Implementing a drug prescription network to evaluate psychiatric polypharmacy using data from IADB.nl

EPH182

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INTRODUCTION

Chronic psychiatric disorders lead to polypharmacy

1 in 5 people has mental disorders[1]

Polypharmacy 13–90% Worldwide prevalence[2]

What influences drug prescription?

- Physician's prescribing habits
- Patient-physician relationship
- Pharmaceutical market
- Decision-making process

Challenges in medication surveillance[3]

- Group results by demographic factors
- Identify increased mortality/morbidity
- Relate to health outcomes and services
- **Describe the importance of polypharmacy**

[1]Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Ustün TB, Wang PS. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. Epidemiology and Psychiatric Sciences. 2009 Mar;18(1):23–33.
[2]Delara M, Murray L, Jafari B, Bahji A, Goodarzi Z, Kirkham J, Chowdhury M, Seitz DP. Prevalence and factors associated with polypharmacy: a systematic review and meta-analysis. BMC geriatrics. 2022 Jul 19;22(1):601.
[3]Sirois, C., Tannenbaum, C., Gagnon, ME. et al. Monitoring polypharmacy at the population level entails complex decisions: results of a survey of experts in geriatrics and pharmacotherapy. Drugs Ther Perspect 32, 257–264 (2016).

METHOD

Source of data and pre-processing steps

Prescription registry from https://IADB.nl/

ID	ATC	DDD	Date	Period
P1	A07EC02	1	2018-01-01	15
P1	G02BA03	1800	2018-01-01	1800
P1	B03BA03	0.8	2018-01-01	13
P2	A07EC02	0.7	2018-01-01	12
P2	B03BA03	100	2018-01-01	5
...	...	...	...	...
PN	A11CC05	0.9	2022-12-31	10

Inclusion:
- Aged 18–65 years old
- Received N05B/N06A at least once
- Data from 2018 to 2022

Cleaning the DDD

DDD, Period → Ratio = DDD / Period → DDD > 1? (Yes: DDD = Ratio; No: Keep DDD) → Filter DDD between {0.1, 10}

Grouping by ATC level 1 3 4

Alimentary & Metabolism	Blood	Cardiovascular
Dermato-logicals	Genito-urinary	Systemic Hormonal
Anti-infectives	Anti-neoplastic	Musculo-skeletal
Anti-parasitic	Respiratory	Sensory
Others	Anesthetic	Analgesics
Anti-epileptics	Anti-parkinsons	Other Neuro Drugs
Anti-psychotics	Anxiolytics	Hypnotics
Anti-depressants	Psycho-stimulants	Anti-dementia

Polypharmacy is a complex and interlinked medication use

Daily prescription data

Patient	Medication
P1	Fluoxetine
P1	Metformin
P1	Amlodipine
P2	Fluoxetine
P2	Metformin
P3	Fluoxetine

Adjacency Matrix

P1

	[1]	[2]	[3]
Fluoxetine [1]	0	1	1
Metformin [2]	1	0	1
Amlodipine [3]	1	1	0

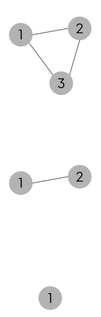
P2

	[1]	[2]	[3]
Fluoxetine [1]	0	1	0
Metformin [2]	1	0	0
Amlodipine [3]	0	0	0

P3

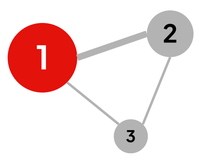
	[1]	[2]	[3]
Fluoxetine [1]	1	0	0
Metformin [2]	0	0	0
Amlodipine [3]	0	0	0

Graph



Drug Prescription Network

	[1]	[2]	[3]
Fluoxetine [1]	1	2	1
Metformin [2]	2	0	1
Amlodipine [3]	1	1	0



Determining relative importance of each medications

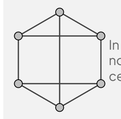
1 The sum of all eigenvector centralities = 1

$$\lambda c_i = \sum_{j \neq i} v_{j,i} \cdot c_j$$

$$\sum_{i \in N} c_i = 1$$

λ : Associated eigenvalue
c_i : Eigenvector centrality of node i
$v_{j,i}$: Connection from j to i

2 Hypothesized regular graph



In a regular graph, all nodes have the same centrality, i.e. 1/N

3 Parameterize 1/N as a normal distribution

$$\bar{c}_i \sim \mathcal{N}\left(\frac{1}{N}, \sigma\right)$$

$\bar{c}_i$: The mean of eigenvector centrality at node i
n : Total number of nodes
σ : Standard deviation

The mean of eigenvector centrality follows normal distribution

4 One-sample Student's T-Test

- Assess how much the observed eigenvector centrality differs from the expected value (1/N)
- If > 1/N → High
- If < 1/N → Low

Rationale and the general ideas

- Regular graph is the null reference
- In a DPN, regular graph implies that all medications are highly likely to be co-prescribed
- The sum of all eigenvector centralities is 1
- In a regular graph, the eigenvector centrality is equal for all nodes, i.e., 1/N
- Null hypothesis: The eigenvector centrality follows 1/N
- One-sample Student's T-Test was performed to test the hypothesis

Askar M, Cañadas RN, Svendsen K. An introduction to network analysis for studies of medication use. Research in Social and Administrative Pharmacy. 2021 Dec 1;17(12):2054–61.
Bazzoni G, Marengoni A, Tettamanti M, Franchi C, Pasina L, Djade CD, Fortino I, Bortolotti A, Merlino L, Nobili A. The drug prescription network: A system-level view of drug co-prescription in community-dwelling elderly people. Rejuvenation Research. 2015 Apr 1;18(2):153–61.
Cavallo P, Pagano S, Boccia G, De Caro F, De Santis M, Capunzo M. Network analysis of drug prescriptions. Pharmacoepidemiology and drug safety. 2013 Feb;22(2):130–7.

