CS 3891 - Final Report

Drug-Drug Interaction (DDI)

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Abstract

Polypharmacy, the concurrent use of multiple medications, is increasingly prevalent in healthcare, posing challenges due to complex drug-drug interactions (DDIs). These interactions can lead to unexpected and potentially harmful side effects. This study employs network analysis to systematically examine the side effects of drug combinations, utilizing the PK-DDI-SADR dataset to construct a detailed network of DDIs. Our analysis uncovers the most prevalent side effects and identifies key drugs and drug pairs associated with adverse reactions. We compute various centrality measures, such as degree centrality and eigenvector centrality, both weighted and unweighted, to pinpoint drugs that are either highly interconnected or have interactions with significant impact. Notably, drugs like Simvastatin emerged as central in numerous interactions. Our findings reveal the potential of network analysis in enhancing the understanding and management of polypharmacy. The insights gained are crucial for tailoring personalized treatments, improving medication adherence, and aiding regulatory bodies in evaluating the safety of drug combinations. This study highlights the vital role of vigilant pharmacist intervention in mitigating risks associated with specific drug combinations, ultimately contributing to safer and more effective treatment strategies for patients.

Background

In the realm of contemporary healthcare, polypharmacy, prescribing or consuming multiple medications simultaneously, holds significance. While this approach can offer specialized treatment avenues, it's imperative to meticulously scrutinize potential drug interactions and adverse effects to guarantee both safety and efficacy. The use of network analysis offers a systematic method to explore the ramifications of polypharmacy. According to the National Center for Health Statistics, the percentage of the US population taking two or more drugs in combination has increased from 25.4% to 31.2% from 1999-2000 to 2007-2008. An interesting fact is that while for children of age 12 or younger, 10% took two or more drugs, and 1% were taking more than 5 drugs, for people of age 60 and over, 76% took two or more drugs, and 37% took five or more drugs [1]. This statistics shows that people are taking more and more medication as they age.

At the forefront, network analysis brings the possibility of uncovering synergistic effects inherent in polypharmacy, as presented in the work of Zhao et al (2021) in “Journal of Clinical Pharmacy and Therapeutics”. Such effects, where combined drug efficacy surpasses their individual potentials, can revolutionize treatment approaches by enabling reduced dosages and thus mitigating side effect risks. Beyond this, there's the promise of personalizing medical treatments. By discerning the most harmonious drug combinations, clinicians can tailor treatments to individual needs, maximizing benefits and

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minimizing adverse reactions. In the same vein, this analysis can pinpoint redundant or counterproductive drug pairings, streamlining medication regimens. This not only enhances treatment outcomes but also bolsters medication adherence by reducing complexities. Regulatory bodies, too, stand to gain. With insights from network analysis, they can judiciously assess drug combinations' safety, ensuring that only the most secure and potent pairings gain market approval.

Drug-drug interaction (DDI) is defined as the change in the efficiency of a drug when it is administered with other drugs. This paper studies the side effects of different DDI through Network analysis, nodes representing the drug, the edge connecting the two nodes representing

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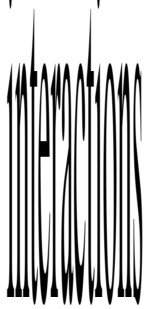

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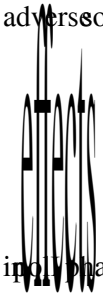

the market

A network of drug-drug interactions has been created using the NetworkX library. There are 4 connected components in the network and the average clustering coefficient of the network is 0.06, meaning that the network has a relatively low tendency for nodes to form tightly knit groups with their neighbors and is relatively sparse in terms of local neighbor-to-neighbor connections.

