The Drug Prescription Process: A Network Medicine Approach

32

Pierpaolo Cavallo, Sergio Pagano, and Luna Carpinelli

32.1 Network Science and Network Medicine

This section presents the definition of Network Science, and its fundamentals and attributes, the main mathematical aspects of the study of networks and the parameters, or quantitative indicators, used to study and analyze a network from a mathematical point of view. It introduces the concept of "Network Medicine," the science that studies biological and medical phenomena from the point of view of networks.

32.1.1 Network Science: Fundamentals and Attributes

A common definition of Network Science is "… a new and emerging scientific discipline that examines the interconnections among diverse physical or engineered networks, information networks, biological networks, cognitive and semantic networks, and social networks" [50]. In simple words, network science is the study of natural and artificial phenomena by representing them as networks, made of nodes and links, and by determining properties, laws, characteristics, and parameters by which the networks are born, evolve, and end or transform their existence. Network Science can be applied to many different fields: physics, biology, psychology, sociology, economics, computer science, etc.

The study of networks has been, almost exclusively, the domain of a branch of discrete mathematics known as graph theory, and the discipline has seen important achievements in some specialized contexts, the most prominent of which are the social sciences. Indeed, the practice of "social networks analysis" started to develop in the 1920s of the twentieth century, and since then has been an important instrument for studying relationships among social entities, for example: the members of a group and their communications; business corporations and their economic trading networks; or nations and their political relationships.

Toward the end of the twentieth century, there was a renewed interest and research in the study of complex networks, with the publication of reference papers on the "small-world" networks [43] and on "scale-free" networks [5]. Complex networks are networks whose structures are irregular, complex, and dynamically evolving in time. Almost any kind of network mentioned at the beginning of the present paragraph (information, biological, cognitive, social, etc.) is a complex network, as reported in another, now classical, review paper [35]. Network Science, initially applied in Social Science Studies, is being adopted by Medicine and Healthcare Organizational studies. A contemporary view is that social perspectives are

P. Cavallo (✉) • S. Pagano • L. Carpinelli
University of Salerno, Via Ponte Don Melillo, 1, 84084 Fisciano (SA), Italy
e-mail: pcavallo@unisa.it

J.P. Sturmberg and C.M. Martin (eds.), *Handbook of Systems and Complexity in Health*,
DOI 10.1007/978-1-4614-4998-0_32,

closely interlinked with healthcare, and that "they remain fundamental for our understanding of health, illness, and care" [36].

32.1.2 Network Study Parameters

A network can be represented as a graph: a graph is a mathematical entity that consists of a set of nodes connected by links. We use the terms "nodes" and "links," but they are also known as "vertices" and "edges," although the two terms, in some notation, are used to indicate different kinds of elements. Figure 32.1 shows a simple example of a network composed of eight nodes and eight links.

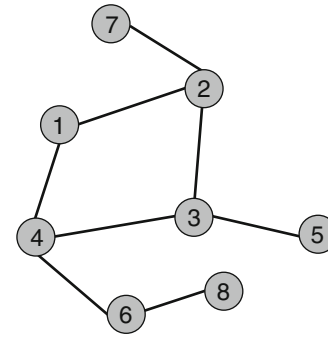

Fig. 32.1 A simple example of a network, composed of 8 nodes and 8 links

In this example, we find a fundamental characteristic of complex networks: the number of links of each node is not constant, as there are nodes with many links (see nodes 2, 3, and 4) and nodes with a small number of links, with the appearance of an insulated individual (see nodes 7 and 8).

Networks are studied with the mathematical instruments of the graph theory, and they have some definite specific features and quantitative parameters. In an undirected graph, the link between two nodes can be considered in either direction; this link is said to be incident, and the two nodes joined are referred to as adjacent or neighboring, while, in a directed graph, the link between two nodes has a specific and irreversible direction. A good example with which to demonstrate the difference between directed and undirected networks is a social one: a parenthood relationship is, for biological and social reasons, a directed one, while a friendship is, commonly, undirected.

Graphs can be unweighted, that is, any link has the same importance, or "weight," or weighted, where each link has a specific "weight": a good example for these parameters could be a road system with and without a toll. In this example, if one has to carry freight on free roads, one would choose the route in terms of shortest distance (unweighted links) on the basis of cost, but if one has to go through toll roads, the route will likely be chosen in terms of lowest cost, summing fuel consumption plus toll costs (weighted links).

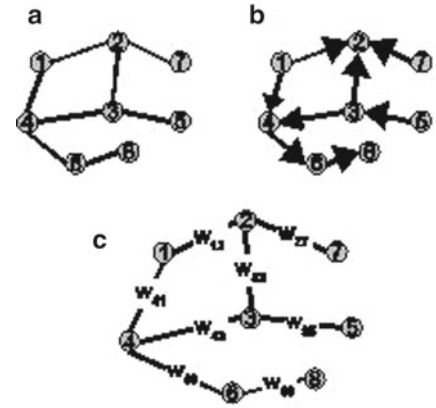

Fig. 32.2 Examples of a simple undirected, directed, and weighted network

Figure 32.2 shows some examples of simple undirected, directed, and weighted networks.

A central concept in graph theory is the possibility of connecting two different nodes of a graph: even if two nodes are not adjacent, they may, nevertheless, be reachable from one to the other, if one jumps from node to node, passing through the available links. This is called a "walk" into the graph, and has a length, that is, defined as the number of edges in the sequence; in graph theory language, a "trail" is a walk in which no link is repeated, while a "path" is a walk in which no node is passed twice. An important parameter of analysis is the "shortest path" or "geodesic distance," that is, the minimal distance between two given nodes, and a graph is said to be "connected"

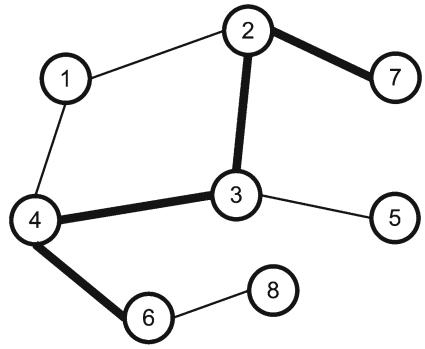

Fig. 32.3 A simple graph with the path between two nodes being highlighted. The distance between the two nodes is four

if, for every pair of distinct nodes, there is a path from one to the other, while if there are nodes present but not reachable from every other node, the graph is said to be "unconnected" or "disconnected." The maximum value of geodesic distance is called the diameter of the graph, as it represents the distance between the two farthest points of the network.

Figure 32.3 shows an example of a simple graph with the path between two nodes highlighted with a thicker line. The distance between the two nodes is four.

Another important parameter for quantitative analysis of a network is the "degree" or "connectivity" of a node. It is the number of links incident with the node; a simple way of explaining this is to compare two airports, a hub with hundreds of flights a day and a small country airport. In terms of degree, measured as the number of airline links, the former will have a degree of hundreds, while the latter will probably have a degree of less than ten.

When we measure the degree of each node in a network, for example, the number of flights on each airport, we can calculate the "degree distribution," that is, the probability that a node chosen at random has a certain degree. For the above example, there are a large number of small airports with a probability of having a small number of flights, while there are a very small number of airports having the probability of a large number of flights and these hubs support most of the activity of the air traffic network.

Table 32.1 describes the most important network parameters, their meanings, and their mathematical symbols.

32.1.3 Types of Networks

Networks can have very different appearances, depending on the number of their nodes and on the average number of the links; we have:

1. Regular networks: usually designed for a certain goal as a chain, a grid, or a regular lattice, e.g., the net of a tennis court.
2. Random networks: networks that are formed by random process: the network we obtain if we scatter a number of buttons across the floor, and tied them in couples at random with thread.
3. Small-world networks: networks that lie somewhere between the extremes of order and randomness, and have the characteristics of short paths and high clustering, i.e., there are many dense groups of nodes, very linked with one another, but single links tie the groups together, making it possible to find a "shortcut" to jump quickly from a group to another.
4. Scale-free networks: networks in which there is a small number of highly connected nodes, the so-called hubs, and a large number of nodes with a low number of links; this architecture has been inspired by the formation of the World Wide Web (WWW). The Barabasi–Albert model of scale-free networks [5] is based on two basic ingredients, growth and preferential attachment, in the sense that a very connected node will have a higher probability to receive many more links than a scarcely connected node.

Figure 32.4 shows examples of regular, random, small-world, and scale-free networks.

Scale-free networks are very important in many fields of scientific research. The scale-free nature of a large number of networks of key scientific interest has been well established [4].

The study of scale-free properties has revealed that the structure and the evolution of networks are inseparable: networks constantly change because new nodes arrive and/or new links are

Table 32.1 Most common terms related to networks

Parameter name	Description
Node or vertex	The objects that are connected together in the network
Edge or link	The connection from one node to another (or the same) in a network
Path	The sequence of links that connect a given node to another one
Shortest path	The smallest number of links between two given nodes
Size	The number of edges in a graph
Diameter	The largest distance in a connected network
Degree	The number of edges connected to a node
Indegree	The number of edges entering a node in a directed network
Outdegree	The number of edges leaving a node in a directed network
Subgraph	A part of a graph containing only part of all vertices, with their links
Complete graph	A graph in which each pair of edges is connected by one link
Weighted graph	A network in which to each link is associated a value, the weight
Strength	An attribute of a node corresponding to the sum of the weights of all the links connected to it
Loop	A link whose endpoints are the same node
Connected graph	It is possible to establish a path from any vertex to any other vertex of the graph
Adjacency matrix	A matrix representation of a network containing for each node all the nodes adjacent to it
Centrality	Measures the relative importance of a vertex within the graph
Closeness centrality	Measures how close, in terms of distance, is a node to all others of the network
Betweenness centrality	Measures the probability of a given node to be in the shortest path between any other randomly chosen nodes in the network
Clustering coefficient	A measure of degree to which nodes in a graph tend to cluster together
Distribution	Arrangement of values taken by one property (typically of nodes or links)
Binning	A way to divide an interval into sections, used to build histograms
Power law	Dependence of a quantity on the power of another, e.g., $P(k) = a\ k^b$
Fat-tail distribution	A distribution of a quantity that does not fall rapidly to zero moving away from the average value

formed and/or older links change, assuming different patterns, and/or assuming different strength. The most prominent example is the WWW that is linked by a very small number of highly connected pages. In the first study of this kind, Barabasi and Albert [5] found that more than 80% of the pages mapped in the WWW had fewer than four links, but a small minority, less than 0.01% of all nodes, had more than 1,000.

