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Network Analysis: an approach to the study of drug-drug relations

co-medication in Norwegian elderly and severe drug-drug interactions as examples

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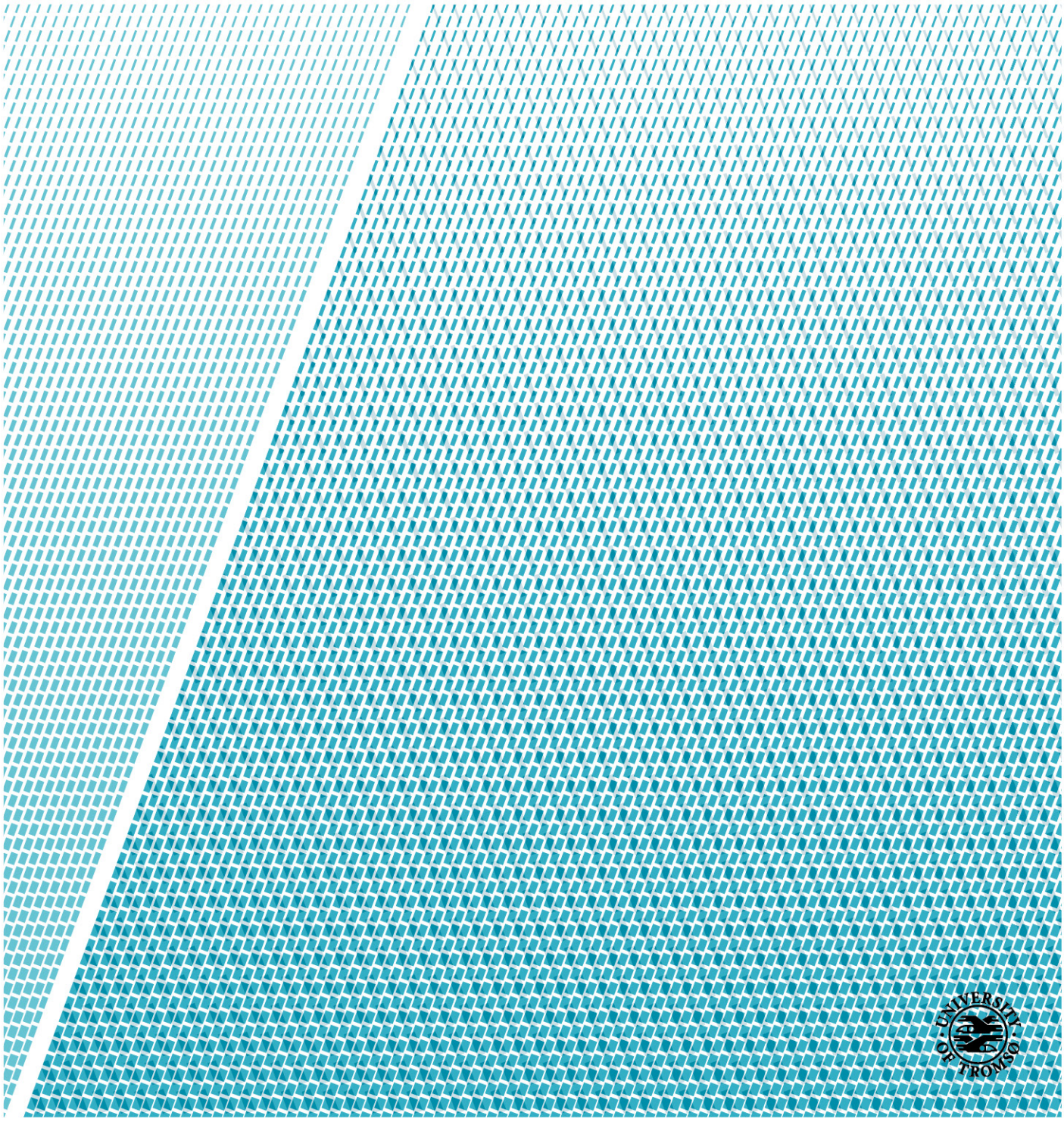

“The fundamental difference between a social network explanation and a non-network explanation of a process is the inclusion of concepts and information on relationships among units in a study”

Katherine Faust

Contents

List of tables v

List of figures vii

Acknowledgment ix

Abbreviations x

Abstract 1

1. Introduction 3

1.1 Background 3

1.2 "Elderly" definition 4

1.3 Co-medication definition 4

1.4 Network analysis 5

1.4.1 A little on network analysis history 5

1.4.2 Graph theory 6

1.4.3 Social Network analysis and public health 6

1.4.4 Drug Prescription Network (DPN) 7

1.5 Structure and types of networks 10

1.5.1 Network matrix 10

1.6 Results of network analysis 11

1.7 Important network measures 12

1.7.1 Density 12

1.7.2 Modularity class 12

1.7.3 Eigenvector centrality 12

1.7.4 Betweenness centrality 13

2. Aims 14

3. Materials and Methods 15

3.1 Data source 15

3.1.1 NorPD 15

3.1.2 FEST database (Prescribing and Dispensing Support Database) 15

3.2 Study population 16

3.3 Inclusion/exclusion criteria 16

3.3.1 Co-medication database exclusions 16

3.3.2 Interactions database exclusions 17

3.4 Data preparation 18

3.4.1 Splitting and merging 18

3.5 Variables 19

3.5.1 Central variables 19

3.5.2 A Little on "time of dispensing" variables 20

3.5.3 Ordinasjonsantall DDD 20

3.6 Defining co-medication 20

3.6.1 A detailed example to clarify the method 23

3.7 For Studying co-medication patterns in 2013 network 24

3.8 For Studying the temporal change in the co-medication pattern 24

3.9 For studying the spatial difference in pattern 25

3.10 Generated networks **25**
3.11 Software **26**
3.12 Ethics: **27**
4. Results **28**
4.1 Part I: Results of Co-medication day 0 network **29**
4.1.1 Network description 29
4.1.2 Modularity classes 32
4.1.3 Patterns of elderly co-medication 37
4.1.4 Studying the six patterns 38
4.1.4.a Cardiac pattern 38
4.1.4.b Anxiety pattern 40
4.1.4.c Acute Respiratory Infection (ARI) pattern 42
4.1.4.d Chronic Obstructive Pulmonary Disease pattern (COPD) 44
4.1.4.e Pain pattern 46
4.1.4.f Menopause pattern 48
4.2 Part II: Comparison of day 0 and 365 networks **50**
4.3 Part III: Comparison of the selected five counties **57**
4.4 Part IV: Drug-drug severe interactions network **60**
4.4.1 Betweenness centrality 62
4.4.2 Applying DDI network on co-medication network (day 0) 65
5. Discussion **68**
Strengths and limitations **86**
6. Future work **89**
8. Conclusion **91**
References **92**
Appendixes **98**
***Appendix 1*: STATA coding** **99**
***A*ppendix 2: Categorization of ATC codes without DDD in the dataset** **104**
***Appendix 3:* Variables description** **105**
***Appendix* 4: The most 200 used drug combinations in 2013 network** **106**
***Appendix 5:* Top 200 combination used in 2014 network** **110**
***Appendix 6:* Eliminated nodes from the generated comparing network** **114**
***Appendix 7:* Top 200 severe DDI in 2013 network** **115**
***Appendix 8:* Anatomical groups severe DDI** **119**

List of tables

Table 3.1: Represents types of study design according to the targeted results 16
Table 4.1 Represents the anatomical groups with their defining colors in the thesis's networks 28
Table 4.2: Day 0 Network main characteristics 29
Table 4.3: Distribution of ATC anatomical groups in day 0 network arranged in terms of being involved in drug-drug combinations from highest to lowest 29
Table 4.4: Represents the most important nodes according to their eigenvector centrality score with the percentage of users in the dataset population 31
Table 4.5: Represents the most 20 combined medicines with the number of times they were combined and the proportion of users in the overall and dataset populations in 2013 31
Table 4.6: Modularity classes with number of nodes and percentage of each module of the whole network 32
Table 4.7: Day 0 network modularity classes after shortening of ATC codes to the second level (3 characters=therapeutic level) sorted after the number of users for each ATC code group 33
Table 4.8: Represents the assumed patterns in each of the four modularity classes after sorting of module [0] 35
Table 4.9: The conducted polypharmacy patterns in the mentioned paper by Exploratory Factor Analysis (EFA) with the used ATC codes in each pattern 37
Table 4.10: Network characteristics for cardiac subnetwork 38
Table 4.11: The most used medicines in cardiac subnetwork, degree centrality shows how many times these medicines were combined with other nodes 38
Table 4.12: Represents the most combined medicines in cardiac network showing number of times each two nodes were combined 38
Table 4.13: Network characteristics for Anxiety subnetwork 40
Table 4.14: The most used medicines in Anxiety subnetwork with degree and eigenvector centrality 40
Table 4.15: The most combined medicines in Anxiety subnetwork showing number of times each two nodes were combined 40
Table 4.16: Network characteristics for ARI subnetwork 42
Table 4.17: The most used medicines in ARI subnetwork, degree centrality shows how many times these medicines were connected to other nodes 42
Table 4.18: The most combined medicines in ARI subnetwork showing number of times each two nodes were combined 42
Table 4.19: Network characteristics for COPD subnetwork 44
Table 4.20: The most used medicines in COPD subnetwork, degree centrality shows how many times these medicines were connected to other nodes 44
Table 4.21: The most combined medicines in COPD subnetwork showing number of times each two nodes were combined 44
Table 4.22: Network characteristics for Pain subnetwork 46
Table 4.23: The most used medicines in Pain subnetwork, degree centrality shows how many times these medicines were connected to other nodes 46
Table 4.24: The most combined analgesics with other drugs in Pain subnetwork showing number of times each two nodes were combined 46
Table 4.25: Network characteristics for Menopause subnetwork 48
Table 4.26: The most used medicines in Menopause subnetwork, degree centrality shows how many times these medicines were connected to other nodes 48
Table 4.27: The most combined medicines in Menopause subnetwork showing number of times each two nodes were combined 48
Table 4.28: Comparing basic network characteristics for network day 0 and 365 50
Table 4.29: Network characteristics for the generated network 50
Table 4.30: Number and percentage of unique edges in both networks 50
Table 4.31: Anatomical ATC distribution in 2014 network, showing difference in percent from 2013 network 51
Table 4.32: Drug-drug combining frequency change in 2013,2014 networks 51
Table 4.33: The top most used drugs in 2014 more 2013 according to ratio of users 52
Table 4.34: The least used drugs in 2014 than 2013 according to ratio of users 52

Table 4.35: The top drug-drug combinations which were more used in 2013 than 2014. Ratio represents number of patients have combined the two medicines in 2013 over the number of patients used the same combinations in 2014. ..... *53*
Table 4.36: The top drug-drug combinations which were more used in 2014 than 2013. Ratio represents number of patients combined the two medicine (edges) in 2014 over 2013 ..... *53*
2014 full Network *56*
2013 full Network *56*
Compare Network (full) *56*
Table 4.37: Prescriptions' distribution in the five counties *57*
Table 4.38: A comparison between network characteristics for the 5 counties *57*
Table 4.39: The most combined medicines in the 5 counties *58*
Table 4.40: Eigenvector Centrality comparison for top 10 high-scored nodes in the 5 counties *58*
Table 4.41: Represents the total number of interactions and number of interactions in each severity level in FEST database *60*
Table 4.42: Drug-drug severe interactions network characteristics. *60*
Table 4.43: The 10 ATC codes with highest number of interactions in the severe drug-drug interactions network *61*
Table 4.44: Represents the medicines with the highest betweenness centrality score in severe DDI network *63*
Table 4.45: Day 0 severe interacted medicines network characteristics, edges range here indicates how many users have combined these interacted drugs *65*
Table 4.46: The most 30 frequent severe DDI in day 0 network *67*

List of figures

Figure 1.1: Uses of Network analysis in Public Health field 9
Figure 1.2: Directed, undirected and weighed (valued) networks 10
Figure 1.3: An example of a "weighed edges" matrix of actors, ATC codes, showing how many times where each ATC codes were combined with other ATC codes (i.e. weighed edges) 11
Figure 1.4: Showing the final form of an undirected weighed network; where ATC codes are nodes and co-medication are edges, thicker edges means more users (combining times) for this drug-drug combination 11
Figure 3.1: Study timeline 15
Figure 3.2: Exclusion criteria for co-medication prescription dataset 17
Figure 3.3: Exclusion criteria for DDI from FEST dataset 18
Figure 3.4: Representing data splitting and merging preparation plan. 19
Figure 3.5: An example of calculating MRP and PDC 21
Figure 3.6: Representing the defining of treatment episodes 22
Figure 3.7: Represents how treatment episodes were defined 24
Figure 3.8: The generated networks in this study 26
Figure 4.1: Represents the full network of day 0, no filters applied. Edges were removed for simplifying. Different colors indicate different anatomical groups. Size of nodes corresponds the number of edges each node has (co-medication with other nodes). 30
Figure 4.2: Representing day 0 network modularity classes. Bigger nodes indicate greater number of users, colors here do not represent the anatomical group colors. 32
Figure 4.3: Cardiac weighted network, filtered for number of users>460 and edge weight >250, bigger nodes indicate greater number of users. 39
Figure 4.4: Anxiety weighted network filtered for number of users >96 and edge weight >100, bigger nodes indicate greater number of users. 41
Figure 4.5: ARI weighted network, filtered for number of users and edge weight >100, bigger nodes indicate greater number of users 43
Figure 4.6: COPD weighted network, filtered for edges >100. Bigger nodes indicate greater number of users 45
Figure 4.7: Pain weighted network, filter for edges weight> 50. Bigger nodes indicate greater number of users 47
Figure 4.8: Menopause weighted network, no filters applied. Bigger nodes indicate greater number of users 49
Figure 4.9: Day 365 (2014 network) with no filters applied, bigger nodes indicate greater number of co-medications 54
Figure 4.10: Compare network, node size indicates ratio of users in 2014/2013 the bigger nodes the greater proportion of users in 2014 compared to 2013. 55
Figure 4.11: Representing the three full networks (2013, 2014 and the compare network) in form of nodes. Bigger nodes indicate being involved in a greater number of co-medication (edges). 56
Figure 4.12: Full networks for the five counties, bigger nodes indicates higher number of edges 59
Figure 4.13: A heat map of anatomical groups severe interactions, the darker the color the more interactions the group is involved in. 60
Figure 4.14: Full severe DDI Network, colors indicate anatomical groups, bigger nodes indicates greater number of interactions 62
Figure 4.15: DDI network filtered for betweenness centrality to show only the top 20 scored drugs in betweenness centrality score (score>2323687), bigger nodes indicate higher score. 63
Figure 4.16: Whole DDI network showing location of top 20 betweenness centrality drugs in the network 64
Figure 4.17: DDI network after removing Histamine HCL node showing disconnection of a part of the network 64
Figure 4.18: Weighted network of severe DDI in day 0 network, no filters applied, thicker edges indicate higher frequency of combinations, bigger nodes indicate greater number of users. 65
Figure 4.19: Weighted network of severe DDI in day 0 network filtered for >900 users for drugs (nodes). Bigger nodes indicate greater number of users 66
Figure 5.1: Represents the main objectives of this thesis 68
Figure 5.2: A summary of network analysis possible functions 70
Figure 5.3 Norwegian ministry of health guidelines for primary prophylaxis in elderly considering both clinical and economic point of views. 74
Figure 5.4: An example of betweenness centrality score on a small graph 83

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Abbreviations

ADEs	Adverse Drug Events	**LABA**	Long-acting Beta2 agonists
ARI	Acute Respiratory Infection	**LAMA**	Long-acting muscarinic antagonists
ASA	Acetylsalicylic acid	**MPR**	Medication Possession Ratio
ATC	Anatomical Therapeutic Chemical	**NA**	Network Analysis
CNS	Central Nervous System	**NorPD**	Norwegian Prescription Database
COPD	Chronic Obstructive Pulmonary Disease	**ONA**	Organizational Network Analysis
DDD	Defined Daily Dose	**PDC**	Proportion of Days Covered
DDI	Drug-drug Interactions	**PPI**	Proton-pump inhibitors
DPN	Drug Prescription Network	**SLV**	Statens legemiddelverk
EFA	Exploratory Factor Analysis	**SNA**	Social Network Analysis
EPR	Electronic Patient Record	**WHO**	World Health Organization
GERD	Gastroesophageal Reflux Disease		
GPs	General Practitioner		
HELFO	The Norwegian Health Economics Administration		
INSNA	International Network for Social Network Analysis		

Abstract

Network analysis (NA) has been used for studying many social aspects. Employing of network analysis as an approach in the field of public health, to study the relations between patients or health workers and their potential effects in many medical perspectives, took a good share of researchers' efforts as well. Few attempts have been conducted to use network analysis to study drug-drug relations using medicines as the main actors in the network instead of persons.

We aimed at two primary objectives; a methodological objective and a clinical one. The methodological is to define the co-medication in a more reliable way and to use NA as an approach to map and extract the co-medication patterns in the elderly. Afterwards, to comment on the relevant clinical information represented in these networks.

We represented two examples of drug-drug relations in the form of networks; i) The elderly co-medication in Norway in three years (2012-2014). The data was extracted from the Norwegian Prescription Dataset (NorPD) and included 61,930,313 prescriptions of 342,451 men (45%) and 419,455 women (55%), in total 761,906 patients. The mean age of the study population is 75 years. ii) The severe Drug-drug Interactions (DDI) based on the drug-drug interactions from the Prescribing and Dispensing Support dataset (FEST) with a total of 57,151 sever interactions.

In our thesis, co-medication was defined as treatment episodes. Determining these episodes depends on the time of prescriptions' dispensing, the Defined Daily Dose (DDD) of each drug, assuming 80% of patients' adherence. We used the Proportion of Days Covered (PDC) to measure the adherence. We allowed a gap of 14 days as an accepted medical-free period between the treatment episodes. After defining the treatment episodes for each patient, a prevalence point was chosen to study the co-medication pattern in it. This approach in defining co-medication allows flexibility in choosing the studied prevalence points.

Six different elderly co-medications patterns were extracted from our primary network. Comparing co-medication patterns in two prevalence time points, with a one-year difference, revealed changes in use, number of users, and prescribed patterns.

We used "betweenness centrality", a specific NA measure, to obtain the drugs with the most contribution in the severe interactions. The network showed 662 severe DDI in the studied treatment episode with a range of 1 to 2320 patients who were exposed to these severe interactions.

We concluded that network analysis, as an approach, can be effectively used in visualizing and studying drug-drug relations with some unique descriptive measures.

1. Introduction

1.1 Background

Studying the patterns of co-medications has increasingly become an essential part of the medical field study. Its importance arises, among others, from that it highlights prescribing quality (1), contributes in finding out undesired medications' side effects, decreasing the risk of drug-drug interactions (DDIs) and studying patterns' change across time and space (2).

As known, the elderly are more exposed to cumulative, continuous and simultaneous polypharmacy (3) than younger ones. Although medicines can reduce elderly morbidity and mortality, they also may have adverse effects (ADEs) which can represent a potential danger (4, 5). Integrative and systematic reviews[1] held on ADEs and DDIs on elderly reinforced that co-medication, polypharmacy and unfortunate prescribing are global significant issues among the elderly. In a systemic review of 14 studies which subjected the elderly (≥ 65 years), the prevalence of inappropriate drug use ranged from 27% to 56% (7). Another integrative review of 47 studies form different countries with about 14 million patients ,in total, aged ≥ 60 years emphasizes that ADEs and DDIs related to polypharmacy in elderly populations are significant issues worldwide (8).

In addition to this; the elderly have many other factors which can increase the risk of undesired medicines' effects such as renal (9), hepatic (10), which are mainly responsible for drugs metabolism, and mental conditions compared to younger people.

In particular, Norwegian elderly have a high mean of age (1 of 9 persons are aged 70 years or older), this percentage is expected to be 1 of each five persons in 2060 (11). Elderly poses a significant proportion of drug users in Norway. Statistics from Norwegian prescription dataset (NorPD) shows that 91% in 2011 and 92% in 2017 of the elderly population had at least one drug dispensed. The data also indicates that 57% in 2011 and 58% in 2017 of the elderly population used more than five drugs. In 2017, 23% of drug users over 65 years were prescribed more than 10 different drugs during the year (12, 13).

[1] The primary difference between systematic and integrative reviews is the types of studies included. The systematic reviews often include randomized clinical trials, while integrative studies may include other types of research. Furthermore, integrative studies are more of discussion to findings. (6. McGrath MJ. Systematic and Integrative Reviews of the Literature: How Are They Changing Our Thoughts About Practice? The Journal of Perinatal & Neonatal Nursing. 2012;26(2):193-5.).

Because of this, it is important to study the co-medication patterns and DDI in the elderly population in order to provide solutions for the potential problems related to polypharmacy (14).

Before moving on, it is important to define and explain some basic concepts and terms. The next paragraphs will therefore focus on defining the elderly, co-medication, and network analysis.

1.2 "Elderly" definition

Although there are commonly used definitions of the elderly (15), there is no general agreement on the age in which a person becomes old. The Norwegian Institute of Public Health has accepted defining elderly as ≥ 65 years in age (13) based on a paper written in 2002 to define the elderly. This paper was published on the website of World Health Organization (WHO) claiming that determining of elderly definition starts with 65 years old (16).

In a statistical study published in 1999 by "Statistics Norway", the elderly were defined as people who are 67 years of age or older (17). In this thesis, we will define the elderly as 65 years old or older.

1.3 Co-medication definition

It's important to shed light on what is meant with co-medication since it will consequently define which kind of results will be extracted. For instance, if co-medication is explained as the group of drugs which were prescribed from the same prescriber, results will reflect the quality of prescribing (18) and to what extent it follows the guidelines, meanwhile if it is interpreted as simultaneously use of some drugs regardless of the prescriber, results will revolve around, among others, co-morbidity, drug-drug interactions (DDI) (19), and undesired drug combinations (1).

The prefix 'co-' means joint; mutual, or common (20). Hence, "co-medication" means jointly using two or more medications. Generally, four main aspects are to be taken into consideration when co-medication is being defined: patient, prescribers, time of prescriptions' dispensing and overlapping use of drugs in a 'time window' either based on Defined Daily Dose (DDD) (21) or not (22).

1.4 Network analysis

According to John Scott (23), the principal types of data are "Attribute data" and "Relational data". Attribute data studies the characteristics of objects (observations), for example, education, income, etc. while relational data care about ties and connections between these objects themselves. The suitable way of studying attributes data is *variable analysis*, however, in the case of relational data, *network analysis* is the appropriate type of analysis (24).

Network Analysis science (NA) has its roots in many sciences such as mathematics, statistics, sociology, and computer science. NA can represent a description of a real world system, a mathematical model or a simulation (25). It introduces also an ecological research approach which is uniquely suited for describing and discovering the structure of relational data. Today, it is increasingly common to employ network analysis for the study of complex systems in fields of biology, sociology and information science.

Like all other fields, the healthcare sector has become rich in electronic databases such as prescription databases and patients' journals. These types of databases are rich sources of information for researchers and decision makers. Different data analytical techniques are now used to understand and interpret many aspects of medical healthcare such as the economic side, effectiveness, and quality of services. Social Network Analysis (SNA) as a quite new analytical approach for healthcare study is believed to introduce a unique ability to explore the medical data (26). Rather than the other analytical approaches, NA focuses on relationships between subjects themselves not relationships between subjects' attributes (i.e., variables) (25).

1.4.1 A little on network analysis history

Developing the concept of the network as a pattern studying tool started about two centuries ago. "Leonhard Euler" (1707-1783) founded the graph theory in order to solve a famous problem in the18th-century. The problem issued if it was possible to walk around the town of Königsberg, (now Kaliningrad, Russia) crossing each of its seven bridges only once and return to the starting point. By using a network of nodes and links Euler showed that the famous mathematical problem wasn't possible to solve and that it was impossible to walk through the city crossing all its seven bridges only once (27).

1.4.2 Graph theory

$$G = (V, E)$$

The theory of NA has its bases in two separate fields; social sciences and mathematics (i.e. graph theory) (28). Graph theory is one of the mathematical foundations for NA in which a graph *(G)* consists of two elements vertices *(V)* or nodes and Edges *(E)*, links or ties.

Another early attempt in the 19th century carried out by the Norwegian ethnologist "Eilert Sundt" (1817-1875), who noticed the formation of social circles among rural Norwegian farmers. Eilert wrote about what he called "*bedelag*" (29) or an "invitation group" which means in the old Norwegian traditions that neighbors who live nearby invite each other to their occasions, such as weddings, and hence forming a sort of isolated circles. (30, 31).

Since that; the attempts from different sociologists, phycologist, and mathematicians were continued to use and develop NA bases, structures and models. Over the past decades, NA use has been developed in an extensive variety of fields such as psychology, sociology, political science, communications, business, statistics, and computer science. Today there is an organization called "International Network for Social Network Analysis" (INSNA), a professional association which publishes only researches concern social network analysis (25).

1.4.3 Social Network analysis and public health

Public health is an important observational field of study with some descriptive and relational characteristics. Using NA in this field is not a new approach. *Transmission networks* have been used to examine the potential risk of diseases transmission based on the relation between the infected people with the surrounding people (28, 32-34). This approach allowed researchers to predict (from the first few cases) the scale of close outbreaks and to take preventive measures.

Another form of the transmission network is the *information transmission network* which helps to show the dissemination of public health information to different organizations and consumers. Some network characteristics (such as centrality measures) reveal which actors contribute the most at spreading of such information.
Furthermore, researchers have developed simulation networks that describe diffusion properties and predict how could the information spread be faster or more efficient (35).

Studying health workers' behavior depending on SNA took a good share of researchers' efforts as well. Interaction social networks have been studied to expose these workers' impact on health services (36). This is considered a form of *Organizational network analysis* (ONA) which cares about the formal/informal relations inside the one organization and their reflection on information spread and business effectiveness. (37).

Researchers moved a step forward in the concept of using SNA nodes to apply the idea on organizations not on individuals and hence starting a new field called *Interorganizational network analysis*, which reveals interactions exist between collaborative agencies and mainly differs from SNA in that networks' nodes comprise of agencies or organizations, not individuals (38, 39).

In the field of *biomedicine* and systems pharmacology network analysis is now widely and effectively used to analyze and map the effects and interactions of different lead compounds and drugs on drug targets, promising to increase the knowledge of the mechanisms underlying the multiple actions of drugs (40, 41).

1.4.4 Drug Prescription Network (DPN)

Another step in-depth, a few tries have been held to apply the approach on drugs themselves as actors; the same fundamental idea of network analysis, but this time with using medicines or drugs as actors instead of individuals or organizations.

To our knowledge, a few studies have been conducted using NA as an approach to understand and analyze drug-drug relations patterns. Cavallo et al. published in 2013 an important paper on the co-medication pattern based on six-month prescriptions by 99 General Practitioner (GPs) in Italy. The study was mainly conducted for visualizing of co-prescription pattern and proposed that it was possible to apply network science as a tool to study public health phenomena from a new, different perspective. To reduce the complexity of networks, they shortened the ATC codes to the second ATC-level (anatomical, therapeutic level) showing and comparing the frequency of combining between different anatomical groups in different age and sex segments of the study population (42).

Another important paper which studied the co-medication pattern was published by Bazzoni et al. in 2015. The study aimed to generate, analyze and compare various drug prescription network (DPN) to unveil possible differences in drug co-prescription patterns across time and space. By time they meant a temporal change in co-prescription pattern in different periods, while space indicates different regions or wider territories in Italy. By studying of density, modularity, and other networks' measures of DPN the researchers concluded the importance of NA as an approach to analyzing co-medication networks with a recommendation of further studies in this concern. They highlighted also that one of the significant features of the new network-based method is the ability to display trends in the co-prescription of a given drug within the context of the general co-prescription practice (2). The paper was a sort of technical study more than a clinical one.

These two studies had some limitations; due to the few nodes scale and shortening of the ATC codes to the second level (i.e. Cavallo) or showing a few relevant clinical results (i.e. Bazzoni). Hence, this thesis is an extension to these attempts on a larger scale of data (on both prescriptions and patients scale) and on the complete ATC level.

In a conference abstract by "Kristian Svendsen" for studying changes in drug utilization in elderly patients before and after being admitted to geriatric ward, the abstract showed a change in the trend of co-medicated drugs after hospitalizing (43).

To our knowledge, no published study has used network analysis to study *the general* DDI as a form of a relation between medicines. Uses of network analysis in public health are summarized in (figure 1.1).

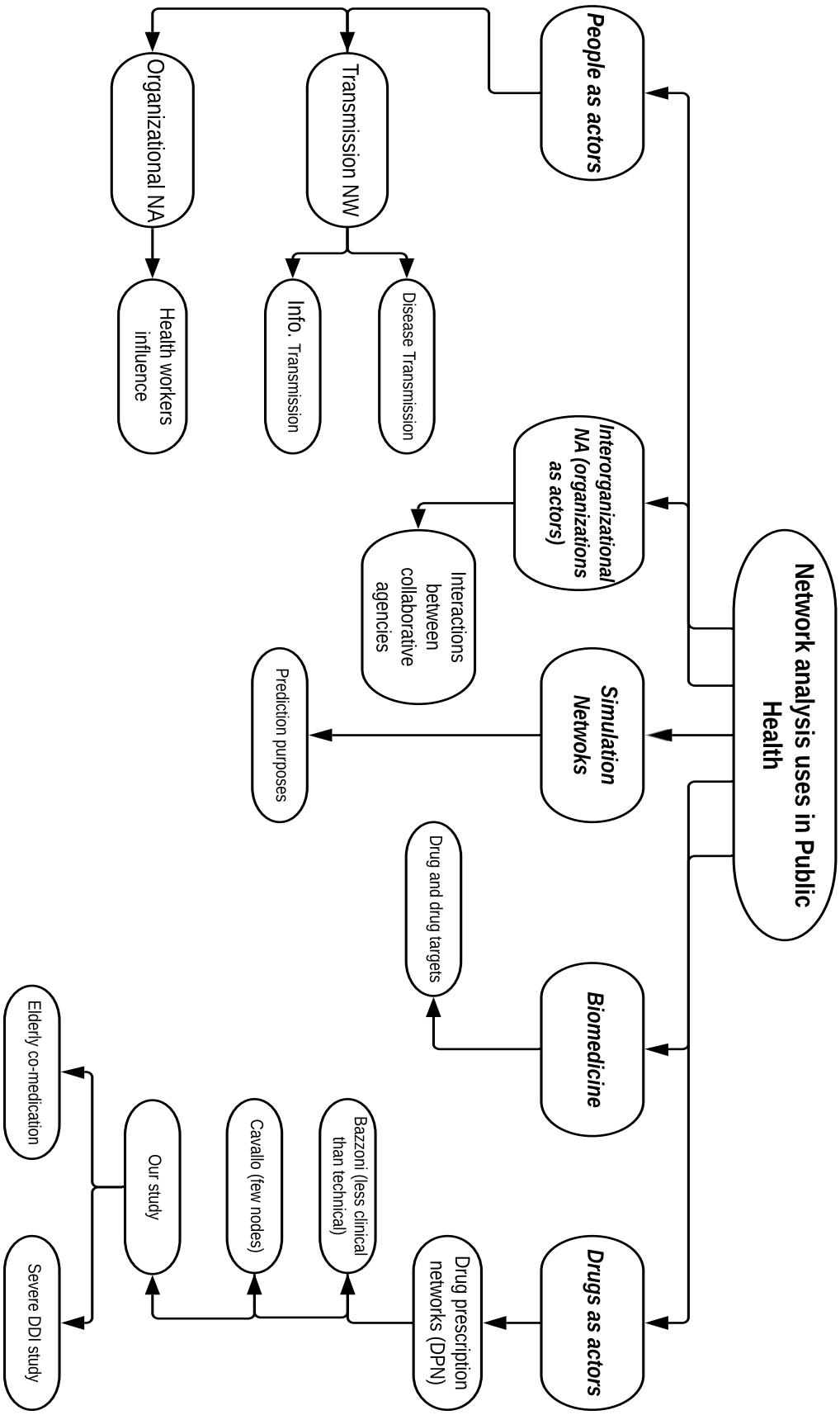


Figure 1.1: Uses of Network analysis in Public Health field

1.5 Structure and types of networks

Networks consist primarily of "Nodes" which represents individuals or actors and "Edges" or "Links" which correspond a kind of relation between these actors (44).

A network can be *directed* which means the edges go in a specific order from a node (A) to (B), for example, or *undirected* which means there is no distinction between the two connected nodes in terms of which one started the relation (figure 1.2).

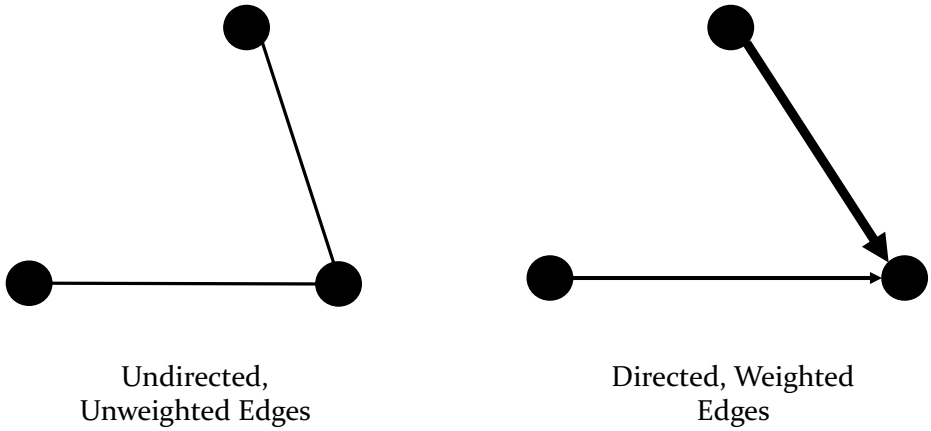


Figure 1.2: Directed, undirected and weighed (valued) networks (Source: The Oxford Handbook of Quantitative Methods in Psychology, Vol. 1)(45)

Network edges can also be weighed or unweighted (figure 1.2), *unweighted* means that the two nodes are either linked or not (0 or 1) (a qualitative type of analysis), while *weighed* considers how many times these two nodes were connected by a sort of relation (also called edge thickness or tie strength) (46). In other words, it shows the intensity of this sort of relationship between these two nodes (a quantitative type of analysis).

1.5.1 Network matrix

To plot a network, the collected data must be held in what is called the *data matrix* (figure1.3) (47). In the case of attribute analysis, the data is arranged in a case-by-variable matrix. For relational data (i.e. network analysis), the matrix represents the intensity of the affiliation between the actors (nodes) in the form of numbers which represent if there is an affiliation or not (0,1) or how many times were these actors connected together in the studied context (weighed matrix) (24).

Figure (1.3) and (1.4) represent a matrix of a simple weighed network and the resulted network. This example matrix gives us the network in the following diagram; the thicker lines between ATC codes indicate higher intensity of co-medication.

	ATC1	***ATC2***	***ATC3***	***ATC4***	***ATC5***	***ATC6***	***ATC7***
ATC1	-	1	14	6	9	11	0
ATC2	1	-	22	5	10	26	2
ATC3	14	22	-	3	15	5	4
ATC4	6	5	3	-	4	0	7
ATC5	9	10	15	4	-	0	8
ATC6	11	26	5	0	0	-	0
ATC7	0	2	4	7	8	0	-

Figure 1.3: An example of a "weighed edges" matrix of actors, ATC codes, showing how many times where each ATC codes were combined with other ATC codes (i.e. weighed edges).

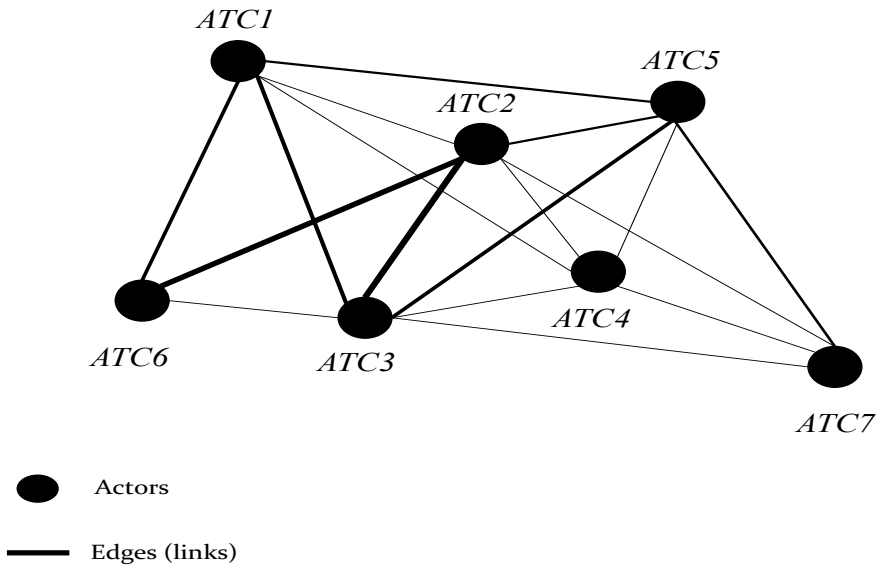


Figure 1.4: Showing the final form of an undirected weighed network; where ATC codes are nodes and co-medication are edges, thicker edges means more users (combining times) for this drug-drug combination.

1.6 Results of network analysis

Generally, in NA there are three broad outcomes are resulted; visualization, descriptive analysis and constructing of inferential or longitudinal network models (25). Visualizing allows researchers to represent the network information in a graphic format (with a wide variety of presenting ways) providing some answers which might not be captured by statistical tests.

A Network is fundamentally descriptive; this capability can highlight roles of important actors, how central they are for the network, which sub-groups and clusters are present in the network in many more other results than traditional descriptive analysis ways. Finally, Inferential (48) and longitudinal models (49) vary and are developed to fit the supposed hypothesis.

1.7 Important network measures

1.7.1 Density

It is one of the NA primary measures. The density of a network is the total number of *actual* edges (ties) divided by the total *possible* number of edges that could occur (50). It is scaled between 0 and 1, in which 1 indicates high density and 0 refers to low density. For instance, if we have six actual edges and all the possible edges that could exist in the network are 10, so the density of this network will be 0,6. The density measure is useful as a tool for comparing networks to show the crowdedness of each network and the difference in coordination between actors in different networks (51).

1.7.2 Modularity class

It is also called "community structure detection" and is concerned about finding sub-networks (clusters) in the large-scale networks. Different algorithms can be used to shed light on the locations of "communities" in the complex networks (52) with advantages and disadvantages of each. Gephi (the software used in this thesis) uses *Louvain* method for community detection. This method has many benefits, such as it is easy to implement, and it can handle complex and weighted networks. This method also provides higher quality results in terms of community detection compared to many other algorithms (53).

1.7.3 Eigenvector centrality

It is a measure of the importance of a node in a network based on the node's connections with the other vital nodes. Relative scores are then given to all nodes in the network based on the concept that; connections to high-scored nodes give a higher score to the node than equal connections to low-scored nodes. In other words, high eigenvector score means that a node is connected to many nodes which, themselves, are connected to important nodes in the network and have high scores of eigenvector centrality. This means that a node with high eigenvector centrality score isn't necessarily linked to the highest number of nodes in a network but is necessarily linked to the most critical ones

(54). This type of centrality differs from *Degree centrality* which counts all the connection to the studied node *equally*.

1.7.4 Betweenness centrality

A node betweenness centrality measures how often this node appears on the shortest paths between the other nodes in the network. In other words, it is the number of times a node connects pairs of other nodes, which ,otherwise, would not be able to reach each other (50). This means if we remove theses nodes first, there is a high probability to cut the network into many unconnected components. Higher betweenness score indicates higher power or efficacy of the node in the network.

2. Aims

The primary objective of this thesis is to test network analysis as a method to study drug-drug relations. To be able to do this, we created a definition for co-medication.

We used network analysis to study two types of drug-drug relations; co-medication and severe drug-drug interactions as examples of the relevant clinical analysis.

- **Studying co-medication patterns**

By mapping the co-medication pattern(s) in the elderly, comparing pattern change between two different years (temporal change), determining if there is a geographic pattern change choosing five different counties in Norway (spatial change), and discovering underlying patterns in the whole network.

- **Studying Drug-drug interactions (DDI) pattern**

We aim also to study severe drug-drug interactions, first, for all substances. Further, to apply this network on the generated co-medication network to highlight the interactions in the elderly population.

3. Materials and Methods

3.1 Data source

3.1.1 NorPD

Elderly prescriptions' dispensing data from the Norwegian Prescription dataset (NorPD) from 2012-2014 was used (figure 3.1). In Norway, it is mandatory for all pharmacies to send a monthly electronic data report of all prescriptions dispensed to patients to the Norwegian Institute of public health since 1. January 2004. All the data is then gathered in NorPD. This means that only the prescriptions were dispensed to patients, rather than prescribed, are included in the database (55).

NorPD dataset variables can be grouped into four main categories:

1. **Prescriber information**: which includes anonymous ID, date of birth and sex
2. **Patient information**: which involves anonymous ID, birth and death date, sex and municipality
3. **Dispensing information**: date of dispensing
4. **Prescription information**: which contains information about dispensed medicines, ATC codes, Defined Daily Dose (DDD), and refund information. (56)

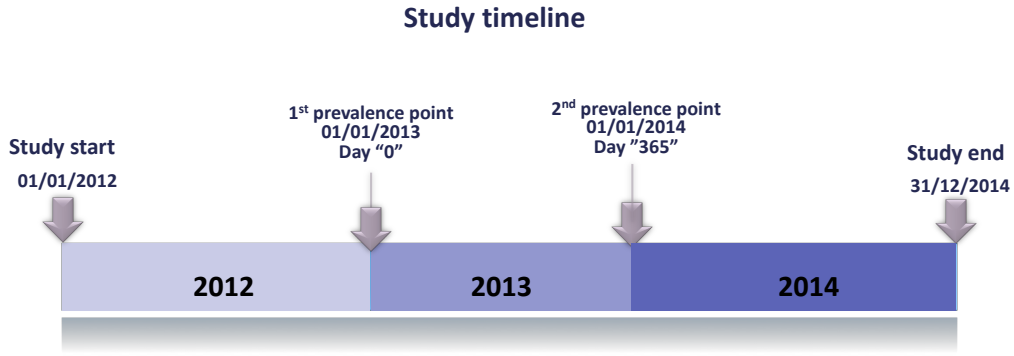


Figure 3.1: Study timeline

3.1.2 FEST database (Prescribing and Dispensing Support Database)

FEST is the Norwegian Medicines Agency's (SLV Statens legemiddelverk) database of information which is used for decision support in electronic prescriptions (E-resepter) and Electronic Patient Record (EPR) systems. The database is also used by the computer systems in the community pharmacies. FEST is used in online services such as e.g. interaksjoner.no (interactions checker) and felleskatalogen.no (Norwegian online drug formulary). The database, generally, contains the basis of information that physicians, hospitals and pharmacies need. Drug-drug interactions is a part of FEST database.