The network analysis will be used to represent polypharmacy side effects of drug pairs. The nodes will represent the drugs and the edges will represent different types of side effects that are associated with each drug pair. The network will be an undirected graph with weight of each edge representing the measure of scientific and clinical significance. In order to measure the significance of the DDI, Selenium was used to find the number of citations each journal had. The highest number of citations a journal had was 516 citations, whereas the lowest number was 0 citation. A higher number of citations would indicate that the scientific community has found the research relevant and useful. Therefore, a drug pair with a higher weight might represent a DDI of higher interest or importance. Citations are the most commonly used metric to measure the impact of a research finding. The more study about a specific DDI is cited, the more influential it may be considered within the scientific and medical communities. Furthermore, frequent citations can suggest that subsequent research has either built upon or validated the findings. A higher cited DDI study could imply that the interaction is well-recognized and verified. Higher citation can reflect the level of awareness in the medical community about a particular DDI and even be associated with clinical importance. If a DDI has significant clinical consequences, it might be more frequently cited in the literature discussing drug safety or specific medical conditions. It is important to note that while citation count can provide valuable insights, citation practices vary between fields and articles may be highly cited for reasons unrelated to the significance of the DDI itself, such as being part of a larger influential body of work or authored by prominent researchers. Additionally, newer research might not yet have accumulated many citations regardless of its potential importance. Relevancy over time, citation velocity, and historical importance of the journals are all factors that need to be considered in the future work. Preprocessing of the data was conducted so that the column names are more user friendly and added an additional column in the dataset that represents citation count of each journal.

Results

The most common side effect listed in the database was Rhabdomyolysis, showing up 42 times, and the most common drug listed was Simvastatin, showing up 21 times. The drug pair with the most number of side effects associated was (Terfenadine, Ketoconazole), having 7 different side effects. Average degree of each node was 2.81 and the network density is calculated as 0.024, meaning there are few edges, and the network is sparsely connected. The assortativity, which measures the similarity of

connections in the graph with respect to the node degree, was calculated as -0.098, meaning there is a very slight tendency for high-degree nodes to connect with low-degree nodes.

	drug1	drug1_code	drug2	drug2_code	side_effect	side_effect_code	research_num	research_pub_yr	num_cited
0	Simvastatin	36567	Ribociclib	1873916	Rhabdomyolysis	10039020	36718280	2023	2
1	Simvastatin	36567	Ribociclib	1873916	Acute kidney injury	10069339	36718280	2023	2
2	Pimozide	8331	Sertraline	36437	Cardiac arrest	10007515	36181876	2022	2
3	Ticagrelor	1116632	Amiodarone	703	Rhabdomyolysis	10039020	34987920	2021	2
4	Ticagrelor	1116632	Amiodarone	703	Acute kidney injury	10069339	34987920	2021	2

Table 1. Snippet of the database

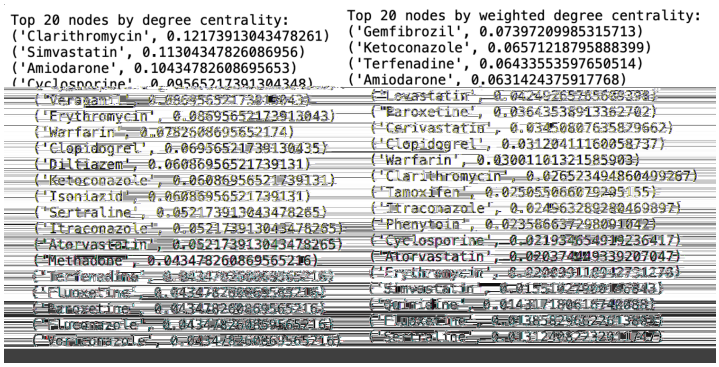

Figure 1. Weighted and Unweighted Degree Centrality of top 20 nodes

As shown in Figure 1, the top 20 nodes by degree centrality and the top 20 nodes by weighted degree centrality are calculated. The drugs with the highest degree centrality would suggest that they are involved in a substantial number of drug interactions. Healthcare professionals would need to pay close attention to drugs with high degrees as they are more likely to be involved in adverse events and have a more widespread impact on patient outcomes. The drug with the highest weighted degree centrality would suggest that they not only interact with many other drugs but also that these interactions are significant in terms of their impact or strength, as measured by the weights assigned to the edges. These drugs have interactions that are highly cited in the literature, suggesting these interactions are well known, and potentially of high clinical importance. These drugs could be significant in clinical making decisions. The juxtaposition of unweighted and weighted centrality measures sheds light on two different aspects of drug interactions: the sheer volume of interactions versus the depth and significance of these interactions. Understanding both dimensions is vital for comprehensive pharmaceutical research and effective healthcare delivery, enabling a more nuanced approach to assessing the risks and benefits of drug therapies.This dual perspective is particularly valuable in identifying potential targets for further

pharmacological research, optimizing therapeutic strategies, and enhancing drug safety surveillance systems.