In a scale-free network, the distribution of the number of links for each node follows a so-called power law, that is, the probability $P(k)$ for a node to have k connections depends on a power of k, as $P(k) = a\ k^{-b}$ where b is a characteristic exponent.

In other words, in this mathematical relationship, the frequency of an event varies as a negative power of a quantitative attribute of that event, in the above case k is the number of connections of a certain node.

Such networks are characterized by a continuous transition from a large number of nodes having very few connections to few nodes (the hubs) having a very large number of connections.

32.1.4 Network Medicine

Network Medicine can be defined as the science that studies the network effects of biologic and medical occurrences [3]. The studies of Network Medicine range from the network-based understandings of diseases, in terms of

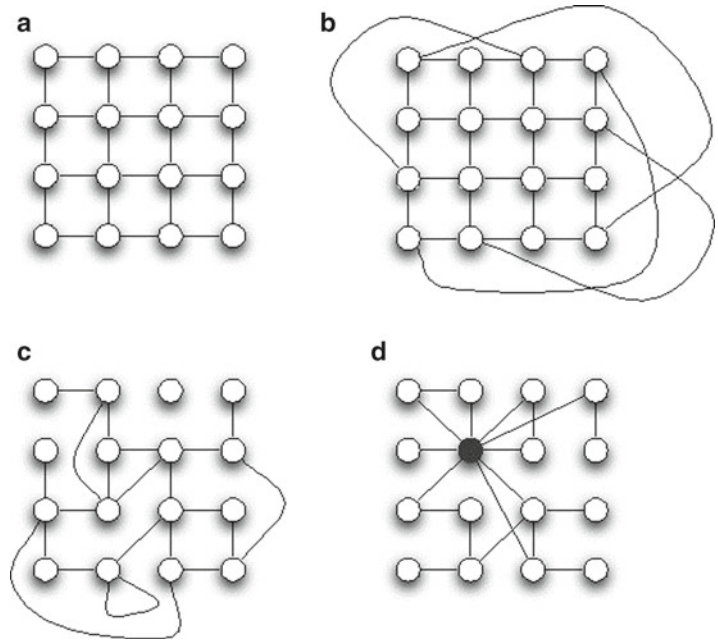

Fig. 32.4 Examples of regular, random, small-world, and scale-free networks

disease classification, to network pharmacology, in order to discover new drugs or to deepen knowledge of existing drugs' mechanisms of action in the "interactome."

To define the interactome, we have to consider that nearly all the cellular components of any living organism exert their functions through interactions with other cellular components; these "partner components" can be located either in the same cell or across cells, and even across different organs.

> In humans, the potential complexity of the resulting network—the human interactome—is daunting: with about 25,000 protein-coding genes, about 1,000 metabolites and an undefined number of distinct proteins and functional RNA molecules, the number of cellular components that serve as the nodes of the interactome easily exceeds 100,000. The number of functionally relevant interactions between the components of this network, representing the links of the interactome, is expected to be much larger [6].

The definition of the interactome, as a network of normal biologic and metabolic processes, is mirrored by the "diseasome," that is, the network of the disease, in which each disease is a node and the links are the common biological features between the diseases.

Considering the interactome from the point of view of the relationships between genes and diseases, a question emerges: are disease genes placed randomly on the interactome, or are there detectable correlations between their location and their network topology? The search for answers has led to a series of hypotheses that tie the interactome to human diseases.

Figure 32.5 shows the relationships between interactome, diseasome, and social networks.

In this scheme, we can see how the interconnections operate: the existence of intricate molecular links between subcellular components implies the possibility that one or more of these components and/or their links might fail. The failure is connected, in turn, to the possibility that a disease, the manifestation of the failure, appears, and there are links into the interactome that make possible to walk through the network, going from node to node. In other words, diseases may not be as independent of each other as medical practitioners currently consider them to be, as it has been demonstrated for the association between obesity and diabetes, in which several genes are associated to both diseases [3], and the presence of obesity elevates the risk of diabetes.

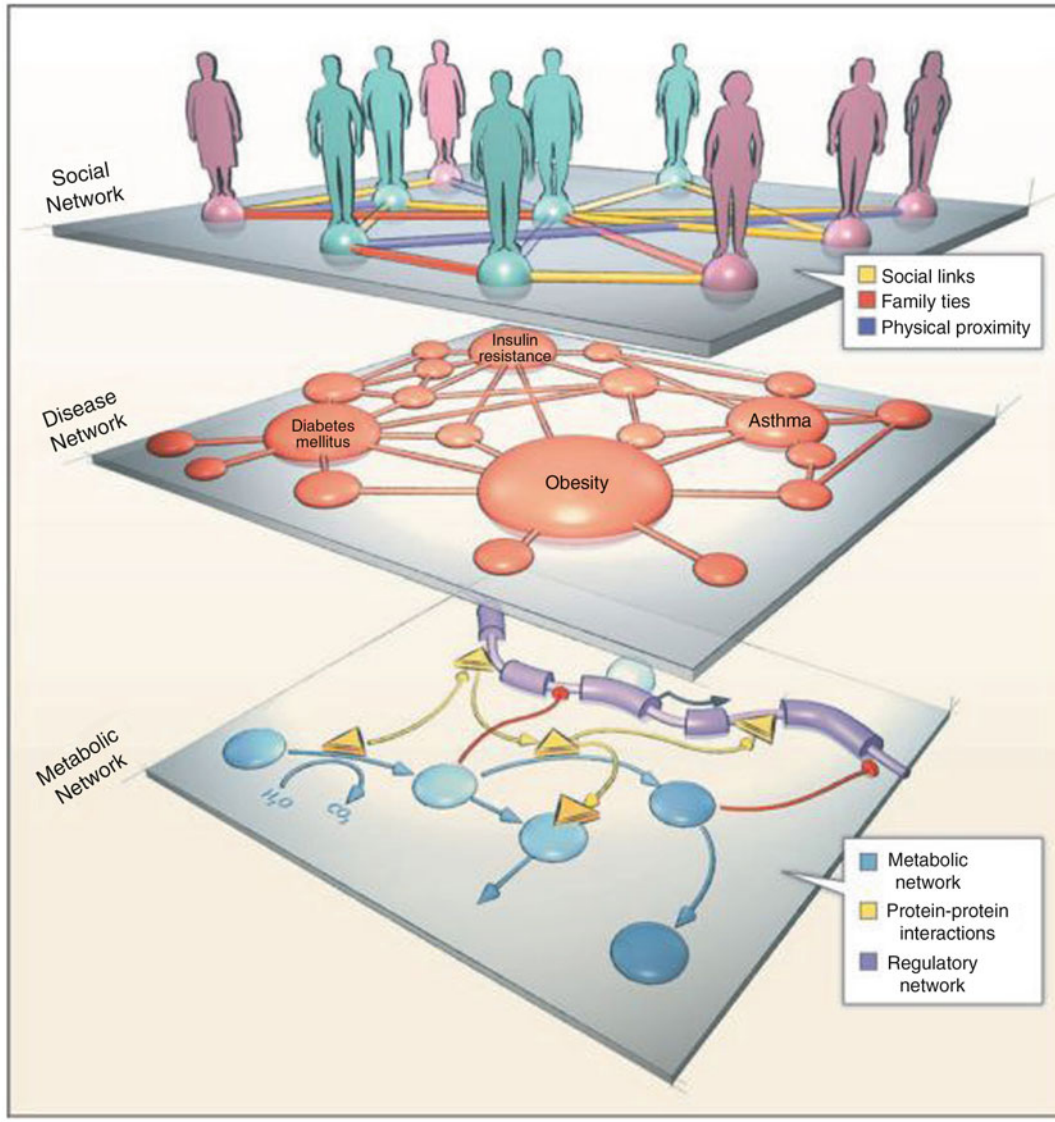

Fig. 32.5 The relationships between interactome, diseasome, and social networks

At the level of our everyday life is the social network. Networks may account for the many environmental and social influences on diseases as well. If we reflect on the numerous and disparate human interactions that encompass social and family links, proximity-based contacts, transportation networks, and the determinants of health, we can appreciate the huge scope for ongoing network research and application in this field.

The Determinants of Health [46] are the factors that combine together to affect the health of individuals and communities, and can be divided into three main groups:

1. The social and economic environment
2. The physical environment
3. The person's individual characteristics and behaviors

These are the main groups, and among them there are modifiable and non-modifiable factors.

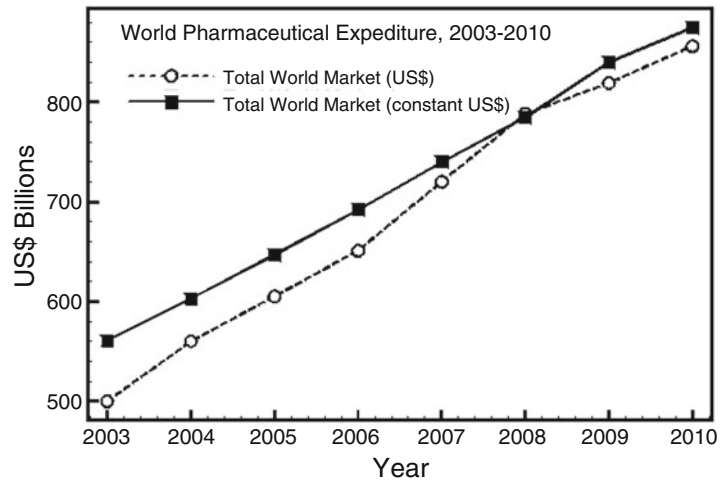

Fig. 32.6 World pharmaceutical expenditure 2003–2010

While one cannot modify one's age or genome, everyone can modify—if willing—his/her behavior, or the environment, at least to some extent.

Our social environment has a deep impact on our behavior. The social networks in which we are embedded and live contain culture, customs, traditions, and beliefs, passed on to us by our family and community, and all influence individual and community health. A clear demonstration of this has been described in a paper on the spread of obesity into a social network [11], in which the results suggest that obesity may spread in social networks in a quantifiable and discernible pattern that depends on the nature of social ties, and on the social distance between two individuals. Among mutual friends—two subjects who both declare each other to be a friend—one becoming obese increases the risk for the other becoming obese by 171%. The social tie between two subjects, each one with his/her own interactome, has acted on the spread of a disease that is largely influenced by behavioral factors.

