Network Analysis of Drug Repurposing Across Therapeutic Areas: A Clinical Trials Perspective

Objective

The objective of this investigation is to identify and characterise opportunities for drug repurposing by examining the co-occurrence of pharmaceutical interventions across diverse therapeutic domains. Using structured clinical trial data sourced from ClinicalTrials.gov, this project employs network science methodologies to construct and analyse bipartite and projected networks linking drugs and disease areas. The aim is to surface candidate compounds with evidence of efficacy across multiple conditions, thus informing potential avenues for therapeutic repositioning.

Phase 1 – Design and Scope

1.1 Repurposing Hypothesis

The foundational hypothesis underpinning this project is that drugs tested in clinical trials across multiple disease indications may possess unrecognised or secondary therapeutic potential beyond their originally licensed use. This hypothesis is motivated by the assumption that overlapping pathophysiological mechanisms or pharmacological responses can be inferred through shared trial patterns.

The study focuses exclusively on active pharmaceutical ingredients, explicitly excluding trials involving devices, procedural interventions, or behavioural therapies.

Repurposing potential is assessed using established network centrality measures:

- Degree Centrality: Reflects how widely a drug has been tested across distinct conditions, suggesting versatility.
- Betweenness Centrality: Identifies drugs that bridge otherwise disconnected disease domains — an indication of strategic repurposing value across therapeutic clusters.
- Eigenvector Centrality: Highlights compounds with embedded influence within dense clinical testing networks, reflecting indirect importance and systemic relevance.

1.2 Population of Interest

To ensure scientific validity and relevance, only interventional trials that meet the following inclusion criteria were considered:

- Intervention Type: Trials involving drug-based interventions only.
- Trial Status: Trials classified as Completed, Recruiting, Active but not recruiting, or Enrolling by invitation.
- Study Phase: Phase I, II, III, or IV trials were included to ensure candidates had surpassed basic safety profiling and were being evaluated for clinical efficacy and broader therapeutic outcomes.

This focused inclusion strategy ensures that the analysis is based on clinically substantiated evidence, optimising the reliability of any repurposing hypotheses generated.

Phase 2: Candidate Drug Profiling and Evidence Mapping

2.1 Selection Criteria

Candidate drugs for follow-up profiling were prioritised based on their prominence across three centrality measures:

- Degree Centrality – breadth of disease associations
- Betweenness Centrality – bridging disconnected disease clusters
- Eigenvector Centrality – influence within the drug co-occurrence network

The following compounds consistently ranked in the top tier across these measures (placebo entries excluded):

Drug	Degree Centrality	Betweenness Centrality	Eigenvector Centrality
Dexamethasone	0.726	0.056	0.084
Midazolam	0.504	0.026	0.031
Rituximab	0.452	0.011	0.069
Prednisone	0.452	0.011	0.069
Fentanyl	0.425	0.013	0.063
Aspirin	0.417	0.010	0.063
Upadacitinib	0.406	0.013	0.060
177Lu-Dotatoc	0.378	0.007	0.027
Epclusa	0.378	0.007	0.027
Prednisolone	0.366	0.009	0.024

2.2 Profiling Example: Dexamethasone

Trial Landscape

Using structured trial data, dexamethasone was found in completed and active trials across diverse conditions, including:

Disease	Trial Title	Phase	Status	NCT ID
Asthma	Dexamethasone for Excessive Menstruation	Phase II	Completed	NCT01769820
Cancer	Bendamustine and Dexamethasone in Myeloma	Phase II	Completed	NCT01222260
Depression	Long-term Efficacy of Adjunctive Dexamethasone	Phase IV	Completed	NCT01580020
HIV/AIDS, Hypertension	Dexamethasone in Cryptococcal Meningitis	Phase II	Completed	NCT00000776
Cancer	Combination Chemotherapy (Including Dexamethasone)	Phase II	Completed	NCT00002494
Cancer	Palbociclib + Dexamethasone in Triple-Negative Breast Cancer	Phase I	Recruiting	NCT04996160

Therapeutic Scope

Dexamethasone bridges the following disease communities (based on disease–disease shared drug networks):

- Cancer
- Depression
- Asthma
- HIV/AIDS
- Hypertension
- Rheumatoid Arthritis

This spread suggests dexamethasone may have systemic or immunomodulatory effects that are being explored across inflammation, oncology, and neurological disease clusters.