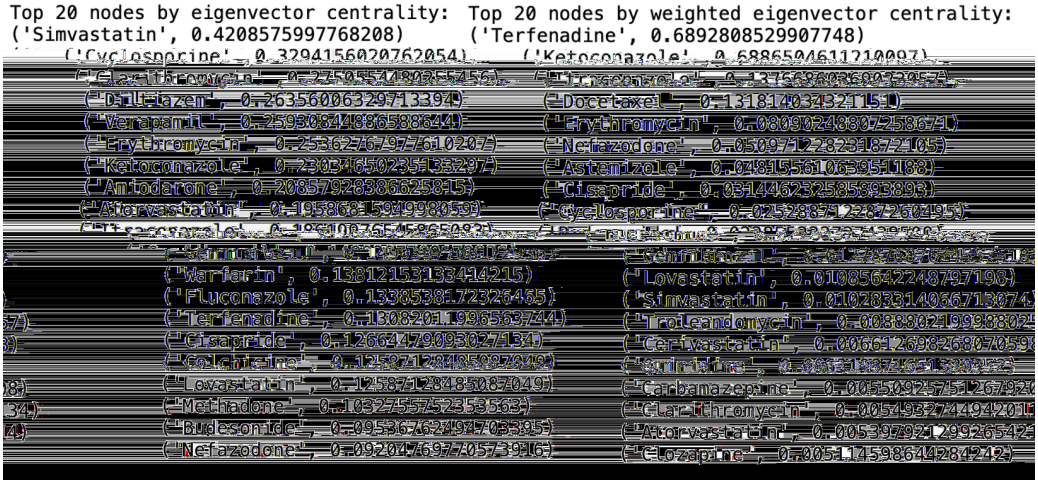

Figure 2. Weighted and Unweighted Eigenvector Centrality of top 20 nodes

In figure 2, the top 20 nodes by eigenvector centrality and the top 20 nodes by weighted eigenvector centrality are calculated. Eigenvector centrality is the measure of the influence of a drug, as the value is not just based on the number of its direct interactions, but also based on considering the significance of the drugs it interacts with. The drugs with high eigenvector centrality are not only connected to many other drugs, but are also connected to drugs that themselves are highly connected or influential. The drugs with high weighted eigenvector centrality are not only connected to many other drugs, but are also connected to drugs that are themselves highly cited. This suggests that the drugs are widely recognized and often cited in the literature, indicating the potential significance in the medical and research community. Again, the comparison between unweighted and weighted eigenvector centrality provides a layered understanding of drug influence in the network. This dual perspective is crucial for healthcare professionals and researchers, as it helps in identifying drugs that are not only structurally important in the network but also involved in clinically significant interactions. Such insights are invaluable for guiding further research, informing clinical decisions, and understanding the broader implications of drug interactions in polypharmacy.