32.2 Pharmaceutical Expense and Drug Prescription Process

This section is presents a general description of international pharmaceutical expenditure and the process of medical prescribing is summarized in its principal aspects.

32.2.1 Health and Pharmaceutical Expense

Article 25.1 of the Universal Declaration of Human Rights [41] states: "*Everyone has the right to a standard of living adequate for the health of himself and of his family, including food, clothing, housing and medical care and necessary social services.*"

As of year 2011, about 100 countries include health provisions in their constitutions, and access to medications is a fundamental aspect of the right to health. Spending on prescription drugs continues to be an important health care concern, particularly in light of rising pharmaceutical costs, the aging population, and upcoming new "molecular" drugs, which are very promising in terms of higher and wider therapeutic effectiveness and opportunities, but are also very expensive.

The Global Pharmaceutical Market value [21] rose from 500 billion US $ in 2003 to 856 billion US $ in 2010, with a growth forecast rate of 3–6% per year from 2011 to 2015 [20]. Figure 32.6 shows the world pharmaceutical expenditure from 2003 to 2010.

Unfortunately, an amount variably calculated to range from between one-third to half of the US annual health expenditure, i.e., between US $600 and 1,000 billion, is wasted, as it is spent for useless, ineffective, or inappropriate reasons.

Table 32.2 Top sources of inefficiency in medicine, according to World Health Organization (2010)

Source of inefficiency 1	Medicines: underuse of generics and higher than necessary prices for medicines
Common reasons for inefficiency	Inadequate controls on supply-chain agents, prescribers and dispensers; lower perceived efficacy/safety of generic medicines; historical prescribing patterns and inefficient procurement/distribution systems; taxes and duties on medicines; excessive mark-ups.
Ways to address inefficiency	Improve prescribing guidance, information, training and practice. Require, permit or offer incentives for generic substitution. Develop active purchasing based on assessment of costs and benefits of alternatives. Ensure transparency in purchasing and tenders. Remove taxes and duties. Control excessive mark-ups. Monitor and publicize medicine prices.
Source of inefficiency 2	*Medicines: use of substandard and counterfeit medicines*
Common reasons for inefficiency	Inadequate pharmaceutical regulatory structures/mechanisms; weak procurement systems.
Ways to address inefficiency	Strengthen enforcement of quality standards in the manufacture of medicines; carry out product testing; enhance procurement systems with pre-qualification of suppliers.
Source of inefficiency 3	*Medicines: inappropriate and ineffective use*
Common reasons for inefficiency	Inappropriate prescriber incentives and unethical promotion practices; consumer demand/expectations; limited knowledge about therapeutic effects; inadequate regulatory frameworks.
Ways to address inefficiency	Separate prescribing and dispensing functions; regulate promotional activities; improve prescribing guidance, information, training, and practice; disseminate public information.

In addition, it is likely that a large part of the annual world healthcare expenditure of US $5.3 trillion a year follows the same pattern.

Medicines account for 20–30% of global health spending [45], slightly more in low- and middle-income countries, and, therefore, constitute a major part of the budget of whoever is paying for health services. The rise in costs of prescription medicines affects all sectors of the health care industry, including private insurers, public programs, and patients. In recent history, increases in prescription drug costs have outpaced other categories of health care spending. The same report [45] puts the word "medicines" at the very first three places of the "Ten leading sources of inefficiency" in world healthcare. Table 32.2 highlights the detailed description of these first three sources of inefficiency.

The underuse of generics and higher than necessary prices for medicines is connected to a number of factors from market to prescription. This includes factors such as inadequate controls, lower perceived efficacy/safety of generic medicines, and "die-hard" prescribing patterns. There are a number of solutions which can be deployed, such as more prescribing guidance and training, assessment of cost and benefices, and an increase in transparency and monitoring.

The use of substandard and counterfeit medicines, indeed, is connected essentially to markets, being determined by inadequate pharmaceutical regulatory structures/mechanisms, weak procurement systems and, simply, illegal activities, and could be fixed by more control on quality standards. Inappropriate and ineffective use is connected essentially to prescribing, including inappropriate prescriber incentives, unethical promotion practices, induced consumer demands and inadequate regulatory frameworks. This could be addressed by separating the functions between prescribers and pharmacists, and—again, like underuse of generics—by more prescribing guidance and training.

Pharmaceutical expense, thus, is a leading topic in the larger area of healthcare expense, the former being a significant proportion of the latter, but this topic so far has been only barely touched in terms of network theory [52]. Probably a large area of research "is out there," ready to be explored, in which interesting and promising will

be to apply complex systems and networks analysis instruments onto pharmacologic, clinical, and pharmacoeconomic data.

32.2.2 Medical Prescription

Medical prescription significance can vary from country to country, but, in general, its definition can be "*… a health-care program implemented by a medical practitioner in the form of instructions that govern the plan of care for an individual patient*" [49].

Medical prescription may regard a diagnostic test and/or a therapeutic intervention, and can show a very variable range of complexity, from a simple diagnostic prescription for a single test or drug to very complex combination of tests and/or therapies, with a wide range of duration, from a single administration to lifelong therapy.

The prescription of drugs takes place in a complex environment and involves a number of factors, whose impact may be difficult to unravel, as the habits and behavior of the physician, the physician–patient relationship, the pharmaceutical market and its actions/effects, and the decision-making process itself, may be "*partly unconscious, based on heuristics rather than structured analysis of all relevant information, and partly based on socially less desirable motives*" [10].

Prescribing is becoming increasingly complicated, and there is evidence of poor prescribing by a range of doctors across different settings, whether from errors, under-prescribing, over-prescribing, inappropriate or irrational prescribing [1]. Overall the prescribing process is a complex task which from training to ongoing practice, is difficult to separate into its components of theoretical knowledge and safe quality-based performance [32].

Factors affecting prescribing relate to the prescriber, patient and society, medication, and/or other interventions being performed at the same time, practice environment and organization, available information and other external factors [34].

The role of these factors, excluding the prescriber-related ones, can be summarized as follows:

1. *Patient and societal related*. This group includes the patient's family and medical history, which can be related to single, specific and/or undifferentiated, or multiple illnesses. These factors include also the lifestyle, in an enlarged aspect, including not only lifestyle of patients, but also of the relatives/cohabitants, and the preferences for use of OTC (over-the-counter) medication and natural health products.
2. *Medication related*. This group includes the properties of drugs, in terms of their pharmacology, pharmacokinetics, pharmacodynamics, dosage, formulation, taste, route and ease of administration, side effects and cost.
3. *Practice environment and organization-related*. This group of factors includes the influences from the group of peers, norms, and interaction with specialists and/or opinion leaders.

   The practice environment includes both the technical support (patients and drug data) and the human resource support, which is the various possible interactions with other healthcare professions, such as nurses, pharmacists, educators, dieticians, psychologists, and health informatics experts to improve prescribing. A specific role could be played by organizational factors, such as type of practice (individual or group), number, length and frequency of patient visits, availability of access to specialists and diagnostic facilities, and the transport network, for its role to make possible for the patient to move to the physician or to the center indicated by the physician.
4. *Information and other external factors*. This group includes a huge number of sources of information about drugs, medications and every kind of therapeutic intervention.

   Some sources are directed toward the physician, including the detailing (i.e., the office visits of drug sales representatives), but also a growing activity of "cyberdetailing," also called "e-detailing," that is, a form of web-based detailing, and the provision of drug samples; to the medical world, of course, are also directed the classic marketing instruments, like targeted mailings, websites and call centre calls, plus—last but not

least—the specific medical instrument of sponsored scientific conferences.

Some sources are directed to the patients, and are called DTC (or "DTC-ad") that is "direct-to-consumer" advertising; even if this kind of advertising is not permitted in all the countries, or at least is permitted with specific limitations, its role acts everywhere, using Internet, or simply accessing through satellite TV to programs aired by DTC permitting countries.

5. *Other external factors*. This group includes drug reimbursement laws/rules/policies, which can be different between countries with a National Health Systems (NHS) and countries without an NHS.

Even between countries with a national health service, the policies of drug reimbursement, with or without co-payments, vary in relation to the two basic healthcare system designs, the "Bismarck" and the "Beveridge" systems.

The Bismarck system is based primarily on social insurance contributions, while the financing of the Beveridge system comes from tax revenue. These differences also include government policies on physician remuneration, standards of practice from professional organizations, prescribers' concerns about legal liability, regulatory and control measures, and political considerations.

The prescriber-related factors require special attention, starting with the decision-making process [10]. In this process, the physician, rather than the patient, is the key decision maker, but the decision may be subject to a range of influences:

1. Patients can influence prescribing [37], with much greater impact on prescriptions by general practitioners (GPs) than on those by specialists.
2. The physician's prescribing decisions may be influenced by specific demands from relatives, as happens when the prescribing of more drugs is believed to ensure better and quicker improvement [2].
3. Formal and informal interactions with other physicians and medical staff can influence decisions.

In the latter case, the interactions are associated with the type of practice, being stronger in hospital and group practices and weaker for single practitioners and/or for clinical consultants. Hospital pharmacists can greatly influence prescriptions through composition of the hospital formulary to which the prescriber has to adhere.[1]

Moreover, there is evidence that emotive and cognitive factors play an important role in medical prescribing. In many cases, prescribing depends on ready memory [48]. The treatment decision may not follow a scientific rationale, at least for certain illnesses [29], or in the choice of generic drugs [38]. In these cases, attitudes and motivations of GPs play an important role [31].

In order to understand the nature of medical prescribing, it is thus important to identify psychological, professional, and organizational components of medical prescribing processes, in General Practice and over and above, to using a complex systems approach [27].

32.3 Prescription Behavior and Decision Making

This section presents the conceptual framework of the decision-making process from a psychological point of view, and then the practical implications of this process in the daily activity of drug prescription by physicians. The last part presents the patterns and rules of drug prescription and administration, in the general case from an international perspective, and in the specific setting in which the authors' research has been performed.

32.3.1 The Decision-Making Process and Problem Solving

The decision is the process in which an individual, or a group (decision maker), makes a choice between several alternatives considered (options). The necessary condition to define a *decision* is that the decision maker has before him a number of

[1] Note: hospital formularies, on face value a great way to safe on drug expenditure, have been shown to be more costly, as their protagonists invariably have failed to consider "unintended consequences." For more detail, see John Sterman's talk at the IHI: Systems Methodologies for Solving Real-World Problems: Applications in Public Health. March 22, 2007 (http://videocast.nih.gov/Summary.asp?file=13712).

options: if there is only one choice, in the absence of alternatives, the activity is not a decision.

