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Evidence selection for a prescription drug's benefit-harm assessment: challenges and recommendations

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Abstract

Objectives: To describe challenges and make recommendations for researchers in how they select evidence to quantitatively assess a prescription drug's benefits and harms.

Study Design and Setting: These challenges and recommendations are based on our recent experience conducting a benefit-harm assessment for the prescription drug roflumilast. We considered the selection of evidence to quantify (1) the drug's treatment effects in patients, (2) the patient population's baseline risks for beneficial and harmful outcomes without treatment, and (3) the patient population's preferences for these beneficial effects and harms. These are fundamental steps for most benefit-harm assessment methods.

Results: We identify critical issues in selecting evidence for each of these steps. We justify in particular the need to incorporate (1) clinical trials for the drug's specific treatment effect; (2) observational studies with the most valid, precise, and applicable effect estimates for the baseline risk; and (3) flexible weighting approaches for balancing the drug benefits and harms.

Conclusion: We identify challenges and make recommendations for selecting evidence at the critical steps in a prescription drug's benefit-harm assessment. Our findings should assist other researchers conducting these assessments for prescription drugs, which could help regulators, medical professionals, and patients make better decisions about prescription drug use.

Keywords: Prescription drugs; Benefit-harm assessment; Pharmacoepidemiology; Roflumilast; Patient preferences; Prescription drug regulation

1. Background

Prescription drugs are critical for the prevention and treatment of diseases, but regulators and medical professionals often face challenges in assessing an individual drug's benefits and harms for use by a general population or specific patient. Various methods for evaluating and balancing a drug's benefits and harms have been developed in recent years [1−3]. For example, Gail et al. [4] developed a model using absolute outcome risks and treatment effects to estimate and compare the benefits and harms of tamoxifen for reducing breast cancer risk, which has been adapted in more recent analyses [5]. Some of these methods incorporate also patient preferences for specific outcomes in weighing the beneficial effects of a drug against its harms [2].

Benefit-harm assessments are important for regulators to determine whether a prescription drug should be approved and, for clinicians, to recommend in what instance a patient should use the drug. In the United States, the Food and Drug Administration (FDA) is legally required to evaluate a prescription drug's safety and efficacy in determining whether to approve the drug for marketing [6]. FDA regulations do not specify how the agency qualitatively or quantitatively compares a drug's benefits with its harms, although FDA is working to develop a more structured and transparent approach for assessing and balancing drug safety and effectiveness [7].

We recently evaluated the benefits and harms of roflumilast, an inhibitor of inflammatory processes in patients with severe chronic obstructive pulmonary disease (COPD) [8]. Roflumilast, like other phosphodiesterase inhibitors, has a long and complicated regulatory history because of the difficulty in assessing the benefit-harm

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What is new?

Key findings

- This article shares the authors' recent experience with evidence selection for a prescription drug's benefit-harm assessment and describes the challenges frequently faced in selecting evidence for these assessments.

What this adds to what is known?

- To assist researchers conducting benefit-harm assessments, the article makes recommendations for selecting evidence in the three critical steps to quantify (1) the drug's treatment effects in patients; (2) the patient population's baseline risks for beneficial and harmful outcomes without treatment; and (3) the patient preferences for these beneficial effects and harms.

What is the implication, what should change now?

- Benefit-harm assessments should identify and select (1) clinical trials for the drug's specific treatment effect; (2) observational studies with the most valid, precise, and applicable effect estimates for the baseline risk; and (3) flexible weighting approaches for balancing the drug benefits and harms.
- These steps provide a foundation for evaluating and comparing a prescription drug's benefits and harms through transparent benefit-harm assessments, which can assist regulators in determining whether a drug can be approved and clinicians in advising whether a patient should use the drug.

balance given the many complex factors to consider. We found, using a systematic and comprehensive method to compare benefits and harms, that the benefits (i.e., reduction in exacerbations) only exceeded the harms (mainly gastrointestinal, psychiatric, and neurological) in patients with at least moderate risk for severe exacerbations requiring hospital admission [8].

This evaluation demonstrated the value of specifying a structured and transparent method for assessing and balancing a prescription drug's benefits and harms. The selection of evidence quantifying these benefits and harms is a critical step [9]. In this article, we share challenges we faced and recommend steps for investigators to select evidence for benefit-harm assessments.

2. Three critical steps for the assessment

In assessing a prescription drug's safety and efficacy, we considered how to quantify (1) the drug's treatment effects in patients, (2) the patient population's baseline risks for beneficial and harmful outcomes without treatment, and (3) the patient population's preferences for these beneficial effects and harms. These three data inputs are key for most methods to quantitatively assess the benefits and harms of medical treatments [2].

For example, in calculating these measures for roflumilast's benefits and harms, we first quantified the drug's treatment effect as an absolute number of events prevented or caused by the drug (per person and unit time) for the desired outcome (benefits) and each unwanted adverse event (harms). We compared the absolute number of events in the patient population who take the drug to those estimates in the patient population not taking the drug (i.e., the baseline outcome risks). Finally, we assigned weights for each outcome and summed these numbers to calculate whether roflumilast's overall benefits are greater than its overall harms.

We selected evidence at each step to quantify these treatment effects, baseline risks, and patient preferences to determine the drug's benefit and harm. The importance of evidence selection underlies most benefit-harm assessments and is not limited to the method we used. For this reason, we focus on evidence selection in this article, recognizing that this topic is relevant to all quantitative methods for benefit-harm assessment. We do not provide guidance for assessing an individual study's quality or the strength of evidence for a particular question but refer to guidance like the one provided by the Grading, Assessment, Development, and Evaluation (GRADE) Working Group [10] or the Cochrane Handbook for systematic review of interventions [11].

Finally, it is important to clarify how our research relates to other important efforts assisting clinicians and guideline developers in assessing a therapy's benefits and harms. For example, the GRADE Working Group recommends steps for rating evidence quality and grading recommendation strength [10]. The GRADE guidance has generally focused on providing frameworks for assessing evidence and developing recommendations, rather than describing specific analytical methods to determine if a therapy's benefits outweigh its harms for certain patients [10]. By contrast, our roflumilast analysis used specific quantitative methods to assess whether the benefits outweighed the harms for a specific drug.

2.1. Treatment effects for the drug

2.1.1. Evidence for benefits

In assessing a drug's treatment effect on the intended outcome, we relied on clinical trial results because well-designed randomized clinical trials (RCTs) are the gold standard for drug evaluation [12]. As a first step, we believe high-quality systematic reviews (with or without meta-analyses) including Cochrane systematic reviews [13] are optimal resources to identify those RCTs studying a drug's benefits and/or harms (see Fig. 1). In the next step, the relevant RCTs from systematic reviews must be selected. Only