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From Epidemiological Signals to Therapeutic Leads: A Scoping Review of Pharmacovigilance-Based Drug Repurposing and Experimental Validation

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 April 2026 and was last updated on 20 April 2026.

INTRODUCTION

Review question / Objective This scoping review aims to systematically map the current state of the art in drug repurposing strategies based on pharmacovigilance data mining. The primary objectives are:
1. To chart the computational and methodological frameworks used, distinguishing between simple disproportionality analyses and advanced multi-database or omics-integrated approaches.
2. To map the current therapeutic landscape to identify which clinical areas (e.g., Neurology, Oncology, Infectious Diseases) are most frequently targeted by this discovery strategy.
3. To explore the translational trajectory and level of evidence by assessing how many statistical "inverse signals" have progressed to in vitro, in vivo, or clinical experimental validation.
4. To highlight the "Validation Gap" between epidemiological correlation and pharmacological causation.

Background The pharmaceutical industry is facing a productivity paradox ("Eroom's Law"), where R&D costs are doubling despite technological advances. Drug repurposing has emerged as a vital strategy to de-risk development by identifying new indications for existing approved medications. Within the ecosystem of Real-World Data, pharmacovigilance databases (e.g., FAERS, VigiBase) represent a unique resource for hypothesis generation. Traditionally used for toxicity detection, these repositories are now being used for "Inverse Signal Analysis" — identifying significantly under-reported drug-event pairs as potential therapeutic leads. However, the transition from statistical disproportionality (e.g., ROR < 1) to biological plausibility and clinical application remains a complex challenge that requires a systematic mapping of the evidence.

Rationale Despite the proliferation of studies leveraging pharmacovigilance (PV) data for drug repurposing, there is no consensus on the optimal methodological frameworks or the reliability of the generated hypotheses. A systematic mapping of the evidence is therefore essential to clarify the methods used (frequentist vs. Bayesian algorithms, integration with transcriptomics or molecular

docking), identify key achievements in different therapeutic areas, and highlight critical gaps in experimental validation. A scoping review is the ideal method to comprehensively capture this heterogeneous landscape and provide a methodological roadmap for future research.

METHODS

Strategy of data synthesis A comprehensive and systematic literature search will be conducted by two investigators (M.G. and S.T.) in major electronic databases: PubMed, Web of Knowledge, Scopus, and OpenGrey. The search will cover the period from database inception to the present, with no language restrictions. To ensure a standardized and consistent identification of relevant literature across all platforms, the following search string will be utilized for all search engines: (drug repurposing OR drug repositioning) AND (FAERS OR FDA adverse event OR VigiBase OR WHO database OR EudraVigilance OR JADER OR AERS OR AEMS OR spontaneous reporting OR ICSR OR individual case safety report OR pharmacovigilance)
Any disagreements between investigators will be resolved through discussion and consensus.

Eligibility criteria The eligibility criteria were defined using the Population, Concept, and Context (PCC) framework to ensure a comprehensive selection process.
Population or participants: Studies must utilize patient data from spontaneous reporting systems (SRS) such as FAERS, VigiBase, or JADER.
Intervention (concept): The core concept is the application of "Inverse Signal Analysis" or similar data mining techniques (e.g., disproportionality analysis, Bayesian algorithms) on pharmacovigilance databases with the explicit aim of identifying new therapeutic indications for existing drugs. Studies that integrated these signals with additional data sources (e.g., omics, EHRs) or experimental validation are included.
Context: All therapeutic areas and geographical settings.
Exclusion criteria: Narrative reviews, editorials, commentaries, conference abstracts, and studies focused exclusively on adverse drug reaction (ADR) detection without a repurposing/therapeutic objective.

Source of evidence screening and selection The selection procedure will be carried out in two successive stages. First, two reviewers (M.G. and S.T.) will independently screen the titles and abstracts of all identified records against the predefined eligibility criteria. In a second step, the full texts of all articles identified as potentially relevant will be retrieved and reviewed by the same two independent reviewers for final inclusion. Discrepancies will be resolved through formal discussion to reach consensus.

Data management A structured data collection form will be developed in Microsoft Excel to ensure systematic extraction. Two reviewers will extract data independently across three domains: (1) Study Characteristics (author, year, database used, data volume); (2) Analytical Frameworks and Bias Mitigation (statistical algorithms used [ROR, PRR, IC, EBGM], inverse signal thresholds, multi-modal integration [transcriptomics, EHRs, molecular docking], and epidemiological strategies to address confounders); (3) Therapeutic Candidates (drug names, original indications, newly proposed indications, signal strengths, and proposed mechanisms).

Reporting results / Analysis of the evidence The analysis of the evidence will be conducted in two main steps. First, a descriptive numerical analysis will summarize the general characteristics of the included studies (publication year, databases used, sample size). Second, findings will be classified into a hierarchical validation framework consisting of four levels: (1) Statistical Only; (2) In Silico Validation; (3) In Vitro / In Vivo Experimental Validation; and (4) Clinical/Real-World Validation. The therapeutic landscape will be mapped by clinical domain.

Presentation of the results The results will be presented through a combination of tables, figures, and narrative synthesis.
Narrative Synthesis: A detailed description of the methodological evolution from simple disproportionality to "Systems Pharmacology" and an analysis of the "validation funnel."
Tables: Summary tables detailing study characteristics, analytical frameworks, and prioritized drug candidates.
Figures: A PRISMA-ScR flow diagram for the selection process and a Sankey diagram to visually synthesize the translational trajectory of identified candidates from original therapeutic area to the level of experimental validation.

Language restriction No language restrictions will be applied.

Country(ies) involved Italy.

Other relevant information None.

Keywords Pharmacovigilance; Drug Repurposing; Inverse Signal Analysis; FAERS; VigiBase; Disproportionality Analysis; Spontaneous Reporting Systems.

Dissemination plans The findings will be submitted for publication in a peer-reviewed international journal specializing in pharmacology, drug discovery, or clinical informatics. Key findings will also be presented at relevant scientific conferences.

Contributions of each author

Author 1 - Martina Giacon - Conceptualization; Methodology; Data Collection; Data Analysis; Writing – Original Draft.
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Author 2 - Salvatore Terrazzino - Conceptualization; Methodology; Data Collection; Supervision; Writing – Review & Editing.
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