The first studies on decision-making processes begun in the discipline of economics, but since the early 1950s, psychology has studied this question from a different point of view and identified some models that aim to explain the steps by which people make a decision:

1. *The rational–normative model/absolute rationality* [26]. This model assumes that the human is a perfectly rational decision maker who reaches the best solution satisfying the principle of maximizing results.
2. *The heuristic model or limited rationality* [33]. The representation of the decision maker as an "infallible scientist" was inadequate and was replaced with that of a decision maker who has a limited and intentional rationality.
3. *Theory of the prospectus* [39]. The prospect theory is based on the assumptions that people seem to evaluate each possible outcome of a decision on the basis of a reference point (or status quo) as can be, for example, their situation at the time of the decision. This theory gives great importance to the way it is interpreted the decision problem, since the experimental evidence shows that the same problems, but described differently, giving rise to different decisions [40].

Usually, people decide using a problem solving perspective in contexts where it is not easy to readily interpret all the available information [8]. Often the terms decision making and problem solving are considered equivalent. Yet they are two different and distinct activities: the decision making takes place after the process of problem solving has identified a number of possible guidelines. A problem is considered as a gap or a difference between the desired performance and the real one [28].

It is necessary to use a variety of strategies to find the best solution to a problem, usually following these steps [15]:

1. Identify the problem: when we are aware of the problem, we can take action to resolve it as best we can.
2. Define the objectives: a process that describes precisely what we want to obtain.
3. Collect relevant information: first we need to find adequate information. It may be difficult to decide which data are important and which are not. In this process, the collection of relevant data is generally one of the most difficult stages of the process.
4. Identify alternatives: the decision-making process can take place if we have alternatives of action. There is no way, however, to be sure that the best alternative can be included in those considered. It is possible to try to make sure that all "conventional" solutions have been considered, and then try to suggest innovative proposals.
5. Select the criteria for evaluating the better alternative: logically, we want to choose the best alternative. However, this can only be done if we describe the concept of "better." There should be a criteria or a set of criteria to assess which alternative is the best.
6. Building the model: to establish the relationship between the objective, alternatives, data collection, and evaluation criteria.
7. Estimate the expected results of each alternative: the model built is then used to estimate early the outcome of each alternative.
8. Choose the best alternative with respect to the objective: if all other process steps were done accurately, we can make the choice of the best (which best meets the selection criteria adopted).

Certainly when we take decisions we try to gather as much information in an accurate manner that accounts for the costs and benefits for each of the options available to us. This is done through our "intellectual component" that allows us to reduce the uncertainty margins, and then consequently errors, in everyday situations. However, to make a decision in a "totally rational condition" is only possible if we know all the data and the possible interferences of a situation [9]. Emotions play an important role in the decision-making process, they have a "constructive role in the higher forms of human experience." Numerous studies [12,13] have shown that, generally, people turn to emotions or emotional sensations when situations are complex to evaluate or when time constrains the ability to accurately evaluate of each alternative. In the process of alternative selection there is a continuous interaction between evaluation and emotional regulation [18].

32.3.2 Therapeutic Drug Prescription Behavior

The complexity and sensitive nature of the physician's decision-making behavior appears to be more hybrid and less rational in nature than is often assumed in quantitative, model-based analyses of prescription behavior. The decision-making process is typically complex and influenced by several sorts of factors, each in turn grouping multiple influences [10]:

1. The multiple-party-setting
2. The prescriber's multiple goals
3. The prescriber's multiple sources of information overload
4. The multiple diagnostic and therapeutic uncertainties

The multiple-party setting. The physician rather than the patient is the key decision maker. This observation, however, needs to be put in perspective. First, the patients may still influence prescribing, their impact being markedly stronger on prescriptions by GPs than on that by specialists. Secondly, the physician's prescribing decisions may be influenced by specific demands from relatives, formal and informal interactions with other physicians, and other medical staff [19,25].

Multiple goals. A predominant goal pursued by physicians, is to rationally and exclusively assume their medical responsibility. This hypothesis does not confirm the logical assumption that medical goals generally dominate prescribing decisions, other goals—such as the prescriber's personal financial and socio-psychological goals are also found to be of influence [10].

Multiple sources of information overload. The information processing capacity of physicians is structurally insufficient. They cannot possibly process all the information reaching them, from many different scientific and/or commercial sources, and concerning many different aspects like pathologies, treatments, and pharmacological supply. The typical time pressure plaguing physicians—in combination with the high risk and uncertainty of the prescribing decisions—worsens this structural problem [10].

Multiple diagnostic and therapeutic uncertainties. A major element in the physician's decision-making process is the difficulty of assessing the results of a treatment. There are three groups of structural causes of uncertainty [14,24]:

1. Uncertainty concerning patients, caused by such eventualities like subjective, imperfect reporting by patients, numerous—often unknown—exogenous elements affecting the patient, and also the changing set of patients.
2. Uncertainty concerning the pathology, caused by the fact that there might be multiple explanations for specific complaints, multiple complaints resulting from a single pathology, or multiple pathologies coinciding.
3. Uncertainty concerning the effects of drugs, due to the limited opportunity for experimentation throughout a treatment, the possibly multiple effects of drugs and the possible carry-over effects of drugs.

These elements may stimulate the adoption of risk reducing prescribing strategies, like following opinion leadership or remaining brand loyal. When analyzing decision-making processes, on must distinguish between situations that are routine and non-routine, as the criteria of choice are different [10]. In non-routine situations, involving new products and/or new patients with a complex pathological profile, prescribers typically go through a fairly extensive evaluation, and rely on multiple criteria:

1. Disjunctive or conjunctive rules—often based on main medical effects—reduce the number of alternatives.
2. The remaining options are eliminated in a lexicographic fashion, either on an aspect-by-aspect basis or on an alternative-by-alternative basis (product, product form, brand).
3. Compensatory rules intervene to arrive at an actual choice.

In routine situations, the physician will implicitly and/or explicitly go through a learning process. In fact, physicians apparently have a particularly strong need to remain in control of events, even under a high degree of uncertainty, and—as a result—predominantly acquire information through an active rather than a passive learning process. Pharmaceutical companies' marketing mix instruments that both affect non-routine deci-

sions and reinforce or disrupt established routines. Price, advertising, detailing, samples, and gifts may affect prescription rates of the company's drug products [10].

Price. The price is generally unimportant. However, price may be salient in brand selection for very expensive products, or products prescribed for patients on a very tight budget. Also, GPs and younger physicians seem somewhat more alert to price, and increased government pressure is bound to increase price attention in years to come [19].

Advertising. Traditionally, pharmaceutical companies' promotional efforts almost exclusively concentrated on detailing and free product samples directed to physicians. The impact of *advertising* directed to the physician is assessed by considering drug information published in different media (medical journals, official publications) and originating from different sources (pharmaceutical companies vs. government and professional organizations) [17,25,51].

Detailing. In the highly complex and rapidly evolving drug market, sales representatives have an important information function, both for new and existing products [53].

Samples. Samples are, for instance, thought to create commitment toward sales representatives and their company, and to serve as a reminder of the sales representatives' visit once they have left.

Gifts. In addition to samples, many pharmaceutical companies also offer various gifts (sponsoring of conference participation, travel and lodging, medical education, meals, honoraria, promotional material, and other small gifts such as pens) [44], which mainly aim to enhance the long-term relationship between the company and physicians [14]. Like for samples, the fact that giving gifts has more or less become common practice may be responsible for their diminished effectiveness, but may also imply that not giving these advantages may elicit negative reactions [22].

32.3.3 Drug Prescription and Administration Rules

Drug prescription and administration are performed in many different ways, according to local uses, habits, informal rules, and formal laws. The main behavior patterns that can be found are referred to:

1. The authority to prescribe, limited to the physician or extended to other health professionals (nurses, midwives, etc.) and/or to the pharmacist.
2. The authority to supply/sell the drug, limited to the pharmacies or extended to the physician and/or healthcare institutions.

In other words, we can range from healthcare settings in which the physician only can prescribe and the pharmacist only can sell the drug, or supply it to those who have the right to receive it for free, to settings in which a drug can be prescribed by almost any healthcare professional and it can be sold/supplied by pharmacists, physicians, and other professionals.

National or local legislation regulates who can write a prescription: for example, in the United States, all States and Columbia District allow prescription from Medical Doctors but also, with some limitations, from nurses, midwives, dentists, podiatrists, optometrists, and somewhere from clinical pharmacists, while in Thailand the drugs are supplied directly to outpatients by the prescribing physician into the district hospital [30]. Moreover, there are some classes of drugs that are not subject to medical prescription, the so-called over the counter (OTC) drugs. These are not strictly regulated as a prescription drug, and, in certain healthcare settings, prescribers can write prescriptions for OTC drugs because drug benefit plans may reimburse the patient only if the OTC medication is taken under the direction of a medical practitioner.

32.3.3.1 Drug Prescribing in Italy

According to the Italian rules, only medical doctors, i.e., people with a degree in Medicine and registration to the professional order, can prescribe drugs. Drugs to be supplied on behalf of the Italian National Health Service (INHS) can be prescribed only by a medical doctor employed or in agreement with the INHS, and GPs are the only physicians who can prescribe drugs for the outpatients.

Drug prescriptions are made by GPs using prescription sheets on which a maximum of four different drugs can be prescribed, each with a maximum of two pieces (boxes of other kind of package); however, more than one prescription sheet can be given to a patient as a result of a visit.

Drug prescriptions for outpatients can also be made by physicians operating in an institution, such as a hospital, but usually these physicians limit their prescribing to the discharge report, that the patient takes to the GP, who will carry on all continuing prescribing, and this behavior is usual for referrals, too. In fact, the referred specialist usually recommends therapy and/or diagnostic tests, but the prescription of all is always made by the GP.

According to current Italian law, only a pharmacist can sell a drug or supply it on behalf of the INHS, and drugs are divided into three categories:

1. Type A are supplied to patients by pharmacies free of charge
2. Type B are supplied after a co-payment (so-called ticket)
3. Type C are sold after the full payment, but their price is controlled by the INHS

Also patients are divided into categories, in respect of their right to receive drugs without co-payment: children up to 6 and adults over 65, if their income (family income for the children) is under a certain threshold, do not have to pay anything, the so-called ticket exemption. Ticket exemption is also provided, regardless of age and/or income, for specific diseases carrying patients, and these pathologies are typically chronic and/or rare diseases, such as diabetes, adrenoleukodystrophy, Alzheimer disease, rheumatoid arthritis, etc., officially listed.