What can a network-based approach offer?

Cavallo (2013)

- Complement inferential statistics in pharmacoepidemiology
- Extract and isolate co-prescription for detailed analysis
- Demonstrate that high connections only occur in a few medications
- Evaluate physician's prescription habit

Bazzoni (2015)

- Highlight dynamic changes in medication uses
- Reflect changes in physician's prescription habit
- Display the co-prescription trends of selected medications
- Extract and isolate distinct clusters in a network

Askar (2021)

- Observe the influence of multiple drugs using centrality measures
- Suggest centrality measures for variable selection
- Identify clusters of patients with similar co-prescription patterns
- Detect topological differences by comparing different networks

Future Direction: Encourage network science application for public health evaluation

Future Direction: Evaluate medicine prescription and expenditure using a network-based approach

Future Direction: Apply network analysis in social pharmacy and pharmacoepidemiology

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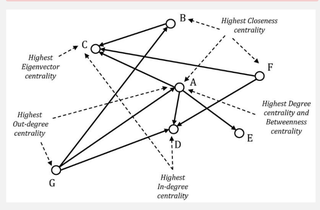
Network centrality as a score for each medication

- Network Measures
  - Modularity analysis
  - Networks comparison
  - N-partite networks
- Topology analysis
- Node measures
  - Edge measures
    - Edge thickness
  - Global description
    - Number of nodes
    - Density
    - Assortativity
- Centrality
  - Ego-networks
  - Degree centrality
  - Betweenness centrality
  - Closeness centrality
- Eigenvector centrality

Evaluating Medication in DPN



Operational Definition

Centrality
Indicates how influential a medication is in a network

Eigenvector Centrality
Measures how well-connected a medication is to highly co-prescribed medications

Centrality measures the relative importance of the medications by assigning a score to each of them

$$\lambda c_i = \sum_{j \neq i} v_{j,i} \cdot c_j$$

$$\sum_{i \in N} c_i = 1$$

λ : Associated eigenvalue
c_i : Eigenvector centrality of node i
$v_{j,i}$: Connection from j to i

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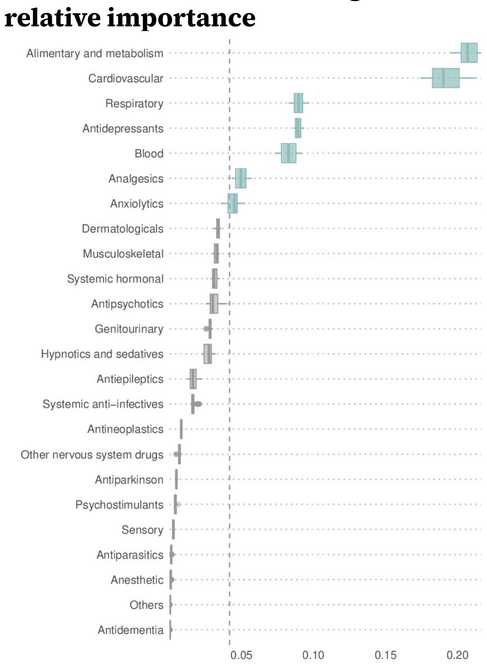
RESEARCH QUESTION

What does eigenvector centrality tell us about polypharmacy in patients with psychiatric disorders?

RESULTS

Seven medications had a high relative importance



Medication Group	N Claims 2018 – 2022	Eigenvector Centrality Mean [95% CI]		Dose Mean [SD]
Alimentary and metabolism	11,512,424	0.2074 [0.2066,	0.2081]	0.60 [0.33]
Cardiovascular	9,778,030	0.1914 [0.1901,	0.1926]	0.54 [0.31]
Respiratory	5,492,900	0.0895 [0.0890,	0.0899]	0.66 [0.33]
Antidepressants	6,108,776	0.0894 [0.0891,	0.0896]	0.54 [0.31]
Blood	2,908,944	0.0827 [0.0821,	0.0833]	0.69 [0.39]
Analgesics	2,557,528	0.0499 [0.0494,	0.0504]	0.42 [0.26]
Anxiolytics	2,644,309	0.0443 [0.0438,	0.0449]	0.46 [0.29]

Strength

- Network analysis is a complementary approach to the general practice of inferential statistics
- DPN is proven useful as a data exploration and variable selection strategy

Limitation

- IADB.nl provides prescription registry data, not drug administration nor diagnosis
- We need a way to standardize DDD when excluding the record
- Constructing a DPN is computationally expensive

Future Direction

- Extract entries with high eigenvector centrality to assess individual patient's period of use
- Formulate a bipartite network to link medication with diagnosis or prescribing habits

TAKE-HOME MESSAGES

DPN is a complementary approach to the general practice of inferential statistics

Network analysis methodology is a powerful tool to address highly connected data

More studies incorporating network analysis of medication uses are encouraged

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lpdp lembaga pengelola dana pendidikan
iadb.nl DRUG USE RESEARCH

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PharmacoTherapy, -Epidemiology & -Economics