Our data file has eight variables; ATC code, name, and group for drug 1" and same for drug 2, interaction ID (on FEST system) and the severity grade of interaction. In the severity of

interactions variable; [1] indicates dangerous interactions which is the concern of this thesis, [2] indicates moderate, and [3] indicates minor interactions. In the dataset we have, the interactions between ATC codes are, mostly, mentioned in a directed way, this means if there is an interaction between A and B substances for example, these interactions will be mentioned two times once from A→B and another from B→A. Meanwhile, some interactions were just mentioned once.

3.2 Study design

Study design varies according to the targeted result as follows in (table 3.1).

Table 3.1: Represents types of study design according to the targeted results

Targeted result	Type of study
Co-medication pattern visualizing	Cross-sectional
Drug-drug interaction	Cross-sectional
Temporal change (change over time)	Longitudinal
Spatial change (change over the place)	Cross-sectional

3.2 Study population

Patients who were ≥ 65 in 2013 and had one or more prescription in the NorPD dataset are included in our study. The dataset we got from NorPD contains 61,930,313 prescriptions of 342,451 men (45%) and 419,455 women (55%), in total 761,906 patients. The mean age of the study population is 75 years. According to Statistical Yearbook of Norway (the year 2013), the total elderly population in 1st January 2013 was 790,614 (57) which means that our study has involved approximately 96,4 % of the total elderly population in this period.

3.3 Inclusion/exclusion criteria

All patients who were 65 or older in 2013 and had at least one prescription or more in NorPD in the study period.

3.3.1 Co-medication database exclusions

a) **Age**: Only patients aged 65 years or older in 2013 were included, patients who were born after 1948 (younger than 65 years in 2013) with total 49,244 prescriptions excluded.
b) **Missing ATC values:** 0 observations were excluded
c) **ATC code without DDD**: As comes after (methods 3.6), DDD is central for our definition of co-medication, so ATC codes without DDD were filtered out (figure 3.2). Major drug groups which have no definite DDDs are: topical products (most products in anatomical group D), immune sera (ATC group J06), vaccines (ATC

group J07), antineoplastic agents (ATC group L01), anesthetics (ATC group N01), ophthalmological and otologicals (most ATC in group S) (58).

Total unique ATC codes without DDD found were 357 codes, divided into 217 non-systemic medicines and 140 systemic medicines. Total prescriptions excluded out was 2,411,888 which forms 3,9 % of overall prescriptions. Detailed information of excluded ATC codes and their classifications are attached in (appendix 2).

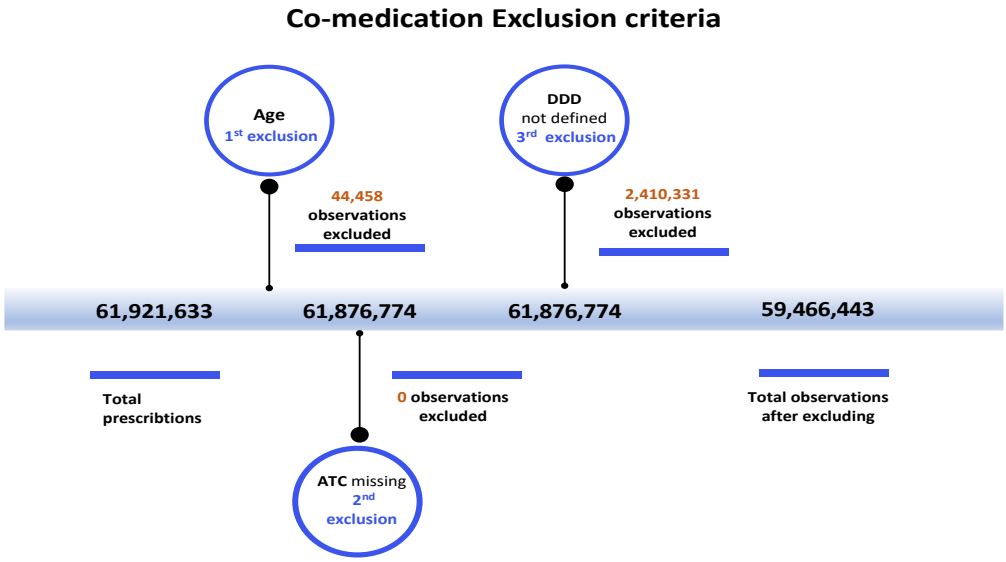


Figure 3.2: Exclusion criteria for co-medication prescription dataset

3.3.2 Interactions database exclusions

a) We excluded substances without ATC codes, for example, substances which may have interactions with medicines but have no ATC codes (e.g. Alcohol and natural products).
b) All ATC codes shorter than 5th level (incomplete ATC) were excluded.
c) Repeated names and ATC codes to avoid having the same substances which have more than one ATC code.
d) Only severe interactions were included.
e) A separate variable for combination products (i.e. drugs which contains more than one active ingredient) is created to be able to exclude/include them in the analysis if needed, (figure 3.3) (combinations were included in the study).

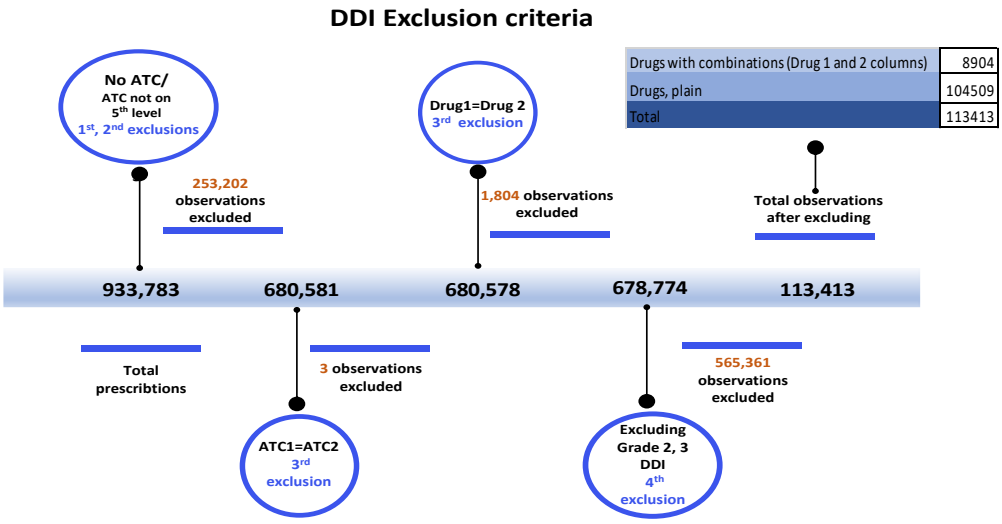


Figure 3.3: Exclusion criteria for DDI from FEST dataset

3.4 Data preparation

3.4.1 Splitting and merging

The raw material of data we had was chunked into 15 files. We split each of these 15 files into two files in terms of the time format of prescriptions dispensing variable, we had two different time of dispensing forms (as follows in 3.5.2) one for patients who were hospitalized (in form of *difference in days* of the of hospitalizing) and the other for NorPD prescriptions (in the form of *date* of dispensing).

Then each group of files with the same form of time of dispensing were merged to form two big files for each; difference in days of dispensing (hospitalized) with (21,067,741) prescriptions and normal dispensing date includes (40,853,892) prescriptions (figure 3.4).

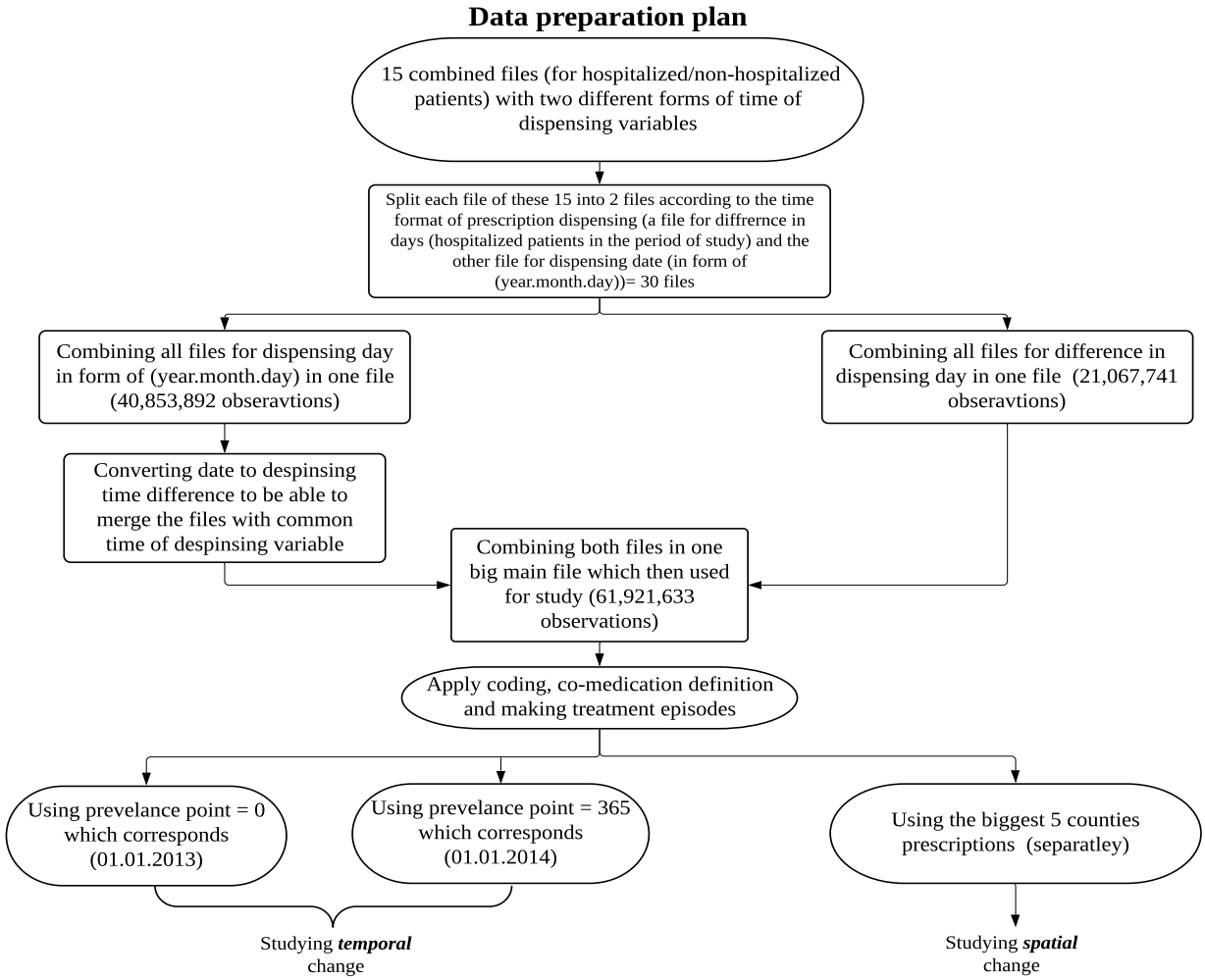


Figure 3.4: Representing data splitting and merging preparation plan.

3.5 Variables

The dataset consists of 29 variables (detailed prescription on variables attached in appendix 3). Not all the variables are used; only a few variables are central for our study.

3.5.1 Central variables

The variables of the most interest are “pasientlopenr” (patient’s anonymized identification number), “diff_utleveringdato” (difference, in days, of prescriptions’ dispensed dates from the first day of hospitalization for the patients who were hospitalized in the study period), “utleveringsdato” (date of prescriptions’ dispensing), “ordinasjonantallddd” (number of defined daily doses (DDD) dispensed in a prescription) and “atckode” (ATC codes). Sorting of observations is done in the following order; first, the patient number, then ATC codes and at last on date of dispensing.

3.5.2 A Little on "time of dispensing" variables

Our dataset has two different forms of time of dispensing. The time of dispensing variable for non-hospitalized patients in the study period in the form of a complete date "YYYY-MM-DD" and this the normal time dispensing format in NorPD (59), while for patients who were hospitalized during the period of study the time variable is in a form of difference in days between the prescription dispensing date and the date of *first* hospitalizing which is unknown for us (for anonymization purposes) and differs from a patient to another. For example, if a patient was hospitalized in 1st of March 2012 and later picked up a prescription in the pharmacy in 15th of April 2012 then the time of dispensing for this particular prescription will be "46" which corresponds the difference in days between the day of hospitalizing and the day of prescription dispensing.

We created a new variable for dates in order to have a single form of time format. We converted the dispensing date variable to a difference in days from a particular day we chose which is 1st of January 2013.

3.5.3 Ordinasjonsantall DDD

It represents the total number of DDDs dispensed to a patient for each dispensed prescription. For example, if a patient picked up two boxes of a drug (A) which has 100 tablets each, and the defined daily dose of this drug is two tablets daily, then the "ordinasjonantallddd" is 100 which corresponds 100 days' supply.

3.6 Defining co-medication

Our study period is three years, this period can contain many medication (i.e. treatment) episodes with a probability of medicine-free periods or periods with different medications, thus taking the whole three years (as a number of days) will create a potential information bias. Therefore, another approach depends on Defined Daily Dose (DDD), prescription date of dispensing combined with assumed patients' adherence (defined as the proportion of days covered (PDC)) and a specific gap period, was obtained. After that, we chose specific dates to study the co-medication as prevalence time points as follows.

DDD is central for co-medication definition in this thesis. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication for adults (58).

Treatment episodes are made up based on DDD of each medicine after sorting prescriptions after patient and ATC codes, then DDD of each ATC code is summed, and the difference in days between two followed prescriptions for the same ATC codes is calculated.

Adherence is defined as to what extent a person' compliance to medical instructions corresponds with agreed recommendations from a health care provider (60) (61).
Studies show that most elderly with polypharmacy are associated with poor adherence (62). There is no absolute guarantee for researchers to assure 100% of patients' compliance. However, the advantage of including adherence in our defining approach is that it will, somehow, specify the patients' actual use of medicines. Consequently, this will make the results more reliable.
The threshold of adherence was chosen to be 80% adherence (63); this means the patient has a 80% of compliance to his daily dose.

We chose to use the Proportion of days covered (PDC) as an approach of measuring adherence. In PDC we count the *actual* number of days covered by a prescription, taking into consideration if there was an overlapping of medicines refill (carryover) (64) (figure 3.5). This carryover concept of PDC method may give an advantage over the other ways of measuring adherence such as Medication Possession Ratio (MPR).

PDC formula:

$$\frac{\text{Number of days in period "covered" by medication}}{\text{Number of days in period}}$$

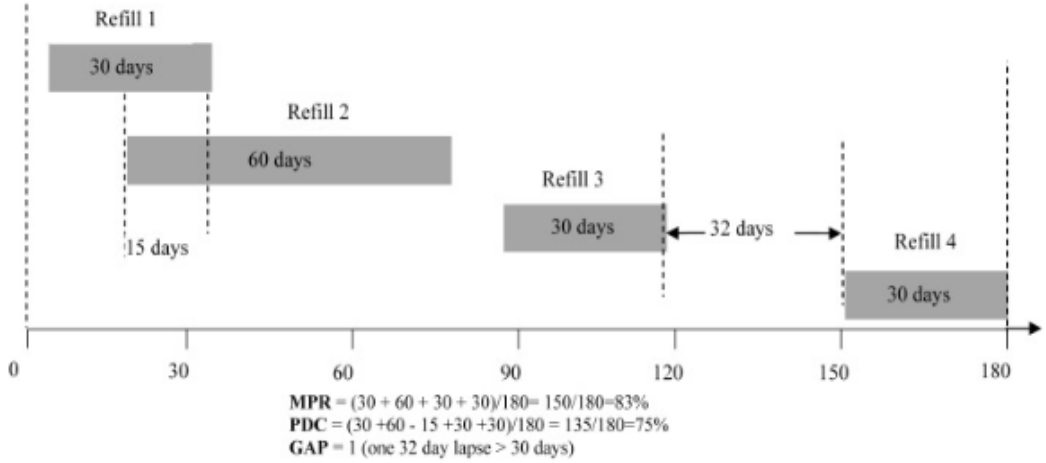


Figure 3.5: An example of calculating MRP and PDC, source: Zhu VJ, A Comparison of Data Driven-based Measures of Adherence to Oral Hypoglycemic (65)

By comparing the number of days which are ,theoretically, covered by the delivered amount of medicine ,using the sum of DDD multiplied by with 80% which is assumed adherence, with the difference of days between each two followed prescriptions of the same drug can we also calculate how much medicine is assumed to be left with patient (i.e. carryover) for next treatment episode. Hence, if we have an overlapping of two refills, this overlapped amount will be transferred to the next treatment episode and so on.

The start and end points for each treatment episode were created allowing 14 days as an acceptable medicine-free gap between the supposed and the actual dispensing dates and still considered within the same treatment episode. In other words, if the gap between the refill due and actual refill is more than two weeks, then a new treatment episode is started, (figure 3.6). The treatment episodes start with first prescription picking date and end if the gap between the assumed number of days covered by the amount of drug the patient had and the next prescription dispensing date is more than 14 days or if the patient is not using this medicine anymore.

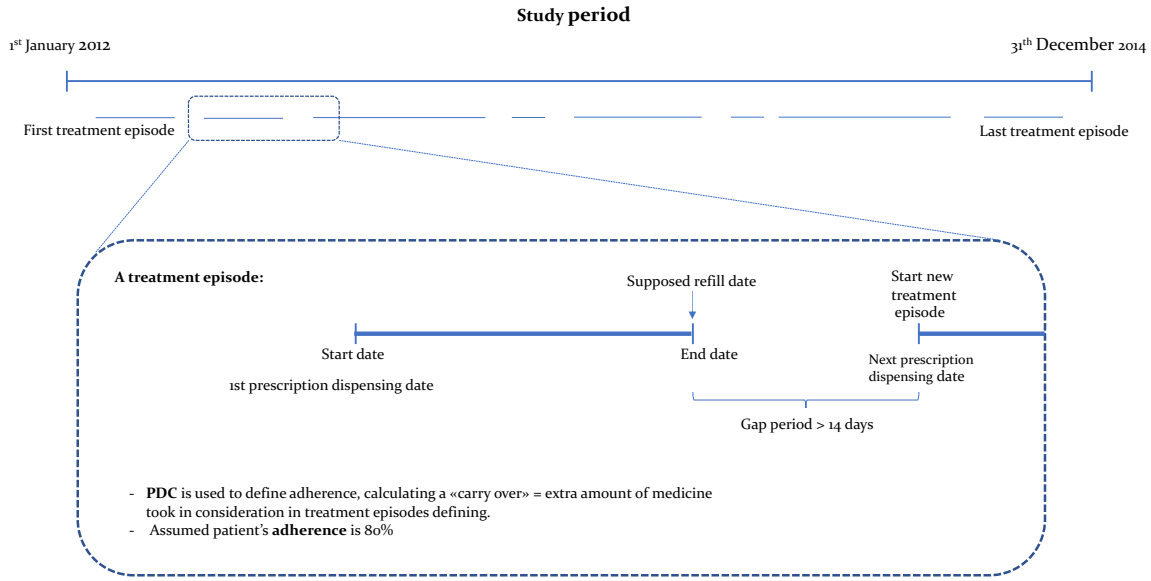


Figure 3.6: Representing the defining of treatment episodes (inspired from "Use of analgesics in the general population" PhD of Samuelsen, Per-Jostein 2016 at Uit) (66)

After defining the starts and the ends of the treatment episodes, we selected the prevalence points in which we will study the co-medication. Two prevalence point were chosen in this thesis; day 0 which corresponds 1st of January 2013 and day 365 which corresponds 1st of January 2014. These two-prevalence time points will allow us to study if there is any difference

in co-medication patterns from the perspective of the time change. In all other studied networks, day 0 will be our prevalence point.

3.6.1 A detailed example to clarify the method

If we suppose we have a patient who's receiving a drug (X) which has 100 tablets per package and this drug (X) define daily dose is 2 tablets a day, then one package of this medicine corresponds, theoretically, to 50 days of consumption. Then we assume that the patient's compliance is not perfect, and his medical adherence is only 80%. This means that this package will cover the patients need for (62,5 days) instead of 50 days (50/0.8).

If we now say that the patient picked up his first prescription of drug (X) at 1st of December 2012 (-31 day of 1st of January 2013 which is our day 0) then we have four scenarios. The first is that the patient will pick up his next prescription within 62 days (e.g. 1st of February 2013) of his earlier pickup. In this case, there will be no problem since the drug is still in the same treatment episode. The second scenario is that the patient picks up his second prescriptions later than 1st of February, but within less than 14 days, and similarly, the drug is still also in the same treatment episode.
The third one is to pick up the refill later than 14 days from 1st of February 2013. In this case, the first treatment episode of this drug is expired, and the patient started a new treatment episode of this drug.

If the second prescription dispensing was before 62 days from the first one let's say in (e.g. 15th of January 2013) and the patient received another package of 100 tablets. This means that the patient has an extra (overlapping) amount of medicine more than he needs for this treatment episode (16,5 days). This amount is transferred to the end of next treatment episode (carryover) and will be calculated in this episode first before we begin to calculate the allowed 14 days of medicine-free gap, and this is the fourth scenario, (figure 3.7).

The same was applied for all prescriptions which have the same ATC code. After this was done, we are able to pick up a day in our study period and study the treatment episode this day is involved in.

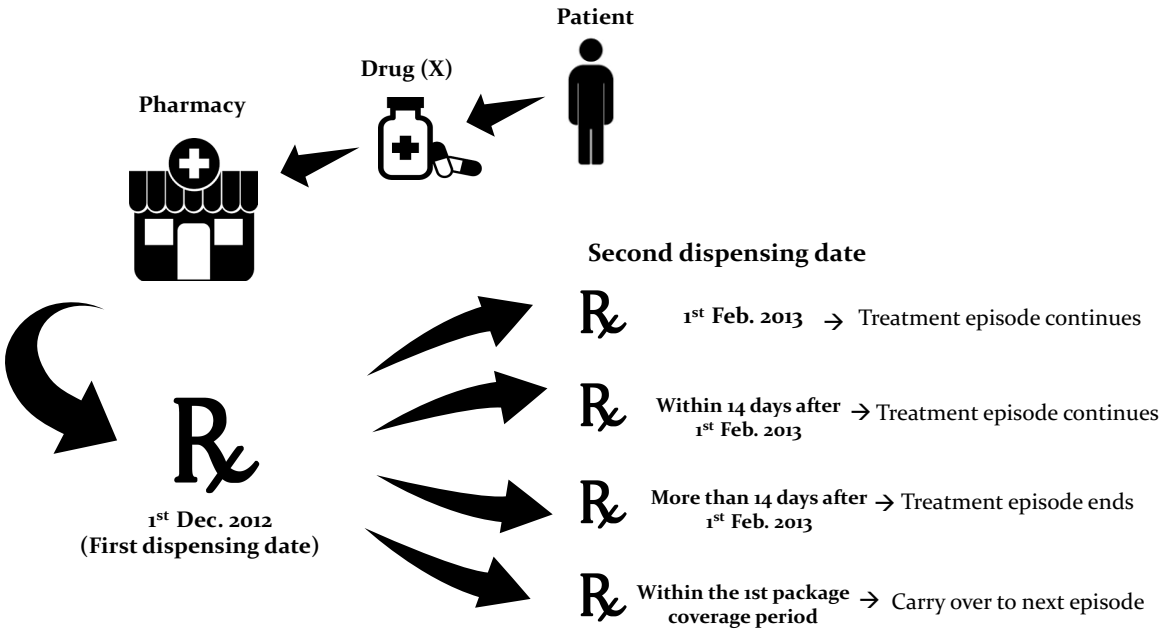


Figure 3.7: Represents how treatment episodes were defined

3.7 For Studying co-medication patterns in 2013 network

To identify which co-medication patterns included in the network of 2013 we used a network measure called "Modularity". We grouped the ATC codes in the same "module" according to the therapeutic indications. The extracted patterns were then compared to the findings of another study depended on Factor Analysis (FA) to discover the underlying patterns. The study was done in Spain in 2008 to demonstrate polypharmacy patterns using exploratory factor analysis (EFA) on drug medical records dispensing information, the patterns they extracted is in (table 4.9) (67). Each pattern was then studied in a separate network. More information on Modularity and Factor analysis comes at the discussion chapter.

3.8 For Studying the temporal change in the co-medication pattern

Two different time points, prevalence points, were selected, the first is day "0" which indicates 1st of January 2013 and the second is day "365" which corresponds the 1st of January 2014. We will directly compare between these two networks.

In addition to directly comparing these two networks, we will generate a new network which is the difference between 2013 network and 2014 network. This is to be done by dividing the number of users of each combination (*i.e. edges*) in the

two networks and eliminate the unmatched edges between the two networks. As an example, if we have two medicines which were combined 20 times in day 0 network and 10 times in day 365 network the new edge in the generated network will equal to two which means that this combination was used twice as many times in 2013 compared to 2014.

3.9 For studying the spatial difference in pattern

Five counties are chosen to explore if there was a change in the co-medication patterns in different counties in Norway. We selected five out of 19 counties that represent north, west, east and south of Norway with the highest population. These five counties are Oslo, Akershus, Hordaland, Rogaland, and Nordland. The five counties form 68 666 km^2 (68) and total 2 526 895 citizens of the total population in 2018. For studying of co-medication in these counties; day "0" was selected as a prevalence point.

For spatial difference we investigated if a patient were registered in more than one municipality. Total patients registered in more than one municipality makes about 1% of the total population. As this percent is low and won't remarkably affect the result, we chose to; if a patient is registered in more than one municipality, only one registration of them is considered when we study spatial change.

3.10 Generated networks

In the figure below (figure 3.8), the generated networks in this thesis are listed. Detailed description of each comes gradually in results and discussion sections.

In this thesis, the nodes will represent medicines and edges will represent either simultaneous use of these medicines (co-medication) or severe drug-drug interactions relations. All our networks in this thesis are undirected. Generated networks are weighed for co-medication to show how often is a combination between two or more medicines are used and unweighted in case of the general DDI network.

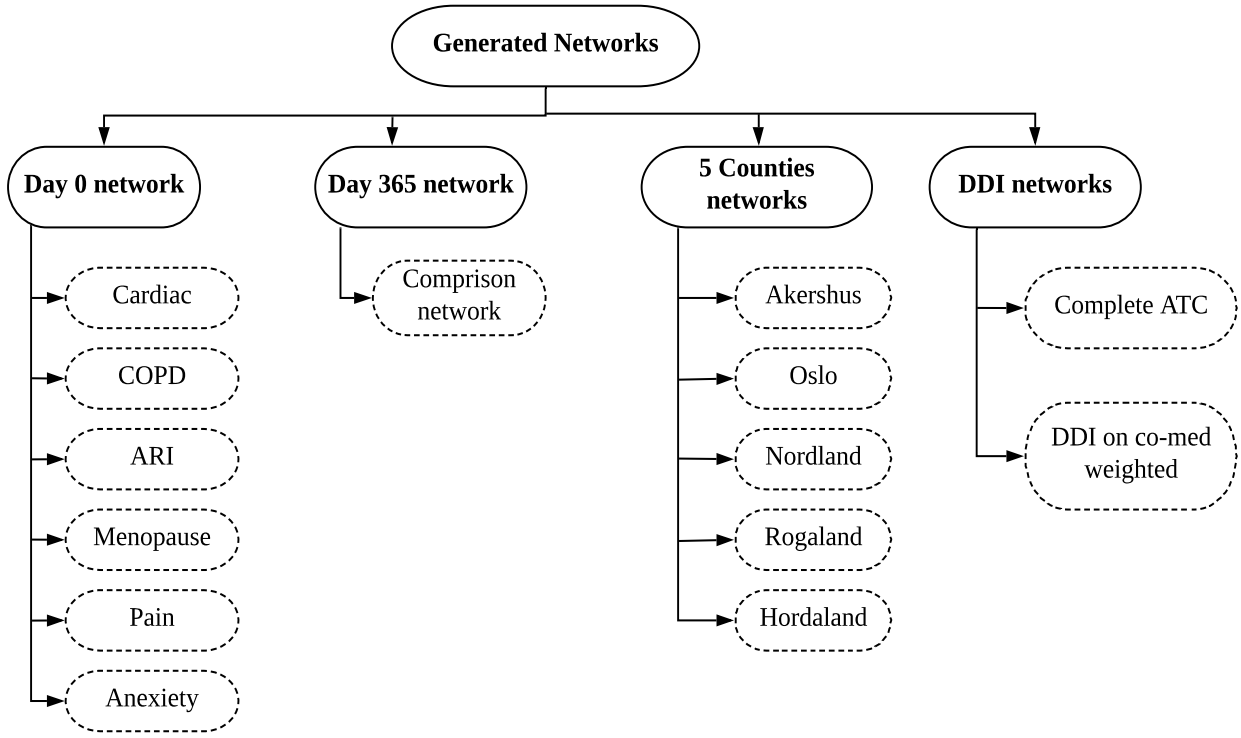


Figure 3.8: The generated networks in this study

3.11 Software

- Stata 15.1
- Microsoft office package version 16.19 and later updates
- Endnote 9 as a reference organizing program
- Gephi 0.9.2

Gephi is a visualizing tool for all types of networks. It is a free open-source software which can, beside visualizing, perform network measures and some statistical analysis. After generating networks using Stata, all networks are imported to Gephi which allows a variety of filters which makes the networks' patterns understandable and interpretable.

- General filters used in Gephi:

  The structure of most networks is complex. In order to make networks more understandable and interpretable a group of filters in some networks are applied in the visualizing program (Gephi). The filters used were one or more of the following filters:

  1. Number of users for each node
  2. Edges weight
  3. Nodes degree
  4. Modularity class

In the results chapter the networks are labelled if they are filtered or not, and which filters that were used.

3.12 Ethics:

The project uses patient data from a national registry, the NorPD. This registry does not require patient consent to collect and use data. The master project is part of a larger project looking at medicine use in the elderly and this study has approval from the regional ethics committee (REK number: 2014/2182). The project also has a permission from the Norwegian Data Protection Authority. The master student has been included as a part of the overall project and did not need any further approvals for conducting the master project. The data is encrypted for identifying information of either patients or physicians.

4. Results

The Results are subdivided into four sections:

Part I: Co-medication day 0 network (primary network):

In this section, we will study the network of treatment episode around 1st of January 2013 in terms of:

a. Descriptive analysis and some network measures of this network
b. Network modularity (clusters)
c. Studying of six different elderly co-medication patterns

Part II: Temporal change study: Comparing day 0 and day 365 (1st January 2014) networks.

a. Direct comparison of descriptive analysis and network measures for day 365 network and day 0 network.
b. Indirect comparison by generating a new network in which its edges are the division of the two prevalence points networks.

Part III: Spatial change study: Comparing co-medication in five selected counties in Norway in a direct comparison.

Part IV: Drug-drug interactions networks.

a. DDI network for severe interactions (general network with all complete ATC codes).
b. Applying of DDI network on the day 0 co-medication network.

For all the coming network graphs, the nodes (ATC codes) are colored according to their anatomical classes to make them easier to notice (table 4.1).

Table 4.1 Represents the anatomical groups with their defining colors in the thesis's networks

Anatomical class	Description	Color
A	Alimentary tract and metabolism	
B	Blood and blood forming organs	
C	Cardiovascular system	
D	Dermatologicals	
G	Genito-urinary system and sex hormones	
H	Systemic hormonal preparations, excluding sex hormones and insulins	
J	Anti-infectives for systemic use	
L	Antineoplastic and immunomodulating agents	
M	Musculo-skeletal system	
N	Nervous system	
P	Antiparasitic products, insecticides and repellents	
R	Respiratory system	
S	Sensory organs	
V	Various	

For all networks some important network measures will be mentioned first, these measures are: Density, number of edges, minimum and maximum edges' weight if the network is weighted.

4.1 Part I: Results of Co-medication day 0 network (primary network)

4.1.1 Network description

Table 4.2: Day 0 Network main characteristics

Day 0 network	
No. of nodes	762
No. of edges	75052
Density	0.26
Edges range	1-82948
Weight	Weighted

Number of nodes represents the number of actors (medicines) in the network, while the number of edges corresponds how many times were these two nodes (i.e. drugs) were co-medicated together. In other words, how many patients who have combined these two medicines (table 4.2).

Table 4.3: Distribution of ATC anatomical groups in day 0 network arranged in terms of being involved in drug-drug combinations from highest to lowest

Day 0 Network		
Anatomical group	**No. of times involved in a combination**	**Percent**
N (Nervous system)	15423	20.55 %
C (Cardiovascular system)	14077	18.76 %
A (Alimentary tract and metabolism)	11280	15.03 %
R (Respiratory system)	8334	11.10 %
B (Blood and blood forming organs)	4318	5.75 %
J (Antiinfectives for systemic use)	4196	5.59 %
G (Genito-urinary system and sex hormones)	4092	5.45 %
M (Musculo-skeletal system)	4057	5.41 %
L (Antineoplastic and immunomodulating agents)	3905	5.20 %
H (Systemic hormonal preparations, excluding sex hormones and insulins)	2350	3.13 %
S (Sensory organs)	2164	2.88 %
P (Antiparasitic products, insecticides and repellents)	382	0.51 %
D (Dermatologicals)	282	0.38 %
V (Various)	192	0.26 %

Table 4.3 shows that nervous and cardiovascular systems (N and C-groups) are the most frequently used medicines in the drug-drug combinations in the day 0 network, while dermatologicals and various (D and V-groups) are the least frequently combined medicines with other medicines.

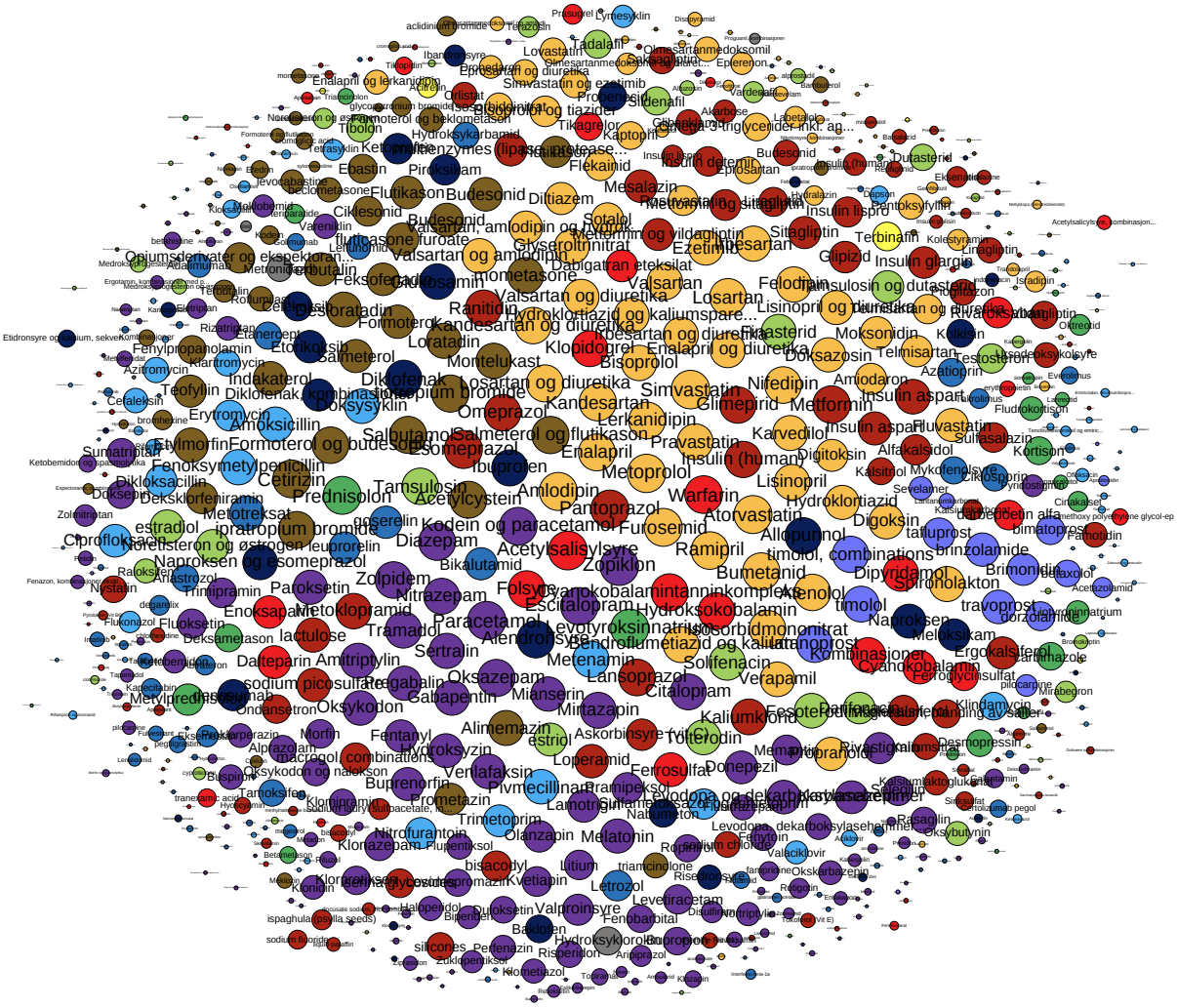


Figure 4.1: Represents the full network of day 0, no filters applied. Edges were removed for simplifying. Different colors indicate different anatomical groups. Size of nodes corresponds the number of edges each node has (co-medication with other nodes).

The full network in PDF format (full resolution) is available here: https://www.dropbox.com/s/evmf3a6o0v9g5yu/Dag%200%20colored%20no%20filters%2C%20no%20edges.pdf?dl=0

The network (figure 4.1) shows cardiovascular system anatomical group drugs, in the orange color, to be most frequent in the network's center along with nervous system, in purple, and respiratory systems substances, in the brown color, (with a lower frequency).

Table 4.4: Represents the most important nodes according to their eigenvector centrality score with the percentage of users in the dataset population

ATC	Substance	No. of users	% patients in dataset population	Eigenvector centrality	Degree cen.
B01AC06	Acetyl salicylic acid	228535	30 %	1.0	663
C10AA01	Simvastatin	155725	20 %	0.994	630
N05CF01	Zopiklon	85229	11 %	0.994	629
C07AB02	Metoprolol	100780	13 %	0.989	606
N02BE01	Paracetamol	47351	6 %	0.987	607
C08CA01	Amlodipin	73881	10 %	0.980	581
H03AA01	Levotyroksinnatrium	55106	7 %	0.979	586
C10AA05	Atorvastatin	78377	10 %	0.979	580
A02BC05	Esomeprazol	35651	5 %	0.979	573
A02BC02	Pantoprazol	34983	5 %	0.978	579
H02AB06	Prednisolon	31653	4 %	0.977	578
C03CA01	Furosemid	42564	6 %	0.976	569
R06AE07	Cetirizin	30150	4 %	0.973	563
B01AA03	Warfarin	47794	6 %	0.970	556
N02AJ06	Kodein og paracetamol	20702	3 %	0.969	552

Table 4.4 shows Acetyl salicylic acid to be the node with highest eigenvector centrality score (i.e. most important in network). Simvastatin and zopiclone come next with equal score for both. Last of the highest 15 scores in network was codeine/paracetamol combination (Paralgin forte®).

Table 4.5: Represents the most 20 combined medicines with the number of times they were combined and the proportion of users in the overall and dataset populations in 2013

No.	Drug 1	Drug 2	No. of patients combined them	% of elderly population	% of dataset population
1	Acetyl salicylic acid	Simvastatin	82948	10 %	11 %
2	Acetyl salicylic acid	Metoprolol	52577	7 %	7 %
3	Acetyl salicylic acid	Atorvastatin	42753	5 %	6 %
4	Metoprolol	Simvastatin	36792	5 %	5 %
5	Acetyl salicylic acid	Amlodipin	32628	4 %	4 %
6	Acetyl salicylic acid	Zopiklon	29173	4 %	4 %
7	Amlodipin	Simvastatin	22554	3 %	3 %
8	Acetyl salicylic acid	Ramipril	19660	2 %	3 %
9	Simvastatin	Zopiklon	18845	2 %	2 %
10	Metformin	Acetyl salicylic acid	18507	2 %	2 %
11	Acetyl salicylic acid	Furosemid	18175	2 %	2 %
12	Metoprolol	Atorvastatin	17266	2 %	2 %
13	Acetyl salicylic acid	Levotyroksinnatrium	16654	2 %	2 %
14	Acetyl salicylic acid	Paracetamol	16380	2 %	2 %
15	Metoprolol	Amlodipin	16271	2 %	2 %
16	Warfarin	Metoprolol	16005	2 %	2 %
17	Metformin	Simvastatin	15647	2 %	2 %
18	Acetyl salicylic acid	Kandesartan	14306	2 %	2 %
19	Acetyl salicylic acid	Isosorbidmononitrat	14236	2 %	2 %
20	Acetyl salicylic acid	Losartan og diuretika	14007	2 %	2 %

Table 4.5 shows the most 20 combined medicines (i.e. thickest edges in the network) in the network with the proportion of users in the overall elderly population in Norway in 2013 (790,614), and the study population (761,906). The combination of Acetylsalicylic acid with simvastatin had the highest number of patients in this treatment episode representing 10% of the total population, while Acetylsalicylic acid with Losartan/diuretics, on the other hand, was

the least frequent combination of the 20 combinations listed with 2% users of entire elderly population (a list of the most 200 combined medicines is attached in appendix 4).

4.1.2 Modularity classes

Modularity or community detection:

Table 4.6: Modularity classes with number of nodes and percentage of each module of the whole network

Module	Number of nodes	Percent
0	530	68 %
1	49	24 %
2	167	6 %
3	16	2 %
Total	762	100 %

Four modularity classes were detected in the network [0,1,2,3] (table 4.6). Module [0] is the biggest one with 530 ATC codes out of 762 which forms 68% of the network. Module [3] on the other hand, is the smallest one with only 2% of the overall ATC codes. The following figure (figure 4.2) represents the four classes with different color of each.

