Prediction of the Evolution of Bipolar Disorder using Semantic Web Technologies

Chryssa Thermolia

Department of Electronics and Computer Engineering
Technical University of Crete

Dissertation Thesis Committee:
Euripides G.M. Petrakis, Professor (Supervisor)
Michail Zervakis, Professor
Michail G. Lagoudakis, Assistant Professor

2012

Acknowledgments

This thesis would not have been possible without the help of several people who contributed in the preparation and completion of this study.

Firstly and foremost I would like to thank my advisor, Professor Euripides G. M. Petrakis for his constant supervision. For guiding, advising and supporting me in every step of this thesis. For widening my scientific horizons by giving me the opportunity to occupy with this issue,helping me getting concious of the abilities of my science.

Also, I would like to thank Professor Michail Zervakis and Assistant Professor Michail G. Lagoudakis for their constructing comments and guidance.

Moreover i would like to thank Dr Katerina Bei, for her valuable help on problem definition and guidance throughout my work for this thesis. Katerina supported me greatly during the writing of this thesis by offering me her research experience.

Moreover, I would like to thank my laboratory colleagues for their patient and constructive comments.

I would like to thank all my friends for these great years we spent together and for the many wonderful memories.

Most of all, I would like to thank my family for their enormous help, understanding and support throughout these years as a student.

Abstract

The quality of medical health care as well as increasing the efficiency of clinical practices can be significantly improved by incorporating information technology in the medical procedures which are routinely used in the medical environment. Diseases that evolve in time require patient's condition of the disease monitored by the clinicians for providing optimal medical treatment to patients in real time. Often clinicians have to manage with crucial incidents that require direct response based on their good knowledge of the patient's history medical record and the medical guidelines that are in effect for the disease.That is not an easy task especially when clinicians have to deal with many patients or the disease evolves constantly.

In this thesis we focus on Bipolar Disorder, a disease with the characteristics refered to above. It evolves constantly in time and often leads to crucial incidents with hazardous effects for the patient's life. Nonetheless, our management and design focuses on Breakthrough Depressive Episode Scenario, a scenario that is common among Bipolar Disorder patients. Using Semantic Web Technologies we developed **SybillaTUC** -a recommendation system based on an ontology designed to represent and manage the information about each patient's medical record and the management of the disease. By reasoning over patient's data, SybillaTUC is able to recommend clinicians the best treatment for each patient.

SybillaTUC provides clinicians with the ability to individualize the monitoring of Bipolar Disorder, offering constant view of the patient's condition and easy access to his medical record. Combining the clinical guidelines for Bipolar Disorder with a patient's condition and his medical record, SybillaTUC can predict the evolution of each patient, alert the clinician on the possibility of a critical incident and propose the best treatment suggested in the clinical practice guidelines asserted into the system. Notice that, not only patient information but also expert's knowledge can be updated to accommodate recent deployments of the state-of-the-art on the treatment of Bipolar Disorder. Clinical cases bases on synthetic (but realistic information) for demonstrating proof of concept are presented and discussed.

Contents

List of Figures

Chapter 1

Introduction

The world wide use of computer technology during the last few years has generated additional interest in methods and tools for improving the productivity and quality of health care processes which are daily applied and by this, improve the quality of health services offered to groups of people or individuals. The benefits of the computerization of health care processes for individuals, group of people or the health care organizations (e.g., hospital, insurance companies, health ministries) are then considerable and range from computer systems that can generate reports of patient's tests, identify when the medication a patient receives is recalled, or accommodate changes in patient's monitoring processes. There can also exist alerting systems that notify clinicians when a patient's test result require prompt attention. Computerized clinical guidelines can help clinicians plan diagnostic and treatment strategies according to selected guidelines, or even warn clinicians when their interventions are straying from a guideline. In addition, large sets of electronic patient data can be analyzed by researchers quickly and cost effectively [1] and by this analysis design better treatment strategies for populations or individuals.

Most of the computer enabled functionalities referred above have been demonstrated in medical, computing research settings, but very few exist in routine clinical settings. The challenge informaticians have to face in order to achieve these functionalities is **not only to provide electronic data storage but to extract information from these data.** These functionalities require not only simple data management but also **knowledge management**. They require a well-designed and functional internal model of the clinical information possessed.

Data is a collection of facts and for their manipulation informaticians use database systems which can process,retrieve and query over data. Nonetheless, databases are not always up to date and typically, the only way of extracting knowledge from data stored data is by querying, a process which can be slow and costly.

Knowledge management is the process of systemically capturing, structuring, retaining and reusing information for the purpose of understanding how a particular system works and subsequently to convey this information meaningfully to other information systems. For example, the output of an micro-array experiment is pure data, that means nothing to human mind. Analyzing the data may reveal that a certain group of genes is over expressed under certain conditions. This can be the extracted knowledge from the dataset.

Semantic Web technologies are being developed in nowadays to meet the challenge of knowledge management in a world with high distributed resources. The Semantic Web promises an infrastructure that comprises machine understandable content and therefore, a World Wide Web made of semantically linked data instead of a mere collection of HTML documents. Semantic Web technologies represent real world entities even with their evolution over time, provide a set of decisions about how and what to observe in a particular domain of discourse, provide support for intelligent reasoning over the domain of discourse according to the needs of a particular community, enable efficient organization and processing of information in a computational environment and also support information sharing [2]. Applying ideas from the Semantic Web for supporting enhanced information management (i.e., representation, sharing and reasoning) over medical information is the main problem this work is dealing with.