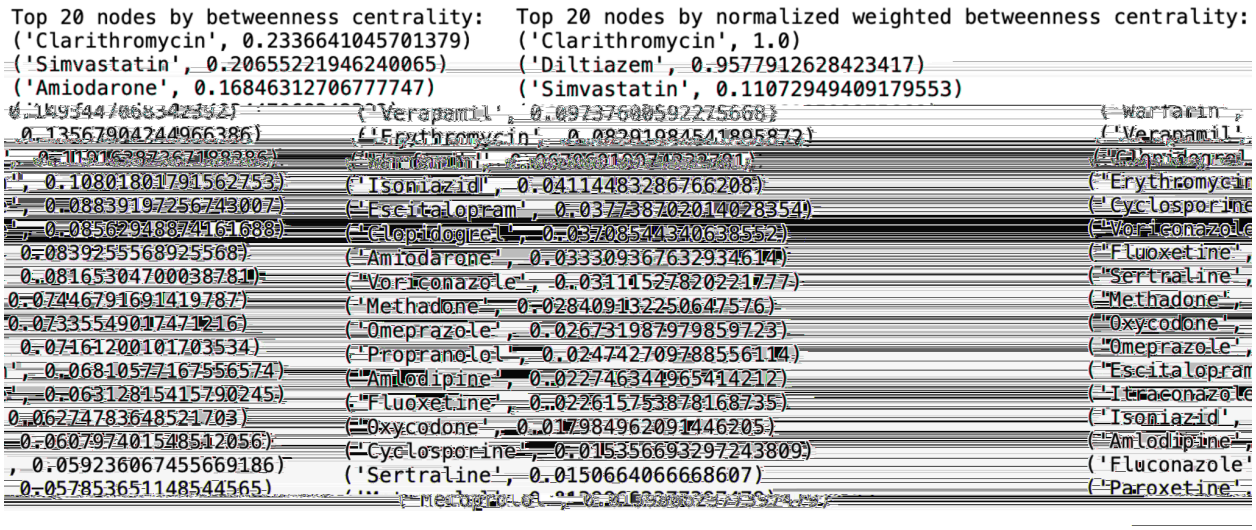

Figure 3. Weighted and Unweighted Betweenness Centrality of top 20 nodes

In figure 3, the top 20 nodes by betweenness centrality and the top 20 nodes by weighted betweenness centrality are calculated. The drugs with high unweighted betweenness centrality could mean that it acts as a key intermediary in the network of drug interactions, possibly connecting many pairs of drugs through shared side effects. Such a drug might be involved in multiple drug interaction pathways or may influence the emergence of side effects when used in combination with various other drugs. The drugs with high weighted betweenness centrality could indicate that they are not only central in the network of drug interactions but also that these interactions are significant or well-established in the scientific literature. Such a drug might be a critical point in the network of well-studied or clinically significant drug interactions, potentially involving side effects that are of high interest or concern in pharmacology and medicine. However, it is important to note that drug interactions often involve direct effects between specific pairs of drugs, rather than a single drug mediating interactions among many other drugs. A simple network model may not capture the multidimensional nature of interactions as it can involve multiple pathways, mechanisms, and effects. The network also has 4 disconnected components, and centrality measures within one component do not give information about the drug's role in the entire network. Furthermore, the edge weights may not accurately reflect the clinical significance of the drug interactions and there might be limitations in the database, such as incomplete reporting of interactions, bias in literature, and lack of information in the clinical context of interactions. When considering the betweenness centrality of drugs within the network, it's important to bear in mind these potential constraints and limitations.

Figure 4. Weighted and Unweighted Node Degree Distributions

In figure 4, the weighted and unweighted node degree distributions of the network are visualized. The distribution resembles a scale free network, which is characterized by a power-law degree distribution. The chart above shows a long tail, wherk of