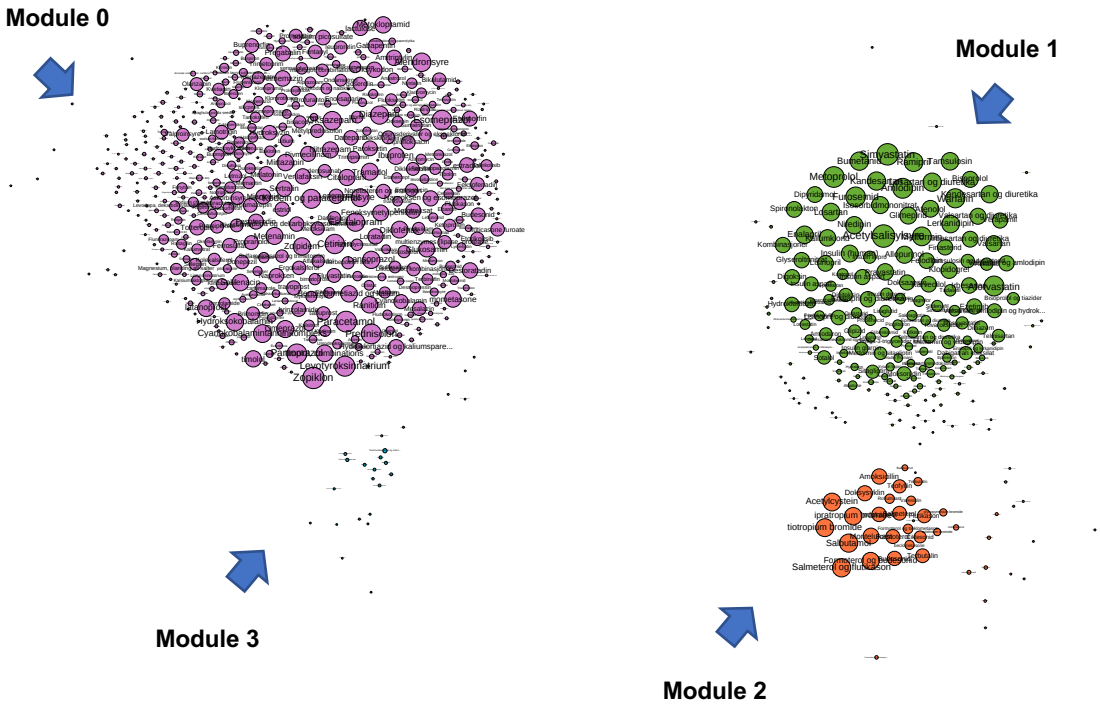


Figure 4.2: Representing day 0 network modularity classes. Bigger nodes indicate greater number of users, colors here do not represent the anatomical group colors.

To figure out the underlying patterns in these modules, the ATC codes were shortened to the second level of ATC (anatomical, therapeutic group) (table 4.7).

Table 4.7: Day 0 network modularity classes after shortening of ATC codes to the second level (3 characters=therapeutic level) sorted after the number of users for each ATC code group.

Group	No. users	Theraputic indications
Modularity class 0		
N05	149142	HYPNOTICS AND SEDATIVES
R03	125913	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
A02	107657	ACID DISORDERS
N02	87051	ANTIMIGRAINE PREPARATIONS
N06	78403	PSYCHOANALEPTICS
M01	60442	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
B03	57100	ANTIANEMIC PREPARATIONS
H03	56354	IODINE THERAPY
R06	53993	ANTIHISTAMINES FOR SYSTEMIC USE
J01	40218	ANTIBACTERIALS FOR SYSTEMIC USE
M05	35792	Bone diseases
H02	35343	CORTICOSTEROIDS FOR SYSTEMIC USE
G04	23622	UROLOGICALS (prostatic hypertrphy)
R01	21306	NASAL PREPARATIONS
G03	20842	SEX HORMONES
N03	17032	ANTIEPILEPTICS
R05	16266	COUGH AND COLD PREPARATIONS
C03	14703	DIURETICS
L04	12827	IMMUNOSUPPRESSANTS
N04	10016	ANTI-PARKINSON DRUGS
A06	7932	DRUGS FOR CONSTIPATION
A07	6774	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVI
L02	5189	ENDOCRINE THERAPY (HORMONS RELATED)
A11	5113	VITAMINS
B01	4793	ANTITHROMBOTIC AGENTS
A03	4159	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
C07	3349	BETA BLOCKING AGENTS
C10	3309	LIPID MODIFYING AGENTS
N07	1823	OTHER NERVOUS SYSTEM DRUGS
A12	1631	MINERAL SUPPLEMENTS
A09	1519	DIGESTIVES, INCL. ENZYMES
P01	1342	ANTIPROTOZOALS
D01	1262	ANTIFUNGALS FOR DERMATOLOGICAL USE
H01	804	PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES
M03	742	MUSCLE RELAXANTS
A04	735	ANTIEMETICS AND ANTINAUSEANTS
A05	595	BILE AND LIVER THERAPY
A08	516	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
L01	476	ANTINEOPLASTIC AGENTS
J05	392	ANTIVIRALS FOR SYSTEMIC USE
L03	288	IMMUNOSTIMULANTS
J04	269	ANTIMYCOBACTERIALS
D05	247	ANTIPSORIATICS
J02	188	ANTIMYCOTICS FOR SYSTEMIC USE
A01	185	STOMATOLOGICAL PREPARATIONS
H05	131	CALCIUM HOMEOSTASIS
G02	115	OTHER GYNECOLOGICALS
B02	113	ANTIHEMORRHAGICS

Modularity class 1		
C03	70736	DIURETICS
B01	52433	ANTITHROMBOTIC AGENTS
M04	15650	ANTIGOUT PREPARATIONS
C01	15616	CARDIAC THERAPY
C07	13343	BETA BLOCKING AGENTS
C08	7445	CALCIUM CHANNEL BLOCKERS
A12	5858	MINERAL SUPPLEMENTS
A11	1635	VITAMINS
B03	1282	ANTIANEMIC PREPARATIONS
V03	487	ALL OTHER THERAPEUTIC PRODUCTS
H05	240	CALCIUM HOMEOSTASIS
A02	194	DRUGS FOR ACID RELATED DISORDERS
C02	163	ANTIHYPERTENSIVES
L04	161	IMMUNOSUPPRESSANTS
Modularity class 2		
C09	293008	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
B01	260482	ANTITHROMBOTIC AGENTS
C10	258050	LIPID MODIFYING AGENTS
C07	128165	BETA BLOCKING AGENTS
C08	126834	CALCIUM CHANNEL BLOCKERS
A10	96241	DRUGS USED IN DIABETES
S01	67468	OPHTHALMOLOGICALS
G04	45302	UROLOGICALS (prostatic hypertrphy)
C01	26825	CARDIAC THERAPY
C03	22963	DIURETICS
L02	11148	ENDOCRINE THERAPY
C02	10313	ANTIHYPERTENSIVES
L01	708	ANTINEOPLASTIC AGENTS
C04	467	PERIPHERAL VASODILATORS
A07	171	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS
Modularity class 3		
J05	237	ANTIVIRALS FOR SYSTEMIC USE

(Table 4.7) shows module [0] to be the largest and most complex module, with 47 out of 75 ATC groups after shortening (approximately 63%). Hypnotics and sedative groups (N05) represent the highest number of users in this module (149,142) users, followed by the drugs for obstructive airways diseases (R03) with (125,913) patients.

We tried to find the underlying pattern(s) in this large module by rearranging the ATC groups, according to the assumed clinical indication (table 4.8). Otherwise, the co-medication patterns in the other modules [1, 2, 3] were quite clear and easy to uncover.

Table 4.8: Represents the assumed patterns in each of the four modularity classes after sorting of module [0]

Group	No. users	Theraputic indications	Pattern
Modularity class 0			
N05	149142	HYPNOTICS AND SEDATIVES	**Anxiety pattern**
N02	87051	ANTIMIGRAINE PREPARATIONS	
N06	78403	PSYCHOANALEPTICS	
N03	17032	ANTIEPILEPTICS	
N04	10016	ANTI-PARKINSON DRUGS	
N07	1823	OTHER NERVOUS SYSTEM DRUGS	
R03	125913	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	**ARI, COPD patterns**
R06	53993	ANTIHISTAMINES FOR SYSTEMIC USE	
R01	21306	NASAL PREPARATIONS	
R05	16266	COUGH AND COLD PREPARATIONS	
J01	40218	ANTIBACTERIALS FOR SYSTEMIC USE	
J05	392	ANTIVIRALS FOR SYSTEMIC USE	
A02	107657	ACID DISORDERS	
M01	60442	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	**Hormones related**
H03	56354	IODINE THERAPY	
M05	35792	BONE DISEASES	
G04	23622	UROLOGICALS (prostatic hypertrphy)	
G03	20842	SEX HORMONES	
L02	5189	ENDOCRINE THERAPY	
L01	476	ANTINEOPLASTIC AGENTS	
H05	131	CALCIUM HOMEOSTASIS	
G02	115	OTHER GYNECOLOGICALS	
C03	14703	DIURETICS	
C07	3349	BETA BLOCKING AGENTS	
C10	3309	LIPID MODIFYING AGENTS	
B01	4793	ANTITHROMBOTIC AGENTS	
B02	113	ANTIHEMORRHAGICS	
L03	288	IMMUNOSTIMULANTS	
B03	57100	ANTIANEMIC PREPARATIONS	**Drugs for Side effects**
A06	7932	DRUGS FOR CONSTIPATION	
A07	6774	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	
A03	4159	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	
A04	735	ANTIEMETICS AND ANTINAUSEANTS	
H02	35343	CORTICOSTEROIDS FOR SYSTEMIC USE	
A11	5113	VITAMINS	**Various drugs or can match with many patterns**
A12	1631	MINERAL SUPPLEMENTS	
A09	1519	DIGESTIVES, INCL. ENZYMES	
P01	1342	ANTIPROTOZOALS	
D01	1262	ANTIFUNGALS FOR DERMATOLOGICAL USE	
M03	742	MUSCLE RELAXANTS	
A05	595	BILE AND LIVER THERAPY	
A08	516	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	
J04	269	ANTIMYCOBACTERIALS	
D05	247	ANTIPSORIATICS	
J02	188	ANTIMYCOTICS FOR SYSTEMIC USE	
A01	185	STOMATOLOGICAL PREPARATIONS	

Modularity class 1			
C03	70736	DIURETICS	**Cardiac**
B01	52433	ANTITHROMBOTIC AGENTS	
M04	15650	ANTIGOUT PREPARATIONS	
C01	15616	CARDIAC THERAPY	
C07	13343	BETA BLOCKING AGENTS	
C08	7445	CALCIUM CHANNEL BLOCKERS	
A12	5858	MINERAL SUPPLEMENTS	
A11	1635	VITAMINS	
B03	1282	ANTIANEMIC PREPARATIONS	
V03	487	ALL OTHER THERAPEUTIC PRODUCTS	
H05	240	CALCIUM HOMEOSTASIS	
A02	194	DRUGS FOR ACID RELATED DISORDERS	
C02	163	ANTIHYPERTENSIVES	
L04	161	IMMUNOSUPPRESSANTS	
Modularity class 2			
C09	293008	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	**Diabetes**
B01	260482	ANTITHROMBOTIC AGENTS	
C10	258050	LIPID MODIFYING AGENTS	
C07	128165	BETA BLOCKING AGENTS	
C08	126834	CALCIUM CHANNEL BLOCKERS	
A10	96241	DRUGS USED IN DIABETES	
S01	67468	OPHTHALMOLOGICALS	
G04	45302	UROLOGICALS (prostatic hypertrphy)	
C01	26825	CARDIAC THERAPY	
C03	22963	DIURETICS	
L02	11148	ENDOCRINE THERAPY	
C02	10313	ANTIHYPERTENSIVES	
L01	708	ANTINEOPLASTIC AGENTS	
C04	467	PERIPHERAL VASODILATORS	
A07	171	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	
Modularity class 3			
J05	237	ANTIVIRALS FOR SYSTEMIC USE	**Anti-virals**

Table 4.8 represents the patterns we found after sorting ATC codes in module [0] according to therapeutic indications. In total six patterns were discovered; three patterns of them were under module [0]. Module [1] were nearly to be a cardiac pattern while module [2] represents diabetes pattern. The last pattern is module [3] which consisted only of some antivirals for systemic use and has few patients.

4.1.3 Patterns of elderly co-medication

Table 4.9: The conducted polypharmacy patterns in the mentioned paper by Exploratory Factor Analysis (EFA) with the used ATC codes in each pattern

	6 elderly co-mediaction patters		
	Name of pattern	**ATC**	**ATC group**
1	**Cardiovascular pattern**	A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)
		A10A	INSULIN
		A10B	BLOOD GLUCOSE LOWERING
		B01A	ANTITHROMBOTIC AGENTS
		C01A	CARDIAC GLYCOSIDES
		C01D	VASODILATORS FOR CARDIAC DISEAS
		C03	DIURETICS
		C03D	POTASSIUM-SPARING DIURETIC
		C07A	BETA BLOCKING AGENTS
		C08D	SELECTIVE CALCIUM CHANNEL BLOCKER
		C09A	ACE INHIBITORS
		C10A	LIPID MODIFYING AGENTS
2	**Depression-anxiety pattern**	H02A	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
		M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
		M04A	ANTIHOUT PREPARATIONS
		N03A	ANTIEPILEPTICS
		N04B	DOPAMINERGIC AGENTS
		N05A	ANTIPSYCHOTICS
		N05B	ANXIOLYTICS
		N06A	ANTIDEPRESSANTS
		N06B	PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS
3	**Acut respiratorty infection pattern (ARI)**	R01A	DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE
		R01B	NASAL DECONGESTANTS FOR SYSTEMIC USE
		R03A	ADRENERGICS, INHALANTS
		R05CA	Expectorants
		R05D	COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS
		R06A	ANTIHISTAMINES FOR SYSTEMIC USE
		J01	ANTIBACTERIALS FOR SYSTEMIC USE
		J05	ANTIVIRALS FOR SYSTEMIC USE
4	**Chronic obstructive pulmonary disease pattern (COPD)**	R03A	ADRENERGICS, INHALANTS
		R06A	ANTIHISTAMINES FOR SYSTEMIC USE
		S02A	ANTIINFECTIVES
		S01C	ANTIINFLAMMATORY AGENTS AND ANTIINFECTIVES IN COMBINATION
		M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
		H02A	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
		R05D	COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS
		A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)
		R05C	EXPECTORANTS, EXCL. COMBINATIONS WITH COUGH SUPPRESSANTS
		R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS
5	**Pain pattern**	M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
		R05D	COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS
		A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)
		M03B	MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
		N02A	OPIOIDS
		N02BG	Other analgesics and antipyretics
		M02A	TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN
6	**Menopause pattern**	A12A	CALCIUM
		M05B	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION
		G03C	ESTROGENS
		S01G	DECONGESTANTS AND ANTIALLERGICS

Comparing the two previous tables, our sorted modules table and the six patterns identified by factor analysis, reveals quite a consistency between the patterns we found with the patterns was found in the mentioned paper.

4.1.4 Studying the six patterns

4.1.4.a Cardiac pattern

Table 4.10: Network characteristics for cardiac subnetwork

Cardiac network	
No. of nodes (Drugs)	108
No. of edges	2568
Density	0.45
Edges range (min.-max.)	1-82,948
Weight	Weighted

Table 4.11: The most used medicines in cardiac subnetwork, degree centrality shows how many times these medicines were combined with other nodes

ATC	Substance	No. of users	Degree Cen.	Eigenvector Cen.
B01AC06	Acetyl salisylic acid	228535	101	1.0
C10AA01	Simvastatin	155725	57	0.66
C07AB02	Metoprolol	100780	56	0.66
C10AA05	Atorvastatin	78377	53	0.65
B01AA03	Warfarin	47794	94	0.98
C03CA01	Furosemid	42564	56	0.66
A10BA02	Metformin	38995	98	0.99
A02BC05	Esomeprazol	35651	97	0.99
C09AA05	Ramipril	35578	53	0.65
A02BC02	Pantoprazol	34983	95	0.98

Table 4.11 shows acetyl salicylic acid, metformin and esomeprazole to have the highest number of connections to the other nodes (i.e. high degree centrality) and highest scores of eigenvector centrality as well.

Table 4.12: Represents the most combined medicines in cardiac network showing number of times each two nodes were combined

ATC 1	Drug 1	ATC 2	Drug 2	No. of times combined
B01AC06	Acetyl salisylic acid	C10AA01	Simvastatin	82948
B01AC06	Acetyl salisylic acid	C07AB02	Metoprolol	52577
B01AC06	Acetyl salisylic acid	C10AA05	Atorvastatin	42753
B01AC06	Acetyl salisylic acid	C09AA05	Ramipril	19660
A10BA02	Metformin	B01AC06	Acetyl salisylic acid	18507
B01AC06	Acetyl salisylic acid	C03CA01	furosemide	18175
B01AA03	Warfarin	C07AB02	Metoprolol	16005
A10BA02	Metformin	C10AA01	Simvastatin	15647
B01AC06	Acetyl salisylic acid	C01DA14	Isosorbide mononitrate	14236
A02BC02	Pantoprazol	B01AC06	Acetyl salisylic acid	13560

Acetylsalicylic acid (ASA) is present in eight of the most 10 used combinations in the network. The most used combinations are ASA with simvastatin, then ASA with metoprolol (table 4.12).

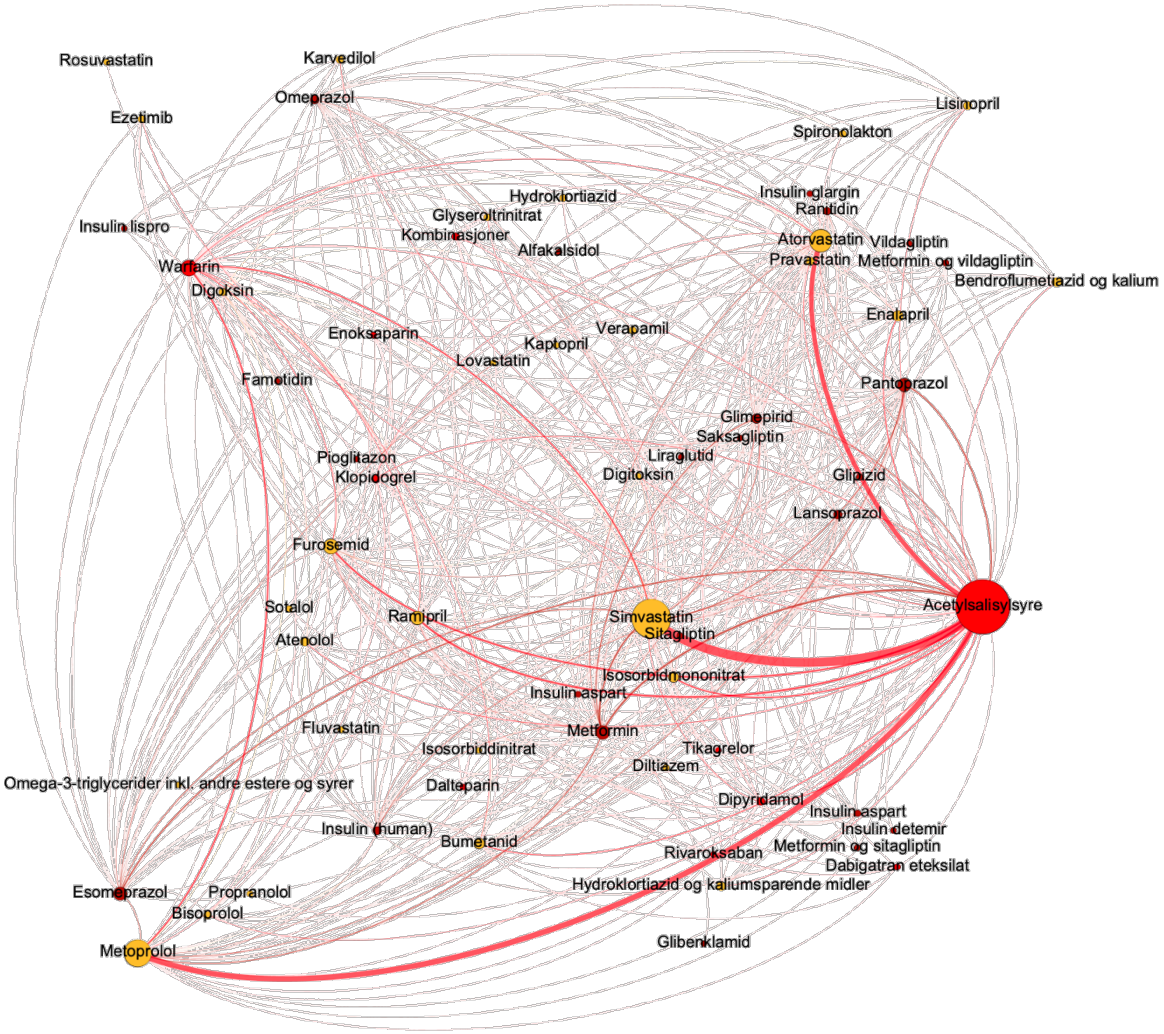


Figure 4.3: Cardiac weighted network, filtered for number of users>460 and edge weight >250, bigger nodes indicate greater number of users.

The full network in PDF format (full resolution) is available here:
https://www.dropbox.com/s/f4e67u5okk0g8dd/cardiac.pdf?dl=0

The cardiac pattern network (figure 4.3) shows some important nodes with the highest number of users (e.g. acetylsalicylic acid, warfarin (in light red color), simvastatin, atorvastatin, and metoprolol (in yellow color). Acetylsalicylic acid with simvastatin, metoprolol, and atorvastatin are the most combined medicine in the network, respectively. Warfarin combination with simvastatin and atorvastatin is also quite frequent in the network.

4.1.4.b Anxiety pattern

Table 4.13: Network characteristics for Anxiety subnetwork

Anxiety network	
No. of nodes (Drugs)	125
No. of edges	2728
Density	0.35
Edges range (min.-max.)	1-1,800
Weight	Weighted

Table 4.14: The most used medicines in Anxiety subnetwork with degree and eigenvector centrality

ATC	Substance	No. of users	Degree Cen.	Eigenvector Cen.
H02AB06	Prednisolon	31653	94	0.99
N06AB10	Escitalopram	21669	96	0.99
N05BA01	Diazepam	15521	97	0.99
M01AB05	Diklofenak	14081	86	0.97
N05BA04	Oksazepam	13956	99	1.0
M04AA01	Allopurinol	13826	80	0.94
M01AX05	Glukosamin	10867	84	0.95
M01AE01	Ibuprofen	10107	87	0.97
N06AX11	Mirtazapin	8570	90	0.97
N06AB04	Citalopram	7790	87	0.97

Table 4.14 shows that oxazepam is the node with the most importance in the network in both eigenvector and degree centrality. Prednisolone on the other hand is the most used medicine in the network.

Table 4.15: The most combined medicines in Anxiety subnetwork showing number of times each two nodes were combined

ATC 1	Drug 1	ATC 2	Drug 2	No. of times combined
N05BA04	Oksazepam	N06AB10	Escitalopram	1800
N06AB10	Escitalopram	N06AX11	Mirtazapin	1421
H02AB06	Prednisolon	N06AB10	Escitalopram	1351
N05BA01	Diazepam	N06AB10	Escitalopram	1337
H02AB06	Prednisolon	N05BA04	Oksazepam	1315
H02AB06	Prednisolon	M04AA01	Allopurinol	1168
H02AB06	Prednisolon	N05BA01	Diazepam	1116
N05BA04	Oksazepam	N06AX11	Mirtazapin	1096
N06AB10	Escitalopram	N06AX03	Mianserin	707
H02AB06	Prednisolon	M01AB05	Diklofenak	679

Table 4.15 shows that prednisolone and escitalopram are involved in most of the combinations among the 10 highest used combinations in the network. Prednisolone is present in five combinations of the top 10 used combinations in the network.

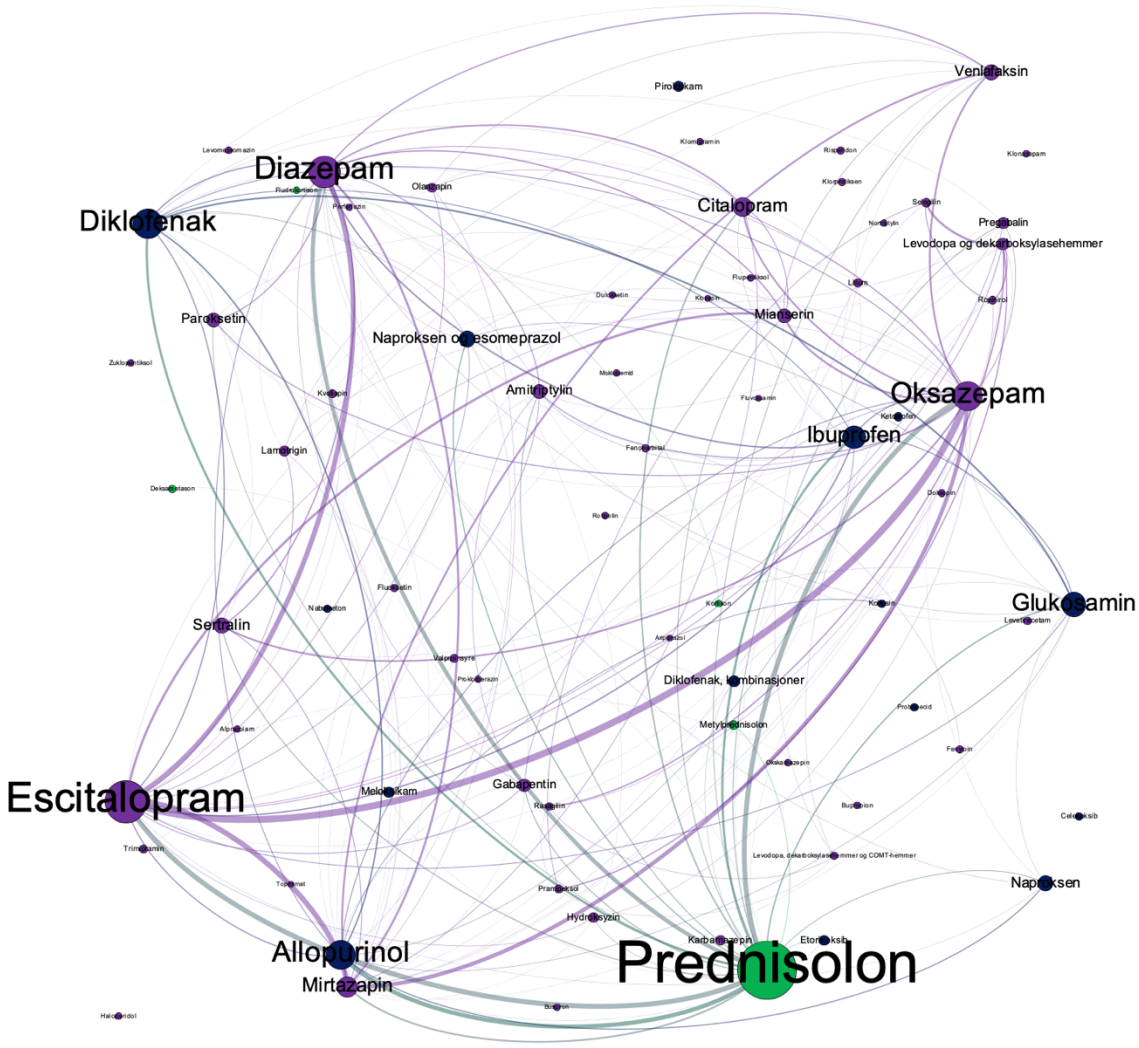


Figure 4.4: Anxiety weighted network filtered for number of users >96 and edge weight >100, bigger nodes indicate greater number of users.

The full network in PDF format (full resolution) is available here:
https://www.dropbox.com/s/j6j8ilqqc0q2q5s/Anxiety.pdf?dl=0

Anxiety network (figure 4.4) shows prednisolone node in the green color to be the most used medicine. Escitalopram, diazepam, oxazepam have also a good share of users. Diclofenac, Ibuprofen, and glucosamine appears in dark blue nodes with a quite high number of users. Combinations between escitalopram with oxazepam, diazepam and mirtazapine are frequent (i.e. thick edges).

4.1.4.c Acute Respiratory Infection (ARI) pattern

Table 4.16: Network characteristics for ARI subnetwork

ARI network	
No. of nodes (Drugs)	105
No. of edges	1255
Density	0.23
Edges range (min.-max.)	1-6,599
Weight	Weighted

Table 4.17: The most used medicines in ARI subnetwork, degree centrality shows how many times these medicines were connected to other nodes

ATC	Substance	No. of users	Degree Cen.	Eigenvector Cen.
R06AE07	Cetirizin	30150	40	1.0
R03AK06	Salmeterol og flutikason	25227	40	0.996
R03AC02	Salbutamol	18450	40	0.990
R03AK07	Formoterol og budesonid	17314	40	0.97
R01AD09	mometasone	10699	40	0.94
R06AX13	Loratadin	7213	40	0.91
R06AX27	Desloratadin	6006	40	0.92
J01CE02	Fenoksymetylpenicillin	5607	40	0.94
J01CA08	Pivmecillinam	4530	39	0.86
R06AD01	Alimemazin	4348	39	0.902

Table 4.17 shows antihistaminic drugs (e.g. cetirizine, loratadine, and desloratadine) and adrenergic inhalations are the most central nodes with the greatest number of links with other nodes and highest number of users.

Table 4.18: The most combined medicines in ARI subnetwork showing number of times each two nodes were combined

ATC 1	Drug 1	ATC 2	Drug 2	No. of times combined
R03AC02	Salbutamol	R03AK06	Salmeterol og flutikason	6599
R03AK06	Salmeterol og flutikason	R06AE07	Cetirizin	2870
R03AC02	Salbutamol	R03AK07	Formoterol og budesonid	2534
R03AC02	Salbutamol	R06AE07	Cetirizin	2187
R03AK07	Formoterol og budesonid	R06AE07	Cetirizin	2020
R01AD09	Mometasone	R06AE07	Cetirizin	1452
R01AD09	Mometasone	R03AK06	Salmeterol og flutikason	1126
R03AC03	Terbutalin	R03AK07	Formoterol og budesonid	804
R01AD09	Mometasone	R03AK07	Formoterol og budesonid	762
R03AK06	Salmeterol og flutikason	R06AX13	Loratadin	740

Table 4.18 shows the most combined medicines are inhalations (long-acting beta II agonist and cortisones) with antihistamines.

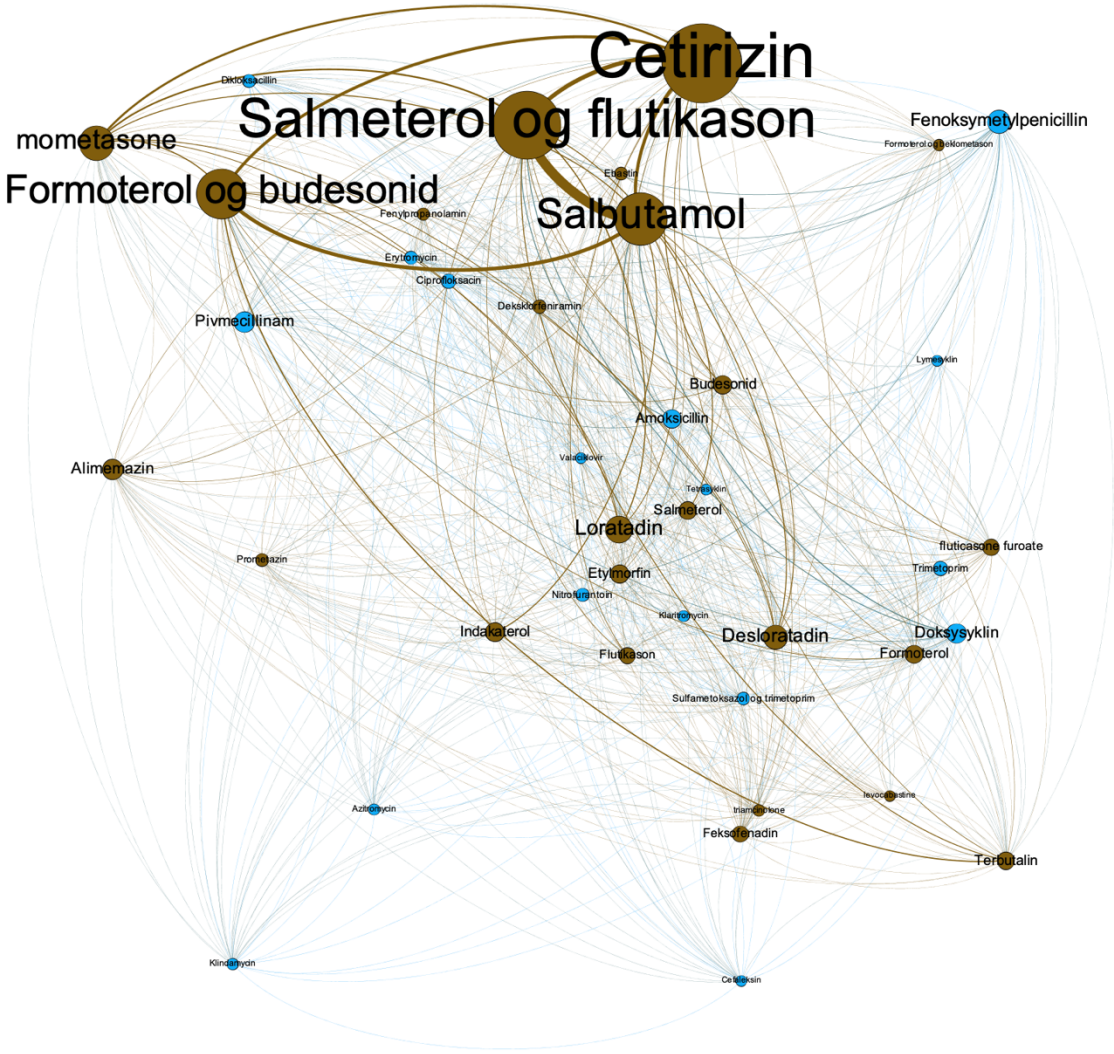


Figure 4.5: ARI weighted network, filtered for number of users and edge weight >100, bigger nodes indicate greater number of users

The full network in PDF format (full resolution) is available here:
https://www.dropbox.com/s/47ef7txfdoxekc2/ARI%20new.pdf?dl=0

The network (figure 4.5) shows two anatomical groups the sky blue one represents the anti-infectives for systemic use, and the brown one represents respiratory system drugs. Cetirizine is the most used medicine in this network along with salbutamol and salmeterol/fluticasone combination. The thickest edge represents the most combined medicines in the network (salbutamol and salmeterol/fluticasone combination).

4.1.4.d Chronic Obstructive Pulmonary Disease pattern (COPD)

Table 4.19: Network characteristics for COPD subnetwork

COPD network	
No. of nodes (Drugs)	78
No. of edges	1601
Density	0.53
Edges range (min.-max.)	1-6,930
Weight	Weighted

Table 4.20: The most used medicines in COPD subnetwork, degree centrality shows how many times these medicines were connected to other nodes

ATC	Substance	No. of users	Degree Cen.	Eigenvector Cen.
A02BC05	Esomeprazol	35651	71	1.0
A02BC02	Pantoprazol	34983	68	0.99
H02AB06	Prednisolon	31653	70	0.99
R06AE07	Cetirizin	30150	66	0.98
R03AK06	Salmeterol og flutikason	25227	70	0.99
R03BB04	Tiotropium bromide	22140	67	0.98
R03AC02	Salbutamol	18450	70	0.99
R03AK07	Formoterol og budesonid	17314	69	0.98
M01AB05	Diklofenak	14081	64	0.96
A02BC03	Lansoprazol	14040	62	0.94

Table 4.20 shows esomeprazole to be the most connected node to other important nodes in the network with greatest number of users. Inhalations and systemic prednisolone along with cetirizine are the most central nodes in this pattern.

Table 4.21: The most combined medicines in COPD subnetwork showing number of times each two nodes were combined

ATC 1	Drug 1	ATC 2	Drug 2	No. of times combined
R03AK06	Salmeterol og flutikason	R03BB04	Tiotropium bromide	6930
R03AC02	Salbutamol	R03AK06	Salmeterol og flutikason	6599
R03AC02	Salbutamol	R03BB04	Tiotropium bromide	5335
R03AC02	Salbutamol	R03BB01	Ipratropium bromide	4536
R03AK07	Formoterol og budesonid	R03BB04	Tiotropium bromide	4202
H02AB06	Prednisolon	R03AC02	Salbutamol	4000
A02BC02	Pantoprazol	H02AB06	Prednisolon	3751
H02AB06	Prednisolon	R03BB04	Tiotropium bromide	3686
H02AB06	Prednisolon	R03AK06	Salmeterol og flutikason	3569
R03AK06	Salmeterol og flutikason	R03BB01	Ipratropium bromide	3193

Table 4.21 shows the most frequented combinations were between selective beta-2-adrenoreceptor agonists Salbutamol (Ventolin®) long-acting beta2 agonists (LABA) combined with corticosteroid like Salmeterol and Fluticasone (Seretide®) and long-acting muscarinic

antagonists (LAMA) like Tiotropium (Spiriva®), Ipratropium bromide (Atrovent®) and systemic Prednisolone.

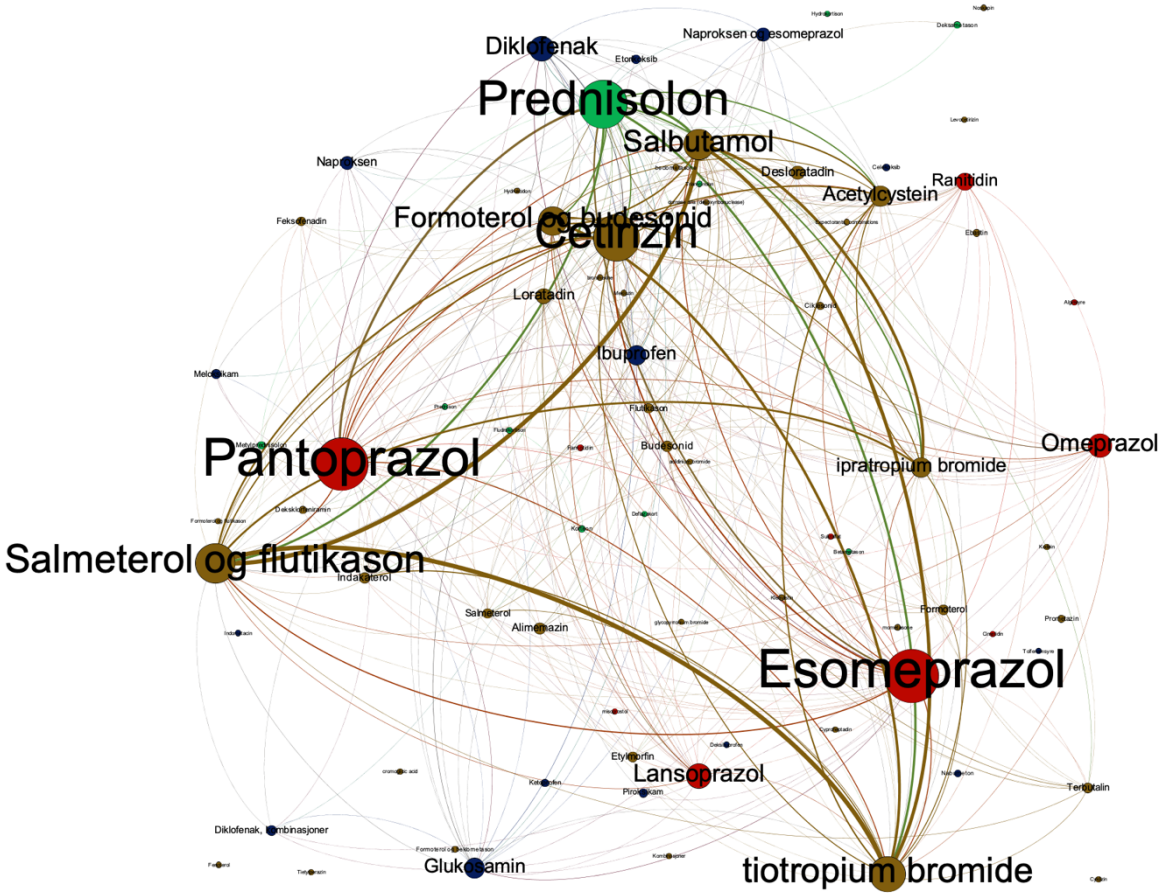


Figure 4.6: COPD weighted network, filtered for edges >100. Bigger nodes indicate greater number of users

The full network in PDF format (full resolution) is available here:
https://www.dropbox.com/s/6zqxb7s79ttdexp/COPD.pdf?dl=0

The network (figure 4.6) shows pantoprazole and esomeprazole, in the red color, are the most used PPIs. Prednisolone, in green, shows a high number of users. Inhalations combination such as salmeterol/fluticasone with tiotropium bromide or with salbutamol are the most used combination in the network.

4.1.4.e Pain pattern

Table 4.22: Network characteristics for Pain subnetwork

Pain network	
No. of nodes (Drugs)	59
No. of edges	926
Density	0.54
Edges range (min.-max.)	1-6,599
Weight	Weighted

Table 4.23: The most used medicines in Pain subnetwork, degree centrality shows how many times these medicines were connected to other nodes

ATC	Substance	No. of users	Degree Cen.	Eigenvector Cen.
A02BC02	Pantoprazol	34983	55	1.0
A02BC05	Esomeprazol	35651	55	0.99
N02AJ06	Kodein og paracetamol	20702	55	0.99
R03AK06	Salmeterol og flutikason	25227	51	0.98
R03AC02	Salbutamol	18450	52	0.98
A02BC03	Lansoprazol	14040	50	0.97
A02BC01	Omeprazol	13645	50	0.96
R03AK07	Formoterol og budesonid	17314	49	0.95
M01AB05	Diklofenak	14081	47	0.94
M01AX05	Glukosamin	10867	44	0.92

Table 4.23 shows PPIs (Pantoprazole and Esomeprazole) are the most vital nodes in the network. Only three types of analgesics exist in the top most used in this network. The other drugs are drugs related to obstructive airways diseases.

Table 4.24: The most combined analgesics with other drugs in Pain subnetwork showing number of times each two nodes were combined

ATC 1	Drug 1	ATC 2	Drug 2	No. of times combined
A02BC05	Esomeprazol	N02AJ06	Codein and paracetamol	1946
A02BC02	Pantoprazol	N02AJ06	Codein and paracetamol	1743
N02AJ06	Codein and paracetamol	R03AK06	Salmeterol og flutikason	1308
N02AJ06	Codein and paracetamol	R03AC02	Salbutamol	1295
M01AB05	Diklofenak	N02AJ06	Codein and paracetamol	1148
A02BC05	Esomeprazol	N02AX02	Tramadol	886
A02BC05	Esomeprazol	M01AB05	Diklofenak	872
N02AJ06	Codein and paracetamol	N02AX02	Tramadol	855
A02BC02	Pantoprazol	N02AX02	Tramadol	825
N02AJ06	Codein and paracetamol	R03AK07	Formoterol og budesonid	818

Table 4.24 shows the most combined drugs with analgesics. In this table we chose to show the most frequented combinations with *analgesics* (i.e. not the most combined medicines in the overall network). The most used analgesic was codeine and paracetamol combination (Paralgin

forte®) either combined with other analgesics or another therapeutic group, then comes tramadol and diclofenac (table 4.24).