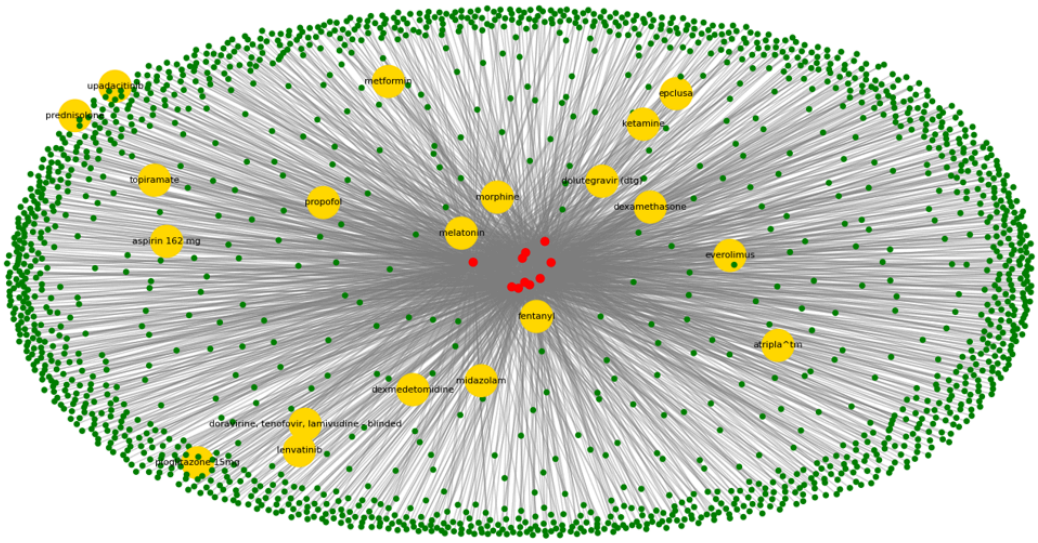
Network Position

1. High Degree: Indicates use in multiple disease trials
2. Moderate Betweenness: Suggests bridging role across distinct disease clusters
3. High Eigenvector: Part of central therapeutic communities with influential links