The nominal difference between the amount paid by patients and the cost of drugs is covered by the INHS, which in turn expects a tight surveillance on the amount and type of prescriptions made by GPs. This complex situation changes in time, as new drugs and therapies are introduced, ticket exemption rules are modified and socio-economic conditions vary.

32.4 An Application of Network Medicine: The Drug Prescription Network

As an example of a Network Medicine study in a Public Health setting, a set of drug prescription data from 99 GPs, working in Italy and covering a 6-month time period, has been studied and analyzed. The data set, containing a total of 42,965 consultations and 631,232 prescribed drugs, has been transformed into a drug prescription network, where each drug is a node, and different drugs prescribed to the same patient on the same day, are linked together. The resulting networks, describing the entire population or subgroups by patient's age and gender, have been analyzed using the tools of network theory.

32.4.1 Introduction

Different types of drug networks can be built [52]. In our study model, it can be described as consisting of two elements: drugs (nodes) and their contemporary prescription for a given patient (links).

In this network model, the link between two drugs, prescribed at the same time in the same patient, can be also called "co-prescription." As in general Network Science studies, once all the nodes (drugs) and links (co-prescription) are known, one can draw pictures of the network, measure its parameters and properties, and discern every node location within it. Each node, thus, is placed in a "co-prescription" space, analogous to a social space, as mapped by social networks methods, or even to a geographic space, as mapped by photographs or drawings.

The rationale of our research has been to consider the drug prescription process from the point of view of its topology, using single drugs as nodes, and their co-prescription for the same patient at the same moment, as links.

Such an approach could make possible to represent and measure relationships between drugs, as there could possibly be "hub drugs," i.e.,

Table 32.3 Summary of data used in this research

Total	Patients	Prescriptions	Nodes	Links
All ages	42,965	631,232	964	52,915
Age < 30	6,882	35,052	494	3,398
30 < age < 60	20,515	196,787	820	23,775
Age > 60	17,177	399,393	830	39,580
	Males			
All ages	19,321	281,435	794	29,864
age < 30	3,297	16,078	372	1,709
30 < age < 60	9,290	89,129	664	12,801
age > 60	7,656	176,228	697	22,730
	Females			
All ages	24,832	349,797	896	37,356
Age < 30	3,793	18,974	400	2,155
30 < age < 60	11,978	107,658	743	15,438
Age > 60	10,212	223,165	759	28,506

drugs that are often prescribed in association with other drugs, and "isolated drugs," i.e., drugs usually prescribed alone. Moreover, the utilization of hub drugs could change among different groups of patients, as the pathology changes between different genders and age groups. This leads to the need to measure and represent different patterns of drug prescription network in different subgroups.

32.4.2 Materials and Methods

32.4.2.1 Prescription Data Used

The networks we have built are based on the set of prescriptions made by a group of 99 GPs operating in Salerno, a city of 140,000 inhabitants in southern Italy, in the first 6 months of year 2009. The Italian rules for drug prescriptions allow a maximum number of drugs for each prescription sheet, but more than one prescription sheet can be given to a patient as result of a visit. The total number of drug prescriptions collected is 631,232 corresponding to 42,965 patient consultations. The data have been collected from the database of "Consorzio Mega Ellas," a GP medical association based in Salerno, including a total of 150 physicians, and treated in the full respect of current legislation on privacy.

32.4.2.2 Network Construction

The rationale for linking the network nodes is the following: two drugs are connected if they have been prescribed to the same patient during the same medical consultation. The number of times two given drugs have been co-prescribed is recorded as link weight. Similarly the number of times a drug is prescribed, alone and in association, is also computed and associated to each node. These procedures resulted in a network of 964 nodes and 52,915 links. By separating the patients by gender and age (in the ranges 0–30, 30–60, and over 60 years), we have built several sub-networks to investigate possible effects due to patient characteristics.

The main characteristics of the networks obtained are reported in Table 32.3.

The obtained networks can be graphically represented in many different ways, and this processing has been performed using "Pajek" software [7], a free large network analysis and visualization tool.

32.4.2.3 Coding: The Anatomical Therapeutic Chemical Classification System

From the ensemble of prescriptions we have build several networks relating the different drugs. The nodes of the networks are made by the drugs, identified by their common name and ATC code.

Table 32.4 Description of ATC code at anatomical level

ATC code	Anatomical region affected
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	Antiinfectives 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

The Anatomical Therapeutic Chemical Classification (ATCC) System [47] is used for the classification of drugs. It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC), and was first published in 1976. In the ATC classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties.

Drugs are classified in groups at five different levels: at the first level (anatomical) the drugs are divided into 14 main groups, shown in Table 32.4.

The following four levels are the therapeutic subgroup (second level), the pharmacological subgroup (third level), the chemical subgroup (fourth levels), and the chemical substance (fifth level).

Table 32.5 shows an example of the ATC code structure for a common diabetic drug.

In the Appendix, the complete list of ATC codes at level 2 is reported.

32.4.3 Results

The appearance of a network can be very complex even if suggestive: Fig. 32.7 shows drug network at ATC level 2.

Figure 32.7 (left) shows that the network is a complete graph, i.e., all the nodes at ATC level 2 are connected to each other, although the links have different weights, because each drug of each ATC group has been prescribed with each of the other different ATC groups.

If we remove the lower 10% in weight links, that are the less frequent co-prescriptions, we obtain a very different picture of the network, as shown in Fig. 32.7 (right). In this representation, the strong links between drugs belonging to the A (alimentary tract), B (blood), C (cardiovascular), and J (infection) groups are clearly evident.

In order to extract more quantitative information on the way this network is formed, the network analysis tools have been used, and the results are reported in the following.

32.4.3.1 Scale Invariance in Drug Co-Prescription Network

The graphic representation of networks can be very suggestive but, sometimes, not very informative. Important information on the network connectivity is given by the degree distribution,

Table 32.5 Description of the ATC code structure

ATC code	Description
A	Alimentary tract and metabolism (first level, anatomical main group)
A10	Drugs used in diabetes (second level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins (third level, pharmacological subgroup)
A10BA	Biguanides (fourth level, chemical subgroup)
A10BA02	Metformin (fifth level, chemical substance)

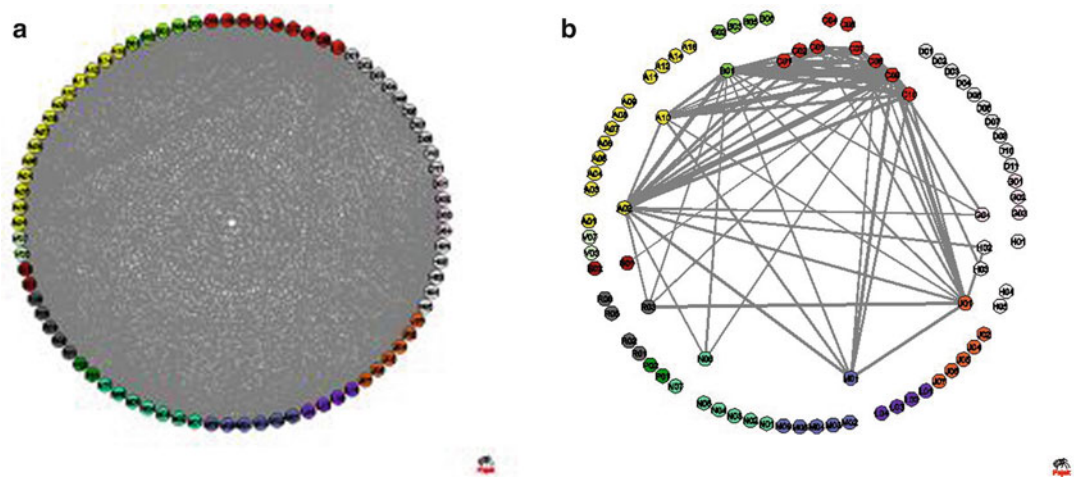

Fig. 32.7 The network is a complete graph (*left*), removing the lower 10% in weight links, shows the strong links between drugs belonging to the A (alimentary tract), B (blood), C (cardiovascular), and J (infection)

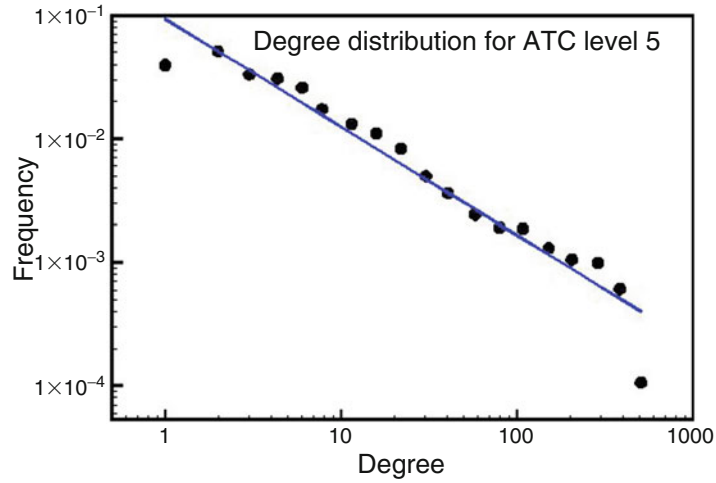

Fig. 32.8 The network of drug co-prescription shows a scale-free behavior

i.e., the relationship between the number of connections (degree; k) of a node and the relative frequency in the network.

Regular networks have a very narrow degree distribution, while random networks show an average degree value, with a given spread around it. Scale-free networks show a characteristic power law dependence of the degree distribution that appears as a negative slope line in a log–log plot.

Surprisingly, the network of drug co-prescription shows a marked scale-free behavior, as shown in Fig. 32.8.

By looking at Fig. 32.8, we note that the degree distribution data points are very well aligned on a line, with the exclusion of the very first and last, a fact due to the finite size of the network. The best fit of the data in log scale gives a slope of -0.88 ± 0.05.

In weighted networks, links do not have the same importance: some links are more important than others, i.e., have a higher weight. In such case, a parameter that could better describe the way the network is connected is the strength, defined as the sum of the connections reaching a node, each multiplied by its weight.