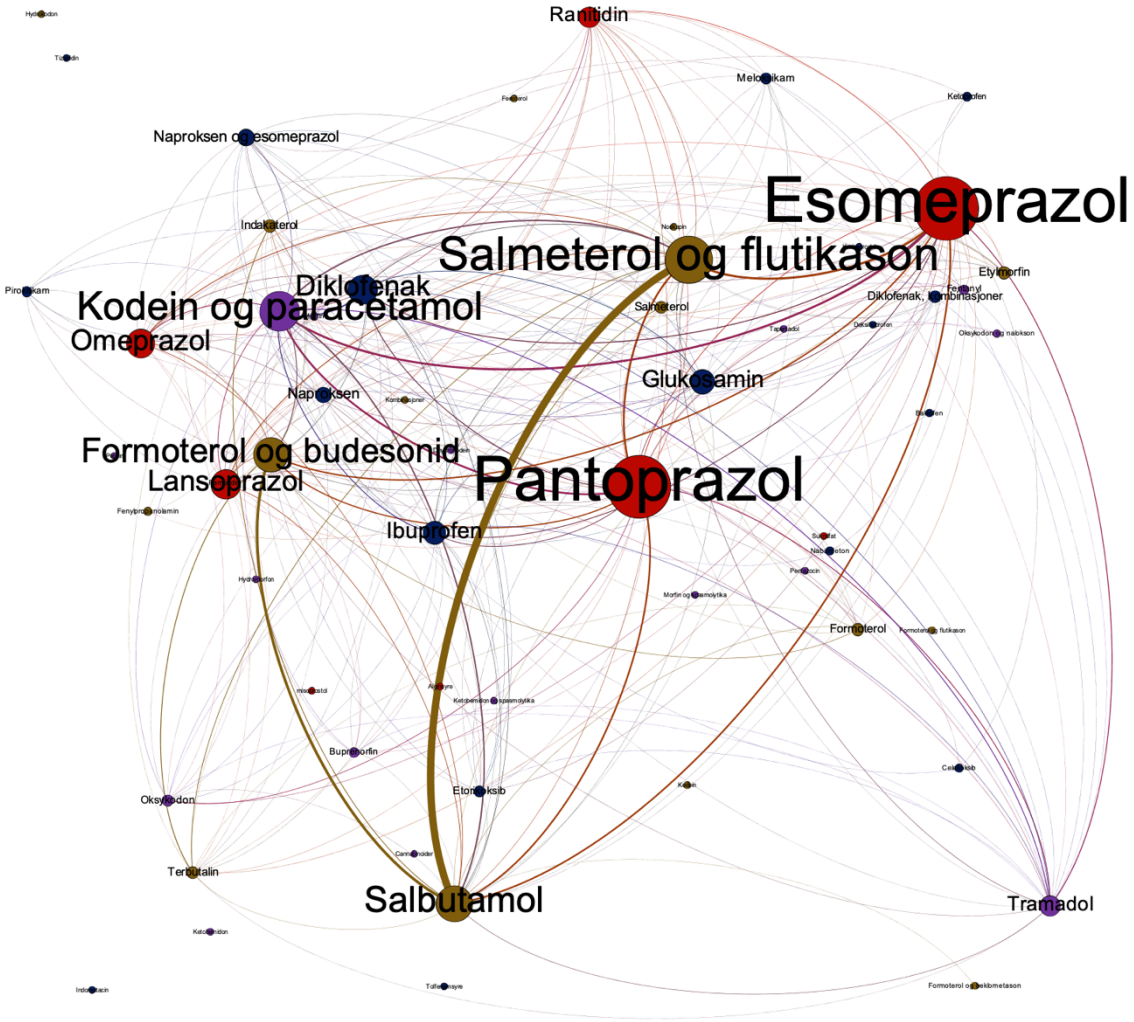


Figure 4.7: Pain weighted network, filter for edges weight> 50. Bigger nodes indicate greater number of users

The full network in PDF format (full resolution) is available here:
https://www.dropbox.com/s/q6ow7ov0evrxtsk/Pain.pdf?dl=0

Figure 4.7 shows Proton Pump Inhibitors (PPIs), in the red color, to represent the highest number of users. Codeine with paracetamol combination with Tramadol, in purple color, show also a high number of users. Non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. diclofenac, ibuprofen) in the dark blue color have a good share of users as well. Combinations of salbutamol with salmeterol/fluticasone and formoterol/budesonide inhalations are frequently used from patients in this network.

4.1.4.f Menopause pattern

Table 4.25: Network characteristics for Menopause subnetwork

Menopause network	
No. of nodes (Drugs)	13
No. of edges	43
Density	0.55
Edges range (min.-max.)	1-16,325
Weight	Weighted

Table 4.26: The most used medicines in Menopause subnetwork, degree centrality shows how many times these medicines were connected to other nodes

ATC	Substance	No. of users	Degree Cen.	Eigenvector Cen.
A12AX	Kalsium, vitamin D	44690	12	1.0
M05BA04	Alendronic acid	33484	8	0.82
G03CA03	estradiol	6381	10	0.94
G03CA04	estriol	4691	11	0.96
G03CX01	Tibolon	1542	7	0.77
M05BX04	denosumab	1436	8	0.85
M05BA07	Risedronsyre	471	6	0.69
M05BA06	Ibandronsyre	243	6	0.64
A12AA06	Kalsiumlaktoglukonat	225	7	0.77
M05BB01	Etidronsyre og kalsium	133	4	0.46

Table 4.26 shows calcium combination with vitamin D and Alendronic acid had the biggest share of users. The most important nodes were calcium combination which is attached to all nodes in the network. Estriol and estradiol comes next in terms of importance with high eigenvector centrality score.

Table 4.27: The most combined medicines in Menopause subnetwork showing number of times each two nodes were combined

ATC 1	Drug 1	ATC 2	Drug 2	No. of times combined
A12AX	Kalsium, komb. vit. D	M05BA04	Alendronic acid	16325
A12AX	Kalsium, komb. vit. D	M05BX04	Denosumab	860
A12AX	Kalsium, komb. vit. D	G03CA04	Estriol	629
A12AX	Kalsium, komb. vit. D	G03CA03	Estradiol	511
G03CA04	Estriol	M05BA04	Alendronic acid	466
G03CA03	Estradiol	M05BA04	Alendronic acid	366
A12AX	Kalsium, komb. vit. D	M05BA07	Risedronic acid	178
A12AX	Kalsium, komb. vit. D	G03CX01	Tibolon	95
A12AX	Kalsium, komb. vit. D	M05BA06	Ibandronsyre	86
G03CA03	Estradiol	G03CA04	Estriol	42

Calcium/vitamin D with Alendronic acid combination had the highest frequency of being used together with a significant difference from the next most frequented combination in the network (i.e. calcium/vitamin D with denosumab).

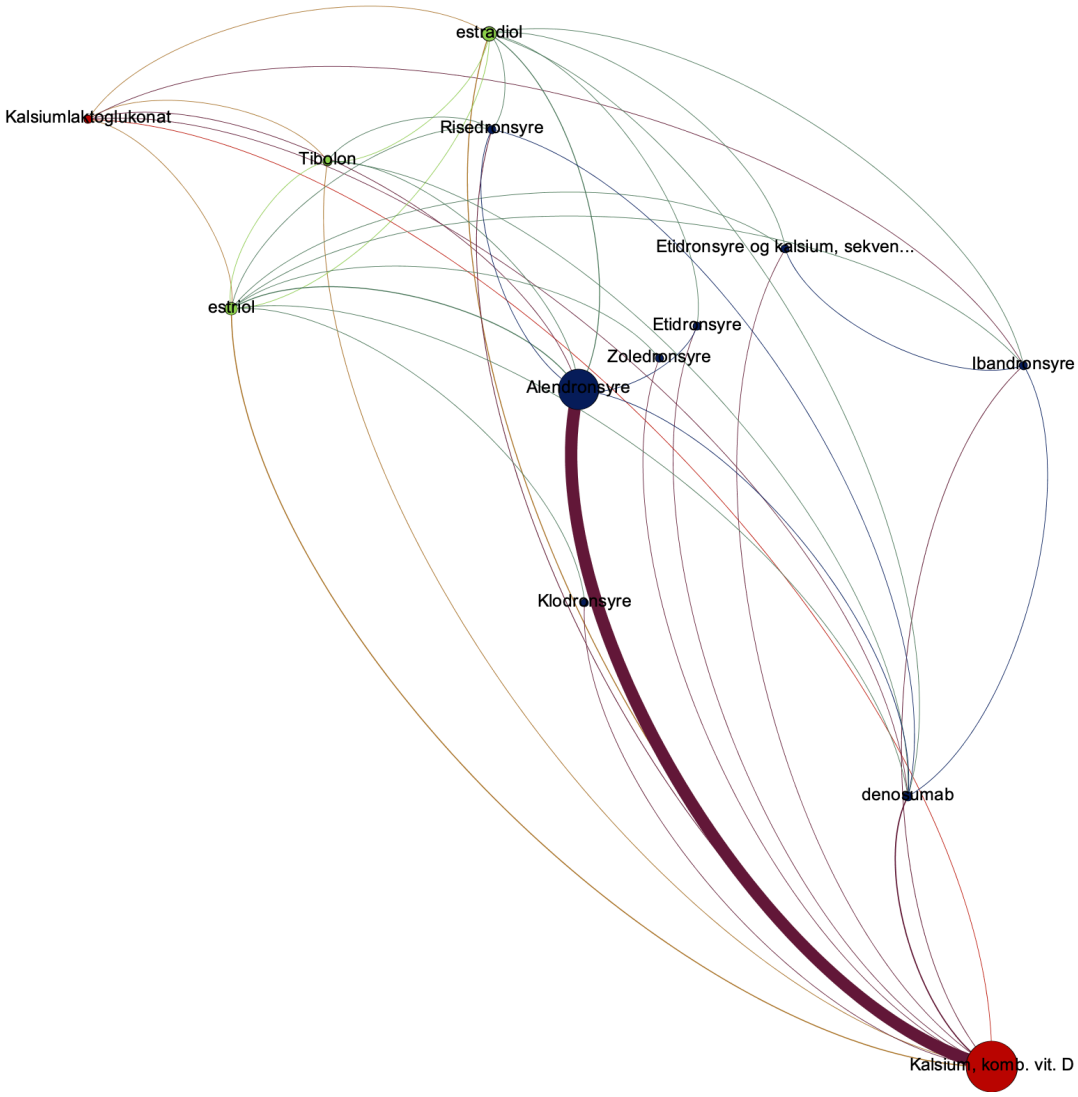


Figure 4.8: Menopause weighted network, no filters applied. Bigger nodes indicate greater number of users

The full network in PDF format (full resolution) is available here:
https://www.dropbox.com/s/qrlgxh9ckvmunt6/menopause.pdf?dl=0

Figure 4.8 shows few nodes with clear priority to Alendronic acid with calcium combination with vitamin D.

4.2 Part II: Comparison of day 0 and 365 networks (Temporal change)

Table 4.28: Comparing basic network characteristics for network day 0 and 365

Day 0 Network		Day 365 Network	
No. of nodes (Drugs)	762	No. of nodes (Drugs)	765
No. of edges	75,052	No. of edges	74,702
Density	0.26	Density	0.26
Edges range (min.-max.)	1-82,948	Edges range (min.-max.)	1-73,456
Weight	Weighted	Weight	Weighted

Table 4.28 represents a minor change in number of nodes, edges and maximum edges' weight.

Table 4.29: Network characteristics for the generated network

Generated (Proportion) Network	
No. of nodes (Drugs)	704
No. of edges	62,809
Density	0.25
Edges range (Proportion min.-max.)	1 to 21
Weight	Weighted

Table 4.29 shows some characteristics of the generated division network. Density remains almost the same. Edges range here represents a ratio of usage not a number.

Table 4.30: Number and percentage of unique edges in both networks

Unique edges distribution in both networks		% of total network edges
Unique edges in 2014 network	11893	16 %
Unique edges in 2013 network	12243	16 %
Total unique edges in both networks (unmatched)	24136	16 %
Common edges in both networks (=compare network)	62809	84 %

About 84 % percent of edges were common in both networks (basically generated network). Each of 2013 and 2014 networks had approximately 16% of unique edges. In other words, 16% of both networks were not matched to the corresponding edges in the other network (table 4.30). The list of eliminated nodes from both networks is attached in (appendix 6).

Table 4.31: Anatomical ATC distribution in 2014 network, showing difference in percent from 2013 network

Anatomical group	No. of times involved in a combination	Pecent (change from 2013)
N Nervous system	15241	20.40 (-0.15%)↓
C Cardiovascular system	13911	18.62 (-0.14%)↓
A Alimentary tract and metabolism	11457	15.34 (+0.31%)↑
R Respiratory system	8556	11.45 (+0.35%) ↑
B Blood and blood forming organs	4507	6.03 (+0.28%)↑
G Genito-urinary system, sex hormones	4154	5.56 (-0.03%) ↓
M Musculo-skeletal system	3885	5.20 (-0.25%)↓
L Antineoplastic, immunomodulating agents	3871	5.18 (-0.23%)↓
J Anti-infectives for systemic use	3829	5.13 (-0.07%)↓
H Systemic hormonal, ex. sex hormones and insulins	2356	3.15 (+0.02%)↑
S Sensory organs	2119	2.84 (-0.04%)↓
P Antiparasitic products, insecticides and repellents	319	0.43 (-0.07%)↓
D Dermatologicals	303	0.41 (+0.03%)↑
V Various	194	0.26 (0.0%)=

Anatomical class ATC distribution (table 4.31) shows slight differences in percentages of different anatomical classes being involved in drug-drug combinations in day 0 and day 365 networks. R-, A-groups had the highest change in percentages respectively. N-group remains with the highest proportion (20.4%) while V-group comes last with (0.26%). The 2014 network shows though less percentages of J-group ATC codes.

Table 4.32: Drug-drug combining frequency change in 2013,2014 networks

Drug combination frequency comparison (2013-2014)		
	Frequency	Percent
Lower combination frequency in 2013 than 2014	19381	31 %
No change	11861	19 %
Higher combination frequency in 2013 than 2014	31567	50 %
Total	62809	100 %

Table 4.32 show that 50% of all drug combinations to be higher used in 2013 than 2014 compared to 31% in 2014 to 2013, while 19% of combinations remains at the same frequency.

Table 4.33: The top most used drugs in 2014 more 2013 according to ratio of users

ATC	Substance	Drug name in Norway	Ratio no. of users 2014/2013
A10BK01	Dapagliflozin	Forxiga®	64.7
B01AF02	Apiksaban	Eliquis®	31.6
R01AD58	Flutikason, combinations	Dymista®	20.4
G04BD12	Mirabegron	Betmiga®	16.4
A10BJ03	Liksisenatid	Lyxumia® inj	16
L02BB04	Enzalutamid	Xtandi®	14.3
A10BD11	Metformin og linagliptin	Jentadueto®	12.4
A06AX04	linaclotide	Constella®	12.0
C01EB17	Ivabradin	Procoralan®	9.0
R03BB06	glycopyrronium bromide	Seebri® breezhaler	8.07
R03AK11	Formoterol og flutikason	Flutiform® inh aeros	7.5
R03BB05	aclidinium bromide	Eklira Genuair inh pulv ®	6.4
A06AX05	Prukaloprid	Resolor ®	6.0
B03BA05	Mekobalamin	Mekobalamin® inj	6.0
B01AF01	Rivaroksaban	Xarelto®	5.9

The top prevalent ratios of drugs users in 2014 network compared to 2013 network (table 4.33) shows dapagliflozin (Forxiga®) is the highest medicine to be used in 2014 with about 65 times more compared to 2013. Apixaban (Eliquis®) comes next with almost 32% more users in 2014 than 2013.

Table 4.34: The least used drugs in 2014 than 2013 according to ratio of users

ATC	Substance	Drug name in Norway	Ratio no. of users 2014/2013
G04CA01	Alfuzosin	Xatral ®	0.04
J04AC01	Isoniazid	Isoniazid NAF ®	0.14
J05AB04	ribavirin	Copegus ®	0.2
J05AH02	Oseltamivir	Tamiflu caps ®	0.2
C01AA04	Digitoksin	Digitoxin nycomed ®	0.202
R03CC02	Salbutamol	Ventoline mixture ®	0.24
N02CA52	Ergotamin, comb. except psykoleptics	Cafergot®	0.25
N02CA72	Ergotamin, comb. with psykoleptics	Anervan supp ®	0.254
J01FA02	Spiramycin	Rovamycin tab 3mill IE ®	0.286
L01XE07	Lapatinib	Tyverb tab®	0.285
C10AD02	Nikotinsyre	Niaspan ®	0.33
J01MA14	Moksifloksacin	Avelox tab ®	0.33
R01AB06	xylometazoline	Otrivin Comp ®	0.36
N05AA01	Klorpromazin	Chlorpromazine ®	0.42
A06AH01	methylnaltrexone bromide	Relistor inj ®	0.42

On the other hand, the least used medicines in 2014 were alfuzosin (Xatral®) with significant lower ratio. Isoniazid, ribavirin, oseltamivir and digitoxin comes next with notably lower percentage of users compared to 2013 users.

Table 4.35: The top drug-drug combinations which were more used in 2013 than 2014. Ratio represents number of patients have combined the two medicines in 2013 over the number of patients used the same combinations in 2014.

ATC	Substance	ATC2	Substance 2	Ratio of users (2013/2014)
C01AA04	Digitoxin	L04AX03	Methotrexate	21
B01AB04	Deltaparin (Fragmin ®)	M01AB55	Diclofenac, combinations	19
C01AA04	Digitoxin	R03BA02	Budesonide	17
A11CC01	Ergocalciferol (AFI-D2 forte ®)	J01CA04	Amoxicillin	16
C01AA04	Digitoxin	C09AA01	Captopril	16
M01AB05	Diclofenac	N02AB01	Ketobemidone (Ketorax ®)	16
A04AA01	Ondansetron (Zofran ®)	J01EE01	Sulfamethoxazole and Trimethoprim	15
C01AA04	Digitoxin	N06AA09	Amitriptyline	15
C01DA08	Isosorbide dinitrate	J01CE02	Phenoxymethylpenicillin	15
C03EA01	HCT/Pot.sparing agents	P01AB01	Metronidazole	15
G04CA01	Alfuzosin (Xatral ®)	G04CA02	Tamsulosin	15

The table 4.35 shows digitoxin combined with methotrexate is the combination with highest proportion of users in 2013 than 2014. Digitoxin is also involved in three other combinations in the most used combinations in 2013. Alfuzosin combination with Tamsulosin comes last of the list with 15 times higher usage in 2013 compared to 2014.

Table 4.36: The top drug-drug combinations which were more used in 2014 than 2013. Ratio represents number of patients combined the two medicine (edges) in 2014 over 2013

ATC	Substance	ATC2	Substance 2	Ratio of users (2014/2013)
A10BK01	Dapagliflozin (Forxiga ®)	C10AA05	Atorvastatin	143
B01AF02	Apixaban (Xarelto ®)	C07AB07	Bisoprolol	102
C09DA04	Irebsartan/HCT (CoAprovel®)	G04BD12	Mirabegron (Betmiga ®)	74
A10BA02	Metformin	A10BK01	Dapagliflozin (Forxiga ®)	73
A10BK01	Dapagliflozin (Forxiga ®)	B01AC06	Acetyl salicylic acid	71
B01AF02	Apixaban (Xarelto ®)	C01DA14	Isosorbide mononitrate	71
A10BK01	Dapagliflozin (Forxiga ®)	C10AA01	Simvastatin	70
A02BC02	Pantoprazole	B01AF02	Apixaban (Xarelto ®)	68
B01AF02	Apixaban (Xarelto ®)	C09CA01	Losartan	64
A10BD08	Metformin/Vildagliptin (Eucreas®)	A10BK01	Dapagliflozin (Forxiga ®)	62

Table 4.36 shows that dapagliflozin (antidiabetic) and apixaban (antithrombotic agent, factor Xa-inhibitor) are involved in almost all the combinations that were higher used in 2014 than 2013.

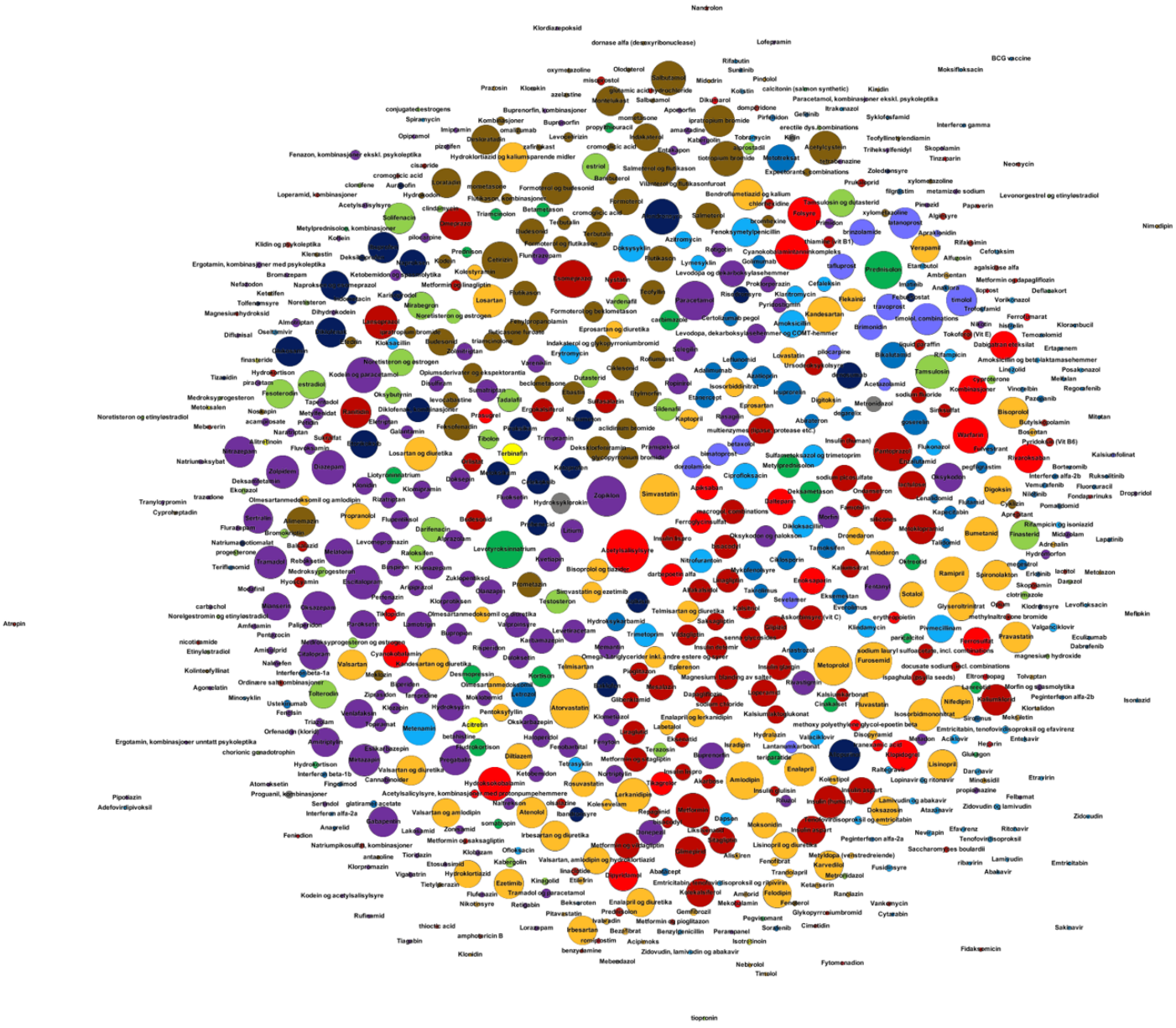


Figure 4.9: Day 365 (2014 network) with no filters applied, bigger nodes indicate greater number of co-medications

The full network in PDF format (full resolution) is available here:
https://www.dropbox.com/s/9e128evrkl1f395/dag%20365%20nw%20no%20filters%20no%20edges.pdf?dl=0

Cardiovascular systems nodes in the orange color shows many large nodes indicating being involved in many drug-drug combinations (e.g. simvastatin, metoprolol). Nervous system drugs in purple has also many big nodes (e.g. zopiclone, paracetamol). Acetyl salicylic acid represents the biggest and most centered node in the network along with simvastatin.

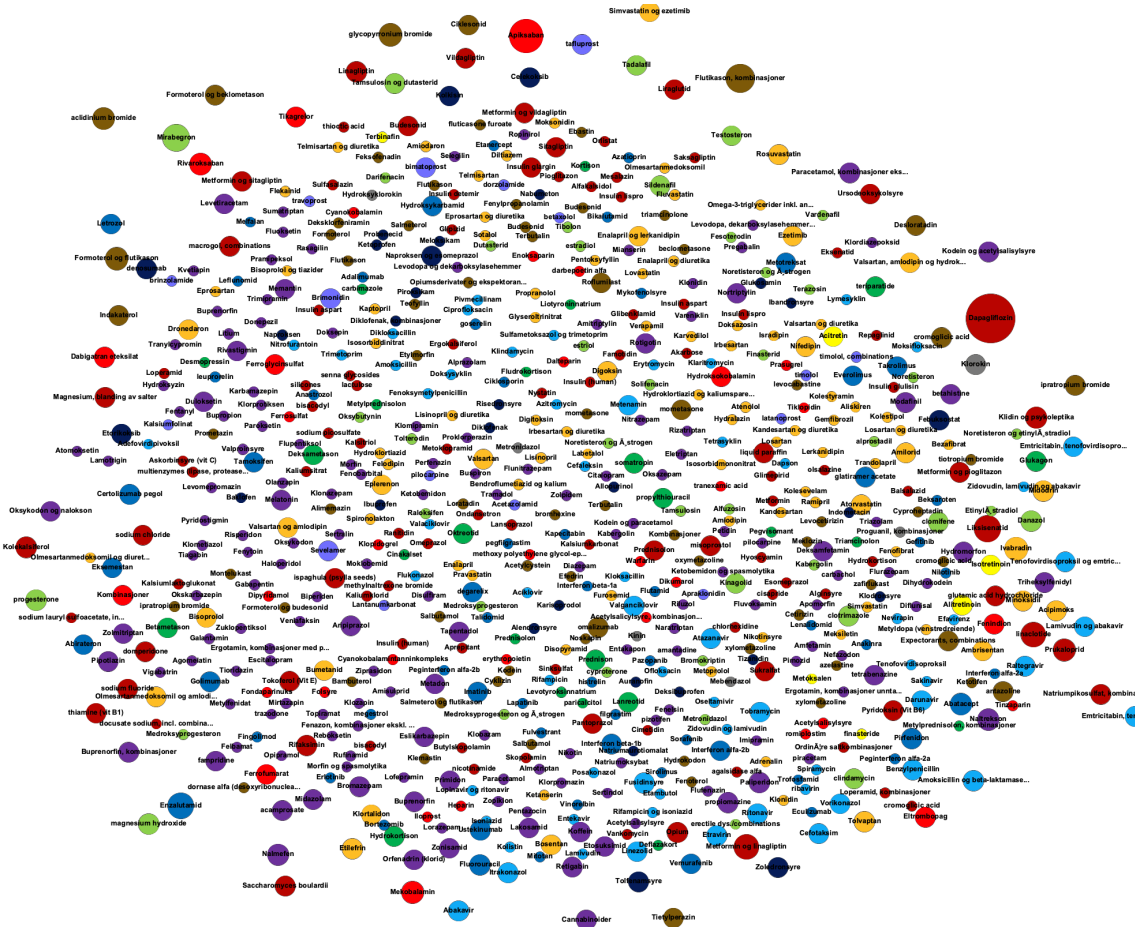
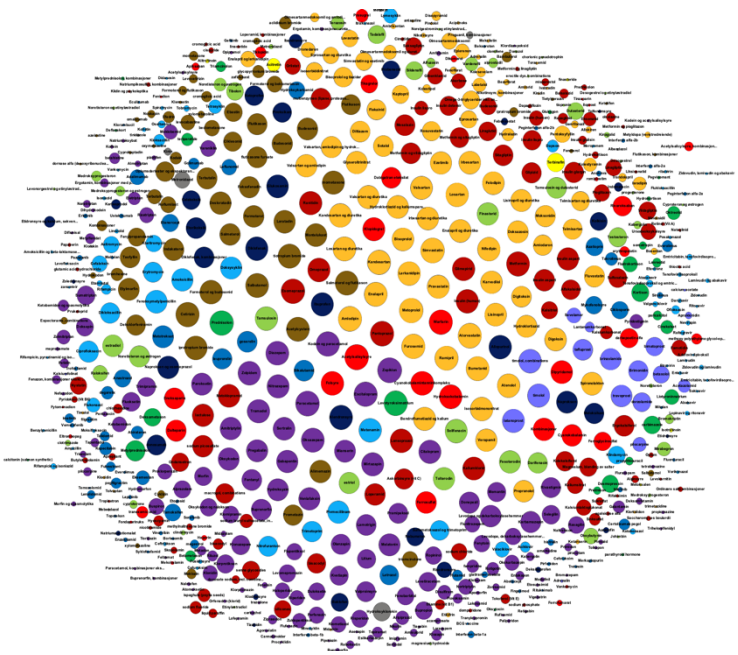


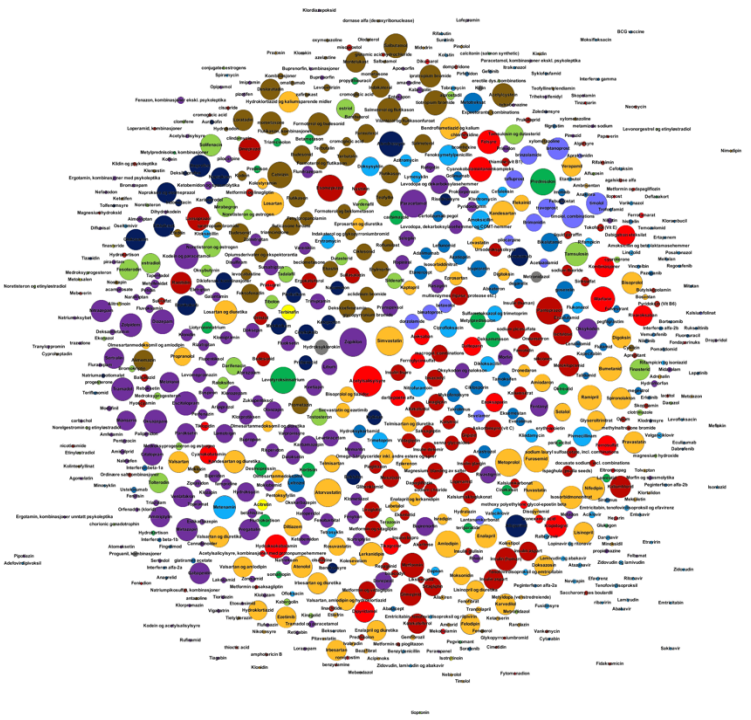
Figure 4.10: Compare network, node size indicates ratio of users in 2014/2013 the bigger nodes the greater proportion of users in 2014 compared to 2013.

The full network in PDF format in which node size indicates ratio of users is available here: https://www.dropbox.com/s/0vllaawnod9ud9a/compare%20nw%20no%20of%20users.pdf?dl=0

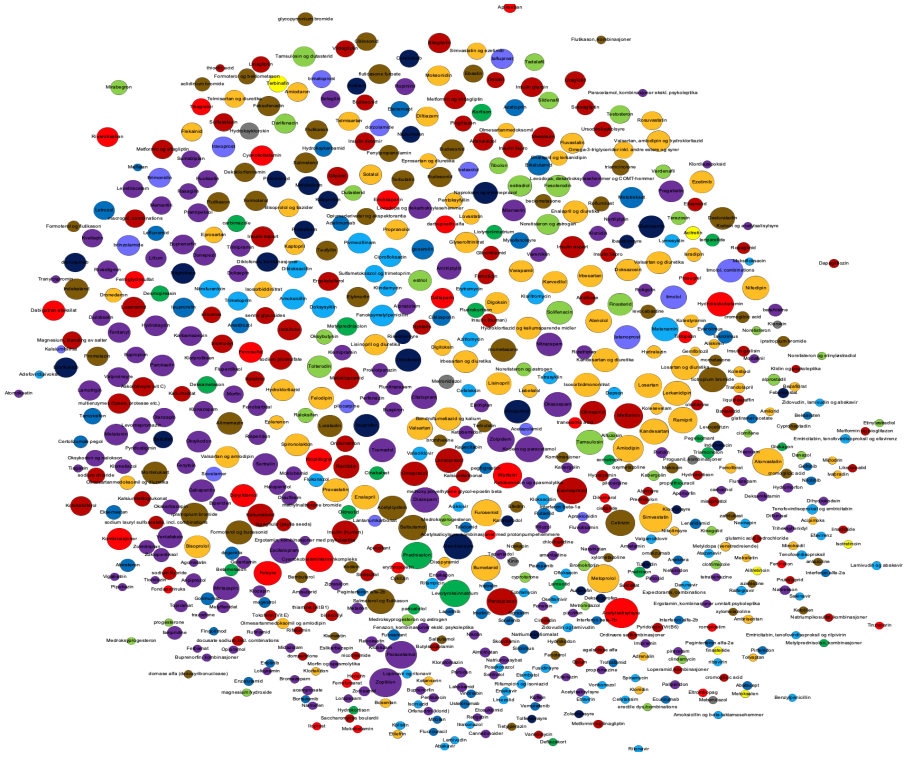
The network (figure 4.10) shows relatively smaller nodes than the other two networks because it represents the ratio of users between day 0 and day 365 network not the number of users. Dapagliflozin and apixaban are the biggest nodes in the network indicating more users in day 365 network. It is noticed that platelet aggregation inhibitors in the light red color (e.g. apixaban, ticagrelor, rivaroxaban) have many big nodes in the network. In general, relatively newer substances or combinations have bigger nodes indicating more users. Notice that this network differs from the following network (figure 4.11) in that node size here indicates ratio of users while the following network node size indicates the number edges (i.e. bigger nodes indicates being involved in more combinations with other nodes).



2013 full Network



2014 full Network



Compare Network (full)

Figure 4.11: Representing the three full networks (2013, 2014 and the compare network) in form of nodes. Bigger nodes indicate being involved in a greater number of co-medication (edges).

Full compare network in PDF in which node size indicates edges degree is available here:
https://www.dropbox.com/s/4u7tj64lrxng3qd/compare%20nw%20no%20filters%20bigger%20nodes%20degree.pdf?dl=0

4.3 Part III: Comparison of the selected five counties

Table 4.37: Prescriptions' distribution in the five counties

Distribution of prescriptions in the 5 counties		
Name of county	No. Of prescriptions	precentage
Akershus	1885949	10 %
Hordaland	1704633	9 %
Nordland	1015113	6 %
Oslo	1622358	9 %
Rogaland	1319689	7 %
Total prescriptions for the chosen counties	7547742	41 %

Table 4.37 represents number and percentage of prescriptions of the overall prescriptions in the dataset in the five counties. The prescription from all the five counties forms 41% of the overall prescriptions in the dataset.

Table 4.38: A comparison between network characteristics for the 5 counties

	Network characteristics					
	No. of nodes	No. of edges	Edges max. value	Density	Weight	Direction
Akershus	592	37009	8150	0.21	Weighted	Undirected
Hordaland	572	35176	6996	0.22	Weighted	Undirected
Nordland	524	27618	5095	0.20	Weighted	Undirected
Oslo	598	34901	6998	0.20	Weighted	Undirected
Rogaland	555	32902	6220	0.21	Weighted	Undirected

Table 4.38 shows slight differences in networks characteristics in the five counties. Number of nodes, edges, and density are convergent. Akershus shows higher scale in terms of edges weight.

Table 4.39: The most combined medicines in the 5 counties

The 5 counties' most combined drugs								
Akershus			Hordaland			Nordland		
Drug 1	**Drug 2**	**No. Comb.**	**Drug 1**	**Drug 2**	**No. Comb.**	**Drug 1**	**Drug 2**	**No. Comb.**
Acetylsalisylsyre	Simvastatin	8150.0	Acetylsalisylsyre	Simvastatin	6996.0	Acetylsalisylsyre	Simvastatin	5093.0
Acetylsalisylsyre	Metoprolol	5313.0	Acetylsalisylsyre	Atorvastatin	4594.0	Acetylsalisylsyre	Metoprolol	3468.0
Acetylsalisylsyre	Atorvastatin	4935.0	Acetylsalisylsyre	Metoprolol	4140.0	Acetylsalisylsyre	Amlodipin	2712.0
Metoprolol	Simvastatin	3607.0	Acetylsalisylsyre	Amlodipin	3103.0	Metoprolol	Simvastatin	2291.0
Acetylsalisylsyre	Amlodipin	3137.0	Metoprolol	Simvastatin	2592.0	Acetylsalisylsyre	Atorvastatin	2056.0
Acetylsalisylsyre	Zopiklon	3081.0	Acetylsalisylsyre	Zopiklon	2447.0	Amlodipin	Simvastatin	1734.0
Amlodipin	Simvastatin	2158.0	Amlodipin	Simvastatin	2162.0	Acetylsalisylsyre	Zopiklon	1649.0
Acetylsalisylsyre	Ramipril	2140.0	Acetylsalisylsyre	Ramipril	2018.0	Metoprolol	Amlodipin	1424.0
Metoprolol	Atorvastatin	2005.0	Acetylsalisylsyre	Furosemid	1744.0	Acetylsalisylsyre	Furosemid	1374.0
Metformin	Acetylsalisylsyre	1948.0	Metformin	Acetylsalisylsyre	1576.0	Acetylsalisylsyre	Levotyroksin	1233.0

Oslo			Rogaland		
Drug 1	**Drug 2**	**No. Comb.**	**Drug 1**	**Drug 2**	**No. Comb.**
Acetylsalisylsyre	Simvastatin	6998.0	Acetylsalisylsyre	Simvastatin	6220.0
Acetylsalisylsyre	Metoprolol	4211.0	Acetylsalisylsyre	Atorvastatin	3405.0
Acetylsalisylsyre	Atorvastatin	3412.0	Acetylsalisylsyre	Metoprolol	3357.0
Metoprolol	Simvastatin	3095.0	Metoprolol	Simvastatin	2626.0
Acetylsalisylsyre	Zopiklon	2670.0	Acetylsalisylsyre	Zopiklon	2220.0
Acetylsalisylsyre	Amlodipin	2621.0	Acetylsalisylsyre	Amlodipin	2205.0
Simvastatin	Zopiklon	1783.0	Simvastatin	Zopiklon	1787.0
Amlodipin	Simvastatin	1755.0	Amlodipin	Simvastatin	1730.0
Metformin	Acetylsalisylsyre	1557.0	Acetylsalisylsyre	Ramipril	1601.0
Acetylsalisylsyre	Levotyroksin	1436.0	Metoprolol	Atorvastatin	1311.0

(Table 4.39) shows almost the same combinations in all counties with slight differences of combinations' order.

Table 4.40: Eigenvector Centrality comparison for top 10 high-scored nodes in the 5 counties

Eigenvector Centrlality									
Akershus		Hordaland		Nordland		Oslo		Rogaland	
Drug	**Score**	**Drug**	**Score**	**Drug**	**Score**	**Drug**	**Score**	**Drug**	**Score**
Acetylsalisylsyre	1.0	Acetylsalisylsyre	1.0	Acetylsalisylsyre	1.0	Acetylsalisylsyre	1.0	Acetylsalisylsyre	1.0
Zopiklon	0.985	Simvastatin	0.986	Simvastatin	0.984	Simvastatin	0.988	Zopiklon	0.994
Simvastatin	0.983	Zopiklon	0.985	Zopiklon	0.976	Zopiklon	0.987	Simvastatin	0.993
Metoprolol	0.978	Metoprolol	0.974	Metoprolol	0.976	Metoprolol	0.979	Paracetamol	0.978
Paracetamol	0.976	Furosemid	0.969	Amlodipin	0.973	Atorvastatin	0.969	Metoprolol	0.975
Atorvastatin	0.974	Atorvastatin	0.968	Paracetamol	0.971	Paracetamol	0.965	Amlodipin	0.968
Amlodipin	0.967	Esomeprazol	0.967	Esomeprazol	0.968	Levotyroksinnatrium	0.963	Prednisolon	0.965
Levotyroksinnatrium	0.9667	Paracetamol	0.962	Pantoprazol	0.967	Amlodipin	0.963	Levotyroksinnatrium	0.964
Esomeprazol	0.966	Amlodipin	0.962	Levotyroksinnatrium	0.962	Kodein og paracetamol	0.959	Atorvastatin	0.958
Warfarin	0.959	Levotyroksinnatrium	0.959	Furosemid	0.959	Pantoprazol	0.954	Pantoprazol	0.955

(Table 4.40) shows the top 10 high-scored nodes to be almost the same between the five counties with slight difference in order between them. Acetyl salicylic acid has the highest score representing the most important node in all networks.