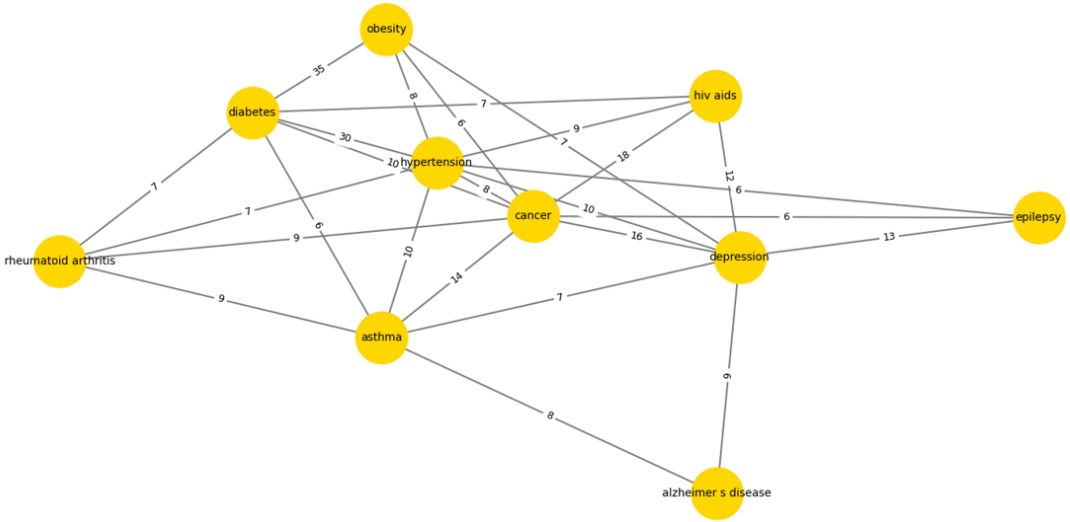
2.3 Network Visualisation Insights

To support and contextualise the centrality-based identification of potential repurposing candidates, four key network visualisations were developed. These figures provide structural insight into the interconnectedness of pharmaceutical agents and disease domains, reinforcing the network-derived hypotheses.

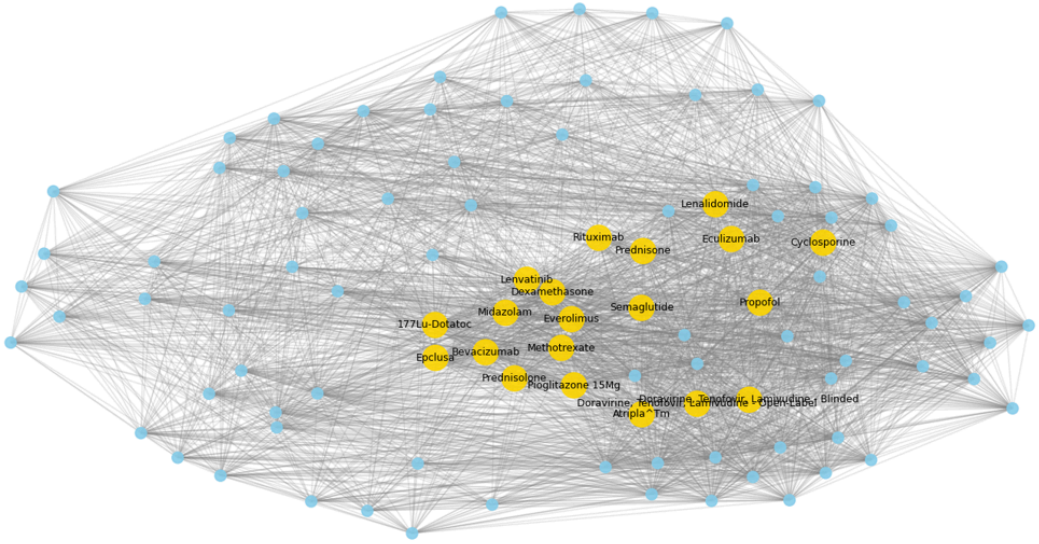
1. Bipartite Drug–Disease Network: This plot visualises the full bipartite network connecting drugs (green nodes) to therapeutic areas (red nodes). High-degree drug candidates are highlighted in gold. The network layout reveals that certain pharmaceutical agents, such as dexamethasone and midazolam, serve as high-connectivity hubs, tested across diverse indications. This visual representation affirms their potential repurposing value due to their broad clinical relevance.



