Comparative Effectiveness Research/Health Technology Assessment (HTA)

Treatment Dynamics of Newly Marketed Drugs and Implications for Comparative Effectiveness Research

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A B S T R A C T

Objectives: Clinicians and payers require rapid comparative effectiveness (CE) evidence generation to inform decisions for new drugs. We empirically assessed treatment dynamics of newly marked drugs and their implications for conducting CE research. **Methods:** We used claims data to evaluate five drug-outcome pairs: 1) raloxifene (vs. alendronate) and fracture; 2) risedronate (vs. alendronate) and fracture; 3) simvastatin plus ezetimibe fixed-dose combination (simvastatin + ezetimibe) (vs. simvastatin alone) and cardiovascular events; 4) rofecoxib (vs. nonselective nonsteroidal anti-inflammatory drugs [ns-NSAIDs]) and myocardial infarction; and 5) rofecoxib (vs. ns-NSAIDS) and gastrointestinal bleed. We examined utilization dynamics in the early marketing period, including evolving utilization patterns, outcome risk among those treated with new versus established drugs, and prior treatment patterns that may indicate treatment resistance or intolerance. We addressed these challenges by replicating active CE monitoring with sequential matched cohort analysis. **Results:** Patients initiating new

drugs were more likely to have used other drugs for the same indication in the past, but the majority of patients in all new drug cohorts were treatment naive (82.0% overall). Patients initiating rofecoxib had higher predicted baseline risk of gastrointestinal bleed than did patients initiating ns-NSAIDs. Patients initiating risedronate and alendronate had similar predicted baseline risks of fracture, while those initiating raloxifene and simvastatin + ezetimibe had lower risks of outcomes of interest relative to their comparators. Prospective monitoring yielded results consistent with expectation for each example. **Conclusions:** Many challenges to assessing the CE of new drugs are borne out in empirical data. Attention to these challenges can yield valid CE results.

Keywords: effectiveness, new drugs, prospective monitoring, validity.

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Introduction

Optimizing patient-centered outcomes requires more than knowing whether a medication works better than placebo in highly proto-colized clinical trial settings [1]. At the time of approval, however, few new drugs have been compared with active alternatives [2] and among those that have, a limited set of alternatives is used even when many potential treatment options exist [3]. Patients, clinicians, and payers therefore do not have all the evidence required for fully informed treatment decisions involving new drugs.

Several mechanisms exist to generate comparative effectiveness (CE) evidence in the early marketing period, but they carry important limitations. Large head-to-head trials of multiple drugs tend to be costly and require many years to complete. The generalizability of results of open-label extensions of phase III trials and indirect comparisons or network meta-analyses of efficacy trials [4] are limited to populations enrolled in the

preapproval trials [5], which do not tend to reflect populations of patients that use the drugs in the postmarketing setting [6–8].

Once approved, new drugs are often consumed by many thousands of patients despite the lack of evidence of so-called real-world effectiveness. Patients' prescription-filling histories and health care encounters are captured in near real time in payers' and providers' electronic health care databases. Analyzing these data as they accrue offers great potential for providing continuous information support for decision makers and other stakeholders in a "learning health care system" [9]. These data can provide in-the-moment insight into the comparative effectiveness and safety of new drugs as experience with the products grows [10,11], which could form the basis of coverage with evidence development strategies, including risk-sharing arrangements [12], and are being used in the US Food and Drug Administration's Sentinel Initiative to assess the safety of newly approved drugs [13]. Using observational data to determine the comparative effectiveness of new

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drugs in the early marketing period is challenging [5,11]. In particular, selective prescribing of new drugs may lead to confounding by indication and patients initiating a new drug may be more likely to have failed a prior treatment [5].

By using data covering the early marketing periods of four example drugs (rofecoxib, raloxifene, risedronate, and fixed-dose simvastatin plus ezetimibe combination), we empirically evaluated aspects of treatment dynamics in the early marketing period that can give rise to confounding in observational comparative effectiveness studies. Specifically, we sought to examine 1) the utilization trends of newly marketed drugs, 2) whether users of new drugs are "sicker" than users of more established therapies, 3) whether users of new drugs are more likely to have failed prior treatments, and 4) whether it is possible to find patients initiating alternative drugs who are comparable to patients initiating the new drugs. We then applied a recently proposed ensemble of methods to emulate active monitoring beginning at market authorization of each drug of interest [5,14,15] and assessed whether the approach addressed these sources of confounding.

Methods

Data

We used 12 years (1994–2005) of medical and pharmacy claims data from Medicare beneficiaries in New Jersey and Pennsylvania who were enrolled in pharmaceutical assistance programs in these states (the Pharmacy Assistance for the Aged and Disabled [PAAD] in New Jersey and the Pharmacy Assistance Contract for the Elderly [PACE] in Pennsylvania). Both PAAD and PACE provide medications with no formulary restrictions and at minimal expense to elderly individuals with low income but who do not meet the Medicaid annual income threshold. PACE and PAAD data are linked to Medicare Parts A and B data.