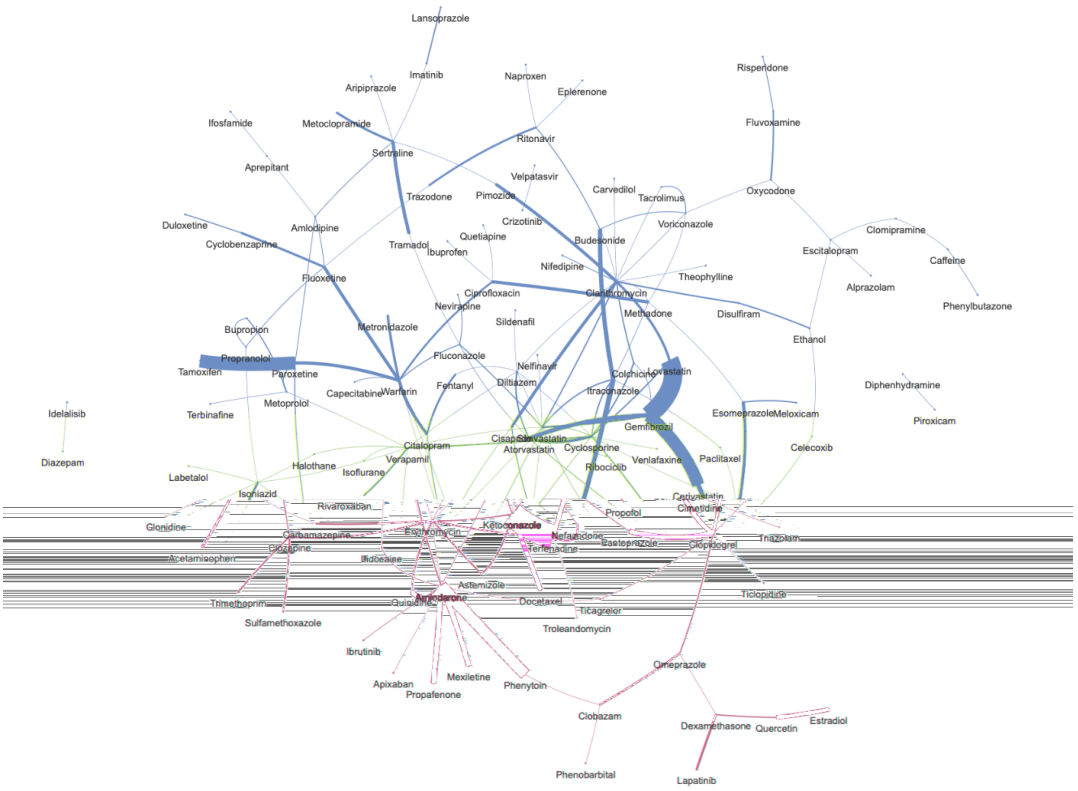

Figure 5. DDI Network Visualization - Repulsion Layout

In figure 5, the DDI network is built using the NetworkX and then translated to the PyVis graph. For effective positioning of the nodes, a ‘Repulsion’ layout algorithm is used. This algorithm arranges the nodes by simulating a repulsive force between them, akin to how like-charged particles repel each other. This repulsion ensures that nodes are spaced out evenly, making the network easier to interpret and analyze visually. The ‘Repulsion’ layout is particularly useful for highlighting the structure of the network, as it tends to separate clusters and reveal the underlying patterns by distancing nodes based on their connections. However, while this method is effective for clarity and aesthetic spacing, it can be computationally intensive, especially for large networks. In the future, if more nodes and edges are added to the database, then the ‘Barnes-Hut’ algorithm can be used, which is more efficient and scalable for rendering large graphs. Although it also utilizes a form of repulsion to position nodes, it does so in a manner that is less computationally demanding. This is achieved by approximating the repulsive forces between distant nodes, significantly speeding up the process. However, it might offer less precision in the control of node positions compared to the standard ‘Repulsion’ layout [4].

Conclusion

In conclusion, this study has effectively leveraged network analysis to explore the intricacies of polypharmacy, focusing on well documented side effects of drug combinations as reported in research literature. Utilizing various network centrality measures, it has identified key drugs that are central to numerous interactions and side effects, such as ‘Clarithromycin’, which emerged as significant nodes in the network as evidenced by its prominence across various centrality measures. These insights demonstrate the value of network analysis in improving therapeutic strategies and guiding drug safety regulations. Moreover, the significant nodes, often well researched, may indicate either their clinical importance or association with many side effects. Conversely, less significant nodes warrant attention for being underrepresented in research, potentially revealing unrecognized risks in polypharmacy. For example, the nodes with high degree centrality but low weighted degree centrality, such as ‘Simvastatin’, might suggest that these drugs are involved in many interactions, but the significance or impact of these interactions is relatively low. This could mean that while the drug interacts with many others, these interactions might not be well-studied, widely recognized, or clinically significant. Such a scenario underscores the need for further research into these drugs to fully understand their roles and impacts in polypharmacy. Further directions include expanding the dataset for a more comprehensive analysis and further refining our understanding of the impact of drug interactions on patient outcomes. Instead of using citation count to measure the significance of each journal that describes the DDI side effects, a different approach could be used that incorporates journal impact factors, such as frequency with which the journal is cited. This research contributes to the advancement of more personalized and safer medication management practices in the context of polypharmacy, with the potential to significantly enhance patient care.

Reference

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