The full networks in PDF format (full resolution) are available here:
Akershus: https://www.dropbox.com/s/wwz77unnqai9rll/Akershus.pdf?dl=0
Hordaland: https://www.dropbox.com/s/424v2mqerusyg4i/Hordaland.pdf?dl=0
Nordland: https://www.dropbox.com/s/m5j4sfznnerk2m6/Nordland.pdf?dl=0
Oslo: https://www.dropbox.com/s/pudxits9a5k9h16/Oslo.pdf?dl=0
Rogaland: https://www.dropbox.com/s/rwwd8k8u8gu2dqb/Rogaland.pdf?dl=0

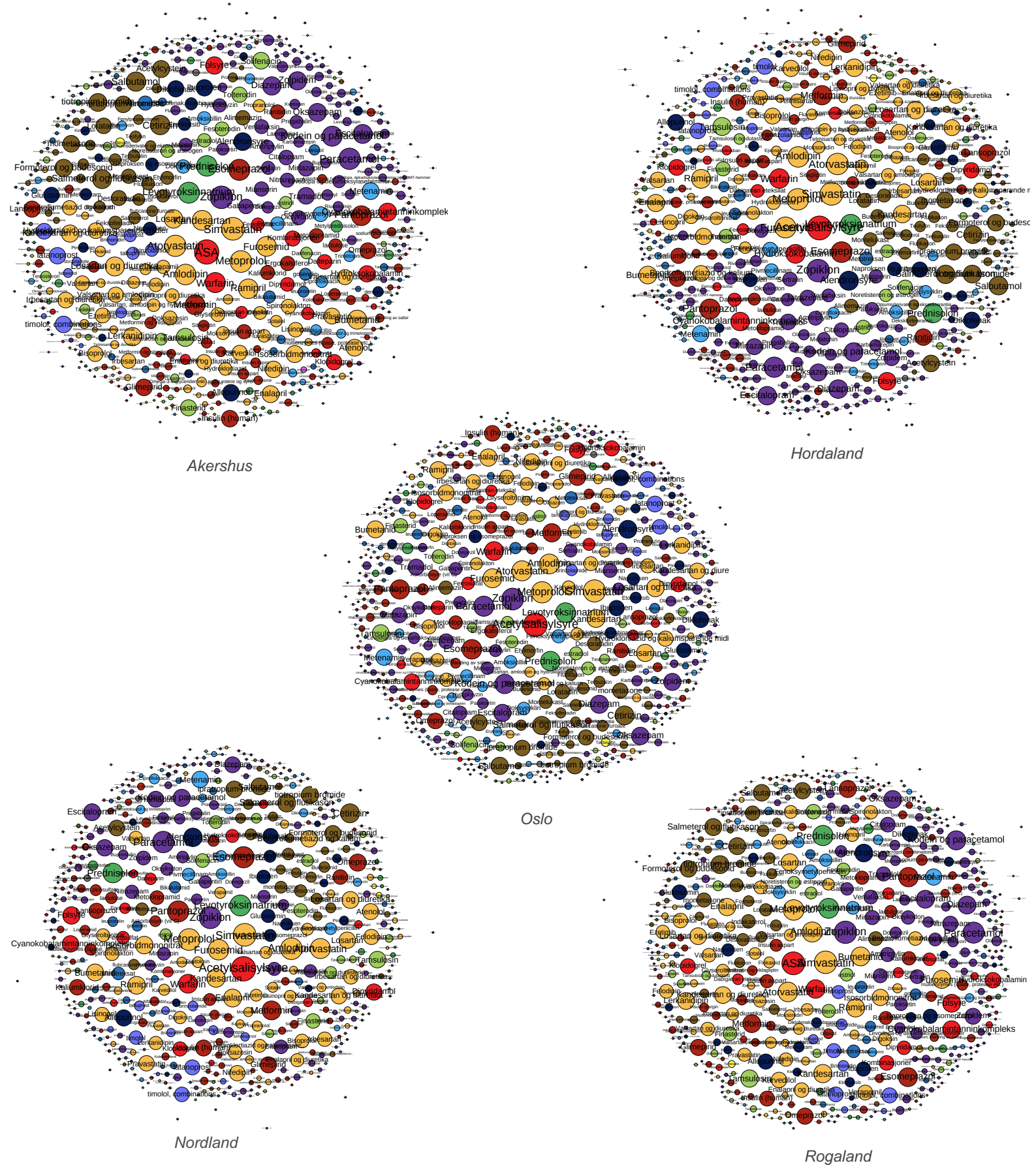


Figure 4.12: Full networks for the five counties, bigger nodes indicates higher number of edges

4.4 Part IV: Drug-drug severe interactions network

Table 4.41: Represents the total number of interactions and number of interactions in each severity level in FEST database

DDI from FEST			
Total Interactions without exclusions	1st grade (severe)	2nd grade (moderate)	3rd (low risk)
933783	153354	477022	303407

Severe interactions represent approximately 16% (table 4.41) of the total drug-drug interaction in the dataset. After exclusions, only 113,413 of the severe interactions were left (methods 3.3.2).

Table 4.42: Drug-drug severe interactions network characteristics.

Drug-drug severe interactions Network	
No. of nodes (Drugs)	1699
No. of edges	57,151
Density	0.04
Edges range (min.-max.)	0-1
Weight	Unweighted

The network represents a qualitative relation; that is why the edges are either 0 or 1 (i.e. the interactions are either found or not) (table 4.42).

Heat map for ATC 1st grade interactions on the anatomical class level														Total
	A	B	C	D	G	H	J	L	M	N	P	R	S	V	
A	380														
B	20	192													
C	84	76	3452												
D	1	0	0	17											
G	0	0	16	0	463										
H	6	0	0	0	0	1									
J	361	60	739	110	852	160	35871								
L	124	119	227	1	107	36	2777	74							
M	7	101	1	0	0	0	42	197	1617						
N	265	91	960	31	1131	11	876	523	61	2027					
P	0	0	12	0	2	0	34	12	0	39	278				
R	1	1	6	1	31	0	163	92	56	922	0	17			
S	0	0	0	0	0	0	1	0	0	209	0	0	15		
V	68	1	744	1	9	2	23	15	3	55	3	10	0	58	
Total	1317	641	6157	161	2595	210	39787	913	1737	3252	281	27	15	58	57151

Figure 4.13: A heat map of anatomical groups severe interactions, the darker the color the more interactions the group is involved in.

The heat map (figure 4.13) shows severe interactions between each anatomical group and the others. The highest number of severe interactions lies between (J-J) anatomical group with a total 35871 DDI.

It shows also how many severe interactions were between each of the anatomical groups. The total number of ATC codes was 1699 (total number of nodes). J- group has the highest number of ATC codes (370) followed by N-group (264) and L-group with (262). ATC classes S, R, V, H and D had the fewest severe interactions.

(L-J), (N-N), (N-G), (N-C) anatomical groups have also a high number of interactions as seen from the red color in the figure. Other groups had no severe interaction, e.g. (H-B) and (S-A) among others.

Total number of severe interactions was (57151). The J-group had the highest number of severe interactions (39787) followed by C-group (6157), while the lowest number of severe interactions was observed in group S- and group R- with 15 and 27 DDI, respectively.

Table 4.43: The 10 ATC codes with highest number of interactions in the severe drug-drug interactions network

ATC	Name	No. of severe DDI
J07AP01	Tyfoid, oral, levende, svekket	537
J01FA01	Erytromycin	343
N06AX25	Prikkperikum (St John's-wort)	335
J01FA09	Klaritromycin	327
J01MA14	Moksifloksacin	312
J01XX08	Linezolid	311
J01XC01	Fusidinsyre	294
J01XX05	Metenamin	289
J01BA01	Kloramfenikol	287
J07AN01	Tuberkulose, levende, svekket	277

As shown in (table 4.43), ATC codes with the greatest number of severe DDI all belong to anatomical J-group (anti-infectives for systematic use) except Prikkpericum (Hypericum perforatum, known as (St John's-wort) which belongs to N-group and used for treating mild to moderate depression and related symptoms. The most interacted medicines and detailed notes on the severe DDI of each anatomical group is attached in (appendixes 8).

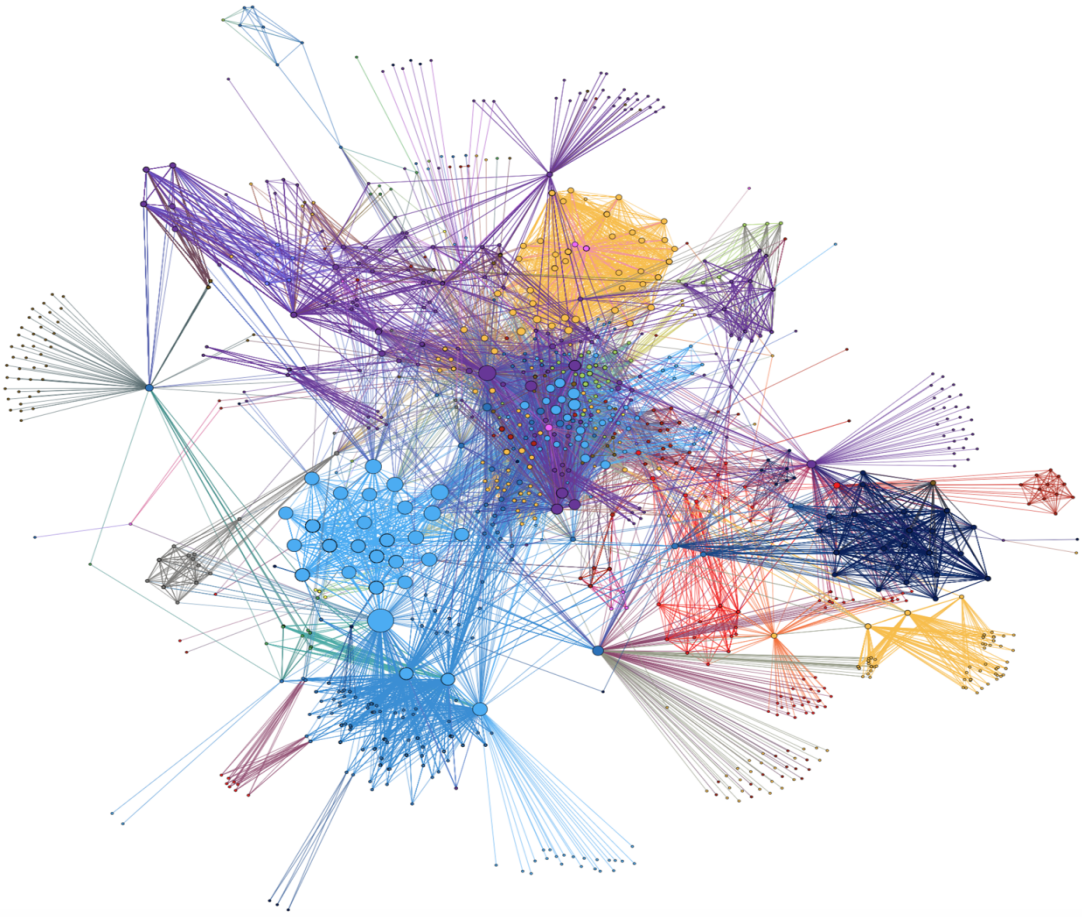


Figure 4.14: Full severe DDI Network, colors indicate anatomical groups, bigger nodes indicates greater number of interactions

The severe DDI network (figure 4.14) shows J-group in the sky-blue color to have the largest nodes of size indicating high number of severe interactions. Nervous system group, in purple, represents spreading in the top half of the network with a share of large nodes as well. Cardiovascular group, in orange color, is extensively in two parts of the network. In general, we can notice a sort of color grouping (clusters) in the network.

Due to the complexity of the network with a considerable amount of information, it may be easier to use the original PDF files with original resolution to visualize and navigate across the whole network.

- The whole severe drug-drug interactions available here (with labels): https://www.dropbox.com/s/55pxvcuz4gifgwd/DDI%20gengeral%20whole%20no%20labels.pdf?dl=0
- The whole severe drug-drug interactions (no labels) available here(figure 4.14): https://www.dropbox.com/s/55pxvcuz4gifgwd/DDI%20gengeral%20whole%20no%20labels.pdf?dl=0
- Labeled severe drug-drug interactions with filtering of nodes which have less than 10 interactions (604 nodes are filtered, about 36% of network) with edges available here: https://www.dropbox.com/s/fe2egep8om7i4mz/DDI%20general%20filtered%3E10%20degree.pdf?dl=0
- Labeled 1st grade drug-drug interactions with less than 10 interactions nodes filtered out (604 nodes about 36% of network) without edges available here: https://www.dropbox.com/s/ry4etbsg3i29e3k/DDI%20general%20filtered%3E10%20degree%20no%20edges.pdf?dl=0

4.4.1 Betweenness centrality

Table 4.44: Represents the medicines with the highest betweenness centrality score in severe DDI network

Betweenness centrality			
Substance	**ATC**	**No. of DDI involoved in**	**Betweenness Cen. Score**
Typhoid vaccine oral	J07AP01	537	191027
Prikkperikum (St John's-wort)	N06AX25	335	172959
Tuberculose vaccine	J07AN01	277	95628
Ginkgo Folium	N06DX02	148	83581
Histamin dihydrochlorid	L03AX14	122	83348
Linezolid	J01XX08	311	65302
Erythromycin	J01FA01	343	64118
Warfarin	B01AA03	90	45646
Itraconazol	J02AC02	157	42317
Klarithromycin	J01FA09	327	41059
Methotrexat	L01BA01	90	40464
Ciclosporin	L04AD01	58	39192
Moxifloxacin	J01MA14	312	37677
Sodium oxybate	N01AX11	72	26242
Aliskiren/HTC	C09XA52	76	26202
Aliskiren/Amlodipin/HCT	C09XA54	76	26202
Panobinostat	L01XX42	76	24878
Chloramfenicol	J01BA01	287	23808

Table 4.44 represents drugs with highest betweenness centrality score, and the number of interactions these drugs are involved in. All drugs with the highest score belong to B-, C-, J-, L-, N- anatomical groups. Typhoid vaccine, tuberculosis vaccine shows the highest score in J-group with 537, 277 interaction with other drugs. The highest scored antibiotic was linezolid followed by erythromycin. Itraconazole was the only anti-fungal drug among the highest-scored drugs. Only one anti-coagulant drug is included in the table which is warfarin.

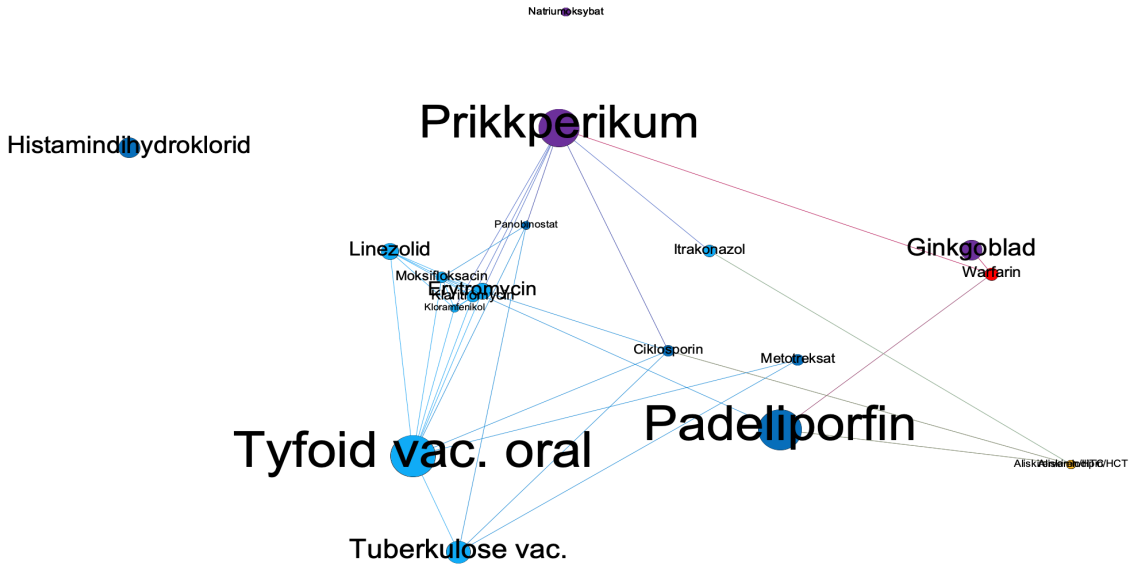


Figure 4.15: DDI network filtered for betweenness centrality to show only the top 20 scored drugs in betweenness centrality score (score>2323687), bigger nodes indicate higher score.

We located the 20 nodes with highest betweenness score in the network (figure 4.16) and filtered them out of the whole network (figure 4.15).

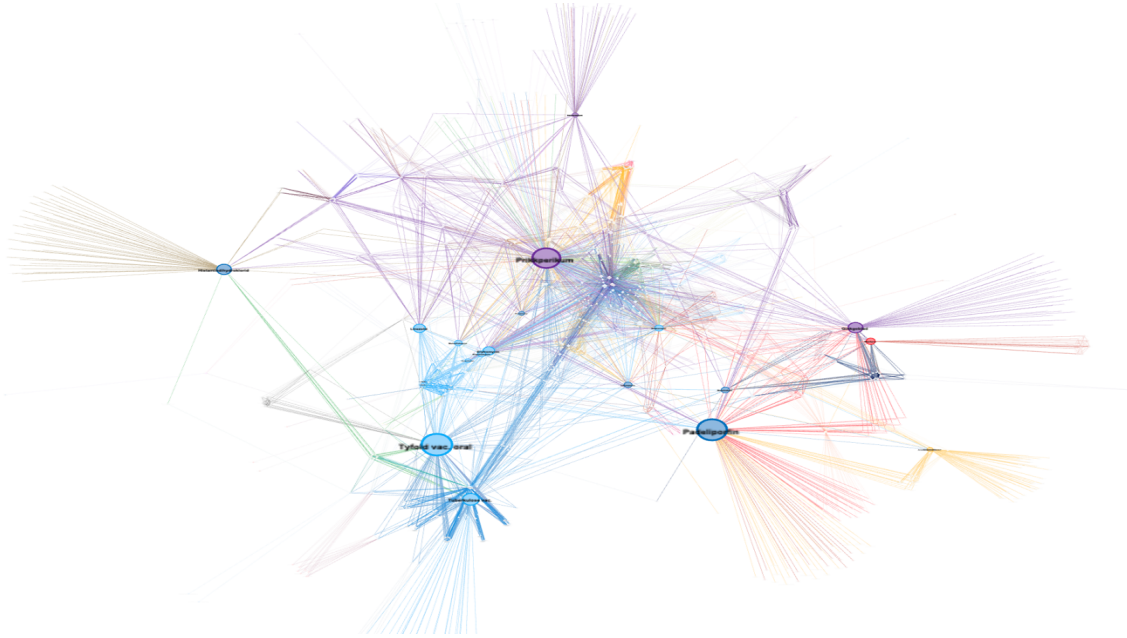
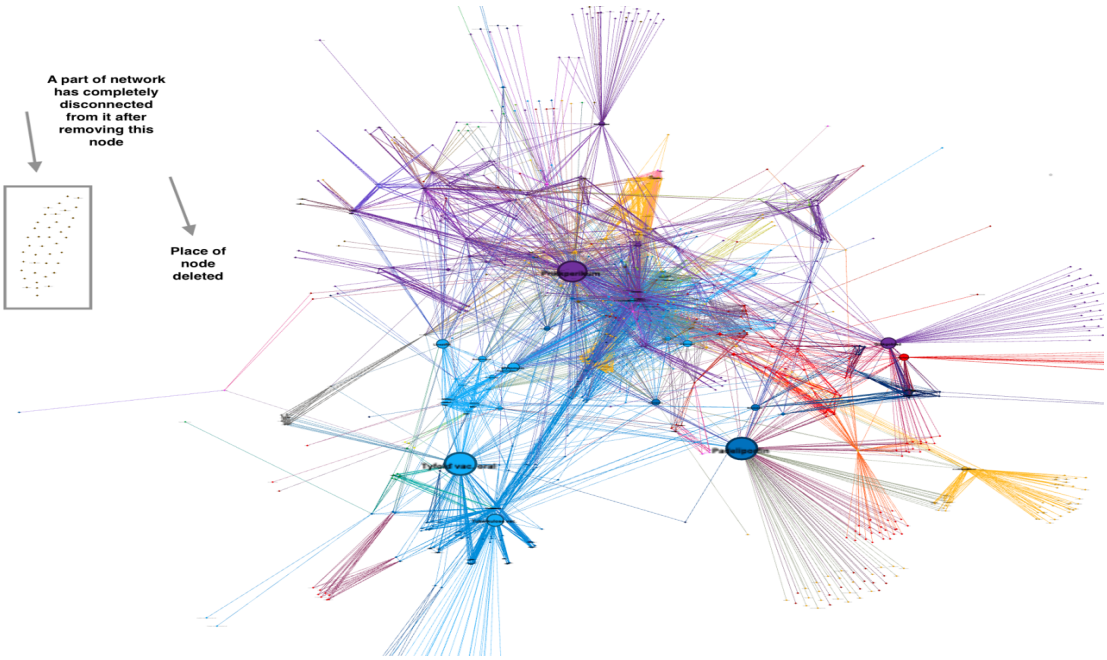


Figure 4.16: Whole DDI network showing location of top 20 betweenness centrality drugs in the network

To clarify the potential importance of using this measure for drug prescription networks we removed one of these highe-scored nodes which is Histamine Hydrochloride and regenerated the network (figure 4.17).

Figure 4.17: DDI network after removing Histamine HCL node showing disconnection of a part of the network



A group of ATC codes were completely isolated from the network after removing histamine node which has high betweenness centrality in the network (figure 4.17).

4.4.2 Applying DDI network on co-medication network (day 0)

Table 4.45: Day 0 severe interacted medicines network characteristics, edges range here indicates how many users have combined these interacted drugs

Day 0 severe DDI Network	
No. of nodes (Drugs)	229
No. of edges	662
Density	0.025
Edges range (min.-max.)	1 to 2320
Weight	Weighted

Matching severe DDI network on co-medication day 0 network allowed us to discover severe interactions in the elderly polypharmacy. Pairing these two networks revealed 229 drugs with total 662 severe drug-drug interactions with combination frequency from 1- 2320 times (table 4.45)

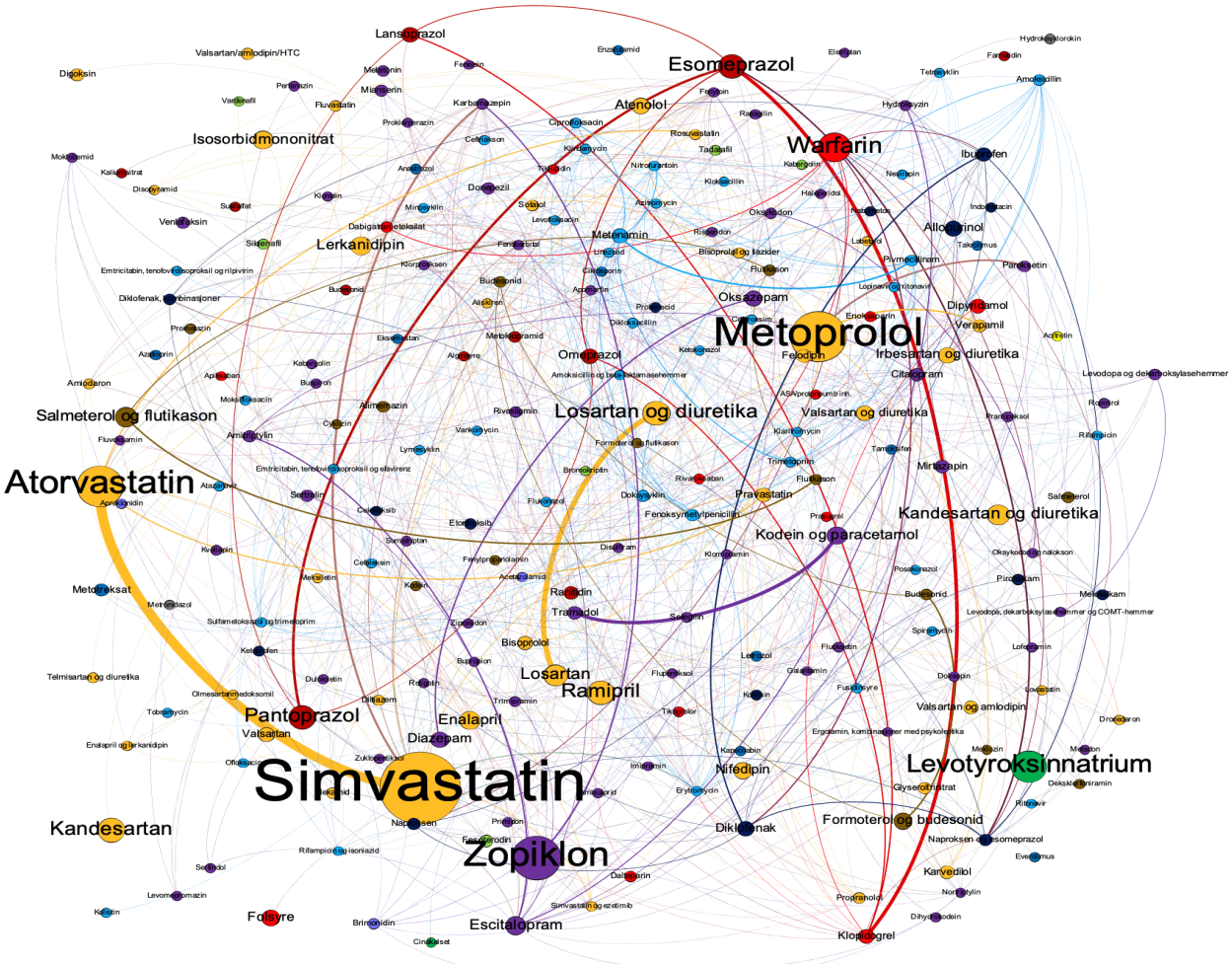


Figure 4.18: Weighted network of severe DDI in day 0 network, no filters applied, thicker edges indicate higher frequency of combinations, bigger nodes indicate greater number of users.

The full network in PDF format (full resolution) is available here (weighted edges): https://www.dropbox.com/s/mojdjpeanpx2mw2/DDI%20co%20no%20filters%20bigger%20nodes%20higher%20users.pdf?dl=0

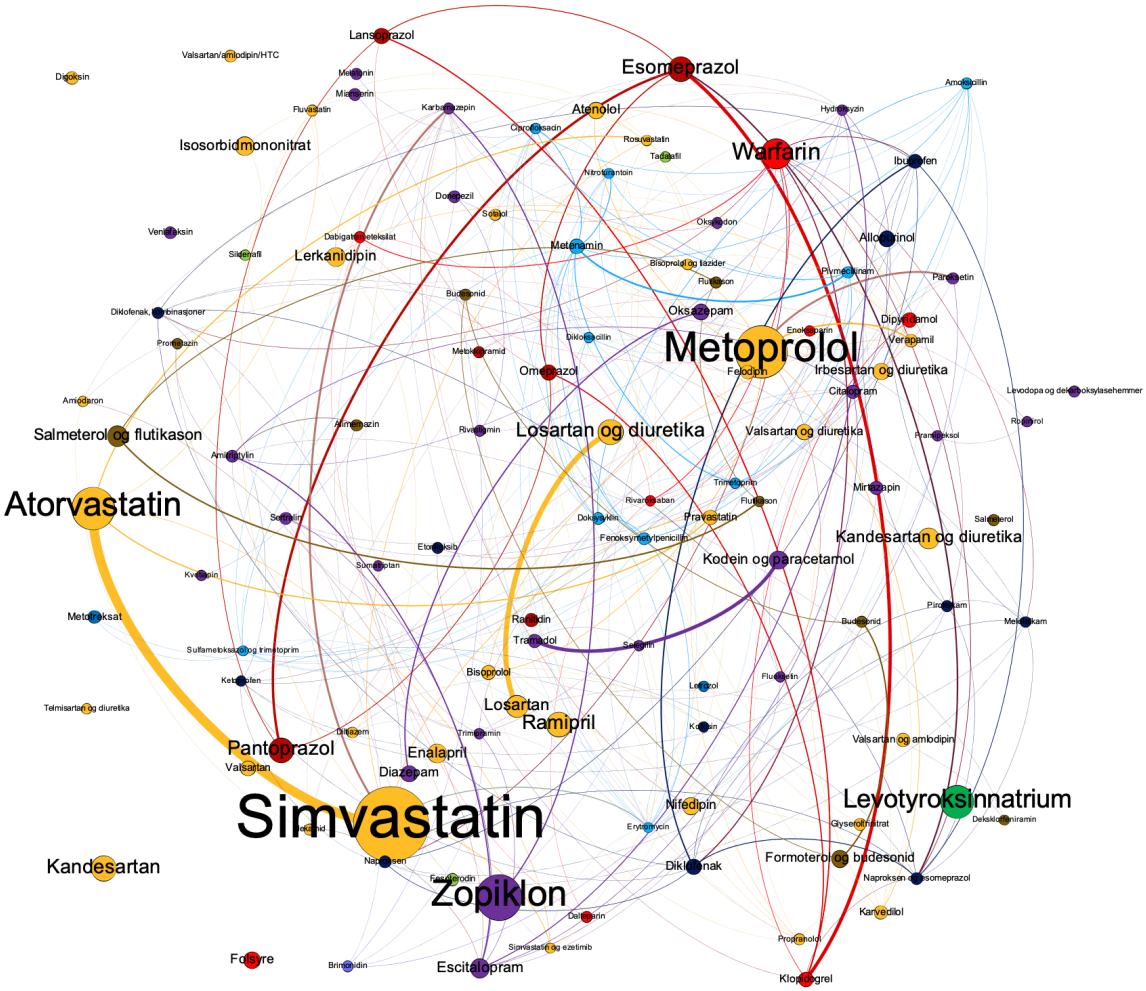


Figure 4.19: Weighted network of severe DDI in day 0 network filtered for >900 users for drugs (nodes). Bigger nodes indicate greater number of users

Figure 4.19 shows the severe DDI in day 0 network. The network shows actual DDI between clopidogrel with PPIs (esomeprazole, lansoprazole, and omeprazole). Tramadol and codeine/paracetamol combinations shows also a thick edge.

The full network in PDF format (full resolution) is available here:
https://www.dropbox.com/s/8rv782gdh48ro5t/DDI%20co-medication%20filtered%20for%20%3E900%20users%20bigger%20nodes%20are%20higher%20users.png?dl=0

Table 4.46: The most 30 frequent severe DDI in day 0 network

No.	Drug 1	Drug 2	No. of times combined (users)
1	Simvastatin	Atorvastatin	2320
2	Losartan	Losartan og diuretika	1253
3	Kodein og paracetamol	Tramadol	855
4	Esomeprazol	Klopidogrel	823
5	Pantoprazol	Esomeprazol	603
6	Simvastatin	Karbamazepin	480
7	Metoprolol	Paroksetin	454
8	Pivmecillinam	Metenamin	411
9	Metoprolol	Verapamil	380
10	Flutikason	Salmeterol og flutikason	359
11	Esomeprazol	Naproksen og esomeprazol	352
12	Budesonid	Formoterol og budesonid	343
13	Lansoprazol	Klopidogrel	308
14	Diklofenak	Ibuprofen	305
15	Diazepam	Oksazepam	300
16	Karbamazepin	Zopiklon	280
17	Pravastatin	Atorvastatin	279
18	Omeprazol	Klopidogrel	277
19	Amitriptylin	Escitalopram	277
20	Omeprazol	Esomeprazol	265
21	Warfarin	Diklofenak	254
22	Atorvastatin	Rosuvastatin	251
23	Simvastatin	Erytromycin	220
24	Hydroksyzin	Escitalopram	212
25	Lansoprazol	Esomeprazol	203
26	Salmeterol og flutikason	Flutikason	199
27	Diklofenak	Naproksen og esomeprazol	183
28	Warfarin	Dabigatran eteksilat	182
29	Nitrofurantoin	Metenamin	180
30	Trimetoprim	Metenamin	174

Table 4.46 shows the top 30 interactions in the network sorted from highest to lowest number of combining times. Combinations in the red color are more likely to be the actual interactions in the network. On the other hand, combinations in black are medicines with less possibility of being actually combined. Combining tramadol and codeine/paracetamol combination comes with the highest frequency of usage (855) patients. Esomeprazole and clopidogrel come next with (823) users. The top 200 drug-drug interactions are attached in (appendixes 7).

For the online access to the folder which contains all the networks (in case of broken links):
https://www.dropbox.com/sh/rid1kxru1ycf0pl/AABTI_TXyNU3bUgZcZxzuddYa?dl=0

5. Discussion

Our study is a population study based on the Norwegian prescriptions dataset (NorPD) for the elderly from 2012 to 2014. There are many differences between the entire population study which is based on electronic registers and studies based on population samples. One difference is that in sample-based studies, the researchers collect and target their own data according to the subject of study, while in case of recorded databases, data is extracted from registers and this somehow limits the control of data collection. Another difference is that in the population-based studies the influence of selection bias is limited. Mathematical oriented statistical analysis, hypothesis testing tests, and sample error, as a source of uncertainty, may not be relevant in the case of register-based studies (69). Finally, in the population studies, we don't need to calculate the power of the study since the study includes almost all the population.

Our thesis has two main objectives (figure 5.1), a *methodological* objective and a *clinical* one. The methodological part is represented in two things; the first is how to define co-medication in the most reliable, flexible, and practical way as much as possible. The second is using network analysis as an approach to the study of drug-drug relations. Since network analysis has been mostly employed for studying many aspects from the social point of view and less effort was done to take network analysis from this template to use it on medicines' relations, this approach needs to be evaluated in terms of usefulness and efficacy to this particular part of public health study. This testing of network analysis allows us to decide if NA can be used efficiently in mapping drug-drug relations and extracting their relevant information or not. The methodological part is the fundamental part for this thesis which leads us to the clinical one.

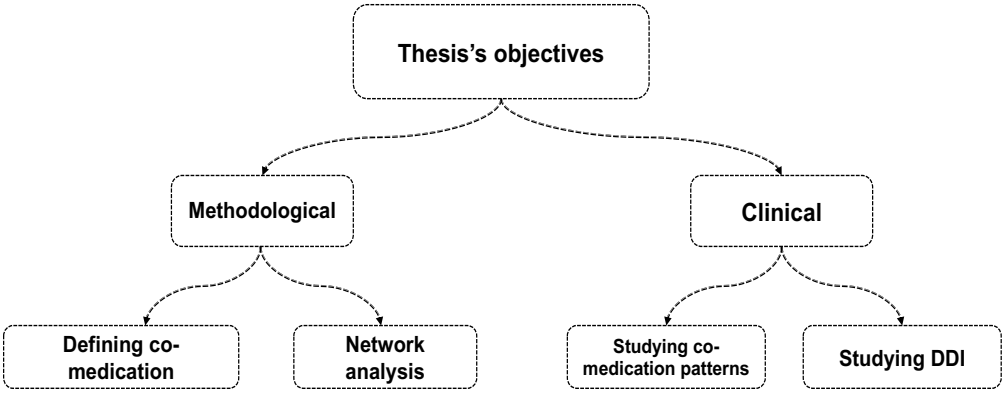


Figure 5.1: Represents the main objectives of this thesis

After representing the results and visualizing them in the form of networks, comes the clinical objectives which are co-medication patterns in elderly and drug-drug severe interactions study. We tried to balance between these two objectives as much as we could but going in details in each point was not possible especially in the clinical part since geriatric medicine is a whole branch of medicine study.

We chose to define co-medication as treatment episodes depending on the time of dispensing of prescription and defined daily dose (DDD) of each medicine combined with Proportion of days covered (PDC) as a measure of patient's adherence, allowing 14 days as an accepted gap between the two treatment episodes. This approach allows us to capture the co-medication in any prevalence time points (i.e. date) we choose. Although determining the GAP period should be based on the pharmacological properties of the drug and the treatment situation (70), it was difficult to agree on a gap period which takes in consideration all the medical recommendations with such variety of medicines and indications with different pharmacological and severity aspects.

There are many alternative approaches to use (1). For example, to consider the whole three years as a one treatment episode, this may create a bias in the study in terms of types and amount of medicines combined (e.g. medicines which are sporadically used). Another approach is to define co-medication as a prevalence period (e.g. 90 days) regardless of the drug defined dose and patient's compliance. This also is not entirely convenient. Other more restricted ways of defining co-medication have been also used, like studying the prescriptions that were prescribed in the same day or from the same prescriber. The advantage of our approach of defining co-medication is that it has combined simultaneous use of medicines and their defined daily dose along with possible patient's adherence giving a more relevant, flexible, and reliable way of defining.

There are plenty of ways to examine the data like spreadsheets, bar graphs, line graphs or timelines. All of these ways help to look at quantities or qualities. However, it is needed sometimes to see the connections between data objects to fully understand the pattern they have. Here is what network analysis can uniquely do among all the previous ways of data visualizing.

In this thesis we introduced Network Analysis (NA) as an approach to studying two forms of relations between medicines; the former was co-medication: by applying this approach on the Norwegian prescription database for elderly in a period of three years (2012-2014), and the latter was severe interactions (severe interactions) by using FEST database which is widely and officially used in Norway. In both types of relations, drugs represented network actors (nodes) in all generated networks, while edges varied according to the studied part representing simultaneous use (quantitatively) in co-medication part and severe interactions (qualitative relation) in the DDI part.

Network analysis can be used in many applications in epidemiological studies as a tool of data visualization with unique descriptive features. Defining what nodes and edges represent allows us to visualize any kind of relational data we have. As an example, here with our data, we can investigate the degree of following the clinical guidelines by physicians by simply replacing what edges represent from co-medication to how many times a physician prescribed these nodes (ATC codes) together.

As a summary of what Network analysis is capable of doing; NA is capable of plotting any kind of relational data in a network form (i.e. visualizing), after visualizing we can describe the network to extract the important information/features of it (i.e. network description); like the most central actors or the most important/frequently used relations. Applying different network measures can allow us to extract/confirm the patterns lies in the network (i.e. pattern study), in some cases networks can also predict/expect some unseen results as we mentioned before (i.e. predicting) (figure 5.2).

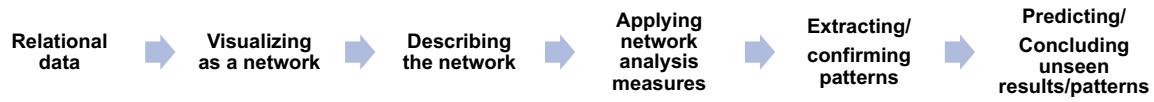


Figure 5.2: A summary of network analysis possible functions

The information and results extracted from the networks are either common with other descriptive/statistical ways or unique in itself. The relation between objects (edges list) is an example of these unique information. Unique measures for network analysis are like Centrality and its different measure (degree centrality, closeness centrality, betweenness centrality), Density and many more (50), these are examples of the unique results that NA can introduce.

Some measures are shared in purpose with other statistical ways but remain unique in the approach like modularity classes extraction which has common functions with factor analysis and clustering analysis, more comes later in modularity classes study.

In this thesis, we used network analysis to *visualize* (all networks), *describe networks' characteristics and information* (Day 0 network), *extract sub-patterns* (Day 0 network), *compare to study temporal change* (network 2013, 2014) and *spatial change* (five selected Norwegian counties in day 0 network), and use *unique network feature* (eigenvector centrality, betweenness centrality).

As mentioned before, we used two different datasets NorPD and interactions dataset from FEST. One of the aims of NorPD dataset which is mentioned in the Regulations on the collection of health information in NorPD §1-3 is to:

1. "Describe drug use patterns, highlighting changes over time" (71) which is one of the main purposes of this thesis.

The NorPD database has its strengthens and weaknesses, one of the strengthens is that it makes it possible to follow up drug dispersion over the years both on public and particular scale. This gives a rich content for pharmacoepidemiologic studies since it gives complete but anonymous information on the patient, prescriber, and medicines (i.e. exposure) and also mortality incidence (i.e. outcome). Another advantage that it gives information on prescriptions dispensing rather than prescribing. This approach, partially, eliminates a potential bias in researching which arises from the probability of non-conformity between prescribing and actual patient usage as in medical records.

Entirely elimination of recall bias is also an advantage of using recorded databases over surveys and questionnaires. At last, owning the database by a researching organization which only allow sharing of anonymized data is ideal ethically.

On the other hand, one of the limitations related to this dataset is that it does not include information on dispensed medications under hospital stay or in nursing homes on the individual scale which results in underestimating the overall drug usage in the population (56).

The other dataset we used is the interactions dataset form FEST dataset. The interactions database was built in FEST to be able to collect groups of the ATC codes or active substances under the same interaction. In other words, the interactions are mentioned in the dataset on both anatomical and therapeutic group level and on the complete ATC level as well.
Active substances with several ATC codes, all relevant ATC codes are included in the appropriate substance group (For example, Ephedrine: C01CA26, R03CA02, the two ATC codes are stored in the database). The dataset is also designed so that they should never be confused with approved substances at WHOCC (with an agreement with them), but they have real interactions (72). ATC is a drug-classification system based on their Anatomical, Therapeutic, Chemical characteristics. The complete ATC code has some levels. The anatomical level forms the 1st part of the code; there are fourteen anatomical groups. The 2nd level represents either therapeutically or pharmacological groups. The 3rd and 4th levels are the therapeutic and chemical subgroups while the 5th one is the chemical substance (73).

The Norwegian Medicines Agency (SLV) informs that the most important sources for FEST are; 1. Systematic studies on patients and healthy subjects, 2. information from pharmaceutical manufacturers, 3. case reports (which are based on the individual experiences and is marked as "case report"), and 4.indirect documentations which means that the interactions are not documented, but can be predicted based on knowledge of the pharmacokinetic or pharmacodynamic properties (74). It should be taken into consideration that FEST does not contain absolutely all of the interactions, other sources could have more DDI based on their interactions' definition like uptodate.com or drugs.com for example.

Interactions in FEST are classified into three categories: the first is severe interactions which Should be avoided, the second is moderate in severity marked with "Precautions should be taken" label and the last is minor in severity and marked with "No action required" (75). Our concern in this study is the first section "severe" or 1st-grade interaction which should be avoided.

We studied our primary network which captures co-medication in the treatment episode around 1st of January 2013. It is the start of a new year and right after Christmas vacation in Norway. The Norwegian Health Economics Administration (Helfo) is responsible for direct payments of medicines which are prescribed as reimbursed prescriptions. After a specific amount of money, the patient pays, Helfo will cover the costs of medicines to the rest of this calendar year.

Patients will start to pay this particular amount of money again at the beginning of the next calendar year (76). This is why December month is considered a rush period for prescriptions' pickups. The reason for why we mention this here is to explain that in 1st of January - theoretically- all patients or the majority of them have their medicines. Therefore, it is a period we can say is most reliable to study co-medicating.

Considering the distribution of anatomical groups in the drug-drug combinations of this network (table 4.3), drugs which affect the nervous system and cardiovascular system were involved in about 21%, 19% of drug combinations (edges) respectively. While dermatologicals and various medicines groups come last with less than 1% of overall combinations. It should be taken into consideration that prescriptions without DDD were excluded; this can affect the frequency of some groups like dermalogicals (D-group).

We should also keep in mind that these percentages are not the amount or number of users or the percent of dispensed drugs which belongs to these anatomical classes, but they represent how frequent were these anatomical groups were involved in drug-drug combinations. Although drugs from (A-, B-, and C- anatomical groups) had the greatest proportion of users in 2013-2017 (77), N-anatomical group drugs represent the highest percentage of being combined with other drugs. This also gives a clear example of what different results can networks represents comparing to traditional descriptive analysis ways.

As mentioned before, most of the interactions in our dataset is mentioned in a directional way. This explains why the number of edges in the network (57,151) (i.e. interactions) is almost half of the number of severe interactions after exclusions (113,413).