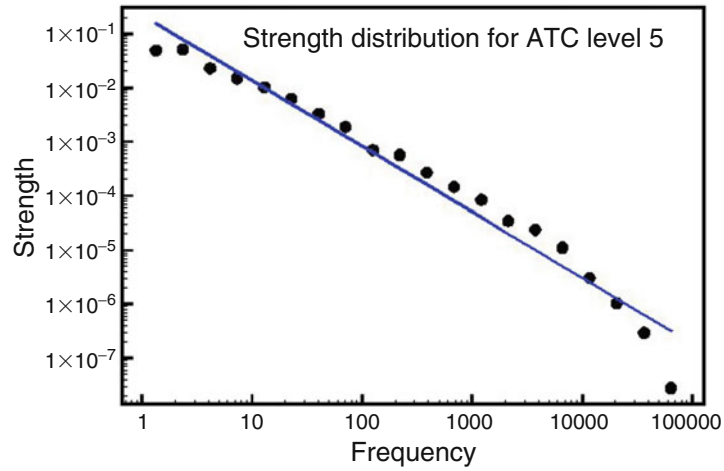

Fig. 32.9 The strength distribution of the drug co-prescription network shows a scale-free behavior

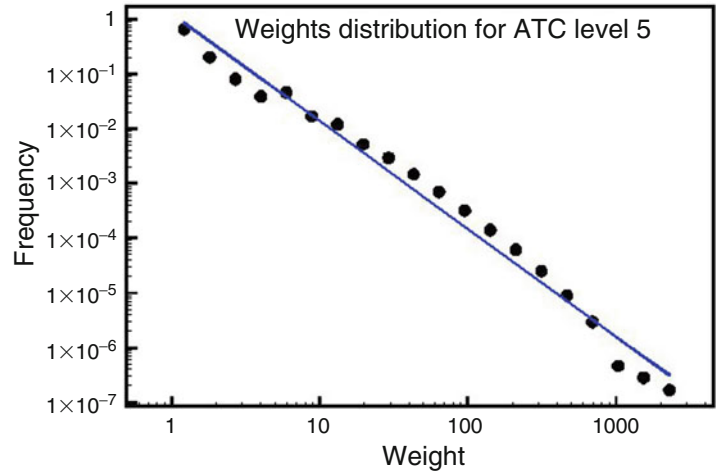

Fig. 32.10 The weight distribution of the drug co-prescription network shows a scale-free behavior

In all networks considered here the links have a weight given by the number of co-prescriptions, therefore an analysis of the strength distribution has also been performed. As a result, the same scale-free behavior, observed for the degree distribution, has been found, as shown in Fig. 32.9, with a characteristic exponent of -1.25 ± 0.06.

Another characteristic often studied in networks is, besides the strength, the weight distribution. Figure 32.10 shows such distribution for the co-prescription network studied.

Also in this case, a clear power law dependence is observed, with a characteristic slope, very close to -2 (-1.97 ± 0.06).

Although all the different graphs in Figs. 32.8–32.10 show a clear linear dependence with a negative slope, for the type of networks considered here, where the links are weighted, the relevant figure for investigating the possible power law dependence of the connections distributions is Fig. 32.9, from which the scale invariance property is maintained over more than six orders of magnitude in the frequency.

By repeating the same analysis in the sub-networks obtained by separating by gender and by age range, we have observed that there is a decisive dependence of the strength distribution exponent (the slopes in Fig. 32.9) on the age range, while there is no significant dependence on gender, as summarized in Table 32.6.

Looking at Table 32.6 it appears that the exponents shows no dependence on the gender and a weak, but significant dependence on the age range of the patients.

Table 32.6 Strength distribution of the networks separated exponents by age and gender

Strength distribution exponent	All	Age < 30	30 < Age < 60	Age > 60
All	−1.25 ± 0.06	−1.52 ± 0.06	−1.29 ± 0.07	−1.27 ± 0.06
Males	−1.27 ± 0.06	−1.57 ± 0.06	−1.35 ± 0.08	−1.30 ± 0.07
Females	−1.27 ± 0.06	−1.58 ± 0.07	−1.27 ± 0.06	−1.29 ± 0.06

Table 32.7 The ten most prescribed drugs at the ATC2 level for each gender group

ATC2	Total				Males				Females			
Most prescribed	All ages	<30	30–60	>60	All ages	<30	30–60	>60	All ages	<30	30–60	>60
1	C09	J01	J01	C09	C09	J01	C09	C09	C09	J01	J01	C09
2	J01	R06	C09	B01	J01	R06	J01	B01	J01	R06	C09	B01
3	A02	H02	A02	A02	B01	N03	A02	A02	A02	G03	M01	A02
4	B01	N03	M01	J01	A02	R03	C10	J01	B01	H02	A02	J01
5	M01	R03	C10	C10	C10	H02	M01	G04	M01	A02	N06	A10
6	C10	A02	C07	A10	A10	A02	A10	C10	A10	R03	H03	C10
7	A10	G03	A10	C08	G04	R01	B01	A10	C10	N03	C07	M01
8	C08	R01	B01	M01	C08	M01	C07	C08	C07	B03	G03	C08
9	C07	M01	N06	C07	M01	N06	C08	R03	C08	R01	C10	C07
10	R03	N06	C08	C01	C07	A07	N03	C07	N06	M01	A10	C03

Table 32.8 The ten most co-prescribed drugs at the ATC2 level for each sex/gender group

ATC2	Total				Males				Females			
Most co-prescribed	All ages	<30	30–60	>60	All ages	<30	30–60	>60	all ages	<30	30–60	>60
1	C09	J01	C09	C09	C09	J01	C09	C09	C09	J01	C09	C09
2	B01	H02	J01	B01	B01	H02	C10	B01	B01	H02	J01	B01
3	A02	R03	A02	A02	C10	R03	B01	A02	A02	R03	A02	A02
4	C10	R06	C10	C10	A02	R06	A02	C10	C10	R06	M01	C10
5	A10	R01	B01	A10	A10	R01	C07	C08	A10	R01	C07	A10
6	J01	A02	C07	C08	C08	A02	A10	A10	J01	A02	B01	C08
7	C08	M01	A10	C03	C07	N03	J01	G04	C08	G03	C10	C03
8	C07	N03	M01	C01	J01	M01	C08	C01	C07	M01	A10	C07
9	C03	G03	C08	C07	G04	N06	M01	C03	M01	B03	N06	C01
10	M01	N06	H02	J01	C03	A07	C03	C07	C03	N03	H03	M01

Although a model connecting strength distribution exponents to patient characteristics (age and gender) does not exist to date, Table 32.6 data suggest a possible connection between drug network characteristics and age-related disease epidemiology.

32.4.3.2 Most Prescribed Versus Most Co-Prescribed

The scale-free behavior of the investigated drug networks suggest the existence of "hub drugs," i.e., drugs which are most frequently prescribed with others. To investigate this phenomenon, the drug co-prescription networks represented at ATC level 2 have been analyzed. The results are summarized in Table 32.7, where the top ten most prescribed drugs are listed for all the sub-networks obtained separating the population by age and gender.

Conversely, in Table 32.8 the top ten most co-prescribed drugs are listed for all the sub-networks obtained separating the population by age and gender.

In other words, Table 32.7 shows statistical information on drug prescription, while Table 32.8 reports a connection-related information, typical of network analysis.

In order to further exploit the information from network connections, the "nearest neighbors" of the most co-prescribed drugs, always at ATC level 2, are reported in in Table 32.9.

Table 32.9 Drugs to which are connected the most co-prescribed drug for each gender group

	Total				Males				Females			
ATC2	All ages	<30	30–60	>60	All ages	<30	30–60	>60	All ages	<30	30–60	>60
Most Co-prescribed	C09	J01	C09	C09	C09	J01	C09	C09	C09	J01	C09	C09
To whom is connected in decreasing order	B01	H02	C07	B01	B01	H02	C10	B01	B01	H02	C07	B01
	C10	R03	C10	A02	C10	R03	B01	C10	A02	R03	A10	A02
	A02	R01	B01	C10	C08	R01	C07	C08	C10	R01	C10	C10
	C08		C08	C08	A02		C08	A02	A10		C08	A10
	A10		A10	A10	A10		A10	A10	C08		B01	C08
	C07		A02	C07	C07		A02	G04	C07		A02	C07
			J01					C07			J01	

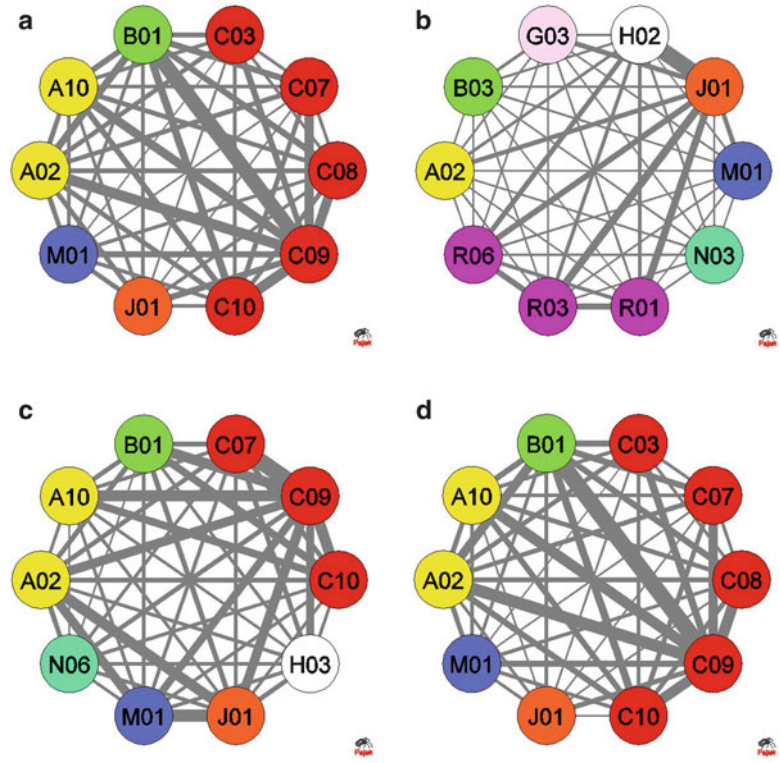

Fig. 32.11 The top ten co-prescribed drugs at ATC level 2, gender by age

For each sub-network analyzed the most co-prescribed drug is presented in the first row of Table 32.9, and, in the corresponding column are listed the drugs with which the head drug is connected, in decreasing order. As an example, for "Males" with age "under 30," the most prescribed drug group, J01 (antibacterials for systemic use) results to be co-prescribed mostly with group H02 (corticosteroids for systemic use), then with R03 (drugs for obstructive airway diseases), and then with R01 (nasal preparations).

