration on patient adherence. *Am J Manag Care.* 2008;14:813-8. [PMID: 19067498]

Question 3: What is the evidence that brand-name and generic medications have similar clinical effects?

- Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA.* 2008;300:2514-26. [PMID: 19050195] doi:10.1001/jama.2008.758
- Kesselheim AS, Stedman MR, Bubrick EJ, Gagne JJ, Misono AS, Lee JL, et al. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs: a systematic review and meta-analysis. *Drugs.* 2010;70:605-21. [PMID: 20329806] doi:10.2165/10898530-000000000-00000
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Appendix Table—Continued

Question 4: What are the barriers to increasing the use of generic medications?

- Brennan TA, Lee TH. Allergic to generics. *Ann Intern Med.* 2004;141:126-30. [PMID: 15262668] doi:10.7326/0003-4819-141-2-200407200-00011
- Shrank WH, Cox ER, Fischer MA, Mehta J, Choudhry NK. Patients' perceptions of generic medications. *Health Aff (Millwood).* 2009;28:546-56. [PMID: 19276015] doi:10.1377/hlthaff.28.2.546
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- Steinman MA, Chren MM, Landefeld CS. What's in a name? Use of brand versus generic drug names in United States outpatient practice. *J Gen Intern Med.* 2007;22:645-8. [PMID: 17443372]

Question 5: What strategies can be used to promote cost savings through greater generic medication use?

- Rector TS, Finch MD, Danzon PM, Pauly MV, Manda BS. Effect of tiered prescription copayments on the use of preferred brand medications. *Med Care.* 2003;41:398-406. [PMID: 12618643]
- Fairman KA, Motheral BR, Henderson RR. Retrospective, long-term follow-up study of the effect of a three-tier prescription drug copayment system on pharmaceutical and other medical utilization and costs. *Clin Ther.* 2003;25:3147-61. [PMID: 14749153]
- Choudhry NK, Cox ER, Fischer MA, Mehta J, Shrank WH. Setting prices for generic medications: a survey of patients' perceptions. *Am J Pharm Benefits.* 2010;2:33-8.
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