We showed then in (table 4.4) the most important drugs in this network according to "Eigenvector centrality"; a unique network measure we mentioned before. Results show that Acetylsalicylic acid (ASA) and simvastatin are the most important nodes in the network. This introduces another measure which can be essential to consider and asses for many aspects like, which medicines should be prioritized for reimbursement from the government and which drugs should the responsible authorities take rapid action in cases of medicines deficiency. This seems to be less important with respect to these 10 medicines listed in (table 4.4) but when it comes to medicines with low usage frequency, this measure can make a difference in the decision-making process.

One of the most important and unique things that network analysis can represent is node-node relation (edges), in (table 4.5) we showed the most 20 combined medicine in the network. Drugs groups in this table are; drugs to prevent blood clotting (Acetylsalicylic acid, Warfarin), Heart and blood pressure medicines from different groups (Amlodipine, Beta-blockers, ACE inhibitors, Diuretics (Furosemide), Calcium antagonists, Isosorbide mononitrates), lipid-modifying drugs (Statins), Anti-diabetic (Metformin), Non-opioid analgesic (Paracetamol), Hypnotics (Zopiclone) and Thyroid hormone (Levothyroxine). Norwegian national geriatric health maintenance guidelines suggest many measures as primary prophylaxis of many expected diseases in the elderly. Acetylsalicylic acid, blood pressure regulation, dyslipidemia are measures which proved efficacy for prevention (primary prevention) of both cardiovascular disease and stroke (78). These results were expected and reflect applying the guidelines Norwegian ministry of health for primary prophylaxis in the elderly (79) (i.e. quality of prescribing).

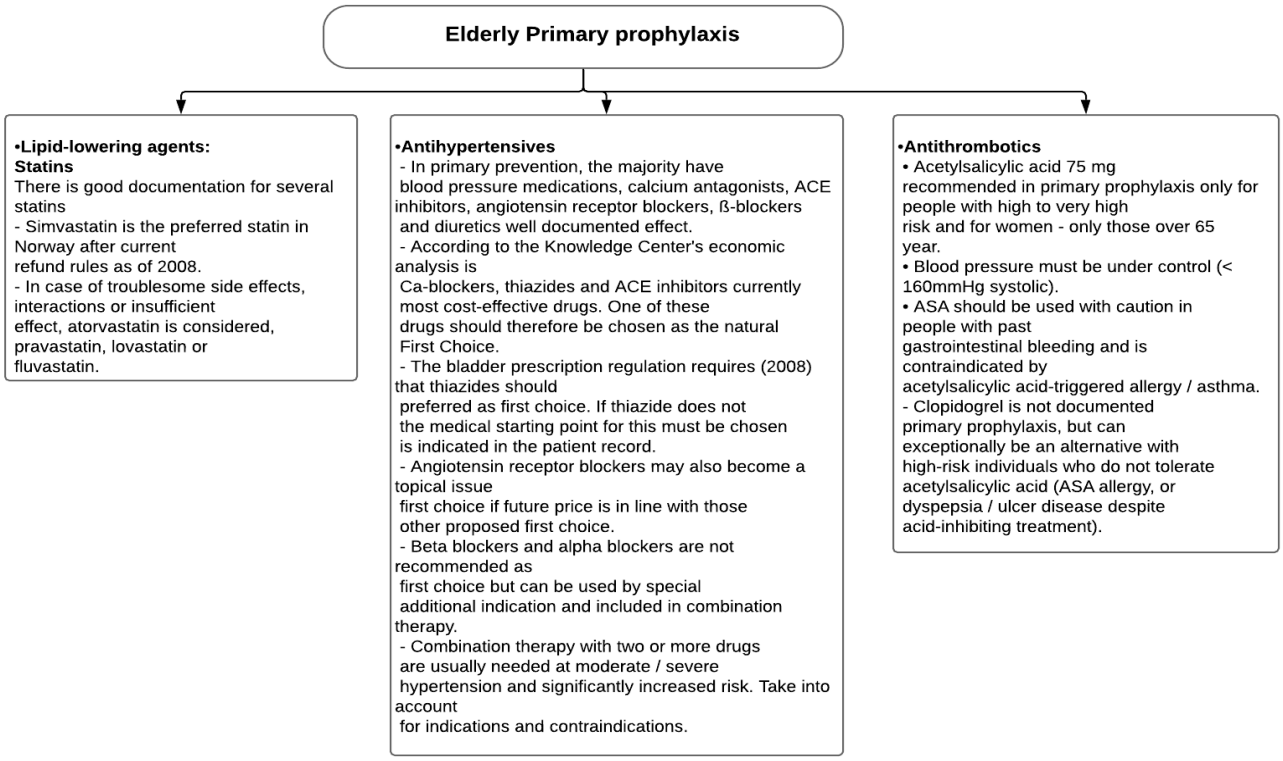


Figure 5.3 Norwegian ministry of health guidelines for primary prophylaxis in elderly considering both clinical and economic point of views. (source: National guidelines, Norwegian ministry of health)

We moved after to another network analysis unique feature which is “Modularity” or “community detection”. In general, there are many statistical ways for identifying patterns in datasets like cluster analysis and Factor Analysis (FA).

Cluster analysis is an exploratory data analysis tool which aims to sorting different objects in the same dataset into specific groups based on the degree of association between these objects. This means, if there is an association (similar objects) then these objects will belong to the same group otherwise not (80). Cluster analysis can be used to discover these hidden structures in data but without providing an explanation/interpretation.

Factor analysis (FA) is another statistical method that has some explanation purposes by reducing number of variables by extracting latent (i.e. unknown or unobservable) variables if any from the observed data and empirically figuring out data structures (creating a theory of data structure) from underlying variables (81) and evaluating whether the observed variables clusters in the theoretic expected way (82).

Another way of detection of data structure is "Modularity" which is a specific feature for network analysis. Four modules were detected in our network (figure 4.2) the most complicated was module [0] which represents almost 70% of the network. To be able to discover the sub-patterns under module [0] we shortened ATC codes to the anatomical, therapeutic level (three characters) (table 4.7) and summed up the number of users for each ATC group. We ended up with (47) different ATC groups under this module (total ATC codes were 530). Sorting these ATC codes needed assessing based on assumed clinical indication and number of users for each group to able to neglect groups with insignificant numbers of users and to give priority to the groups with a high number of users.

As an example of how we tried to sort module [0]; if we notice there (table 4.7), Nervous and respiratory system (N- and R- groups) drugs are just found in module [0], while Cardiac-, Alimentary-, Blood- (C-, A-, B- groups) are common groups with modules [1] and [2], but with looking at the number of users in each module we can locate in which module these ATC groups represent the most importance. For example, some cardiac groups (C03 Diuretics, C07 Beta-blockers, C10 Lipid modifying agents) are common between two or more modules but (C03) is shown to be with the greatest number of users in module [1] (70,736) users, while (C07) comes with the greatest number of users in module [2] (128,165) patients. Most number of users for (C10) is also located in module [2] (258,050). This reveals less importance of these ATC codes for module [0] and much more value for the other modules. In other words, these ATC codes are not central for module [0] as much as they are for the other modules. After sorting,

we were able to obtain some patterns shown in (table 4.8). It is interesting to relate these patterns under module [0] in terms of co-morbidity, but this actually needs further assessment and cannot be confirmed as a clinical outcome based only on mathematical bases.

Some drugs in module [0] couldn't be sorted in these three assumed patterns under it because they can belong to many therapeutic indications or are used to avoid the side effect of some other drugs. Some others have a certain clinical indication but with a lower number of users than they are in other modules (e.g. C03 diuretics, C07 beta-blocking agents).

Module [1] is assumed to be a cardiac pattern as it contains diuretics (C03) with highest proportion of users, antithrombotics (B01), cardiac therapy (C01), beta-blockers (C07) and calcium channel blockers (C08). Module [2] has Renin-Angiotensin agents which are indicated for treatment of hypertension in case diabetes (83), antithrombotic agents (B01) as patient with diabetes have more risk for deep-vein thrombosis and pulmonary embolism (84), lipid modifying agents (C10) and ophthalmologicals (S01) as diabetes can lead to many eye complications.

Another confirmatory step to these patterns was done to verify these patterns; by comparing the patterns we found to the patterns revealed by another study held in Spain in 2008 to demonstrate polypharmacy patterns using Exploratory Factor Analysis (EFA), regarding (79,089) adults, researchers identified seven patterns (six of them were more applicable for the elderly) of co-medication in adults classified depending type of diagnosis. These seven patterns were Cardiovascular pattern, Depression-Anxiety pattern, Acute Respiratory Infection (ARI), Chronic Obstructive Pulmonary Disease (COPD), Rhinitis-Asthma, Pain, and Menopause pattern (67).

The importance of this comparison is that these patterns (ours and the Spanish study patterns) that they were conducted using two different statistical methods. The mentioned paper depended on Exploratory Factor Analysis (EFA), while ours depended on obtaining substructures in the full network (modules). Modularity was done, as mentioned before, by Louvian method which measures the density of edges inside communities to edges outside communities and assigns a theoretical value results in the best possible grouping of the nodes inside a network. Revealing consistency between the two results despite the differences in methods and populations can affirm results' reliability.

Our assessed patterns were Anxiety, Acute respiratory infection (ARI), Chronic obstructive pulmonary diseases (COPD), Hormones-related, Cardiac, and Diabetes patterns. While in the other study they conducted six patterns applicable for elderly which were Anxiety, Cardiovascular, ARI, COPD, Pain and Menopause patterns. We used then these anatomical group to extract and isolate each of sub-networks from the whole network according to the therapeutic indications.

As the highly prevalent diseases are common in the elderly and already known, this pattern extraction is considered a *confirmatory* pattern extraction. However, in the case of ambiguous patterns, this approach of pattern extraction can reveal unknown patterns or negates hypothetic ones.

We moved then to the studying of these sub-networks separately starting with the cardiac pattern. Under this clinical category there are a lot of diseases (e.g. arrhythmia, congestive heart failure, atrial fibrillation, hypertension, etc.). In this network, we had 108 nodes which all belong to three anatomical groups (A-, B-, and C- groups).
Therapeutic groups under these patterns are anticoagulants, lipid-modifying agents, hypertensive drugs, beta-blockers, diuretics, Nitrates, digoxin, acid-related disorders drugs, diabetes drugs, and insulins.

Anticoagulants (warfarin) and antithrombotics (acetylsalicylic acid, clopidogrel) are widely used in many cardiovascular diseases like atrial fibrillation, heart attack, and also for primary prophylaxis. One thing to notice here is that the network shows low number of users of direct factor Xa inhibitors like apixaban and rivaroxaban. These drugs were released in the Norwegian market around 2011 (85) and the reimbursement Helfo approval was after January 2013 (86) (i.e. after the treatment episode we study).

Lipid-modifying agents are used to prevent many coronary and vascular diseases like atherosclerosis. Hypertension drugs, beta-blockers, and diuretics are also related to many indications. Most used drugs of those were metoprolol, furosemide, and ramipril. Vasodilator used in cardiac diseases like isosorbide mononitrates also had a good share of users (21,286) it is used in case of Angina pectoris. Digoxin is used for heart failure and atrial fibrillation. Proton pump inhibitors (PPIs) (esomeprazole, pantoprazole, lansoprazole, and omeprazole) are widely

used in this network. It is interesting here because these drugs are used in case of cardiovascular diseases to protect against the adverse effects of some antiplatelet medications like acetylsalicylic acid and clopidogrel or NSAIDs, for example, but on the other hand, many studies related them to an increased risk of cardiovascular morbidity (87) (88).

Anxiety pattern involves three anatomical groups (H-, M-, and N- groups). It is obvious that medicines belong to N-anatomical group (Anxiolytics, Anti-psychotics, Dopaminergic agents, Anti-depressants) are indicated for anxiety, depression and related sleeping problems. Corticosteroids for systematic use (prednisolone, methylprednisolone, dexamethasone, triamcinolone, etc.) are being used quite frequent by patients in this group. The relation between pain and depression is also quite clear (89). Prednisolone is the most used medicine in this network (table 4.14). Some studies related the using of corticosteroids to the incidence of fear and anxiety by inducing specific chemical changes in particular sets of neurons (90). There are two possible directions here when we think about corticosteroids use, the first is that they were used as anti-inflammatory agents with pain killers and in this case the depression or anxiety is caused by pain and corticosteroids are used as a consequence of pain. The second, is the other way around is that the depression was caused because of long term use of corticosteroids but the common thing between pain-killers and prednisolones that they indirectly related to anxiety or depression incidence.
The network showed also that oxazepam is commonly combined with escitalopram (table 4.15) which is consistent with Norwegian guidelines for the treatment of depression (91) and sleeping disorders (92).

Acute respiratory infection (ARI) is a serious infection that prevents normal breathing function. It usually begins as a viral infection that can lead to many complications including death in case of weak immunity or not being treated. Examples of infections are pneumonia and flu. (67)

All ATC codes in this network belong to R- and J-groups. It is remarkable that few numbers of antibiotics and antivirals were involved in drug-drug combinations in this network despite that we included all antibiotics and antivirals for systemic use (J01, J05) which reflects the low percentage of misprescribing of antibiotics by prescribers. Phenoxy methyl penicillin, erythromycin, sulfamethoxazole/trimethoprim combination were the highest frequently used antibiotics in this network. Valaciclovir and acyclovir were the highest antivirals used here. Some antibiotics which are not indicated for upper respiratory tract infections were also

involved in combinations like Pivmecillinam, this occurred because we involved all systemic antibiotics and antivirals in the network, and they were used by some patients who were using also some medicines belong to this pattern.

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous collection of diseases with different causes, pathogenic mechanisms, and physiological effects (93). It is a poorly reversible disease of the lungs that is one of the major causes of morbidity and mortality worldwide. Typical medical treatment includes Beta2-agonists (both short- and long-acting), anticholinergics (short- and long-acting), inhaled and systemic corticosteroids (94).

Anatomical groups under this pattern (A-, H-, R-, and M-groups). Proton pump inhibitors (PPIs) and other drugs for acid disorders (which belongs to group A) are high-frequently used in this pattern for two main reasons, the first is that studies show that the relative risk of a COPD exacerbation over two years in those with gastroesophageal reflux disease (GERD) higher than in those without (GERD) (95) and the second is to protect the stomach against the adverse effect of systemic corticosteroids (96). Pain (M-group) is a common problem for patients with chronic obstructive pulmonary disease (COPD) (97) that's why many analgesics are present in this pattern. Anatomical group H contains systemic corticosteroids (mainly prednisolone).

In the pain pattern, as pain is not an indication in itself but a symptom for a disease or a disorder, we cannot tell for sure for which indication was each analgesic was prescribed. Analgesics in these groups belong to (M- and N-) anatomical groups.
Unexpectedly, the top ten used drugs in the network had only three analgesics. Other top used drugs were either indicated for COPD or PPIs. Some indications are clear here like pain in case of COPD when the analgesic is combined with an inhaled active substance. Studies show that pain is more prevalent in patients with COPD than others (98).

It is well known that low estrogen level in women in post-menopausal is one of the most influential risk factors for osteoporosis (99). The menopause pattern is clear, and the main actors are few. Calcium/vitamin D3 combination with Alendronic acid was the most combined medicines in the network (16,325) with a significant difference from the next combination (860). Denosumab (Prolia®) combination with calcium/vitamin D3 is also a common combination for treatment of osteoporosis. Other hormones like estriol, estradiol, and tibolone are all used for symptoms of estrogen deficiency.

We moved then to the next part of results which is using network analysis for comparison purposes. Using NA for comparison purposes was also possible. Comparison can occur between different information between two time points, places or patterns. In our thesis, we used network analysis to compare in term of time (Temporal difference) and palace (Spatial difference).

To our knowledge, there is no specific software which can automatically compare two or more networks except for one software called (CompNet) (100) which, unfortunately, was damaged and not completely supported from developers. It could be much easier if such tools are available and well-supported.

For temporal change study, we used two approaches of comparison a direct comparison which means we compared the two network of 2013 and 2014 in terms of characteristics (table 4.28), anatomical groups distribution (table 4.31), top used medicines and combinations, and indirect comparison by generating a new network which represents the division of 2013 network over 2014 network (methods 3.8).

The reason nodes in the generated network were less (table 4.29) is that when we generated the new network by the division of the two networks, unique edges (drug combinations) of both were divided by 0 (were not matched in Stata) which caused these nodes to be eliminated in the new network. Unique edges were identified and stored for comparison purposes (appendix 6).

The generated network allowed us to see many things, for example, the ratio of users, the ratio of combination usage (edges) and unique edges in each network. 16% of total edges in both networks were unmatched to corresponding edges in the other network, while 84% were matched (table 4.30). Only 19% of drug-drug combination remains constant in both years, while 31% of overall combinations are higher frequented in 2014 than in 2013 and 50% of them are higher in 2013 than in 2014 (table 4.32).

This is an example of the change that which occurred on medical dispensing in a short period (i.e. only one year). Even more significant quantitative and qualitative changes are expected if the time gap between studied networks is longer.

Anatomical groups distribution (table 4.31) shows 2014 network to have less percentages of J-group ATC codes which may reflect increased awareness towards anti-infectives for systemic use e.g. antibiotics.

Top most used drugs in 2014 compared to the same period in 2013 were Forxiga® (dapagliflozin) and Eliquis® (apixaban). Forxiga® was approved in the Norwegian market in 1st of February 2013, so it is logic to be higher frequented in 2014. Eliquis® 5mg tablets was approved on the 15th February 2013. The same was with the other drugs; either they were approved in the Norwegian market later in 2013 or during 2014.

Two remarkable medicines were in the list the first is Procoralan® (ivabradine) which is indicated for chronic angina pectoris for patients who can't use beta-blockers, this medicine was approved for selling in the Norwegian market in 1st of June 2015, but it was approved for use (without approval for selling on the general scale=MT-dato) (101) in 25th of October 2005. This means the physician can apply for approval exemption for individual patients although the medicines they need isn't for sale in Norway (102), so it is possible as it is a specific medicine for a few patient's populations that it was imported from another European country. Going back to the original networks shows nine users in 2014 to only one user in 2013 (very few numbers with respect to the total number of patients). Mecobalamin (vitamin B12) is also a medicine which needs a special approval exemption (24 users in 2014 to four users in 2013). Market approval and relevant information can be checked in at https://www.legemiddelsok.no/ website.

On the other hand, some drugs indicate significantly lower ratios of usage from 2014 to 2013 in terms of the number of users (table 4.34). By checking these drugs, we can, mostly, find the reason behind the withdrawal of usage. For example, alfuzosin (Xatral®) was discontinued from the market in 2013 (103). Patients used to receive Digitoxin changed to Digoxin because of the former adverse effects (104) some other drugs need further assessing to see if there was a change in guidelines or date of registering as a reimbursed medicine for example.

Drug combinations that were higher used in 2013 show some discontinued drugs like digitoxin which is involved in four of the highest 10 combinations. Some combinations show a drug-drug interaction (Deltaparin and Diclofenac) increases bleeding risk (105) (table 4.35).

Most of the combinations with higher usage in 2014 contained one of the drugs were approved late 2013 (later than January -our treatment episode-) or in 2014 (dapagliflozin, apixaban, metformin/vildagliptin, mirabegron) (table 4.36).

We moved then to another type of comparison which is spatial comparison. We extracted the prescriptions for five counties in Norway (Akershus, Hordaland, Nordland, Oslo, and Rogaland). It was considered to choose counties from different places in Norway to study if medicine usage patterns represent any change. As expected in advance, the top used medicines and top used combinations are almost the same in the five counties. Norway is a country with a relatively low population (a little over 5 million in 2013) (57), well-established data system and a lot official electronic sources which make it quite easy to check, follow and keep updates concerning guidelines and medicines related information. That is the reason may be that spatial study shows almost typical results in all of the previous places. Spatial change in different countries or countries with higher population and less organized electronic data systems can be imagined to be much greater than what we found here. The primary purpose here was to show that network analysis approach is capable of introducing an alternative way of comparison than the commonly used statistical ways.

The other central part of our thesis is drug-drug network severe interactions study based on FEST database. Severe interaction forms about 16% of the total interactions in the database (table 4.41). We represented the interactions between each anatomical group in the form of a heat map. A Heat map is a matrix that represents the frequency in the form of colors instead of numbers, the darker the color, the higher the frequency the color represents (106). The most severe interaction belongs to J-J group interactions. J- anatomical group includes, among others, antibacterial, antivirals, and vaccines. Injecting with vaccines which have weak or parts of viruses will for sure affect the immunity and any other drugs which affect the immuno-system as well affect the vaccine response. Also, antibacterial groups contain some of the medicines which are well known to have several interactions with other medication, for example, erythromycin, ciprofloxacin, moxifloxacin, and chloramphenicol. (detailed information of interactions for each anatomical group with some notes on this is attached in appendix 8). The top severely interacted drugs with other drugs all belong to J-group except St John's-wort which belongs to N-group. That is why some countries have banned using it like France (107). The lowest frequency of severe interactions was for S- and R- anatomical groups.

We tried to clarify, remove the overlapping between nodes and nodes labels to make the network quite clear for visualizing, so by magnifying the network to maximal size in PDF format (link attached in results figure 4.14) the reader will be able to extract a lot of information out of it. The network consists of about 1700 nodes (quite complex) but quite low density (0.04) which says something about connectivity between its nodes.

The very first look to the network (figure 4.14) after coloring it according to anatomical groups that the most appeared colors in the network is violet and light blue which represent J-, N-anatomical groups and that network visualizing gives an indication of a sort of partitioning (except the middle). This led us to think to use another unique measure for network analysis which is "Betweenness centrality".

Betweenness is based on the number of shortest paths a node lies on between any two other nodes (45). The higher number of shortest paths this node is involved in, the higher betweenness centrality score it gets. The original application of the centrality idea is in the study of communication in small groups. Betweenness centrality importance in any network arises from its potential great impact on the process being examined in a network (108). In our case, we measured betweenness centrality for the drug-drug severe interactions network to find out the drugs which have the most influence in connecting between interacted groups.

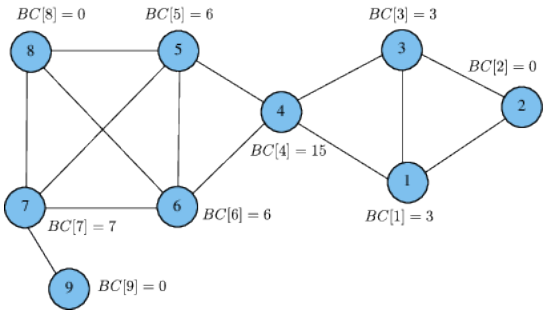


Figure 5.4: An example of betweenness centrality score on a small graph. Source: Accelerating Graph Betweenness Centrality with CUDA by Adam McLaughlin (https://devblogs.nvidia.com/accelerating-graph-betweenness-centrality-cuda/), showing node 4 to have the highest score, while marginal nodes 2, 8 and 9 with score= 0.

We showed then the impact of removing one of these nodes (histamine Hydrochloride). This resulted in separating of a whole part of the network (R06A) Antihistamines for systemic use (Amino alkyl ethers).

If we look closer at Histamine Hydrochloride interactions, we will find that it has interactions with five ATC groups: N05AF03 Chlorprothixene (Antipsychotic), H02AB (Glucocorticoids), H02B (Corticosteroid for systemic use), R06A (Antihistamines for systemic use), N06AA (Antidepressants, Non-selective monoamine reuptake inhibitors). Removing this node from the network has completely cut the connection between R06A group and the network and the group could be filtered out of the network.

More disconnections will take place in the network if we remove nodes with high scores of betweenness centrality which indicates these nodes potentiality for DDI. One or more nodes with high betweenness can attach two nodes/groups in the network which don't interact themselves but will be interacting in the presence of these high-between-centered nodes.

The main point here is to conclude is that the presence of a drug with a high betweenness score will increase the potentiality of the presence of DDI between interacting or even non-interacting parts in the network. Betweenness centrality can also be applied on the co-medication network to highlight the most important medicines in terms of this measure.

We used then the DDI network to obtain the severe interactions in 2013 network by matching the similar edges between the two networks (using DDI as a master network and keeping only the edges which are similar from Day 0 network). Using DDI network and matching its edges to any other Drug prescription network will easily allow us to visualize these interactions in the networks we study.

Something to notice here is that as we defined co-medication as treatment episodes, it should be put into consideration that some interactions could be untrue. As shown in (table 4.46), there are some interacted medicines have the same clinical indication and appear as co-medicated medicines in the same treatment episode. There is a low possibility that the patients have actually used these medicines together. As an example, a patient used one small package of atorvastatin and then his doctor decided to stop it and start over with simvastatin, this combination will appear as a co-medication in the patient's treatment episode, so assessment of such combinations is needed.

We highlighted the combinations which seem to be “true” interactions in (table 4.46) in red. Using tramadol and codeine causes a depressive effective on Central Nervous System (CNS) results in increasing the risk for sedation.

The second interaction is between clopidogrel and esomeprazole. Patients who use this combination have the risk for reduced effect of clopidogrel (risk for thrombus formation). Clopidogrel is a prodrug which is activated through metabolizing inside the body. Esomeprazole is known to be (CYP2C19) metabolism enzyme inhibitor, this will lead to reduced concentration of clopidogrel active metabolite leading to reducing of its effect.

Simvastatin contra carbamazepine is the next most used combination with severe DDI in the network. Carbamazepine is (CYP3A4) inducer, the enzyme which is responsible for metabolizing of simvastatin resulting in a higher metabolism rate of the cholesterol medicine and lacking its effect. These were three examples of observed severe interactions in 2013 network, other examples in (table 4.46) and the 200 most frequented interactions are attached in (appendix 7).
(all interactions and relevant information about their mechanisms can be checked at https://www.felleskatalogen.no/medisin/interaksjon or http://interaksjoner.azurewebsites.net/)

As there were few studies used social network analysis on prescriptions databases, we had not a definitive and organized methodology of how exactly we will do this, and which results/outcomes to expect from this approach. We tried to represent the general features of each network and to summarize the information with short explanations but going in depth in each detail of these networks is a very time and effort consuming. Because we chose to represent the nodes of most influence in each network, some of the results can seem to be unimportant to study with such new complicated approach but going deeper to other nodes which aren’t the same famous or less familiar may represent important/unexpected results. It is important to say here that the main point was to show that this approach (network analysis) is/isn’t capable of introducing an approach to study drugs consumption flow. Some other results were actually surprising like medicine with most severe interactions and medicine with high betweenness score.
We think that the part of extracting sub-patterns from the general network represents one of the most important uses of network analysis in the studying prescription databases. Comparing this

pattern extraction with other statistical ways (e.g. Clustering and FA) is important to confirm the pattern and eliminate errors as much as possible.

Strengths and limitations

1. Large scale of data on both scales patients and observations (prescriptions) (a population study).
2. No selection bias as the data is already registered. Independence between data collection and the research eliminates targeting of certain cases to get specific results.
3. The data are collected prospectively.
4. The entire population is always combined with adjustment for confounders (69).
5. The quality of data in NorPD is quite high; the data system is well-established and has been used for a quite long time.
6. Our co-medication definition combines many useful medical aspects which makes it more reliable and flexible than many other approaches. It allows us to choose any prevalence points which makes comparing different treatment episodes possible.
7. We used network analysis on a large scale of patients and prescriptions. To our knowledge, no published study has used this approach on drug-drug relations on such large scale and with such variety usage of network measures.

While limitations are:

1. Using Network analysis as an approach is challenging in itself because it requires studying social network analysis before starting to use it. In addition to that, there was no scheme or clear steps to follow regarding how we would use this approach on medicines study and which results are expected to get from this method of studying.

2. Differences between using medicines and people as actors (nodes) in a network should be carefully taken into consideration. Motives, behavior, human interactions, and many other aspects which distinguish people from objects will keep the use of network approach relatively limited in case of studying objects rather than people.

3. Depending on the Defined Daily Dose (DDD) as an approach to the defining of co-medication has its limitations. Many drugs have a wide dose range, for instance, Prednisolone (ATC code H02AB06) had a DDD of 10 mg/day while it can be -

practically- used more than 100 mg/day if necessary, besides it can be used less than that upon withdrawal. This can result in biasing the start and end of the treatment episodes for these drugs. Moreover, some drug formulations have no defined DDD like dermatologicals. Another thing related to DDD and should be taken into consideration is patient's compliance which is usually not perfect.

4. Visualizing of networks on a sheet of paper remains to be limited representative, digital visualizing with all the possibilities of using many filters and applying different algorithms is the ideal form for showing a network so far. Therefore, we uploaded all the generated networks in PDF format with the original resolution. To be able to apply filters and different algorithms on networks, visualizing platforms (like Gephi) must be used.

5. Changing the date of dispensing variable to a difference in days from 1st of January 2013 are expected to create some bias in the treatment episodes because the day of hospitalizing of each patient is unknown for us. Meanwhile, this bias is not expected to significantly affect the results for some reasons: first that the total number of hospitalized patients is much smaller than patients of NorPD. The second is that each patient has his own date of hospitalizing which means the date we chose will randomly be right matched with a share of patients and unmatched with another share, we could have said that this way of matching time dispensing variables can greatly affect the results if the hospitalizing difference date was one certain unknown day for all patients. The ideal situation was to study each dataset of these two separately but on the other hand, it would be much more difficult to study the double number of networks and conveniently combine the results of both.

6. Choosing of 1st of January 2013 had its advantages but the disadvantage of it was that we couldn't study the same time at the 2012 year because if we go back in time 365 this will correspond the 1st day of the study and the treatment episode then is interrupted (a part of treatment episode which is before 1st January 2012 isn't included in the study period). A better approach was to take this day in the middle point of the study (June 2013 for example).

7. Adherence percent of 80% is an assumption, there is no known way can safely confirm a certain adherence in addition adherence percentage varies a lot between patients.
8. As we mentioned before some drug combinations showed in results are biased and needs an assessment example (Atorvastatin, Simvastatin in DDI most unfortunate combined drugs as an example, table 4.46).
9. A deeper understanding of different network algorithms and some mathematical basics is necessary to get the rightest results using this approach.
10. Although our study was done on a large scale of patients (approximately 96% of total the elderly population), the dataset we used from NorPD doesn't include absolutely all the elderly prescriptions. Medicines dispensed under hospital stay or in nursing homes aren't included (possible selection bias).

6. Future work

1. Further testing of our co-medication definition approach efficacy can be done by applying other different co-medication definitions on the same dataset and compare the accuracy and reliability of the results.

2. Other network measures which haven't been used in this thesis can be useful as well. For example, Ego Networks for certain important medicines can be done to study the influence of these particular medicines on the other medicine. Ego-centric network is to create a network from only a specific node perspective. In other words, to show only this drug and its relations to other drugs (50). Furthermore, we can use Ego networks for certain co-medications, following these combinations over years will allow us to study the probability of shifting or turning over to other drugs/combinations as a consequence of using these first combinations.

3. Having network analysis as apart of descriptive analysis in medical research can also show some importance even if network analysis is not the primary concern for the study. Using network measures to specify the importance of each drug node in the network compared to others can play an important role in Pharmacoeconomics decision making and prioritizing of for example reimbursed medicines. Using NA to notice the change of intensity of DDI over time or in different places critical for pattern study in the medical field.

4. Using Networks as a visualizing comparing tool can also be useful in studying medicines patterns and flow over the years. We believe yet that networks analysis can open a wide field for researchers in studying drug-drug relation-based information.

5. In the Pharmacoeconomics field, network analysis can introduce new and supportive measures to the normal descriptive ways which are normally used. It can also support the decision makers to take the right decisions when it comes to prioritizing of drugs in terms of their value and importance.

6. Using network analysis to visualize DDI can be used as an important part of discovering unwanted drug combinations on the large scale to evaluate the quality of prescribing and to take the necessary measures against the undesired adverse effects.

7. We think that network analysis can be used for prediction of the possible change in patterns if these specific patterns are followed up over the years. For example, if the patients of a certain co-medication for some cardiac disease and by following these patients' co-medication patterns we can see that some other medicines gradually appears in the pattern over time so we can conduct the possibility of using a drug after a particular drug-drug combination and take the preventative measures if possible.

8. Conclusion

Network analysis can be used as a new, convenient way of studying relations between drugs and extracting medication patterns. Furthermore, it represents a group of measures that the traditional descriptive and statistical analysis cannot measure. Plotting the overall drugs' consumption in a network to visualize it, is interesting in itself but for sure not enough. Further, extracting patterns and using the descriptive measures of network analysis to shed light on the clinical outcomes is a necessary part. A group of network analysis measures can be effectively used in the study of drug-drug relations (e.g. edges intensity, centrality measures, betweenness measures).

Defining co-medication as treatment episodes allows flexibility in choosing of the studied prevalence points. Moreover, including many measures, like DDD and PDC, makes it more reliable to capture the co-medication.

Network analysis was effectively used to obtain the relevant clinical information for both co-medication and drug-drug interactions.

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108. Freeman L, Freeman L. A Set of Measures of Centrality Based on Betweenness. Sociometry. 1977;40(1):35-41.

Appendixes

Appendix 1: **STATA coding**

//1-Data preparation

```
// a. split the 15 data files into 2 types of files according to time of despinsing
variable (date or difference)
preserve
drop if diff_utleveringdato ==. //dropping all missing for diff_utleveringdato
drop utleveringsdato //optional (you can keep it)
save as
restore
drop if utleveringsdato ==""
drop diff_utleveringdato //optional
save as ""
// b. merge using "append comman" all datafiles for dispensing difference 1 file
and 1 file for dispensing date variable
append using "/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato02.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato03.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato04.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato05.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato06.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato07.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato08.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato09.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato10.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato11.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato12.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato13.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato14.dta""/Users/mohsengamalsaad/Desktop/Msc data
full/Utleveringsdato/utleveringsdato15.dta"
// save into 2 big datafiles
save "/Users/mohsengamalsaad/Desktop/Msc data full/Data all in 2
files.nosync/utleveringsdatoall.dta"
// and the same fordifference in date of dispensing
//filter out age
drop if pasientfodtar >1948
drop if atckode==""
drop if atckodedddverdi==""
// to find out mean age
use "/Volumes/Mohsen/Master data after filters/Merged/All filtered.dta"
gen alder=0
replace alder =(2013-pasientfodtar)
// for date of dispensing data file, make a variable which is difference between
dispencing day and 01.01.2013
// change date variable to numeric
gen utleveringsdato2 = date(utleveringsdato, "YMD")
// take difference
gen differnse = utleveringsdato2-19359 // 19359 is the stata date format for
01.01.2013
drop utleveringsdato2
rename differnse diff_utleveringdato
// sort the used variables:
sort pasientlopenr atckode diff_utleveringdato
// must first convert ordinasjonantallddd from string to numeric
gen test = subinstr(ordinasjonantallddd,",",".",9)
destring test, replace
// rename test and drop
drop ordinasjonantallddd
rename test ordinasjonantallddd
```

//2- co-medication coding and creating treatment episodes

```
// make a new variable which sums up ordinasjonantallddd
by pasientlopenr atckode diff_utleveringdato: egen test = sum(ordinasjonantallddd)

keep pasientlopenr atckode diff_utleveringdato ordinasjonantallddd
duplicates drop
// make lag and lead variables to take differece between observations in the same
column (dispensing variable column)
by pasientlopenr atckode: gen lag_dato = diff_utleveringdato[_n-1]
```

```
by pasientlopenr atckode: gen lead_dato = diff_utleveringdato[_n+1]
gen delta_dager = lead_dato - diff_utleveringdato
recode delta_dager (.=0)
// Same with DDD
by pasientlopenr atckode: gen ddd = ordinasjonantallddd
by pasientlopenr atckode: gen lag_ddd = ordinasjonantallddd[_n-1]
by pasientlopenr atckode: gen lead_ddd = ordinasjonantallddd[_n+1]

// ADHERENCE 0.8 and create lag and lead for DDD as well
by pasientlopenr atckode: gen ddd_80p_adh = ordinasjonantallddd /0.8 //0.8 betyr
80% adherence, denne kan endres ved behov
by pasientlopenr atckode: gen lag_ddd_80p_adh = ordinasjonantallddd[_n-1] /0.8
by pasientlopenr atckode: gen lead_ddd_80p_adh = ordinasjonantallddd[_n+1] /0.8

// create a variable for how long a prescription will cover pateint's dose
by pasientlopenr atckode: gen resept_dekning_dager = ddd_80p_adh - delta_dager
//choosing  80% adherence
// removing the negative values (this means a patient has minus number of tablets
for example, this -obviously- can't be taken to next treatment episode
recode resept_dekning_dager (min/0=0)
// create a lag variable for resept coverage period
by pasientlopenr atckode: gen lag_rx_dekn_dag = resept_dekning_dager[_n-1]
recode lag_rx_dekn_dag  (.=0)
// create carryover variable for amount of DDD (tabletter) left with the patient
(pateint still has an amount of medicine to carry over to the end of this treatment
episode (PDC adherence definintion)
by pasientlopenr atckode: gen carryover=  (ddd_80p_adh - delta_dager) +
lag_rx_dekn_dag //må lage lag_resept_dekning_dager så det ikke genereres missings
her
by pasientlopenr atckode: gen lag_carryover = carryover[_n-1]
codebook carryover
// create treatmet episodes
// 1 = defines treatment epsode start time (either missing value= start of a period
(no precriptions before that) or  the patient had a medicine-free period for more
than 14 days (gap period)
gen treatment_episode = 0
replace treatment_episode = 1 if lag_carryover==.
replace treatment_episode = 1 if lag_carryover < -14
// 3= defines treatment episode end (lead date is missing or carry over is less
than -14
recode treatment_episode (0=3) if carryover < -14
recode treatment_episode (0=3) if lead_dato==.

// generate a treatmet_start variable
gen treatment_start = diff_utleveringdato if treatment_episode==1
// filling out missing values
by pasientlopenr: replace treatment_start = treatment_start[_n-1] if
missing(treatment_start)
replace treatment_episode =3 if carryover < -14 //hvis det er mer mindre enn 14
dager minus så er gapet for stort til neste at det avsluttes
replace treatment_episode =3 if lead_dato==. //første behandlingsepisode per
legemiddel vil være

// generate treatment_end variable
gen treatment_end = diff_utleveringdato + ddd_80p_adh if treatment_episode==3
//turning sorting for to fill out treatment end  (so, 3 (slutt) is over and 1 is
under)
gsort pasientlopenr atckode -diff_utleveringdato
// filling out missing values
by pasientlopenr: replace treatment_end = treatment_end[_n-1] if
missing(treatment_end)
sort pasientlopenr atckode diff_utleveringdato
keep if treatment_episode==3
keep pasientlopenr atckode treatment_start treatment_end
//after that we can choose a period of study (prevelence period or point) to study
//for 2013 netwrok
keep if treatment_start <= 0
keep if treatment_end >= 0
```

```
// for 2014 netwrok
keep if treatment_start <= 365
keep if treatment_end >= 365
```
//3- networks generating
```
preserve
keep atckode pasientlopenr
duplicates drop
save ""
rename atckode atckode2
joinby pasientlopenr using ""
bysort atckode atckode2 :egen edges=count(pasientlopenr)
drop if atckode == atckode2
drop pasientlopenr
duplicates drop
nwfromedge atckode atckode2 edges, undirected keeporiginal
nwexport
nwexport, type(pajek) replace
```
//4- coding for importing different attributes to GEPHI
```
import delimited "/Users/mohsenaskar/Desktop/CSV from gephi/DDI co weighed as
edges.csv", clear
drop timeset
//merging wanted attributes (variables)
//merging drug name
merge 1:m label using "/Users/mohsenaskar/Desktop/vareregister.dta"
//merging substance name
merge 1:m label using "/Users/mohsenaskar/Desktop/ATC+substence name.dta"
keep if _merge==3
drop _merge
rename varenavn name
gen gruppe =substr(label,1,1)
//for colors
gen color="."
replace color="#AD2516" if gruppe=="A"
replace color="#EE1E23" if gruppe=="B"
replace color="#F7BE4D" if gruppe=="C"
replace color="#FFFC54" if gruppe=="D"
replace color="#9FCD5F" if gruppe=="G"
replace color="#4FAC5C" if gruppe=="H"
replace color="#4CACF2" if gruppe=="J"
replace color="#2B71B7" if gruppe=="L"
replace color="#0A1F59" if gruppe=="M"
replace color="#673897" if gruppe=="N"
replace color="#7C7B79" if gruppe=="P"
replace color="#7B5E21" if gruppe=="R"
replace color="#6E74F8" if gruppe=="S"
replace color="#6E74F8" if gruppe=="V"
drop gruppe
merge 1:m label using "/Volumes/Mohsen/2. forsøk/All antall brukere av ATC dag
0.dta"
keep if _merge==3
drop _merge
export delimited using "/Users/mohsenaskar/Desktop/CSV from gephi/CSV to
gephi/Rogaland.csv", replace
// import to GEPHI
```
// 5- Six patterns networks
```
// creating a file for each pattern (6 patterns)
//cardiac,ARI,COPD,Anexiety,Menopause,Pain
use "/Volumes/Mohsen/2. forsøk/All nw.dta", clear
keep if treatment_start <= 0
keep if treatment_end >= 0
drop treatment_start treatment_end
keep if substr(atckode,1,1) == "R" | substr(atckode,1,1) == "M" |
substr(atckode,1,1)=="N" //fungerer
keep if strpos(atckode,"R01A")>0 | strpos(atckode,"R01B")>0 |
strpos(atckode,"R03A")>0 | strpos(atckode,"R03A")>0 | strpos(atckode,"R05CA")>0|
strpos(atckode,"R05D")>0 | strpos(atckode,"R06A")>0 | strpos(atckode,"N06A")>0|
strpos(atckode,"N06B")>0 | strpos(atckode,"C09A")>0| strpos(atckode,"C10A")>0
preserve
```

```
keep atckode pasientlopenr
duplicates drop
save "/Users/mohsenaskar/Desktop/Menopause.dta"
rename atckode atckode2
joinby pasientlopenr using "/Users/mohsenaskar/Desktop/Menopause.dta"
bysort atckode atckode2 :egen edges=count(pasientlopenr)
drop if atckode == atckode2
duplicates drop
drop pasientlopenr
nwfromedge atckode atckode2 edges, xvars undirected keeporiginal name(Menopause)
nwexport, type(pajek) replace
save "/Volumes/Mohsen/2. forsøk/7 PATTERNS/Dag 0/ARI.dta"
// use (all nw) to find out how many useres for each ATC
//for Day 0
keep if treatment_start <= 0
keep if treatment_end >= 0
drop treatment_start treatment_end
sort pasientlopenr atckode
by pasientlopenr: gen n3=[_n-1]
sort atckode
by atckode: gen n4=_N
rename n4 antallbrukere
keep atckode antallbrukere
duplicates drop
rename atckode label
// use merge command to merge number of users with 0 network
drop _merge
save "/Volumes/Mohsen/2. forsøk/All antall brukere av ATC dag 0.dta"
// same is done with 365 network and compare network
export delimited using "/Users/mohsenaskar/Desktop/CSV from gephi/CSV to gephi/All
365 m3e antallnrukere.csv", replace
//Now a file for ATC codes with number of users is created
// anatomical groups
keep if substr(atckode,1,1) == "A" | substr(atckode,1,1) == "B" |
substr(atckode,1,1)=="C"
keep if strpos(atckode,"A02B")>0 | strpos(atckode,"A10A")>0 |
strpos(atckode,"A10B")>0 | strpos(atckode,"B01A")>0 | strpos(atckode,"C01A")>0|
strpos(atckode,"C01D")>0 | strpos(atckode,"C03")>0 | strpos(atckode,"C07A")>0|
strpos(atckode,"C08D")>0 | strpos(atckode,"C09A")>0| strpos(atckode,"C10A")>0
sort antallbrukere
//6- Interactions data
//filtering and preparation of data
//keep just ATC codes (remove groups og categories)
drop if length(ATC1)<7
drop if length(ATC2)<7 //114802 deleted
//the opposite can be done if we want to study interactions on the groups level
keep if length(ATC1)<=5
keep if length(ATC2)<=5
drop if ATC1=="NULL"
drop if ATC2=="NULL"
//remove if ATC1=ATC2
drop if ATC1==ATC2
//making a variable indicating combinations
gen komb=0
replace komb=1 if strpos(Lm1,"kombinasjon")>0
replace komb=1 strpos(Lm2,"kombinasjon")>0

//remove if drug 1 and 2 has the same substence
drop if Lm1== Lm2
//keep severe interactions (1st grade) indicated by number 1 in FEST database
keep if Grad==1
keep ATC1 ATC2 Grad
// for creating of frequency DDI tablet between the anatomical groups
gen atckode1=substr(ATC1,1,1)
gen atckode2=substr(ATC2,1,1)
tab atckode1 atckode2
// to confirm the number of edges we founf in the general DDI netwrok
use "/Volumes/Mohsen/2. forsøk/DDI/DDI atc code level 1 grad.dta"
```

```
keep ATC1 ATC2 Grad
gen pairing = ATC1 + ATC2
gen pairing2 = ATC2 + ATC1
stack pairing pairing2, into(combined)
duplicates drop combined,force // we got 114.302 observations which are (57151*2)

// to create DDI nw for co-medication
use "/Volumes/Mohsen/2. forsøk/All nw.dta"
keep if treatment_start <= 0
keep if treatment_end >= 0
drop treatment_start treatment_end
preserve
keep atckode pasientlopenr
duplicates drop
save "/Users/mohsenaskar/Desktop/all joinby.dta"
rename atckode atckode2
joinby pasientlopenr using "/Users/mohsenaskar/Desktop/all joinby.dta"
bysort atckode atckode2 :egen edges=count(pasientlopenr)
drop if atckode == atckode2
drop if length(atckode)<7
drop if length(atckode2)<7
drop pasientlopenr
duplicates drop
rename atckode ATC1
rename atckode2 ATC2
joinby ATC1 ATC2 using "/Volumes/Mohsen/Master oppgave 2018/interaksjoner/DDI med
grad.dta"
keep if Grad==1
//Grade as edges (unweighted)
keep ATC1 ATC2 Grad
nwfromedge ATC1 ATC2 Grad, xvars undirected keeporiginal name(DDI comedication all
grades)
nwexport, type(pajek) replace

//co-medication as edges (weighed)
keep ATC2 ATC1 edges
**network
nwfromedge ATC1 ATC2 edges, xvars undirected keeporiginal name(DDI comedication
comedicationa as edges)
nwexport, type(pajek) replace
```