This finding is consistent with epidemiological experience that relates the highest demand of drugs for this age/gender group to infections, more likely to happen in the respiratory tract.

In order to better visualize the data of Table 32.9, in Figs. 32.11 and 32.12 a graphic representation of the top ten co-prescribed drugs at ATC level 2 are shown, separately by age and gender.

The circles in Figs. 32.11 and 32.12 represent the nodes, i.e., the most co-prescribed drugs. The color/gray shade indicates the anatomical drug

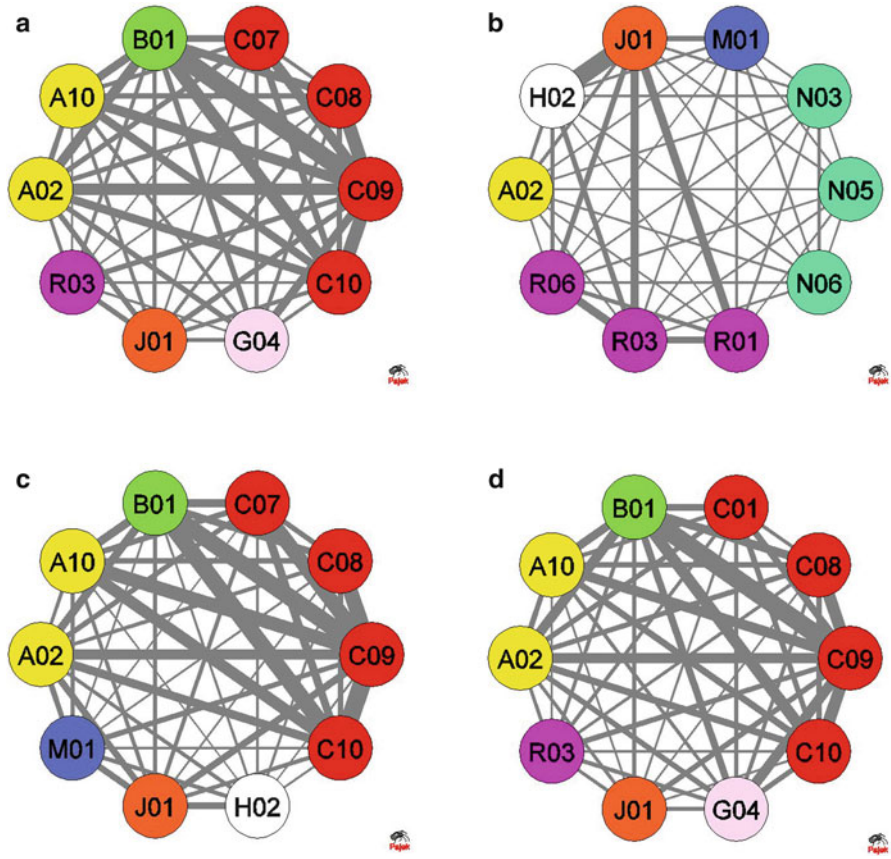

Fig. 32.12 The top ten co-prescribed drugs at ATC level 2, gender by age

group (ATC level 1); while the ATC level 2 code is written in the node. The link thickness is proportional to the number of times the two drugs have been co-prescribed.

This representation shows in a very clear way the difference between age/gender drug co-prescription: in other words, the data commented above, related to the "Males/under 30" column of Table 32.9, are graphically shown in Fig. 32.12, top right.

32.5 Discussion

32.5.1 Significance of Scale Invariance

The main result of this work is the discovery that the network formed by the drugs co-prescription to the patients by GP is scale invariant.

To date there are very few theoretical models that produce scale invariant networks. The most considered is the "Preferential Attachment" network [5,16,23,42].

Within the preferential attachment model, a network is build by adding one node at a time at random in the network, but with a definite probability. In particular the probability that a node is linked to a target node depends linearly on the degree of the target node. The resulting network [5] is a scale free one with a scaling exponent equal to three. We note however that the value of the scaling exponent may depend on the specific choice of relation between node degree and linking probability.

In our case the exponent is always between one and two.

An interpretation of the preferential attachment, in the framework of this work, could be

the following: when confronted with the necessity of prescribing a relatively new drug, i.e., a drug for which all adverse interactions may not be known yet, a general practitioner tends to co-prescribe it with it known drugs, i.e., drugs for which there exist a well-known history of adverse interactions. In essence, a new drug is co-prescribed with higher probability together with drugs that have been safely co-prescribed many other times before, rather than with more rarely used ones.

32.5.2 Prescription Versus Co-Prescription Frequency

From the comparison of Table 32.7 (most prescribed) and Table 32.8 (most co-prescribed) it stems out that there are no large differences between the most prescribed drug class and the most co-prescribed ones, with the notably difference of J01 and possibly R01 and M01.

Drugs of J01 group are antibacterials for systemic use, and they are, for both genders:

1. Highly ranked either as most prescribed and most co-prescribed in lower (0–30) and middle (30–60) age groups.
2. Relatively highly ranked as most prescribed, and low ranked as most co-prescribed, in the older age group (over 60).

This finding could be consistent with the fact that in older patients antibacterials are mostly associated with urinary tract infections, as suggested by general practitioners' experience. In such case, the antibacterial prescription is less frequently associated with other drugs. Conversely, in younger patients antibacterials are mostly associated with respiratory tract infections, and the prescriptions are frequently associated with other drugs.

However the purely statistical information on the most prescribed drug class, does not tell with which other drug it has been prescribed. This information is instead easily obtainable from the network analysis, as shown in Table 32.9, and even better visually in Figs. 32.11 and 32.12.

The table reports the drug classes co-prescribed with the most co-prescribed drug (row 1). In each column are reported only the drug classes with the higher frequency of co-prescription.

Looking at the table and comparing the different sex and age groups, few peculiarities pop up.

For the youngest age group (<30) there is no difference between genders: the most prescribed drug class (alone and in association) is J01 (antibacterials for systemic use) and is always associated to R03 (drugs for obstructive airway diseases) and R01 (nasal preparations).

For the intermediate age range (30–60) there is a notable difference in the frequency of co-prescription of B01 (antithrombotic agents) and A10 (drugs used in diabetes), which is reversed for the two genders.

A somewhat similar effect can be seen in the higher age range (>60) with C02 (antihypertensives) and A02 (drugs for acid-related disorders) having inverted frequencies for the two genders, and the appearance of G04 (urologicals) among the most frequently co-prescribed drugs for males.

32.6 Conclusions

Network Medicine is a new concept that can be exploited in different fields—from the network-based study of diseases to network pharmacology. Studies are currently conducted horizontally at one of the three levels, the interactome, the diseasome, and the social network, but the future will see vertical studies too, connecting the three levels.

These studies will offer a greater knowledge not only of the network molecular mechanisms of physiology and pathology, but also of the relationships between molecular and social mechanisms, which are responsible for the social transmissibility of diseases, once considered "non-transmissible," like obesity, diabetes, ischemic heart disease, various cancers, and so on.

A large part of global health spending is accounted for by medicines, and a large part of this expenditure is led by general practitioners' prescribing. Prescribing, not only for drugs but also for diagnostic tests, is a complex process, that takes place in a complex environment, and involves a large number of factors, related to the knowledge,

professionalism, and culture of the prescriber and their health system context, but also on patient's personal, social, and cultural features.

Emotive factors can play a central role in this process, but, again, the social network of the physician and the patient can make it easier or more difficult to decide on a correct, effective drug choice, which can lead to better or worse results in terms of health outcomes and healthcare expenditure.

Moreover, different settings and prescribing rules, incentives and constraints, throughout the world can be considered as additional complications, but also as a promising ground of research, in which network science instruments can help to find simple answers to complex questions.

The experimental part of the present chapter has investigated a drug co-prescription network obtained from a database of 99 GPs which contained more than 600,000 drug prescriptions. The most interesting result is that all the drug prescription networks show scale invariance behavior, with characteristic exponents related to the patients age but not to gender; this finding is new, and could be related to a prescribing behavior explainable by a preferential attachment model.

Moreover, by looking at the most frequently prescribed versus the most frequently co-prescribed drugs, specific correlations emerge between drugs belonging to different anatomical and therapeutic groups.

The emerging field of Network Medicine can investigate not only biological/social systems and disease factors, but also behavioral and healthcare planning factors. Drug prescription process has a complex structure that can be evidenced and measured using Network Science instruments.

Therefore, Network Medicine could be a new powerful tool for research in Public Health.

Acknowledgments We gratefully acknowledge Dr. Mario De Santis, General Practitioner and Vice-President of "Consorzio Mega Ellas," for kindly providing the data used in this research.

We also thank Prof. Albert Laszlo Barabasi for his encouragement and for the permission to use his very significant and didactic picture, which shows relationships between the levels of molecular, clinical, and social networks.