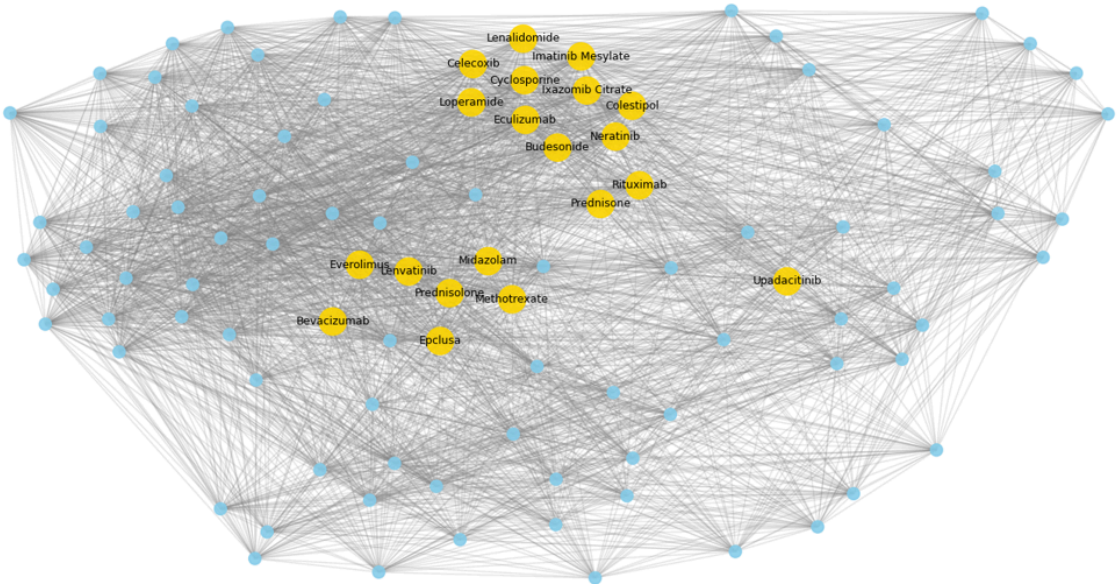
2. Disease–Disease Projection Network: This projection maps diseases based on the number of shared drug interventions, filtered to retain only connections involving more than five shared compounds. Each edge label reflects the count of shared drugs, while node size is fixed for interpretability. Diseases such as cancer and rheumatoid arthritis appear prominently linked, suggesting shared pharmacological management strategies. This highlights potential avenues for drug repositioning between therapeutically adjacent but historically distinct conditions.



3. Drug Network by Eigenvector Centrality: In this projection, drug nodes are connected if they share a common disease. The node colour and size reflect their eigenvector centrality—a measure of influence within the network. Dexamethasone and rituximab emerge as drugs embedded within highly influential clusters. Such compounds are not only broadly tested but are also positioned within densely connected therapeutic communities, enhancing their candidacy for repositioning.



4. Drug Network by Betweenness Centrality: Here, drug nodes are evaluated for their betweenness centrality, highlighting compounds that serve as critical bridges between otherwise disconnected disease modules. Drugs like dexamethasone and fentanyl occupy key transitional positions, suggesting that they mediate pharmacological access across multiple clinical clusters. These agents may be instrumental in guiding future repositioning strategies that bridge disease silos.



Conclusion and Research Significance

This study presents a structured and analytically robust approach to identifying drug repurposing opportunities through the lens of clinical trial co-occurrence networks. By focusing on interventional trials and applying established network science techniques, we have characterised compounds, such as dexamethasone that demonstrate consistent presence across distinct therapeutic areas. These findings suggest underlying pharmacological versatility that may not yet be fully exploited in clinical practice.

The use of centrality measures provides a quantifiable basis for evaluating a drug's positioning within the broader therapeutic landscape, offering both explanatory power and strategic insight. Unlike isolated observational studies, this network-based perspective reflects aggregated trial-level evidence, thereby enhancing both the credibility and translational relevance of the findings. As such, it provides a solid foundation for further investigation into cross-indication efficacy and the rational prioritisation of repurposing candidates.

Moving forward, the work will transition from descriptive network analysis to predictive modelling. A Bayesian statistical framework will be introduced to incorporate prior knowledge, quantify uncertainty, and enable robust inference about the likelihood of future drug–disease associations. In parallel, machine learning methods will be deployed to identify high-probability repositioning candidates, using trial-derived and biologically informed features. This dual pathway combining statistical interpretability with predictive power will support both scientific rigour and real-world applicability, positioning this work to inform decision-making in pharmacological research, trial design, and therapeutic strategy.