//7-studying modularity classes medicines

```
//import from gephi to stata (cvs)
import delimited "/Users/mohsenaskar/Desktop/CSV from gephi/CSV to gephi
substance/All 0.csv", clear

//to covert ATC to the 4th level
gen gruppe =substr(label,1,3) //which indicates theraputic use
preserve
gsort + modularity_class - antallbrukere
keep if modularity_class ==1
keep antallbrukere gruppe
sort gruppe
// to sum all users under the same group
egen sumbrukere = sum(antallbrukere), by(gruppe)
sort antallbrukere
gsort - antallbrukere
duplicates drop gruppe, force
drop antallbrukere
gsort -sumbrukere
// and the same with each modularity class (1,2,3
```

*A*ppendix 2: Categorization of ATC codes without DDD in the dataset

Appendix 2: ATC without DDD in the database (categorized)

Categorizing ATC codes without DDD

Non-systemic

Creams/Topical

Proctosedyl salve	C05AA01	Betnovat m/chinoform krem	D07BC01
Scheriproct rektalsalve+stikkp	C05AA04	Synalar med Chinoform krem	D07BC02
Rectogesic rektalsalve 4mg/g	C05AE01	Fucidin-Hydrocortison krem	D07CA01
Anoheal krem 2%	C05AX	Mycolog salve	D07CB01
Alcos-Anal salve	C05AX03	Fucibet krem	D07CC01
Hirudoid salve 3mg/g	C05BA01	Hydrokort SA krem 1% i karbar	D07XA01
Canesten krem 1%	D01AC01	Diprosalic lin	D07XC01
Daktar krem 2%	D01AC02	Alsol vandig oppl 1%	D08AB
Pevaryl pudder 1%	D01AC03	Brulidine krem 0,15%	D08AC01
Fungoral krem 20mg/g	D01AC08	Hibiscrub lin 40mg/ml	D08AC02
Pevisone krem	D01AC20	Braunovidon salve 10%	D08AG02
Krystallfiolett NAF lin 0,1%	D01AE02	Jod NAF lin 2%	D08AG03
Onytec medis neglelakk 80mg/g	D01AE14	Pyrisept salve 1mg/g	D08AJ03
Terbinafin hexal krem 10mg/g	D01AE15	Sølvnitrat SA lin 0,25%	D08AL01
Loceryl medisinsk neglelakk 5%	D01AE16	Microcid krem 1%	D08AX01
Lassars pasta NAF	D02AB	Kaliumpermang NAF til badev 3	D08AX06
Canoderm krem 5%	D02AE01	Fucidin impr kompress 10x10cn	D09AA02
Salisylsyre NAF olje lin 5%	D02AF	Zipzoc salvestrømpe impr kompr	D09AB01
Miniderm krem 20%	D02AX	Kamferspiritus NAF lin	D10A
Bepanthen krem 5%	D03AX03	Aberela krem 0,05%	D10AD01
Fenistil gel 1mg/g	D04AA13	Avibon pomade	D10AD02
Xylocain salve 5%	D04AB01	Differin krem 1mg/g	D10AD03
Eurax krem 10%	D04AX	Zalna gel 10+0,25mg/g	D10AD51
Alphosyl 2 i 1 sjampo	D05AA	Epiduo gel 0,1/2,5%	D10AD53
Dithrocream krem 0,25%	D05AC01	Basiron AC Wash gel 5%	D10AE01
Calcipotriol san krem 0,05mg/g	D05AX02	Dalacin lin emulsjon 10mg/ml	D10AF01
Silkis salve 3mcg/g	D05AX03	Zineryt pulv t/liniment 40mg	D10AF02
Xamiol gel	D05AX52	Finacea gel 15%	D10AX03
Fumaderm tab	D05BX51	Scott-Mathiesens hudv NAF lin	D10AX30
Aureomycin salve 3%	D06AA02	Selsun sjampo 25mg/ml	D11AC03
Terramycin-Polymyxin B salve	D06AA03	Verucid lin	D11AF
Fucidin salve 2%	D06AX01	Protopic salve 0,1%	D11AH01
Bacimycin salve	D06AX05	Elidel krem 10mg/g	D11AH02
Bactroban krem 2%	D06AX09	Pigmanorm krem (Sveits)	D11AX
Altargo salve 1%	D06AX13	Recrea Forte lin 5%	D11AX01
Flamazine krem 10mg/g	D06BA01	Vaniqa krem 11,5%	D11AX16
Zovirax krem 5%	D06BB03	Solaraze gel 3%	D11AX18
Condyline lin 5mg/ml	D06BB04	Mirvaso gel 3mg/g	D11AX21
Vectavir krem 1%	D06BB06	Uva Ursi Max-V kaps 200mg	G01A
Aldara krem 5%	D06BB10	Eddiksyre SA lin 2%	G01AD02
Veregen salve	D06BB12	Albothyl vaginalvæske	G01AX03
Rozex gel 0,75%	D06BX01	Orudis gel 2,5%	M02AA10
Picato gel 150mcg/g endosetube	D06BX02	Ibumetin gel 5%	M02AA13
Hydrok/Svov i cetyl SA kr 1/3%	D07AA	Voltarol gel 11,6mg/g	M02AA15
Mildison Lipid krem 1%	D07AA02	Termo medisinert plaster	M02AB01
Locoid lin 0,1%	D07AB02	Algesal salve	M02AC
Apolar krem 0,1%	D07AB08	Hvit kamferolje NAF lin	M02AX10
Betnovat krem 0,1%	D07AC01	Diltiazem SA rektalsalve 2%	C08DB01
Ibaril krem 0,25%	D07AC03	Nystatin krem 100000IE	D01AA01
Synalar gel 0,025%	D07AC04	Testosteron SA krem 2%	G03BA03
Metosyn salve 0,05%	D07AC08	Lugols joddråper SA oppl 5%	H03CA
Elocon krem 0,1%	D07AC13	Topicale anesthet gel raspberr	N01BA05
Flutivate krem 0,05%	D07AC17	Xylocain gel 2% engangsspr	N01BB02
Dermovat krem 0,05%	D07AD01	Emla krem 25+25mg/g	N01BB20
Apolar med dekvalin salve	D07BB02	Capsina krem 0,075%	N01BX04
		Morfin SA steril gel 0,1%	N02AA01
		Nix sjampo 1%	P03AC04
		Benzylbenzoat NAF lin 33%	P03AX01
		Prioderm lin 0,5%	P03AX03
		Arnikatinktur NAF lin	M02

Topicals incl. Drops others

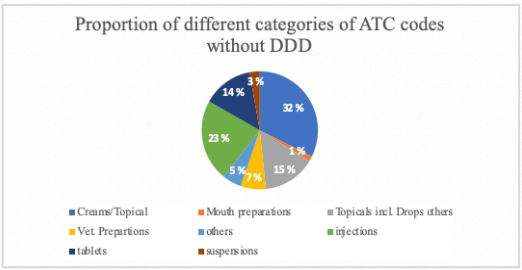
Liposomal B12/Methylfolate drp	B03BA	Kloramfenikol tak øyesalve 1%	S01AA01
Kloramfenikol tak øyesalve 1%	S01AA01	Aureomycin øyesalve 1%	S01AA02
Aureomycin øyesalve 1%	S01AA02	Garamycin øyedr 3mg/ml	S01AA11
Garamycin øyedr 3mg/ml	S01AA11	Sulfatiazol NAF vet salve 10%	QD06BA02
Tobrex Depot dep øyedr 3mg/ml	S01AA12	Fuciderm vet gel	QD07CC01
Fucithalmic øyedr 10mg/g	S01AA13	Jod-kamfersalve NAF vet	QD08AG53
Azyter øyedr 15mg/g endos	S01AA26	Perlutex vet tab 5mg	QG03DA02
Terramycin-Polymyxin B øyesalv	S01AA30	Clamoxyl vet inj 150mg/ml	QJ01CA04
Zovirax øyesalve 3%	S01AD03	Noroclav vet tab 400/100mg	QJ01CR02
Cilox øyedr 3mg/ml	S01AE03	Tribrissen vet tab	QJ01EW10
Betadine ster ophtalm oppl 5%	S01AX18	Antirobe vet kaps 150mg	QJ01FF01
Spersadex øyedr 1mg/ml	S01BA01	Genta-Kel 10 vet inj 100mg/ml	QJ01GB03
Ultracortenol øyesalve 5mg/g	S01BA04	Baytril vet tab 15mg	QJ01MA90
Flurolon øyedr 1mg/ml	S01BA07	Metacam vet miks 0,5mg/ml katt	QM01AC06
Visucloben øyedr 1mg/ml	S01BA09	Rimadyl vet tab 50mg	QM01AE91
Vexol øyedr 10mg/ml	S01BA13	Baycox Bovis vet miksт 50mg/ml	QP51AJ01
Efemolin øyedr	S01BB03	Drontal vet tab	QP52AA51
Voltaren Ophtha øyedr 1mg/ml	S01BC03	Panacur vet past 187,5mg hu/ka	QP52AC13
Maxitrol øyedr 1mg/ml	S01BC10	Banminth vet pasta 2,2% hund	QP52AF02
Yellox øyedr 0,9mg/ml	S01BC11	Exspot vet påflekk 715mg/ml	QP53AC04
Maxitrol øyedr	S01CA01	Scalibor vet halsb 40mg/g hund	QP53AC11
Atropin Minims øyedr 10mg/ml	S01FA01	Frontline vet påfl væ 100mg/ml	QP53AX15
Cyclopentolat Minim øyedr 10mg	S01FA04	Milbemax vet tab 16/40 katt	QP54AB51
Tropikamid Minims øyedr 5mg/ml	S01FA06	Fucithalmic vet øyedr 1%	QS01AA13
Metaoxedrin Minims øyedr 100mg	S01FB01	Optimmune vet øyesalve 2mg/g	QS01XA18
Antistin-Privin øyedr	S01GA51		
Spersallerg øyedr	S01GA52		
Lomudal øyedr 40mg/ml u/kons	S01GX01		
Livostin øyedr 0,5mg/ml	S01GX02		
Tilavist øyedr 20mg/ml	S01GX04		
Emadine øyedr 0,05%	S01GX06		
Lastin øyedr 0,5mg/ml	S01GX07		
Zaditen øyedr 0,25mg/ml	S01GX08		
Opatanol øyedr 1mg/ml	S01GX09		
Oxibuprokain Minims øyedr 4mg	S01HA02		
Tetrakain Minims øyedr 10mg/ml	S01HA03		
Alcaine øyedr 5mg/ml	S01HA04		
Fluoresceinna Minim øyedr 20mg	S01JA01		
Na kl i Emulgon apl øyesalv 5%	S01XA03		
Restasis øyedr 0,05% endos	S01XA18		
Ophtasiloxan øyedr	S01XA20		
Kloramfenikol NAF øred 100mg/g	S02AA01		
Borsyre SA øredr 30mg/ml	S02AA03		
Diproderm øredr 0,05% endos	S02BA07		
Locorten Vioform øredr	S02CA02		
Cetraxal Comp øred 3+0,25mg/ml	S02CA05		
Sofradex øye-/øredr	S03CA01		
Terra-Cortril Polymyx B øredr	S03CA04		
Na kl SA øyedr 50mg/ml	S01		
Kamferdråper NAF	V03AX		
Bactroban Nasal eurom salve 2%	R01AX06		
Koffein/difen SA stikp 100/100	R06AA52		
Cilox øyedr 3mg/ml	S01AE03		

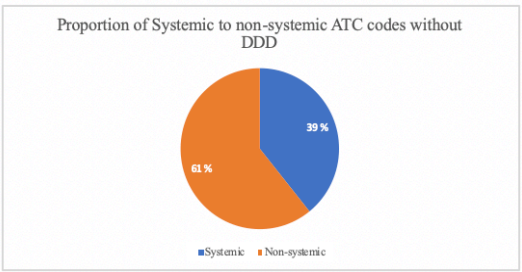
Vet. Preparations

Vitamin E NAF vet drp 50mg/ml	QA11HA03	Karsivan vet tab 50mg	QC04AD90
Fortekor vet tab 2,5mg	QC09AA07	Olje-glyserol NAF rektalvæske	A06AG04
Sulfatiazol NAF vet salve 10%	QD06BA02	Oljeklyster SA rektalvæske	A06AG06
Fuciderm vet gel	QD07CC01	Prednisolon SA stikkpille 15mg	H02AB06
Jod-kamfersalve NAF vet	QD08AG53	Mirena intrauterin 20mcg/24t	G02BA03
Perlutex vet tab 5mg	QG03DA02	Kaliumjodid recip tab 65mg	V03AB21
Clamoxyl vet inj 150mg/ml	QJ01CA04	ReadiSorb Lipo Glutathion miks	V03AB32
Noroclav vet tab 400/100mg	QJ01CR02	Resonium-Calcium pulv	V03AE01
Tribrissen vet tab	QJ01EW10	True Test panel 1+2+3 plaster	V04CL
Antirobe vet kaps 150mg	QJ01FF01	UltraClear PLUS pH pulv vanilj	V06DB
Genta-Kel 10 vet inj 100mg/ml	QJ01GB03	Na kl fres t par br 9mg/ml pl	V07AB
Baytril vet tab 15mg	QJ01MA90	Eter NAF	V07AZ
Metacam vet miks 0,5mg/ml katt	QM01AC06	Utlevering m/tilsyn - Metadon	N07BC02
Rimadyl vet tab 50mg	QM01AE91	VSL#3 pulv neytral	A07FA01
Baycox Bovis vet miksт 50mg/ml	QP51AJ01	Hirudo medicinalis blodigler	C05
Drontal vet tab	QP52AA51	L-glutamin pulv	A16AA03
Panacur vet past 187,5mg hu/ka	QP52AC13	Fortyn saltsyre NAF drp 2mol/l	A09AB03
Banminth vet pasta 2,2% hund	QP52AF02	Gingi-Pak Cord 2-ply 10120	A01AD01
Exspot vet påflekk 715mg/ml	QP53AC04	**Mouth preparations**	
Scalibor vet halsb 40mg/g hund	QP53AC11	Andolex munnskyll 1,5mg/ml	A01AD02
Frontline vet påfl væ 100mg/ml	QP53AX15	Duraphat tannpasta 5mg/g	A01AA01
Milbemax vet tab 16/40 katt	QP54AB51	Klobetasol munngel 0,025%	A01AC
Fucithalmic vet øyedr 1%	QS01AA13	Kenacort A orabase pasta 0,1%	A01AC01
Optimmune vet øyesalve 2mg/g	QS01XA18	Dentinox NAF oppl t tannkjøtt	A01AD11

Systemic	140
Non-systemic	217
Total	357

Creams/Topical	115
Mouth preparations	5
Topicals incl. Drops others	52
Vet. Prepartions	25
others	19
injections	80
tablets	50
suspensions	10





Systemic

Injections

Neurobion inj	A11DB	Tricycline kaps	A
Pabrinex IM high potency inj	A11EB	Marinol tab 2,5mg	A04AD10
Helixate NexGen inj sub 2000IE	B02BD02	OFA urtete NAF	A06AB20
Feiba inf subst 1000E	B02BD03	Pepto-Bismol tyggetab 262mg	A07BB
Octanine inj subst 1000IE	B02BD04	Ther-Biotic Complete kaps	A07FA
Haemate inj subst 1000IE	B02BD06	Bififlor tab	A07FA51
Act-HIB inj subst	J07AG01	Mycopryl 680 kaps	A07XA
NeisVac-C inj 10mcg/spr	J07AH07	Daosin kaps	A09AA
Menveo inj subst	J07AH08	Inte-zyme kaps	A09AA02
Boostrix inj spr	J07AJ52	InterFase Plus kaps	A09AC02
Pneumovax inj	J07AL01	Auralife kaps	A11
Prevenar 13 inj spr	J07AL02	Anabolic flow kaps	A11AA03
Tetavax inj	J07AM01	Carotaben kaps 25mg	A11CA02
DiTeBooster inj	J07AM51	Immunothione kaps	A11EX
BCG-vaksine inj SSI sett I+II	J07AN01	Riboflavin solgar tab 50mg	A11HA04
Vivotif enterokaps	J07AP01	P-5-P kaps 50mg	A11HA06
Typhim Vi inj 25mcg/spr	J07AP03	Phosphate-sandoz brustab 500mg	A12
TicoVac inj 2,4mcg/spr	J07BA01	Calcium citrate tab	A12AX
Ixiaro inj 6mcg/spr	J07BA02	Kalium hausmann brusetab	A12BA30
Vaxigrip inj spr	J07BB02	Magnesium Diasporal kaps 150mg	A12CC10
Engerix-B inj 20mcg/spr	J07BC01	Fosfat SA miksт 1mmol/ml	A12CX
Havrix inj 1440 ELISA U/spr	J07BC02	Pregnenolone depottab 100mg	A14A
Twinrix Voksen inj spr	J07BC20	DHEA douglaskaps 50mg	A14AA07
Imovax Polio inj spr	J07BF03	Beet flow kaps	A16
Rabies-Imovax inj subst	J07BG01	L-Phenylalanine kaps	A16AA
Varilrix inj subst	J07BK01	Molsidomin depottab 8mg	C01DX12
Stamaril inj subst	J07BL01	Elmiron kaps 100mg	C05BA04
Gardasil inj	J07BM01	Venoruton kaps 300mg	C05CA01
Boostrix Polio inj spr	J07CA02	Venastat depotkaps	C05CX03
Albumin baxter inf 50g/l	B05AA01	HypoCol kaps	C10
Glucos fres inf 50mg/ml freef	B05BA03	Remifemin tab 2,5mg	G02CX04
SmofKabiven inf 1600kcal/p	B05BA10	Armour Thyroid tab 30mg	H03AA05
Na kl fres inf 9mg/ml freeflex	B05BB01	Glucosamine Plus kap 500/360mg	M01AX
Karbolyt inf 2000kJ/l freefl	B05BB02	Reumacon ent kaps 50mg	M01CX
Physioneal 40 glu 22,7mg skr	B05DB	Valerina forte tab	N05CM09
Kaliumkl braun infkon 1mmol MP	B05XA01	5-HTP douglas kaps 50mg	N06AX01
Na hyd karb br infkons 0,5mmol	B05XA02	L-Tryptophan ratio tab 500mg	N06AX02
Na kl braun infkon 1mmol/ml MP	B05XA03	Bio-Biloba tab 100mg	N06DX02
Magnesiumsulfat inf kons 1mmol	B05XA05	Dimaval kaps 100mg	V03AB09
Monokaliumfosf inf kons 1mmol	B05XA06	Ferriprox tab 500mg	V03AC02
Calciumklorid inf kons 1mmol	B05XA07	Exjade dispergerbar tab 500mg	V03AC03
Tracel inf kons	B05XA31	Osvaren tab 435/235mg	V03AE04
L-Arginine kaps 700mg	B05XB01	Folinic-folic acid kaps 0,8mg	V03AF
Dipeptiven inf kons 200mg/ml	B05XB02	Uromitexan tab 400mg	V03AF01
Vitalipid adult inf kons	B05XC	Proglicem kaps 25mg	V03AH01
Aethoxysklerol inj 0,5%	C05BB02	Aminess tab	V06DD
Premixel inf pl 840kj/l	B05B	Livertone kaps	V06DX
Vamin Elektrol fri inf 14g N/l	B05BA01	Placebo SA kaps	V07A
Nexavir inj	D	Diabact UBT tab 50mg	V04CX
Protaminsulf leo inf/inj 10mg	V03AB14	Hamburgerte NAF urtete	A06AB56
Naloxon braun inf/inj 0,4mg/ml	V03AB15	**Suspension or liquids**	
Flumazenil hameln inj 0,1mg/ml	V03AB25	Cytra-K crystals pulv t mikst	A02A
Alutard SQ Timot inj 100 000sq	V01AA02	Vismutmikst/vann 1:3 SA mikst	A02BX12
Alutard SQ Der pter 503 100000	V01AA03	Tagitol V mikst 40% w/v	V08BA01
Alutard SQ Bjørk inj 100 000sq	V01AA05	Ketovite Liquid mikst	A11JA
Alutard SQ Vepsegift 100 000sq	V01AA07	Dukoral susp+brusegran t mikst	J07AE01
Alutard SQ Burot inj 100 000sq	V01AA10	Frølichs hostemikstur NAF	R05CA10
Alutard SQ Hundehår inj start	V01AA11	Flow C dråper	V03
Gammanorm inj 165mg/ml	J06BA01	Brekkmiddel til barn NAF mikst	V03AB01
Octagam inf 50mg/ml	J06BA02	A-vitamin oljeoppl NAF mikst	V04CB01
Hepatect CP inf 50 IE/ml	J06BB04	Solhattinktur NAF dråper	R05
Botox inj subst 100E	M03AX01		
Fentanyl hameln inj 50mcg/ml	N01AH01		
Standard EDA blanding SA inf	N01AH51		
Ketalar inj 50mg/ml	N01AX03		
Marcain inj 5mg/ml	N01BB01		
Carbocain inj 20mg/ml	N01BB03		
Ropivacain fre inf 2mg/ml free	N01BB09		
Marcain-Adr inj 2,5mg+5mcg/ml	N01BB51		
Xylocain-Adr inj 2%+5mcg/ml	N01BB52		
Carbocain adren inj 20mg+5mcg	N01BB53		
Citanest Dent Octapressin inj	N01BB54		
Septocaine F inj 40mg+10mcg sy	N01BB58		
Isofluran baxt væ t inh damp	N01AB06		
Valoid inj 50mg/ml	R06AE03		
Na kl SA inh væske 70mg/ml	R07A		
Gastrografin m & r 370mg I/ml	V08AA01		
Omnipaque inj 300mg I/ml USB	V08AB02		
Adrenalin base NAF injkons 1mg	V03A		
Desferal inf/inj subst 500mg	V03AC01		

Appendix 3: **Variables description**

Variable name	Variable description	Variable type [1]	Comment
1. Prescriber information:			
forskriverlopenr	Physician's anonymous ID	Numeric (long)	
forskriverfodtar	Physician's birth date	Numeric (int.)	
forskriverkjonn	Physician's sex	Numeric (byte)	
forskriverutenid	Physician's without an ID [2]	Numeric (byte)	
2. Patient information:			
pasientlopenr	Patient's anonymous ID	Numeric (long)	Central variable [4]
pasientfodtar	Patient's birthdate	Numeric (int.)	
pasientkjonn	Patient's sex	Numeric (byte)	
pasientbostedfylkenr	Patient's municipality no	Numeric (byte)	
pasientbostedfylkenavn	Patient's municipality	String (str30)	
pasientdodsar	Patient's death date	Numeric (int.)	
pasientdodsmnd	Patient's death month	Numeric (byte)	
pasientutenid	Patient's without ID	Numeric (byte)	
3. Dispensing information:			
diff_utleveringdato	Difference between dispensing for hospitalized patients	Numeric (byte)	Central variable [4]
utleveringsaar	Dispensing year	Numeric (int.)	
utleveringsdato	Dispensing date	String (str10)	Central variable [4]
4a. Prescription information (Reimbursement info):			
kategori		String (str83)	
kategorinr		Numeric (byte)	
hjemmel		String (str62)	
hjemmelnr		Numeric (byte)	
refusjonkodeicdnr	Blue prescription, reimbursement ICD code	String (str5)	Indicates type of diagnosis
refusjonkodeicpcnr	Blue prescription, reimbursement ICPC code	String (str3)	Indicates type of diagnosis
4b. Prescription information (Medicines info):			
ordinasjonantallpakninger	No. of packages dispensed	String (str7)	
ordinasjonantallddd	Total DDD dispensed	String (str9)	Central variable [4]
varenr	Medicine number [3]	Numeric (long)	
varenavn	Medicine name	String (str32)	
atckode	ATC code	String (str8)	Central variable [4]
atckodedddverdi	DDD for this ATC code	String (str7)	
atckodedddenhet	Concentration in gram or mg or others	String (str4)	
ordinasjonnr	Prescription number	Numeric (double)	

Table shows dataset variables.
[1] Variables types according to STATA variable types.
[2] In some cases the pharmacist can dispense a prescription without a physician's ID (for instance emergency cases, or a prescription from outside Norway)
[3] Each medicine in Norway has a registration number.
[4] Central variables for this thesis

Appendix 4: The most 200 used drug combinations in 2013 network

Most 200 combined medicines			
No.	**Drug 1**	**Drug 2**	**No. of times combined**
1	118 - Acetyl salicylic acid	224 - Simvastatin	82948.0
2	118 - Acetyl salicylic acid	185 - Metoprolol	52577.0
3	118 - Acetyl salicylic acid	228 - Atorvastatin	42753.0
4	185 - Metoprolol	224 - Simvastatin	36792.0
5	118 - Acetyl salicylic acid	191 - Amlodipin	32628.0
6	118 - Acetyl salicylic acid	608 - Zopiklon	29173.0
7	191 - Amlodipin	224 - Simvastatin	22554.0
8	118 - Acetyl salicylic acid	201 - Ramipril	19660.0
9	224 - Simvastatin	608 - Zopiklon	18845.0
10	70 - Metformin	118 - Acetyl salicylic acid	18507.0
11	118 - Acetyl salicylic acid	172 - Furosemid	18175.0
12	185 - Metoprolol	228 - Atorvastatin	17266.0
13	118 - Acetyl salicylic acid	314 - Levotyroksinnatrium	16654.0
14	118 - Acetyl salicylic acid	520 - Paracetamol	16380.0
15	185 - Metoprolol	191 - Amlodipin	16271.0
16	111 - Warfarin	185 - Metoprolol	16005.0
17	70 - Metformin	224 - Simvastatin	15647.0
18	118 - Acetyl salicylic acid	210 - Kandesartan	14306.0
19	118 - Acetyl salicylic acid	157 - Isosorbidmononitrat	14236.0
20	118 - Acetyl salicylic acid	213 - Losartan og diuretika	14007.0
21	185 - Metoprolol	608 - Zopiklon	13801.0
22	10 - Pantoprazol	118 - Acetylsalisylsyre	13560.0
23	111 - Warfarin	224 - Simvastatin	13483.0
24	172 - Furosemid	185 - Metoprolol	13118.0
25	201 - Ramipril	224 - Simvastatin	12907.0
26	172 - Furosemid	224 - Simvastatin	12536.0
27	12 - Esomeprazol	118 - Acetylsalisylsyre	12430.0
28	520 - Paracetamol	608 - Zopiklon	12193.0
29	185 - Metoprolol	201 - Ramipril	12153.0
30	224 - Simvastatin	314 - Levotyroksinnatrium	12006.0
31	118 - Acetyl salicylic acid	206 - Losartan	10883.0
32	118 - Acetyl salicylic acid	307 - Prednisolon	10347.0
33	118 - Acetyl salicylic acid	217 - Kandesartan og diuretika	10319.0
34	213 - Losartan og diuretika	224 - Simvastatin	10312.0
35	224 - Simvastatin	520 - Paracetamol	10139.0
36	118 - Acetyl salicylic acid	495 - Alendronsyre	9897.0
37	118 - Acetyl salicylic acid	119 - Dipyridamol	9877.0
38	210 - Kandesartan	224 - Simvastatin	9774.0
39	191 - Amlodipin	228 - Atorvastatin	9748.0
40	118 - Acetyl salicylic acid	195 - Lerkanidipin	9731.0
41	118 - Acetyl salicylic acid	292 - Tamsulosin	9511.0
42	118 - Acetyl salicylic acid	173 - Bumetanid	9366.0
43	70 - Metformin	185 - Metoprolol	9292.0
44	118 - Acetyl salicylic acid	199 - Enalapril	9186.0
45	70 - Metformin	73 - Glimepirid	9152.0
46	191 - Amlodipin	608 - Zopiklon	9075.0
47	118 - Acetyl salicylic acid	737 - Cetirizin	8962.0
48	228 - Atorvastatin	608 - Zopiklon	8785.0

49	10 - Pantoprazol	224 - Simvastatin	8757.0
50	157 - Isosorbidmononitrat	224 - Simvastatin	8618.0
51	185 - Metoprolol	520 - Paracetamol	8472.0
52	12 - Esomeprazol	224 - Simvastatin	8310.0
53	157 - Isosorbidmononitrat	185 - Metoprolol	8218.0
54	73 - Glimepirid	118 - Acetylsalisylsyre	8146.0
55	314 - Levotyroksinnatrium	608 - Zopiklon	8020.0
56	185 - Metoprolol	314 - Levotyroksinnatrium	7961.0
57	172 - Furosemid	608 - Zopiklon	7869.0
58	118 - Acetyl salicylic acid	707 - tiotropium bromide	7814.0
59	118 - Acetyl salicylic acid	194 - Nifedipin	7753.0
60	118 - Acetyl salicylic acid	697 - Salmeterol og flutikason	7728.0
61	201 - Ramipril	228 - Atorvastatin	7562.0
62	111 - Warfarin	172 - Furosemid	7489.0
63	118 - Acetyl salicylic acid	626 - Escitalopram	7426.0
64	173 - Bumetanid	185 - Metoprolol	7384.0
65	217 - Kandesartan og diuretika	224 - Simvastatin	7354.0
66	206 - Losartan	224 - Simvastatin	7346.0
67	70 - Metformin	191 - Amlodipin	7115.0
68	140 - Folsyre	466 - Metotreksat	7078.0
69	697 - Salmeterol og flutikason	707 - tiotropium bromide	6930.0
70	199 - Enalapril	224 - Simvastatin	6831.0
71	185 - Metoprolol	213 - Losartan og diuretika	6811.0
72	118 - Acetyl salicylic acid	513 - Kodein og paracetamol	6775.0
73	118 - Acetyl salicylic acid	186 - Atenolol	6751.0
74	10 - Pantoprazol	185 - Metoprolol	6740.0
75	73 - Glimepirid	224 - Simvastatin	6721.0
76	224 - Simvastatin	495 - Alendronsyre	6682.0
77	111 - Warfarin	228 - Atorvastatin	6640.0
78	224 - Simvastatin	737 - Cetirizin	6608.0
79	691 - Salbutamol	697 - Salmeterol og flutikason	6599.0
80	195 - Lerkanidipin	224 - Simvastatin	6591.0
81	185 - Metoprolol	210 - Kandesartan	6472.0
82	111 - Warfarin	608 - Zopiklon	6461.0
83	70 - Metformin	228 - Atorvastatin	6458.0
84	173 - Bumetanid	224 - Simvastatin	6391.0
85	172 - Furosemid	520 - Paracetamol	6366.0
86	118 - Acetyl salicylic acid	137 - Cyanokobalamintanninkompleks	6360.0
87	10 - Pantoprazol	608 - Zopiklon	6316.0
88	118 - Acetyl salicylic acid	216 - Irbesartan og diuretika	6270.0
89	191 - Amlodipin	213 - Losartan og diuretika	6265.0
90	12 - Esomeprazol	608 - Zopiklon	6265.0
91	224 - Simvastatin	292 - Tamsulosin	6243.0
92	224 - Simvastatin	307 - Prednisolon	6240.0
93	65 - Insulin (human)	118 - Acetylsalisylsyre	6207.0
94	228 - Atorvastatin	314 - Levotyroksinnatrium	6187.0
95	118 - Acetyl salicylic acid	754 - timolol, combinations	6165.0
96	513 - Kodein og paracetamol	608 - Zopiklon	6144.0
97	12 - Esomeprazol	185 - Metoprolol	6104.0
98	111 - Warfarin	201 - Ramipril	6060.0

99	118 - Acetyl salicylic acid	691 - Salbutamol	6048.0
100	307 - Prednisolon	608 - Zopiklon	6030.0
101	118 - Acetyl salicylic acid	226 - Pravastatin	5984.0
102	172 - Furosemid	191 - Amlodipin	5959.0
103	172 - Furosemid	201 - Ramipril	5959.0
104	116 - Klopidogrel	118 - Acetylsalisylsyre	5943.0
105	495 - Alendronsyre	608 - Zopiklon	5911.0
106	608 - Zopiklon	626 - Escitalopram	5658.0
107	185 - Metoprolol	195 - Lerkanidipin	5634.0
108	118 - Acetyl salicylic acid	489 - Allopurinol	5622.0
109	118 - Acetyl salicylic acid	138 - Hydroksokobalamin	5435.0
110	210 - Kandesartan	228 - Atorvastatin	5427.0
111	118 - Acetyl salicylic acid	170 - Bendroflumetiazid og kalium	5420.0
112	224 - Simvastatin	697 - Salmeterol og flutikason	5417.0
113	118 - Acetyl salicylic acid	140 - Folsyre	5406.0
114	111 - Warfarin	191 - Amlodipin	5387.0
115	119 - Dipyridamol	224 - Simvastatin	5368.0
116	111 - Warfarin	118 - Acetylsalisylsyre	5356.0
117	691 - Salbutamol	707 - tiotropium bromide	5335.0
118	118 - Acetyl salicylic acid	698 - Formoterol og budesonid	5324.0
119	118 - Acetyl salicylic acid	755 - latanoprost	5263.0
120	185 - Metoprolol	217 - Kandesartan og diuretika	5225.0
121	11 - Lansoprazol	118 - Acetylsalisylsyre	5208.0
122	118 - Acetyl salicylic acid	215 - Valsartan og diuretika	5208.0
123	12 - Esomeprazol	228 - Atorvastatin	5207.0
124	118 - Acetyl salicylic acid	200 - Lisinopril	5160.0
125	224 - Simvastatin	707 - tiotropium bromide	5134.0
126	191 - Amlodipin	520 - Paracetamol	5115.0
127	111 - Warfarin	173 - Bumetanid	5107.0
128	191 - Amlodipin	314 - Levotyroksinnatrium	5098.0
129	185 - Metoprolol	199 - Enalapril	5088.0
130	9 - Omeprazol	118 - Acetylsalisylsyre	5067.0
131	186 - Atenolol	224 - Simvastatin	5056.0
132	185 - Metoprolol	307 - Prednisolon	5050.0
133	118 - Acetyl salicylic acid	593 - Diazepam	5049.0
134	65 - Insulin (human)	224 - Simvastatin	5011.0
135	194 - Nifedipin	224 - Simvastatin	5002.0
136	10 - Pantoprazol	520 - Paracetamol	4969.0
137	595 - Oksazepam	608 - Zopiklon	4955.0
138	172 - Furosemid	228 - Atorvastatin	4955.0
139	224 - Simvastatin	626 - Escitalopram	4937.0
140	201 - Ramipril	608 - Zopiklon	4929.0
141	173 - Bumetanid	201 - Ramipril	4873.0
142	608 - Zopiklon	737 - Cetirizin	4852.0
143	118 - Acetyl salicylic acid	178 - Hydroklortiazid og kaliumsparende midler	4827.0
144	307 - Prednisolon	520 - Paracetamol	4812.0
145	314 - Levotyroksinnatrium	520 - Paracetamol	4754.0
146	10 - Pantoprazol	228 - Atorvastatin	4751.0
147	185 - Metoprolol	206 - Losartan	4718.0
148	173 - Bumetanid	608 - Zopiklon	4694.0

149	224 - Simvastatin	513 - Kodein og paracetamol	4663.0
150	228 - Atorvastatin	520 - Paracetamol	4662.0
151	118 - Acetyl salicylic acid	240 - Ezetimib	4648.0
152	191 - Amlodipin	217 - Kandesartan og diuretika	4603.0
153	216 - Irbesartan og diuretika	224 - Simvastatin	4582.0
154	118 - Acetylsalisylsyre	595 - Oksazepam	4580.0
155	118 - Acetyl salicylic acid	208 - Valsartan	4575.0
156	691 - Salbutamol	706 - ipratropium bromide	4536.0
157	118 - Acetyl salicylic acid	187 - Bisoprolol	4533.0
158	210 - Kandesartan	608 - Zopiklon	4507.0
159	213 - Losartan og diuretika	228 - Atorvastatin	4489.0
160	191 - Amlodipin	201 - Ramipril	4467.0
161	118 - Acetyl salicylic acid	752 - timolol	4444.0
162	593 - Diazepam	608 - Zopiklon	4433.0
163	185 - Metoprolol	194 - Nifedipin	4407.0
164	118 - Acetyl salicylic acid	203 - Enalapril og diuretika	4407.0
165	12 - Esomeprazol	520 - Paracetamol	4404.0
166	65 - Insulin (human)	70 - Metformin	4387.0
167	172 - Furosemid	314 - Levotyroksinnatrium	4352.0
168	118 - Acetyl salicylic acid	295 - Finasterid	4345.0
169	191 - Amlodipin	210 - Kandesartan	4340.0
170	118 - Acetyl salicylic acid	358 - Metenamin	4336.0
171	116 - Klopidogrel	224 - Simvastatin	4324.0
172	157 - Isosorbidmononitrat	608 - Zopiklon	4311.0
173	224 - Simvastatin	489 - Allopurinol	4303.0
174	118 - Acetylsalisylsyre	189 - Karvedilol	4279.0
175	157 - Isosorbidmononitrat	191 - Amlodipin	4254.0
176	185 - Metoprolol	495 - Alendronsyre	4249.0
177	698 - Formoterol og budesonid	707 - tiotropium bromide	4202.0
178	116 - Klopidogrel	228 - Atorvastatin	4173.0
179	495 - Alendronsyre	520 - Paracetamol	4148.0
180	118 - Acetyl salicylic acid	192 - Felodipin	4129.0
181	73 - Glimepirid	185 - Metoprolol	4098.0
182	157 - Isosorbidmononitrat	172 - Furosemid	4097.0
183	608 - Zopiklon	697 - Salmeterol og flutikason	4092.0
184	754 - timolol, combinations	755 - latanoprost	4086.0
185	185 - Metoprolol	489 - Allopurinol	4046.0
186	224 - Simvastatin	754 - timolol, combinations	4026.0
187	118 - Acetyl salicylic acid	721 - Acetylcystein	4013.0
188	307 - Prednisolon	691 - Salbutamol	4000.0
189	12 - Esomeprazol	191 - Amlodipin	3993.0
190	157 - Isosorbidmononitrat	228 - Atorvastatin	3982.0
191	224 - Simvastatin	691 - Salbutamol	3971.0
192	118 - Acetyl salicylic acid	209 - Irbesartan	3963.0
193	70 - Metformin	172 - Furosemid	3950.0
194	608 - Zopiklon	707 - tiotropium bromide	3944.0
195	213 - Losartan og diuretika	608 - Zopiklon	3942.0
196	185 - Metoprolol	292 - Tamsulosin	3939.0
197	10 - Pantoprazol	191 - Amlodipin	3915.0
198	185 - Metoprolol	737 - Cetirizin	3905.0
199	111 - Warfarin	520 - Paracetamol	3857.0
200	170 - Bendroflumetiazid og kalium	224 - Simvastatin	3855.0