32.7 Appendix. ATC Codes (At Anatomical and Therapeutic Level)

A01	Stomatological preparations
A02	Drugs for acid-related disorders
A03	Drugs for functional gastrointestinal disorders
A04	Antiemetics and antinauseants
A05	Bile and liver therapy
A06	Laxatives
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents
A08	Antiobesity preparations, excluding diet products
A09	Digestives, including enzymes
A10	Drugs used in diabetes
A11	Vitamins
A12	Mineral supplements
A13	Tonics
A14	Anabolic agents for systemic use
A15	Appetite stimulants
A16	Other alimentary tract and metabolism products
B01	Antithrombotic agents
B02	Antihemorrhagics
B03	Antianemic preparations
B05	Blood substitutes and perfusion solutions
B06	Other hematological agents
C01	Cardiac therapy
C02	Antihypertensives
C03	Diuretics
C04	Peripheral vasodilators
C05	Vasoprotectives
C07	Beta blocking agents
C08	Calcium channel blockers
C09	Agents acting on the renin-angiotensin system
C10	Lipid modifying agents
D01	Antifungals for dermatological use
D02	Emollients and protectives
D03	Preparations for treatment of wounds and ulcers
D04	Antipruritics, including antihistamines, anesthetics, etc.
D05	Antipsoriatics
D06	Antibiotics and chemotherapeutics for dermatological use
D07	Corticosteroids, dermatological preparations
D08	Antiseptics and disinfectants

D09	Medicated dressings
D10	Anti-acne preparations
D11	Other dermatological preparations
G01	Gynecological antiinfectives and antiseptics
G02	Other gynecologicals
G03	Sex hormones and modulators of the genital system
G04	Urologicals
QG51	Anti-infective and antiseptics for intrauterine use
QG52	Products for teats and udder
H01	Pituitary and hypothalamic hormones and analogues
H02	Corticosteroids for systemic use
H03	Thyroid therapy
H04	Pancreatic hormones
H05	Calcium homeostasis
QI01	Immunologicals for Aves
QI02	Immunologicals for Bovidae
QI03	Immunologicals for Capridae
QI04	Immunologicals for Ovidae
QI05	Immunologicals for Equidae
QI06	Immunologicals for Felidae
QI07	Immunologicals for Canidae
QI08	Immunologicals for Leporidae
QI09	Immunologicals for Suidae
QI10	Immunologicals for Pisces
QI11	Immunologicals for rodents
QI20	Immunologicals for other species
J01	Antibacterials for systemic use
J02	Antimycotics for systemic use
J04	Antimycobacterials
J05	Antivirals for systemic use
J06	Immune sera and immunoglobulins
J07	Vaccines
QJ51	Antibacterials for intramammary use
QJ54	Antimycobacterials for intramammary use
L01	Antineoplastic agents
L02	Endocrine therapy
L03	Immunostimulants
L04	Immunosuppressants
M01	Anti-inflammatory and Antirheumatic products
M02	Topical products for joint and muscular pain
M03	Muscle relaxants
M04	Antigout preparations
M05	Drugs for treatment of bone diseases
M09	Other drugs for disorders of the musculo-skeletal system
N01	Anesthetics
N02	Analgesics
N03	Antiepileptics
N04	Anti-Parkinson drugs
N05	Psycholeptics
N06	Psychoanaleptics
N07	Other nervous system drugs
QN51	Products for animal euthanasia
P01	Antiprotozoals
P02	Anthelmintics
P03	Ectoparasiticides, including scabicides, insecticides, and repellents
QP51	Antiprotozoals
QP52	Anthelmintics
QP53	Ectoparasiticides, including insecticides and repellents
QP54	Endectocides
R01	Nasal preparations
R02	Throat preparations
R03	Drugs for obstructive airway diseases
R05	Cough and cold preparations
R06	Antihistamines for systemic use
R07	Other respiratory system products
S01	Ophthalmologicals
S02	Otologicals
S03	Ophthalmological and otological preparations
V01	Allergens
V03	All other therapeutic products
V04	Diagnostic agents
V06	General nutrients
V07	All other non-therapeutic products
V08	Contrast media
V09	Diagnostic radiopharmaceuticals
V10	Therapeutic radiopharmaceuticals
V20	Surgical dressings

References

1. Aronson JK, Henderson G, et al. A prescription for better prescribing. BMJ. 2006;333(7566):459–60.
2. Awad A, Al-Saffar N. Evaluation of drug use practices at primary healthcare centers of Kuwait. Eur J Clin Pharmacol. 2010;66(12):1247–55.
3. Barabasi AL. Network medicine–from obesity to the "diseasome". N Engl J Med. 2007;357(4):404–7.
4. Barabasi AL. Scale-free networks: a decade and beyond. Science. 2009;325(5939):412–3.
5. Barabasi AL, Albert R. Emergence of scaling in random networks. Science. 1999;286(5439):509–12.
6. Barabasi AL, Gulbahce N, et al. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12(1):56–68.

7. Batagelj V, Mrvar A. Pajek–Program for large network analysis. From http://vlado.fmf.uni-lj.si/pub/networks/pajek/
8. Broadbent DE. Levels, hierarchies, and the locus of control. Quart J Exp Psychol. 1977;29(2):181–201.
9. Buchner A, Funke J, et al. Negative correlations between control performance and verbalizable knowledge: indicators for implicit learning in process control tasks? Quart J Exp Psychol Sect A. 1995;48(1):166–87.
10. Campo K, De Staebel O, et al. (2002) Therapeutic drug prescription behavior: Decision process and marketing mix effects. Antwerp, University of Antwerp, Faculty of Applied Economics, Prinsstraat 13, B-2000 Antwerpen, Web page: http://www.ua.ac.be/tew**:** 1–44.
11. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. N Engl J Med. 2007;357(4):370–9.
12. D'Zurilla TJ, Goldfried MR. Problem solving and behavior modification. J Abnorm Psychol. 1971;78(1):107–26.
13. D'Zurilla TJ, Sheedy CF. The relation between social problem-solving ability and subsequent level of academic competence in college students. Cogn Ther Res. 1992;16(5):589–99.
14. DeSarbo WS, Degeratu AM, et al. Disaggregate market share response models. Int J Res Market. 2002;19(3):253–66.
15. Dewey J (1910) How we think. D.C. Heath
16. Eisenberg E, Levanon EY. Preferential attachment in the protein network evolution. Phys Rev Lett. 2003;91(13):138701.
17. Freudenheim M (1998). The media business: advertising; influencing doctor's orders. New York Times
18. Goldstein FC, Levin HS. Disorders of reasoning and problem-solving ability. In: Meier M, Benton A, Diller L, editors. Neuropsychological rehabilitation. London: Taylor & Francis Group; 1987. p. 327–54.
19. Hurwitz MA, Caves RA. Persuasion or information? Promotion and the shares of brand name and generic pharmaceuticals. J Law Econ. 1988;31:299–320.
20. IMS (2011a) Total unaudited and audited global pharmaceutical market By Region. from http://www.imshealth.com Top-line Market Data.
21. IMS (2011b) Total unaudited and audited global pharmaceutical market, 2003–2010." From www.imshealth.com Top-line Market Data.
22. Jhon P (2001) Drug company dependent? Medscape Med Students 3
23. Jones JH, Handcock MS. An assessment of preferential attachment as a mechanism for human sexual network formation. Proc Biol Sci. 2003;270(1520):1123–8.
24. Kahn B, Greenleaf E, et al. Examining medical decision making from a marketing perspective. Market Lett. 1997;8(3):361–75.
25. Leffler KB. Persuasion or information? The economics of prescription drug advertising. J Law Econ. 1981;24(1):45–74.
26. March JG, Simon HA. Motivational constraints: the decision to participate. New York: Wiley; 1958.
27. Martin CM, Sturmberg JP. General practice–chaos, complexity and innovation. Med J Aust. 2005;183(2):106–9.
28. Newell A, Simon H. Human problem solving. NJ, Prentice Hall: Englewood Cliffs; 1972.
29. Paredes P, de la Pena M, et al. Factors influencing physicians' prescribing behaviour in the treatment of childhood diarrhoea: knowledge may not be the clue. Soc Sci Med. 1996;42(8):1141–53.
30. Plianbangchang P, Jetiyanon K, et al. Physicians' generic drug prescribing behavior in district hospitals: a case of Phitsanulok, Thailand. Pharm Pract. 2010;8(3):167–72.
31. Rodriguez-Calvillo JA, Lana A, et al. Psychosocial factors associated with the prescription of generic drugs. Health Policy. 2011;101(2):178–84.
32. Ross S, Loke YK. Do educational interventions improve prescribing by medical students and junior doctors? A systematic review. Br J Clin Pharmacol. 2009;67(6):662–70.
33. Simon HA. Motivational and emotional controls of cognition. Psychol Rev. 1967;74(1):29–39.
34. Sketris IS, Langille Ingram EM, et al. Strategic opportunities for effective optimal prescribing and medication management. Can J Clin Pharmacol. 2009;16(1):e103–125.
35. Strogatz SH. Exploring complex networks. Nature. 2001;410(6825):268–76.
36. Sturmberg JP, Martin CM. Complexity and health – yesterday's traditions, tomorrow's future. J Eval Clin Pract. 2009;15(3):543–8.
37. Tan NC, Tay IH, et al. Factors influencing family physicians' drug prescribing behaviour in asthma management in primary care. Singapore Med J. 2009;50(3):312–9.
38. Theodorou M, Tsiantou V, et al. Factors influencing prescribing behaviour of physicians in Greece and Cyprus: results from a questionnaire based survey. BMC Health Serv Res. 2009;9:150.
39. Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. Science. 1974;185(4157):1124–31.
40. Tversky A, Kahneman D. The framing of decisions and the psychology of choice. Science. 1981;211(4481):453–8.
41. United Nations A (1948) Universal Declaration of Human Rights. Approved by the General Assembly at its Plenary Meeting on 6 December, 1948, pp. 6. [Lake Success,] 1948.
42. Vazquez A. Growing network with local rules: preferential attachment, clustering hierarchy, and degree correlations. Phys Rev E Stat Nonlin Soft Matter Phys. 2003;67(5 Pt 2):056104.
43. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. Nature. 1998;393(6684):440–2.
44. Wazana A. Physicians and the pharmaceutical industry. JAMA. 2000;283(3):373–80.

45. WHO. The world health report: health systems financing: the path to universal coverage. Geneva: WHO; 2010.
46. WHO (2011) Health Impact Assessment (HIA): the Determinants of Health. WHO programmes and projects. from http://www.who.int/hia/evidence/doh/en/.
47. WHO, Collaborating Centre for Drug Statistics Methodology (2010b) Guidelines for ATC classification and DDD assignment 2011. Oslo, WHO -World Health Organization.
48. Wierenga B, Jong SJ, et al. The decision making process of the family physician in choosing a drug. Ned Tijdschr Geneeskd. 1989;133(3):115–22.
49. Wikipedia.org (2011a). Medical prescription. From http://en.wikipedia.org/wiki/Medical_prescription.
50. Wikipedia.org (2011b) Network science. From http://en.wikipedia.org/wiki/Network_science.
51. Wilkes MS, Bell RA, et al. Direct-to-consumer prescription drug advertising: trends, impact, and implications. Health Affairs. 2000;19(2):110–28.
52. Yildirim MA, Goh KI, et al. Drug-target network. Nat Biotechnol. 2007;25(10):1119–26.
53. Zuger A. Fever pitch: getting doctors to prescribe is big business. New York: New York Times; 1999.