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Off-label treatments were not consistently better or worse than approved drug treatments in randomized trials

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Abstract

Objectives: Off-label drug use is highly prevalent but controversial and often discouraged assuming generally inferior medical effects associated with off-label use.

Study Design and Setting: We searched PubMed, MEDLINE, PubMed Health, and the Cochrane Library up to May 2015 for systematic reviews including meta-analyses of randomized clinical trials (RCTs) comparing off-label and approved drugs head-to-head in any population and on any medical outcome. We combined the comparative effects in meta-analyses providing summary odds ratios (sOR) for each treatment comparison and outcome, and then calculated an overall summary of the sOR across all comparisons (ssOR).

Results: We included 25 treatment comparisons with 153 RCTs and 24,592 patients. In six of 25 comparisons (24%), off-label drugs were significantly superior (five of 25) or inferior (one of 25) to approved treatments. There was substantial statistical heterogeneity across comparisons (I^2 = 43%). Overall, off-label drugs were more favorable than approved treatments (ssOR 0.72; 95% CI = 0.54–0.95). Analyses of patient-relevant outcomes were similar (statistical significant differences in 24% (six of 25); ssOR 0.74; 95% CI = 0.56–0.98; I^2 = 60%). Analyses of primary outcomes of the systematic reviews (n = 22 comparisons) indicated less heterogeneity and no statistically significant difference overall (ssOR 0.85; 95% CI = 0.67–1.06; I^2 = 0%).

Conclusion: Approval status does not reliably indicate which drugs are more favorable in situations with clinical trial evidence comparing off-label with approved use. Drug effectiveness assessments without considering off-label use may provide incomplete information. To ensure that patients receive the best available care, funding, policy, reimbursement, and treatment decisions should be evidence based considering the entire spectrum of available therapeutic choices.

Keywords: Meta-epidemiology; Off-label; Drug regulation; Drug label; U.S. Food and Drug Administration; Systematic review; Meta-analysis; Evidence-based health care

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What is new?

Key findings

- Off-label treatments were not consistently better or worse than approved drug treatments in randomized trials.

What this study adds to what was known?

- Medical effects associated with off-label drug use are highly heterogeneous and do not appear to be systematically inferior when compared with approved drug treatments.

What is the implication and what should change now?

- Relying on the approval status of drugs should not replace thorough assessment of benefits and harms on a case-by-case basis to ensure that patients receive the best available care.
- To ensure that patients receive the best available care, funding, policy, reimbursement, and treatment decisions should be evidence based considering the entire spectrum of available therapeutic choices.

1. Introduction

Many drugs are commonly prescribed outside their approved indications (off-label), and most off-label use is not supported by sufficient evidence [1]. For some sensitive patient populations such as children or pregnant women, off-label drug use is a routine practice because many common treatments have never been tested in randomized clinical trials (RCTs) and have never been formally approved for these populations [2,3]. In some areas, for example pediatrics or oncology, a large part of the spectrum of therapeutic choices in routine care is off-label use [4–6].

Off-label use gives physicians the freedom to treat patients with limited treatment options, in particular when approved (on-label) drugs are unsuccessful and alternative treatment is urgently needed, and it allows adopting innovative practices when new evidence emerges. On the other hand, drug use without regulatory approval may create uncertainty about dosing and contraindications, increase costs, and undermine the motivation to initiate rigorous trials evaluating off-label indications [7]. There are several regulatory and legal mechanisms that hinder off-label use, including patient information requirements, black box warnings, prohibition of direct promotion, regulatory systems generating drug effectiveness assessments without considering off-label use, and reimbursement and coverage policies limiting the access by either complete or only restricted coverage by health insurers [8–13].

Policies preferring approved treatments influence daily patient care. These policies generally serve the interest of patients and society, but sometimes it may preclude patients from receiving valid off-label therapy alternatives. Such policies rely on the assumption of generally lower efficacy and safety of off-label treatment. However, to our knowledge, this assumption has never been empirically assessed using clinical trial evidence.

We conducted a meta-epidemiological analysis of treatment effects of off-label and approved drug treatments based on RCTs across all available treatment comparisons. We aimed to determine the comparative treatment effects of approved vs. unapproved drug options to evaluate the assumption of generally inferior treatment effects associated with off-label use. We also aimed to obtain an empirical estimate of the relative magnitude of the treatment effects of approved vs. unapproved drug options.

2. Materials and methods

2.1. Identification of off-label treatments

We defined off-label drug use as treatment outside of the Food and Drug Administration's (FDA's) approved medical condition or age group and did not consider milder deviations from the approved use, that is, different dosage, disease severity, or route of administration. There is to our knowledge no exhaustive list of the most widely used off-label treatments in routine care. We determined the FDA approval status at various time points using Micromedex DRUGDEX (as of May 2015). We used the most recent available drug label from the drugs@FDA database and confirmed the approval status of all included drugs in September 2017 (there was never a change of status).

We used three different search strategies (Appendix A). First, we searched PubMed, the Cochrane Library, and PubMed Health using the keyword "off-label" and related terms in combination with the database's standard filters for systematic reviews (last search May 8, 2015). Second, we used the Ovid interface to search MEDLINE with an existing search strategy for off-label use [14] and an established systematic review filter [15] (last search May 8, 2015). Third, we identified all indications which were the subject of evidence summaries on unlicensed or off-label medicines (ESUOMs) [16] published by the UK National Institute for Health and Care Excellence (NICE) up to June 2014. We then searched PubMed for each topic for systematic reviews combining keywords for the off-label indications using standard systematic review filters (last search June 27, 2014).

2.2. Selection of off-label vs. on-label treatment comparisons

We included off-label treatments that were evaluated in a systematic review with a meta-analysis of head-to-head