(1)The number before substance indicates node number in th network

Appendix 5: **Top 200 combination used in 2014 network**

No.	Drug 1	Drug 2	No. of times combined
1	125 - Acetylsalisylsyre	234 - Simvastatin	73456.0
2	125 - Acetylsalisylsyre	193 - Metoprolol	47895.0
3	125 - Acetylsalisylsyre	238 - Atorvastatin	46548.0
4	193 - Metoprolol	234 - Simvastatin	32120.0
5	125 - Acetylsalisylsyre	200 - Amlodipin	30796.0
6	125 - Acetylsalisylsyre	609 - Zopiklon	27198.0
7	200 - Amlodipin	234 - Simvastatin	20299.0
8	125 - Acetylsalisylsyre	211 - Ramipril	18871.0
9	193 - Metoprolol	238 - Atorvastatin	18815.0
10	77 - Metformin	125 - Acetylsalisylsyre	17178.0
11	234 - Simvastatin	609 - Zopiklon	16786.0
12	125 - Acetylsalisylsyre	321 - Levotyroksinnatrium	16030.0
13	125 - Acetylsalisylsyre	181 - Furosemid	15970.0
14	125 - Acetylsalisylsyre	523 - Paracetamol	15709.0
15	193 - Metoprolol	200 - Amlodipin	15311.0
16	13 - Pantoprazol	125 - Acetylsalisylsyre	14829.0
17	77 - Metformin	234 - Simvastatin	14080.0
18	125 - Acetylsalisylsyre	220 - Kandesartan	13948.0
19	118 - Warfarin	193 - Metoprolol	13514.0
20	125 - Acetylsalisylsyre	223 - Losartan og diuretika	13063.0
21	193 - Metoprolol	609 - Zopiklon	12973.0
22	125 - Acetylsalisylsyre	164 - Isosorbidmononitrat	12584.0
23	15 - Esomeprazol	125 - Acetylsalisylsyre	12337.0
24	523 - Paracetamol	609 - Zopiklon	11786.0
25	193 - Metoprolol	211 - Ramipril	11621.0
26	211 - Ramipril	234 - Simvastatin	11573.0
27	181 - Furosemid	193 - Metoprolol	11553.0
28	234 - Simvastatin	321 - Levotyroksinnatrium	10938.0
29	118 - Warfarin	234 - Simvastatin	10844.0
30	200 - Amlodipin	238 - Atorvastatin	10742.0
31	181 - Furosemid	234 - Simvastatin	10653.0
32	125 - Acetylsalisylsyre	216 - Losartan	10213.0
33	125 - Acetylsalisylsyre	227 - Kandesartan og diuretika	9953.0
34	125 - Acetylsalisylsyre	126 - Dipyridamol	9669.0
35	238 - Atorvastatin	609 - Zopiklon	9665.0
36	125 - Acetylsalisylsyre	205 - Lerkanidipin	9510.0
37	234 - Simvastatin	523 - Paracetamol	9396.0
38	125 - Acetylsalisylsyre	300 - Tamsulosin	9272.0
39	125 - Acetylsalisylsyre	497 - Alendronsyre	9271.0
40	223 - Losartan og diuretika	234 - Simvastatin	9210.0
41	220 - Kandesartan	234 - Simvastatin	9022.0
42	125 - Acetylsalisylsyre	314 - Prednisolon	9001.0
43	125 - Acetylsalisylsyre	182 - Bumetanid	8925.0
44	13 - Pantoprazol	234 - Simvastatin	8921.0
45	77 - Metformin	193 - Metoprolol	8715.0
46	125 - Acetylsalisylsyre	742 - Cetirizin	8709.0
47	200 - Amlodipin	609 - Zopiklon	8600.0
48	211 - Ramipril	238 - Atorvastatin	8583.0

49	193 - Metoprolol	523 - Paracetamol	8279.0
50	125 - Acetylsalisylsyre	209 - Enalapril	8264.0
51	77 - Metformin	80 - Glimepirid	7971.0
52	321 - Levotyroksinnatrium	609 - Zopiklon	7799.0
53	193 - Metoprolol	321 - Levotyroksinnatrium	7779.0
54	15 - Esomeprazol	234 - Simvastatin	7683.0
55	125 - Acetylsalisylsyre	203 - Nifedipin	7678.0
56	125 - Acetylsalisylsyre	710 - tiotropium bromide	7638.0
57	13 - Pantoprazol	193 - Metoprolol	7630.0
58	182 - Bumetanid	193 - Metoprolol	7325.0
59	147 - Folsyre	467 - Metotreksat	7314.0
60	125 - Acetylsalisylsyre	698 - Salmeterol og flutikason	7231.0
61	164 - Isosorbidmononitrat	193 - Metoprolol	7194.0
62	164 - Isosorbidmononitrat	234 - Simvastatin	7179.0
63	80 - Glimepirid	125 - Acetylsalisylsyre	7153.0
64	181 - Furosemid	609 - Zopiklon	6950.0
65	125 - Acetylsalisylsyre	628 - Escitalopram	6862.0
66	13 - Pantoprazol	609 - Zopiklon	6821.0
67	77 - Metformin	238 - Atorvastatin	6820.0
68	238 - Atorvastatin	321 - Levotyroksinnatrium	6805.0
69	227 - Kandesartan og diuretika	234 - Simvastatin	6776.0
70	216 - Losartan	234 - Simvastatin	6721.0
71	77 - Metformin	200 - Amlodipin	6683.0
72	698 - Salmeterol og flutikason	710 - tiotropium bromide	6627.0
73	118 - Warfarin	238 - Atorvastatin	6524.0
74	193 - Metoprolol	223 - Losartan og diuretika	6357.0
75	13 - Pantoprazol	238 - Atorvastatin	6330.0
76	193 - Metoprolol	220 - Kandesartan	6311.0
77	220 - Kandesartan	238 - Atorvastatin	6216.0
78	209 - Enalapril	234 - Simvastatin	6131.0
79	234 - Simvastatin	497 - Alendronsyre	6108.0
80	205 - Lerkanidipin	234 - Simvastatin	6098.0
81	72 - Insulin (human)	125 - Acetylsalisylsyre	6032.0
82	15 - Esomeprazol	609 - Zopiklon	6025.0
83	15 - Esomeprazol	193 - Metoprolol	5997.0
84	118 - Warfarin	181 - Furosemid	5992.0
85	234 - Simvastatin	742 - Cetirizin	5991.0
86	125 - Acetylsalisylsyre	194 - Atenolol	5982.0
87	234 - Simvastatin	300 - Tamsulosin	5972.0
88	691 - Salbutamol	698 - Salmeterol og flutikason	5961.0
89	181 - Furosemid	523 - Paracetamol	5957.0
90	182 - Bumetanid	234 - Simvastatin	5937.0
91	125 - Acetylsalisylsyre	758 - timolol, combinations	5911.0
92	200 - Amlodipin	223 - Losartan og diuretika	5901.0
93	15 - Esomeprazol	238 - Atorvastatin	5799.0
94	125 - Acetylsalisylsyre	226 - Irbesartan og diuretika	5798.0
95	125 - Acetylsalisylsyre	144 - Cyanokobalamintanninkompleks	5733.0
96	80 - Glimepirid	234 - Simvastatin	5697.0
97	125 - Acetylsalisylsyre	492 - Allopurinol	5561.0
98	125 - Acetylsalisylsyre	145 - Hydroksokobalamin	5545.0
99	497 - Alendronsyre	609 - Zopiklon	5538.0
100	238 - Atorvastatin	523 - Paracetamol	5520.0

101	125 - Acetylsalisylsyre	236 - Pravastatin	5507.0
102	125 - Acetylsalisylsyre	691 - Salbutamol	5458.0
103	118 - Warfarin	609 - Zopiklon	5455.0
104	193 - Metoprolol	205 - Lerkanidipin	5438.0
105	13 - Pantoprazol	523 - Paracetamol	5437.0
106	125 - Acetylsalisylsyre	514 - Kodein og paracetamol	5406.0
107	181 - Furosemid	200 - Amlodipin	5389.0
108	118 - Warfarin	211 - Ramipril	5374.0
109	181 - Furosemid	238 - Atorvastatin	5288.0
110	181 - Furosemid	211 - Ramipril	5277.0
111	314 - Prednisolon	609 - Zopiklon	5237.0
112	125 - Acetylsalisylsyre	699 - Formoterol og budesonid	5161.0
113	125 - Acetylsalisylsyre	147 - Folsyre	5156.0
114	200 - Amlodipin	523 - Paracetamol	5120.0
115	609 - Zopiklon	628 - Escitalopram	5118.0
116	234 - Simvastatin	314 - Prednisolon	5111.0
117	514 - Kodein og paracetamol	609 - Zopiklon	5110.0
118	200 - Amlodipin	321 - Levotyroksinnatrium	5021.0
119	125 - Acetylsalisylsyre	250 - Ezetimib	4999.0
120	125 - Acetylsalisylsyre	225 - Valsartan og diuretika	4975.0
121	182 - Bumetanid	211 - Ramipril	4966.0
122	193 - Metoprolol	227 - Kandesartan og diuretika	4952.0
123	691 - Salbutamol	710 - tiotropium bromide	4946.0
124	125 - Acetylsalisylsyre	759 - latanoprost	4942.0
125	126 - Dipyridamol	234 - Simvastatin	4920.0
126	234 - Simvastatin	698 - Salmeterol og flutikason	4832.0
127	234 - Simvastatin	710 - tiotropium bromide	4825.0
128	223 - Losartan og diuretika	238 - Atorvastatin	4819.0
129	14 - Lansoprazol	125 - Acetylsalisylsyre	4792.0
130	211 - Ramipril	609 - Zopiklon	4762.0
131	321 - Levotyroksinnatrium	523 - Paracetamol	4716.0
132	203 - Nifedipin	234 - Simvastatin	4703.0
133	125 - Acetylsalisylsyre	218 - Valsartan	4685.0
134	118 - Warfarin	182 - Bumetanid	4684.0
135	609 - Zopiklon	742 - Cetirizin	4665.0
136	182 - Bumetanid	609 - Zopiklon	4645.0
137	125 - Acetylsalisylsyre	178 - Bendroflumetiazid og kalium	4615.0
138	125 - Acetylsalisylsyre	210 - Lisinopril	4615.0
139	123 - Klopidogrel	125 - Acetylsalisylsyre	4613.0
140	193 - Metoprolol	209 - Enalapril	4598.0
141	12 - Omeprazol	125 - Acetylsalisylsyre	4592.0
142	118 - Warfarin	200 - Amlodipin	4539.0
143	125 - Acetylsalisylsyre	195 - Bisoprolol	4531.0
144	15 - Esomeprazol	523 - Paracetamol	4529.0
145	72 - Insulin (human)	234 - Simvastatin	4519.0
146	220 - Kandesartan	609 - Zopiklon	4507.0
147	193 - Metoprolol	314 - Prednisolon	4496.0
148	193 - Metoprolol	216 - Losartan	4484.0
149	200 - Amlodipin	227 - Kandesartan og diuretika	4450.0
150	234 - Simvastatin	628 - Escitalopram	4416.0

151	193 - Metoprolol	203 - Nifedipin	4407.0
152	118 - Warfarin	125 - Acetylsalisylsyre	4392.0
153	597 - Oksazepam	609 - Zopiklon	4384.0
154	200 - Amlodipin	211 - Ramipril	4379.0
155	13 - Pantoprazol	200 - Amlodipin	4377.0
156	194 - Atenolol	234 - Simvastatin	4373.0
157	200 - Amlodipin	220 - Kandesartan	4356.0
158	314 - Prednisolon	523 - Paracetamol	4319.0
159	125 - Acetylsalisylsyre	595 - Diazepam	4272.0
160	123 - Klopidogrel	238 - Atorvastatin	4250.0
161	125 - Acetylsalisylsyre	359 - Metenamin	4249.0
162	699 - Formoterol og budesonid	710 - tiotropium bromide	4222.0
163	125 - Acetylsalisylsyre	756 - timolol	4204.0
164	164 - Isosorbidmononitrat	238 - Atorvastatin	4177.0
165	216 - Losartan	238 - Atorvastatin	4150.0
166	125 - Acetylsalisylsyre	303 - Finasterid	4136.0
167	125 - Acetylsalisylsyre	186 - Hydroklortiazid og kaliumsparende midler	4125.0
168	497 - Alendronsyre	523 - Paracetamol	4089.0
169	234 - Simvastatin	492 - Allopurinol	4086.0
170	205 - Lerkanidipin	238 - Atorvastatin	4039.0
171	226 - Irbesartan og diuretika	234 - Simvastatin	4034.0
172	72 - Insulin (human)	77 - Metformin	4026.0
173	125 - Acetylsalisylsyre	597 - Oksazepam	4025.0
174	15 - Esomeprazol	200 - Amlodipin	4022.0
175	13 - Pantoprazol	181 - Furosemid	4012.0
176	227 - Kandesartan og diuretika	238 - Atorvastatin	4004.0
177	125 - Acetylsalisylsyre	213 - Enalapril og diuretika	3979.0
178	691 - Salbutamol	709 - ipratropium bromide	3973.0
179	758 - timolol, combinations	759 - latanoprost	3965.0
180	125 - Acetylsalisylsyre	198 - Karvedilol	3957.0
181	193 - Metoprolol	492 - Allopurinol	3943.0
182	193 - Metoprolol	497 - Alendronsyre	3925.0
183	193 - Metoprolol	300 - Tamsulosin	3923.0
184	193 - Metoprolol	742 - Cetirizin	3907.0
185	181 - Furosemid	321 - Levotyroksinnatrium	3895.0
186	609 - Zopiklon	698 - Salmeterol og flutikason	3849.0
187	609 - Zopiklon	710 - tiotropium bromide	3829.0
188	125 - Acetylsalisylsyre	201 - Felodipin	3826.0
189	164 - Isosorbidmononitrat	609 - Zopiklon	3790.0
190	13 - Pantoprazol	314 - Prednisolon	3777.0
191	182 - Bumetanid	523 - Paracetamol	3775.0
192	164 - Isosorbidmononitrat	200 - Amlodipin	3774.0
193	238 - Atorvastatin	742 - Cetirizin	3750.0
194	234 - Simvastatin	758 - timolol, combinations	3721.0
195	223 - Losartan og diuretika	609 - Zopiklon	3691.0
196	125 - Acetylsalisylsyre	219 - Irbesartan	3683.0
197	200 - Amlodipin	216 - Losartan	3673.0
198	314 - Prednisolon	497 - Alendronsyre	3661.0
199	125 - Acetylsalisylsyre	230 - Valsartan og amlodipin	3647.0
200	234 - Simvastatin	514 - Kodein og paracetamol	3639.0

Appendix 6: Eliminated nodes from the generated comparing network

Unique nodes 2013 network		Unique nodes 2014 network	
ATC	Substeance name	ATC2	Substeance name3
A03AD01	Papaverin	A01AB04	amphotericin B
A04AA03	Tropisetron	A01AD02	benzydamine
A06AD17	sodium phosphate	A02AA04	Magnesiumhydroksid
A10BX03	Nateglinid	A03AA04	Mebeverin
A11CA01	Retinol (Vit A)	A03AB02	Glykopyrroniumbromid
A16AA01	Levokarnitin	A03AD01	Papaverin
B02BA01	Fytomenadion	A03BA01	Atropin
C01BA01	Kinidin	A06AD12	lactitol
C01EB15	trimetazidine	A07AA01	Neomycin
C03CA04	Torasemid	A07AA12	Fidaksomicin
C07AA03	Pindolol	A10BD10	Metformin og saksagliptin
C07AA06	Timolol	A10BD15	Metformin og dapagliflozin
C10AD52	Nikotinsyre, kombinasjoner	A14AB01	Nandrolon
G03AA07	Levonorgestrel og etinyløstradiol	B02BA01	Fytomenadion
G03AA09	Desogestrel og etinyløstradiol	C01BA01	Kinidin
G03AA13	Norelgestromin og etinyløstradiol	C01EB18	Ranolazin
G03AC09	Desogestrel	C02CA01	Prazosin
G03GA01	chorionic gonadotrophin	C03BA08	Metolazon
G03HB01	Cyproteron og østrogen	C07AA03	Pindolol
G04BE04	Johimbin	C07AA06	Timolol
G04BX16	tiopronin	C07AB12	Nebivolol
H01BB02	Oksytocin	C08CA06	Nimodipin
H05AA03	parathyroid hormone	C10AA08	Pitavastatin
H05BA01	calcitonin (salmon synthetic)	G01AF05	Ekonazol
J01AA08	Minosyklin	G03AA07	Levonorgestrel og etinyløstradiol
J01CA01	Ampicillin	G03AA13	Norelgestromin og etinyløstradiol
J01CF05	Flukloksacillin	G03CA57	conjugated estrogens
J01DC02	Cefuroksim	G03GA01	chorionic gonadotrophin
J01DD04	Ceftriakson	G04BX16	tiopronin
J01DH02	Meropenem	H05BA01	calcitonin (salmon synthetic)
J01MA12	Levofloksacin	J01AA08	Minosyklin
J01XA01	Vankomycin	J01DH03	Ertapenem
J02AB02	Ketokonazol	J01MA12	Levofloksacin
J04AM05	Rifampicin, pyrazinamid og isoniazid	J04AB04	Rifabutin
J05AF01	Zidovudin	J05AF01	Zidovudin
J05AF02	Didanosin	J05AF09	Emtricitabin
J05AH01	zanamivir	L01AA01	Syklofosfamid
L01AA01	Syklofosfamid	L01AA02	Klorambucil
L01AA02	Klorambucil	L01AX03	Temozolomid
L01AX03	Temozolomid	L01BC01	Cytarabin
L01BB02	Merkaptopurin	L01XE04	Sunitinib
L01CB01	Etoposid	L01XE18	Ruksolitinib
L01XC02	Rituksimab	L01XE21	Regorafenib
L01XE10	Everolimus	L01XE23	Dabrafenib
L01XX14	Tretinoin	L01XX35	Anagrelid
L01XX17	Topotekan	L03AB03	Interferon gamma
L03AX03	BCG vaccine	L03AX03	BCG vaccine
M05BA01	Etidronsyre	L04AA31	Teriflunomid
M05BB01	Etidronsyre og kalsium, sekvensielle	L04AX06	Pomalidomid
N04AA04	Procyklidin	M01CC01	Penicillamin
N04BX01	Tolkapon	N02AJ13	Tramadol og paracetamol
N05AH05	Asenapin	N02BB02	metamizole sodium
N05BC01	meprobamate	N03AX22	Perampanel
P01AB02	tinidazole	N05AD08	Droperidol
P01BC02	Meflokin	N05CM05	Skopolamin
P02CA03	Albendazol	P01BC02	Meflokin
S01EA01	Adrenalin	R03AC19	Olodaterol
V03AE07	calcium acetate	R03AK10	Vilanterol og flutikasonfuroat
		R03AL04	Indakaterol og glykopyrroniumbromid
		R03DA02	Kolinteofyllinat
		R03DA05	Teofyllinetylendiamin

Appendix 7: Top 200 severe DDI in 2013 network

Unfortunate combinations (DDI) in day 0 network			
No.	**Drug 1**	**Drug 2**	**No. of combinations**
1	61 - Simvastatin	65 - Atorvastatin	2320.0
2	49 - Losartan	53 - Losartan og diuretika	1253.0
3	148 - Kodein og paracetamol	149 - Tramadol	855.0
4	6 - Esomeprazol	15 - Klopidogrel	823.0
5	4 - Pantoprazol	6 - Esomeprazol	603.0
6	61 - Simvastatin	157 - Karbamazepin	480.0
7	35 - Metoprolol	194 - Paroksetin	454.0
8	82 - Pivmecillinam	106 - Metenamin	411.0
9	35 - Metoprolol	44 - Verapamil	380.0
10	213 - Flutikason	216 - Salmeterol og flutikason	359.0
11	6 - Esomeprazol	138 - Naproksen og esomeprazol	352.0
12	212 - Budesonid	217 - Formoterol og budesonid	343.0
13	5 - Lansoprazol	15 - Klopidogrel	308.0
14	131 - Diklofenak	135 - Ibuprofen	305.0
15	179 - Diazepam	180 - Oksazepam	300.0
16	157 - Karbamazepin	183 - Zopiklon	280.0
17	63 - Pravastatin	65 - Atorvastatin	279.0
18	3 - Omeprazol	15 - Klopidogrel	277.0
19	189 - Amitriptylin	197 - Escitalopram	277.0
20	3 - Omeprazol	6 - Esomeprazol	265.0
21	12 - Warfarin	131 - Diklofenak	254.0
22	65 - Atorvastatin	66 - Rosuvastatin	251.0
23	61 - Simvastatin	92 - Erytromycin	220.0
24	181 - Hydroksyzin	197 - Escitalopram	212.0
25	5 - Lansoprazol	6 - Esomeprazol	203.0
26	216 - Salmeterol og flutikason	220 - Flutikason	199.0
27	131 - Diklofenak	138 - Naproksen og esomeprazol	183.0
28	12 - Warfarin	21 - Dabigatran eteksilat	182.0
29	105 - Nitrofurantoin	106 - Metenamin	180.0
30	90 - Trimetoprim	106 - Metenamin	174.0
31	3 - Omeprazol	4 - Pantoprazol	171.0
32	4 - Pantoprazol	5 - Lansoprazol	153.0
33	145 - Oksykodon	147 - Oksykodon og nalokson	151.0
34	12 - Warfarin	22 - Rivaroksaban	150.0
35	12 - Warfarin	135 - Ibuprofen	144.0
36	135 - Ibuprofen	138 - Naproksen og esomeprazol	142.0
37	212 - Budesonid	219 - Budesonid	142.0
38	99 - Ciprofloksacin	106 - Metenamin	135.0
39	12 - Warfarin	136 - Naproksen	129.0
40	12 - Warfarin	138 - Naproksen og esomeprazol	127.0
41	61 - Simvastatin	154 - Fenobarbital	127.0
42	61 - Simvastatin	67 - Simvastatin og ezetimib	124.0
43	61 - Simvastatin	156 - Fenytoin	120.0
44	77 - Doksysyklin	81 - Amoksicillin	118.0
45	77 - Doksysyklin	83 - Fenoksymetylpenicillin	118.0
46	83 - Fenoksymetylpenicillin	106 - Metenamin	118.0
47	15 - Klopidogrel	17 - Dipyridamol	116.0
48	217 - Formoterol og budesonid	219 - Budesonid	115.0
49	35 - Metoprolol	39 - Karvedilol	114.0
50	35 - Metoprolol	37 - Bisoprolol	113.0

51	61 - Simvastatin	63 - Pravastatin	111.0
52	82 - Pivmecillinam	90 - Trimetoprim	110.0
53	35 - Metoprolol	36 - Atenolol	108.0
54	189 - Amitriptylin	193 - Citalopram	106.0
55	189 - Amitriptylin	223 - Alimemazin	105.0
56	213 - Flutikason	220 - Flutikason	103.0
57	34 - Sotalol	35 - Metoprolol	101.0
58	131 - Diklofenak	136 - Naproksen	96.0
59	158 - Levodopa og dekarboksylasehemmer	159 - Levodopa, dekarboksylasehemmer og COMT-hemmer	96.0
60	81 - Amoksicillin	106 - Metenamin	94.0
61	82 - Pivmecillinam	99 - Ciprofloksacin	94.0
62	61 - Simvastatin	66 - Rosuvastatin	93.0
63	174 - Klorprotiksen	197 - Escitalopram	90.0
64	195 - Sertralin	197 - Escitalopram	90.0
65	193 - Citalopram	197 - Escitalopram	89.0
66	135 - Ibuprofen	136 - Naproksen	88.0
67	81 - Amoksicillin	83 - Fenoksymetylpenicillin	87.0
68	81 - Amoksicillin	94 - Klaritromycin	84.0
69	83 - Fenoksymetylpenicillin	92 - Erytromycin	83.0
70	37 - Bisoprolol	44 - Verapamil	82.0
71	12 - Warfarin	132 - Diklofenak, kombinasjoner	81.0
72	154 - Fenobarbital	183 - Zopiklon	80.0
73	65 - Atorvastatin	67 - Simvastatin og ezetimib	79.0
74	28 - Flekainid	197 - Escitalopram	78.0
75	61 - Simvastatin	94 - Klaritromycin	78.0
76	77 - Doksysyklin	106 - Metenamin	78.0
77	35 - Metoprolol	192 - Fluoksetin	77.0
78	82 - Pivmecillinam	105 - Nitrofurantoin	74.0
79	65 - Atorvastatin	154 - Fenobarbital	70.0
80	42 - Nifedipin	157 - Karbamazepin	69.0
81	43 - Lerkanidipin	44 - Verapamil	68.0
82	181 - Hydroksyzin	193 - Citalopram	68.0
83	12 - Warfarin	134 - Meloksikam	66.0
84	132 - Diklofenak, kombinasjoner	135 - Ibuprofen	66.0
85	136 - Naproksen	138 - Naproksen og esomeprazol	66.0
86	187 - Trimipramin	197 - Escitalopram	66.0
87	65 - Atorvastatin	126 - Ciklosporin	65.0
88	132 - Diklofenak, kombinasjoner	138 - Naproksen og esomeprazol	64.0
89	81 - Amoksicillin	99 - Ciprofloksacin	62.0
90	29 - Amiodaron	197 - Escitalopram	61.0
91	83 - Fenoksymetylpenicillin	84 - Dikloksacillin	58.0
92	131 - Diklofenak	133 - Piroksikam	58.0
93	81 - Amoksicillin	82 - Pivmecillinam	57.0
94	43 - Lerkanidipin	126 - Ciklosporin	56.0
95	82 - Pivmecillinam	91 - Sulfametoksazol og trimetoprim	56.0
96	156 - Fenytoin	183 - Zopiklon	56.0
97	83 - Fenoksymetylpenicillin	96 - Klindamycin	55.0
98	91 - Sulfametoksazol og trimetoprim	106 - Metenamin	53.0
99	194 - Paroksetin	197 - Escitalopram	53.0
100	64 - Fluvastatin	65 - Atorvastatin	51.0

101	77 - Doksysyklin	92 - Erytromycin	51.0
102	33 - Propranolol	35 - Metoprolol	50.0
103	181 - Hydroksyzin	189 - Amitriptylin	50.0
104	131 - Diklofenak	132 - Diklofenak, kombinasjoner	49.0
105	15 - Klopidogrel	138 - Naproksen og esomeprazol	48.0
106	83 - Fenoksymetylpenicillin	99 - Ciprofloksacin	47.0
107	82 - Pivmecillinam	83 - Fenoksymetylpenicillin	46.0
108	90 - Trimetoprim	105 - Nitrofurantoin	44.0
109	205 - Donepezil	206 - Rivastigmin	44.0
110	120 - Tamoksifen	123 - Letrozol	42.0
111	36 - Atenolol	44 - Verapamil	40.0
112	131 - Diklofenak	134 - Meloksikam	40.0
113	133 - Piroksikam	135 - Ibuprofen	40.0
114	43 - Lerkanidipin	157 - Karbamazepin	39.0
115	201 - Mirtazapin	228 - Brimonidin	39.0
116	12 - Warfarin	133 - Piroksikam	37.0
117	61 - Simvastatin	126 - Ciklosporin	37.0
118	77 - Doksysyklin	99 - Ciprofloksacin	37.0
119	174 - Klorprotiksen	193 - Citalopram	36.0
120	21 - Dabigatran eteksilat	30 - Dronedaron	35.0
121	61 - Simvastatin	64 - Fluvastatin	35.0
122	133 - Piroksikam	138 - Naproksen og esomeprazol	35.0
123	134 - Meloksikam	135 - Ibuprofen	35.0
124	3 - Omeprazol	5 - Lansoprazol	34.0
125	15 - Klopidogrel	19 - Tikagrelor	34.0
126	39 - Karvedilol	44 - Verapamil	34.0
127	43 - Lerkanidipin	48 - Enalapril og lerkanidipin	34.0
128	165 - Selegilin	166 - Rasagilin	34.0
129	43 - Lerkanidipin	92 - Erytromycin	33.0
130	99 - Ciprofloksacin	105 - Nitrofurantoin	33.0
131	12 - Warfarin	141 - Nabumeton	32.0
132	91 - Sulfametoksazol og trimetoprim	99 - Ciprofloksacin	32.0
133	96 - Klindamycin	99 - Ciprofloksacin	32.0
134	17 - Dipyridamol	140 - Etorikoksib	31.0
135	84 - Dikloksacillin	106 - Metenamin	31.0
136	187 - Trimipramin	223 - Alimemazin	29.0
137	11 - Kaliumsitrat	106 - Metenamin	28.0
138	21 - Dabigatran eteksilat	22 - Rivaroksaban	28.0
139	12 - Warfarin	137 - Ketoprofen	27.0
140	134 - Meloksikam	138 - Naproksen og esomeprazol	27.0
141	170 - Haloperidol	197 - Escitalopram	26.0
142	13 - Dalteparin	22 - Rivaroksaban	25.0
143	15 - Klopidogrel	140 - Etorikoksib	25.0
144	83 - Fenoksymetylpenicillin	91 - Sulfametoksazol og trimetoprim	25.0
145	84 - Dikloksacillin	96 - Klindamycin	25.0
146	90 - Trimetoprim	99 - Ciprofloksacin	25.0
147	200 - Mianserin	228 - Brimonidin	25.0
148	49 - Losartan	156 - Fenytoin	24.0
149	84 - Dikloksacillin	99 - Ciprofloksacin	24.0
150	92 - Erytromycin	106 - Metenamin	24.0

151	131 - Diklofenak	137 - Ketoprofen	24.0
152	181 - Hydroksyzin	205 - Donepezil	24.0
153	186 - Klomipramin	223 - Alimemazin	24.0
154	187 - Trimipramin	193 - Citalopram	24.0
155	189 - Amitriptylin	224 - Prometazin	24.0
156	192 - Fluoksetin	197 - Escitalopram	24.0
157	28 - Flekainid	193 - Citalopram	23.0
158	43 - Lerkanidipin	45 - Diltiazem	23.0
159	77 - Doksysyklin	91 - Sulfametoksazol og trimetoprim	23.0
160	135 - Ibuprofen	137 - Ketoprofen	23.0
161	37 - Bisoprolol	40 - Bisoprolol og tiazider	22.0
162	63 - Pravastatin	66 - Rosuvastatin	22.0
163	81 - Amoksicillin	90 - Trimetoprim	22.0
164	99 - Ciprofloksacin	184 - Melatonin	22.0
165	149 - Tramadol	165 - Selegilin	22.0
166	77 - Doksysyklin	95 - Azitromycin	21.0
167	81 - Amoksicillin	92 - Erytromycin	21.0
168	145 - Oksykodon	157 - Karbamazepin	21.0
169	17 - Dipyridamol	139 - Celekoksib	20.0
170	35 - Metoprolol	38 - Labetalol	20.0
171	77 - Doksysyklin	82 - Pivmecillinam	20.0
172	81 - Amoksicillin	105 - Nitrofurantoin	18.0
173	191 - Doksepin	197 - Escitalopram	18.0
174	193 - Citalopram	195 - Sertralin	18.0
175	6 - Esomeprazol	109 - Flukonazol	17.0
176	13 - Dalteparin	21 - Dabigatran eteksilat	17.0
177	26 - Disopyramid	35 - Metoprolol	17.0
178	34 - Sotalol	39 - Karvedilol	17.0
179	35 - Metoprolol	40 - Bisoprolol og tiazider	17.0
180	36 - Atenolol	39 - Karvedilol	17.0
181	43 - Lerkanidipin	154 - Fenobarbital	17.0
182	123 - Letrozol	124 - Eksemestan	17.0
183	10 - Budesonid	217 - Formoterol og budesonid	16.0
184	14 - Enoksaparin	22 - Rivaroksaban	16.0
185	28 - Flekainid	30 - Dronedaron	16.0
186	41 - Felodipin	157 - Karbamazepin	16.0
187	71 - Fesoterodin	157 - Karbamazepin	16.0
188	81 - Amoksicillin	91 - Sulfametoksazol og trimetoprim	16.0
189	83 - Fenoksymetylpenicillin	87 - Cefaleksin	16.0
190	83 - Fenoksymetylpenicillin	94 - Klaritromycin	16.0
191	135 - Ibuprofen	141 - Nabumeton	16.0
192	174 - Klorprotiksen	181 - Hydroksyzin	16.0
193	181 - Hydroksyzin	187 - Trimipramin	16.0
194	181 - Hydroksyzin	206 - Rivastigmin	16.0
195	189 - Amitriptylin	222 - Deksklorfeniramin	16.0
196	43 - Lerkanidipin	94 - Klaritromycin	15.0
197	44 - Verapamil	92 - Erytromycin	15.0
198	87 - Cefaleksin	106 - Metenamin	15.0
199	131 - Diklofenak	141 - Nabumeton	15.0
200	132 - Diklofenak, kombinasjoner	136 - Naproksen	15.0

Appendix 8: Anatomical groups severe DDI

ATC	Name	No. of DDI involoved in	Notes
Group A anatomical class			
Most interacted ATC codes (combined or none combined)			
A02BD07	Lansoprazol, amoksicillin og klaritromycin	62	1. Proton pump inhibitors: Esmoprazole has more interactions than omeprazole, lansoperzaole and the least is pantoprazole 2. H2-receptor antagonists: Cimetidin, ranitidine, famotidin has same no. Of interactions (19)
A02BD04	Pantoprazol, amoksicillin og klaritromycin	61	
A02BD05	Omeprazol, amoksicillin og klaritromycin	61	
A02BD06	Esomeprazol, amoksicillin og klaritromycin	61	
A02BD09	Lansoprazol, klaritromycin og tinidazol	61	
A02BD11	Pantoprazol, amoksicillin, klaritromycin og metronidazol	61	
A02BA53	Famotidin, kombinasjoner	43	
A06AH03	Naloksegol	39	
A16AX10	Eliglustat	27	
A02AB01	Aluminiumhydroksid	26	
Most interacted ATC codes uncombined (singel active sustance)			
A06AH03	Naloksegol	39	
A16AX10	Eliglustat	27	
A02AB01	Aluminiumhydroksid	26	
A02AB02	Algeldrat	26	
A02AB03	Aluminiumfosfat	26	
Group B anatomical class			
Most interacted ATC codes (combined or none combined)			
B01AA03	Warfarin	90	combinations are rare in this group
B01AC24	Tikagrelor	57	
B01AE07	Dabigatran eteksilat	51	
B01AF01	Rivaroksaban	35	
B01AF02	Apiksaban	33	
B01AC04	Klopidogrel	32	
B01AF03	Edoksaban	27	
B01AE01	Desirudin	25	
B01AE02	Lepirudin	25	
B01AE03	Argatroban	25	
Group C anatomical class			1. Among diuretics: Tolvaptan has most interactions (18). 2. Among Beta-blockers propranolol most DDI with 99 interactions and Labetalol has least with 78 as a single substance. 3. Among Calcium channel blockers Verapamil has most 97 and Nimodipine has least with 22. 4.Among Angiotensin reuptake inhibitors Aliskiren is themost with 75, -sartans are the least 5-4 interactins (C09) 5.Among lipid modifying (C10) simvastatin is most with 81, the leat is Gemfibrozil with 4 (as single substances)
Most interacted ATC codes (combined or none combined)			
C01BA03	Disopyramid	133	
C07FX05	Metoprolol og ivabradin	122	
C07FX06	Karvedilol og ivabradin	120	
C07FB02	Metoprolol og felodipin	114	
C07FB03	Atenolol og nifedipin	114	
C07AA05	Propranolol	99	
C07BA05	Propranolol og tiazider	98	
C07FX01	Propranolol og andre kombinasjoner	98	
C08DA01	Verapamil	97	
C08DA51	Verapamil, kombinasjoner	97	
Most interacted ATC codes uncombined (singel active sustance)			
C01BA03	Disopyramid	133	
C07AA05	Propranolol	99	
C08DA01	Verapamil	97	
C01BA01	Kinidin	94	
C07AA07	Sotalol	92	
C10AA01	Simvastatin	81	
C10AA02	Lovastatin	81	
C07AB02	Metoprolol	80	

Group D anatomical class			
Most interacted ATC codes uncombined (singel active sustance)			
D05AD02	Metoksalen	18	Almost no combinations in this group
D05BA02	Metoksalen	18	
D03BA03	Bromelener	16	
D05BB01	Etretinat	16	
D05BB02	Acitretin	16	
D10AD04	Isotretinoin	15	
D11AH04	Alitretinoin	15	
D07AC09	Budesonid	14	
D01BA02	Terbinafin	5	
Group G anatomical class			
Most interacted ATC codes (combined or none combined)			
G03AB08	Dienogest og østradiol	64	
G03AA14	Nomegestrol og østradiol	63	
G02BB01	Vaginalring med progestogen og østrogen	62	
G03CA01	Etinyløstradiol	62	
G03HB01	Cyproteron og østrogen	62	
G03AA01	Etynodiol og etinyløstradiol	62	
G03AA02	Kingestanol og etinyløstradiol	62	
G03AA06	Norgestrel og etinyløstradiol	62	
G03AA08	Medroksyprogesteron og etinyløstradiol	62	
G03AA12	Drospirenon og etinyløstradiol	62	
Most interacted ATC codes uncombined (singel active sustance)			
G03CA01	Etinyløstradiol	62	1. A lot of combinations in this group (Hormons). 2. Among the Drugs used in erectile dysfunction sildenafil most (42), tadalafil least (31).
G04BE03	Sildenafil	42	
G04BE10	Avanafil	42	
G03AD02	Ulipristal	41	
G03XB02	Ulipristal	41	
G03AC01	Noretisteron	38	
G03AC02	Lynestrenol	38	
G03AC03	Levonorgestrel	38	
G03AC04	Kingestanol	38	
G03AC05	Megestrol	38	
G03AC06	Medroksyprogesteron	38	
G03AC07	Norgestrienon	38	
G03AC08	Etonogestrel	38	
G03AC09	Desogestrel	38	
G03AC10	Drospirenon	38	
G04BE09	Vardenafil	35	
G04BE08	Tadalafil	31	
Group H anatomical class			
Significantly low interactions (cortisones), interactions are mostly with vaccines or immunosuppresents (J,L) groups			
Group J anatomical class			
Most interacted ATC codes			
J07AP01	Tyfoid, oral, levende, svekket	537	1. J02 Antimycotics for systematic use: Most Itraconazol 157, Hakimycin is lowest with 13. 2.J04 Antimycobacterial: Rifampicin and isoniazid 15 many comes with just 1 DDI. 3. J05 Antivirals sys. Use: Telbivudin least with 1 DDI, many combinations. 4. Vaccines J07: most Tyfoid, oral, levende, svekket with absolute most DDI of all ATC 537, least is Yellow fever vac. with 248.
J01FA01	Erytromycin	343	
J01FA09	Klaritromycin	327	
J01MA14	Moksifloksacin	312	
J01XX08	Linezolid	311	
J01XC01	Fusidinsyre	294	
J01XX05	Metenamin	289	
J01BA01	Kloramfenikol	287	
J07AN01	Tuberkulose, levende, svekket	277	
J01MA02	Ciprofloksacin	273	
Antibiotics for systematic use			
ATC	**Antibitioc group name**	**No. of DDI**	
J01A	Tetracyclines	273	
J01B	AMPHENICOLS	287-265	
J01C-J01D	B-lactam	265	
J01E	Sulphonmides	around 260	
J01F	Macrolides	343 Erythromycin, 327 Klarithromycin, Azithromycin 266 all other are 265.	
J01G	Aminoglycosides	268	
J01M	QUINOLONE	265, 266 except Moxifloxacin 312	
J01R-J01X	Combinations and others	265 DDI	

			1. Antineoplastic L01: most Padeliporfi with 192, least are Erlotinib, Sunitinib and Ruksolitinib with (1). 2. Endocrine theraby L02: most Enzalutamid with 111, least Abirateron with 1. 3.Immunostimulants L03: most Histamindihydroklorid with 122, least Peginterferon alfa-2a with (1). 4. Immunosuppressants L04: most Ciklosporin with 58, least Kladribin with (10).
Group L anatomical class			
Most interacted ATC codes			
L01XD07	Padeliporfin	192	
L01XE42	Ribosiklib	134	
L03AX14	Histamindihydroklorid	122	
L02BB04	Enzalutamid	111	
L01XE23	Dabrafenib	110	
L01BA01	Metotreksat	90	
L01XX42	Panobinostat	76	
L01BA04	Pemetreksed	73	
L01XE28	Ceritinib	66	
L01XX46	Olaparib	66	
Group M anatomical class			
Most interacted ATC codes Uncombined			
M01AB01	Indometacin	63	
1. Almost 70% of ATC in this group had around 60 interactions. 2. Coxibs GROUP shows sig. Lower interactions than all the other infalmmatory ATCs. 3. All NSAIDs, Oxicams have equal interactions.			
Group N anatomical class			
Most interacted ATC codes Uncombined			1. Anaethtics N01: most Natriumoksybat with 72, least Alfentanil with (1). 2.Analgesics N02: most Dihydroergotamin with 39, least Cannabinoider with (1) 3. Antiepileptics N03: Metylfenobarbital, Fenobarbital, Primidon, Barbeksaklon, Metarbital most with 207, Beklamid lowest with (1). 4. Anti-parkinson drugs N04: most Selegilin with 32, Melevodopa with lowest 23.
N06AX25	Prikkperikum	335	
N03AA01	Metylfenobarbital	207	
N03AA02	Fenobarbital	207	
N03AA03	Primidon	207	
N03AA04	Barbeksaklon	207	
N03AA30	Metarbital	207	
N03AF01	Karbamazepin	204	
N03AB01	Etotoin	203	
N03AB02	Fenytoin	203	
N03AB03	Aminodifenylhydantoinvaleriansyre	203	
5. PSYCHOLEPTICS N05: highst Hydroksyzin with 87, lowst Klometiazol with (1). 2. PSYCHOANALEPTICS N06: ginkoblad and citalopram comes first with 148 and 83, lowest is Reboksetin with (1).			
Group P anatomical class			No special notes
Group R anatomical class			1. high combinations frequency. 2. Nasal preparations R01: fluticason combination comes with highst DDI 18, while Fenylpropanolamin comes lowst with (13). 3. Throat preparations R02: just one medicine Flurbiprofen comes with highst number of interactions of all with 61 DDI. 4. Obstructive air ways drugs R03: salmetrol highst 18, Roflumilast lowst (1).
Most interacted ATC codes			
R02AX01	Flurbiprofen	61	
R07AX30	Ivakaftor og lumakaftor	53	
R06AX28	Rupatadin	31	
R05DA04	Kodein	25	
R03AK06	Salmeterol og flutikason	23	
R05DA12	Acetyldihydrokodein	23	
R06AB01	Bromfeniramin	22	
R06AB02	Deksklorfeniramin	22	
R06AB03	Dimetinden	22	
R06AB04	Klorfeniramin	22	
5.Cough and cold prep. R05: codein most with 25, least are Etylmorfin, Hydrokodon with 2. 6. Antihistaminic for sys. Use R06: Rupatadin 31 highst, most famous lowest Desloratidine among others with 1 DDI. 7. Others N07: most is Natriumoksybat with 72, many comes lowst with 2 interaction most famous Buprinorphine.			
Group S anatomical class			No special notes
Group V anatomical class			No special notes