Patients

We identified initiators of four drugs of interest beginning at their market authorization and initiators of an active comparator drug or class for each: 1) rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs (ns-NSAIDs), 2) raloxifene versus alendronate, 3) risedronate versus alendronate, and 4) simvastatin plus ezetimibe fixed-dose combination (Vytorin; simvastatin + ezetimibe) versus simvastatin alone. Each pair was chosen to create a set of examples with new drugs that represent slightly different types of advances on the comparator. For example, rofecoxib offered a more selective mechanism of action over ns-NSAIDs; raloxifene offers a different mechanism of action than does alendronate; risedronate is a follow-on product in the same class as alendronate; and simvastatin plus ezetimibe is a combination product containing an established therapy and is thought to be more effective for some patients, though conclusive evidence is lacking. Pairs were also selected to ensure that the comparator had been available for some time prior to the authorization of the new drug.

Outcomes

Our outcomes of interest were myocardial infarction (MI) and gastrointestinal (GI) bleeding for the rofecoxib versus ns-NSAIDs example, a composite fracture end point for the raloxifene versus alendronate and risedronate versus alendronate examples, and a composite cardiovascular event end point for the simvastatin plus ezetimibe fixed-dose combination versus simvastatin alone. The composite fracture outcome involved fractures at the hip, humerus, pelvis, and radius, and the cardiovascular event outcome comprised MI, cerebrovascular events (i.e., ischemic and hemorrhagic stroke), and acute coronary syndromes with revascularization. We

defined all outcomes by using claims-based algorithms. Validation studies comparing the algorithms to medical chart reviews have found positive predictive values of 94% for MI [16], 88% for GI bleeds [17], 86% for cerebrovascular events [18], and between 93% and 98% for each fracture outcome [19,20].

For each example, we followed patients for the outcome(s) of interest by using an intention-to-treat approach beginning the day after the initiation of their index drug and for a maximum of 180 days. We censored patients at the first of the following events: 1) occurrence of the outcome of interest, 2) death, or 3) end of study period (December 31, 2005).

Analysis

We examined trends in utilization by plotting the number of initiators of the new drugs, the comparators, and similar drugs in each calendar quarter starting 1 year before the new drugs' market authorization. We defined initiators as those patients with no prior use of the index drug in the preceding 180 days [21]. We characterized prior treatment patterns by calculating the proportion of patients initiating the new drugs and their respective comparators who had exposure to other drugs used to treat the same condition in the 180 days before index drug initiation. Specifically, we calculated the proportion of patients in the new drug group who had used the comparator and vice versa, the proportion of patients in each group who had used various alternatives (e.g., celecoxib and valdecoxib for the rofecoxib example, other statins for the simvastatin + ezetimibe example, and other bisphosphonates or calcitonin for the raloxifene and risedronate examples), and the proportion of patients in each group who were treatment naive.

We tabulated demographic and clinical characteristics of patients initiating the new drugs in the very early marketing period (i.e., the first 6 months following market authorization) and compared the characteristics to those initiating the active comparator during the same time. We identified a large number of predefined covariates for each example, including patient demographics (e.g., age, gender, and race), health service utilization variables (e.g., number of physician visits, number of hospitalizations, number of unique drugs dispensed, and a comorbidity score that combines the Charlson and Elixhauser indices [22]), and specific risk factors for the outcome(s) of interest in each example. All covariates were ascertained during the 180 days preceding the index prescription date and are listed in the Appendix Tables in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval. 2013.05.008. To compare the baseline risk of the outcomes of interest between treatment groups, we estimated a disease risk score, defined as a patient's likelihood of experiencing the outcome of interest conditional on baseline covariates [23–26]. Following the approach of Glynn et al. [26], we developed the disease risk score model for each example among patients exposed to the comparator drug prior to the market authorization of the new drug. We then applied the resulting model coefficients in the form of a prediction rule to all patients in both treatment groups after the introduction of the new drug. We considered all predefined covariates listed in the Appendix Tables in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.05.008.

Finally, we replicated prospective comparative effectiveness monitoring by analyzing each example as if new data became available on a quarterly basis following the introduction of each new drug. We updated estimates of effect over time as experience with the new drug grows [14,15,27]. We divided the databases into sequential data sets defined by claims occurring in each calendar quarter. For each example, patients who initiated the new drug of interest within 6 months of its market authorization formed monitoring period one. Subsequent monitoring periods were defined by 3-month intervals. We 1:1 matched initiators of the new drug in each monitoring period to initiators of the