1.1 Problem Definition

With the vision of providing better and direct health care services and improving and strengthen clinician-patient relationship, decision -support tool systems have been developed. These tools may include reminder systems that identify patients who are due for preventative care interventions, alerting systems that detects contraindications among designed medications and coding systems that facilitate the selection of correcting billing codes for patients encounters [1]. Dealing with diseases whose evolution depends on time is of particular interest to us.

In this case **preventative care recommendations systems** can be developed to predict the evolution of the disease for each patient, identify patients who are eligible to vaccinations and patient counseling and recommend clinicians the appropriate therapy for each patient.

In this thesis we focus our attention on **Bipolar Disorder**, which is characterized by **long periods of evolution in time** and whose treatment (clinical) guidelines change often causing certain difficulties in providing trustworthy medical care to patients.

1.2 Proposed Solution

We introduce **SybillaTUC** an information system built-upon Semantic Web Technologies and designed to model and stimulate Bipolar Disorder. Through SybillaTUC clinicians are provided with the means to access each patient's file information, and view the evolution of their patient's condition in time. SybillaTUC is also designed to provide recommendations regarding the treatment each patient should receive. For this purpose it takes into consideration the medical guidelines that are in effect for the disease at each particular time and the patient's medical history.

Sybilla TUC represents patient's and disease information as well as expert's knowledge by means of an ontology. Dealing with the evolution of bipolar disorder disease in time calls for temporal ontologies. Recent advances in Semantic Web technology suggest that such a representation can be achieved by adding the concepts of time and change in an ontology representation allowing time to effect the status of the described concepts. In this work, a temporal ontology is realized by implemented the so called "N-ary" relations approach. Decision making over existing information on patient data and expert's knowledge and clinical guidelines (e.g., for, issuing an alerts when patient condition changes from stable to unstable) is realized as a reasoning system which is implementing by means of SWRL, a rule-based semantic-web language.

1.3 Thesis Outline

Background knowledge and related work are discussed in Chapter 2. This includes description of Semantic Web and Ontologies technologies such as OWL, temporal reasoning and SWRL Rules, such as the tool we used to develop our ontology, Protégé OWL Editor. We describe SOWL, an ontology for handling spatial and temporal knowledge and the developed plugins for handling temporal knowledge and ontologies such as Chronos Plugin and 4-d Fluents Plugin for Protégé OWL Editor. Also we present previous work that was done in this field. In Chapter 3 we describe Bipolar Disorder along with the scenario we designed for our implementation. In Chapter 4 we present the ontology design for patient's suffering from Bipolar Disorder. In this chapter we discuss the reasoning system and we present the use cases suggested by our experts for dealing with the patients and we discuss their implementation in SWRL. Finally, the system, its User Interface as well as the use cases implemented are discussed in Chapter 4, followed in Chapter 5 by conclusions and issues for further research.

Chapter 2

Background and Related Work

2.1 Semantic Web

The Semantic Web is not a separate Web but an extension of the current one, in which information is given well-defined meaning, better enabling computers and people to work in cooperation". It is a source to retrieve information from the web (using the web spiders from RDF files) and access the data through Semantic Web Agents or Semantic Web Services [4].

2.2 Ontologies

There have been several attempts to define the word "ontology" in computer science. Some of them approach "ontology" from a more philosophical scope, while some others have tried to give a more practical definition of the term. In our work,we go with the practical definition, that an ontology is a method of representing items of knowledge (ideas, facts, things—whatever) in a way that defines the relationships and classifications of concepts within a specified domain of knowledge. [5] The four fundamental ingredients of an ontology are classes, properties, individuals and datatypes.

Individuals represent objects in the domain of interest.

Properties represent relationships. They are distinguished in two types, *Object properties* and *Data properties*. Object properties relate two individuals to each other and data properties relate an individual to a data value.

Classes represent sets of individuals (or sets of objects) that share some common features, constraints and semantics.

Ontologies provide the semantic foundation, that allows agents and their human users to identify,collect and process suitable information by interpreting the semantic metadata based on the task at hand. They also allow the exchange of results and the communication by sharing such resources. [5]

2.3 OWL

The Web Ontology Language OWL is a semantic markup language for publishing and sharing ontologies on the World Wide Web. It is developed as a vocabulary extension of RDF (the Resource Description Framework) and is derived from the DAML+OIL Web Ontology Language. OWL is intended to provide a language that can be used to describe the classes and relations between them that are inherent in Web documents and applications. OWL provides three increasingly expressive sublanguages:

1. OWL Lite supports classification hierarchy and simple constraints.
2. OWL DL supports maximum expressiveness without loosing computational completeness and decidability.
3. OWL Full provides maximum expressiveness and the syntactic freedom of RDF, but without computational guarantees.

Each of these sublanguages is an extension of it's simpler predecessor.

OWL is part of W3C's Semantic Web technology stack. In October 2007 a new W3C working group was started to extend OWL with several new features. This new version was called OWL 2 [3].

2.4 SWRL

Semantic Web Rule Language (SWRL) [6] is a proposal for a semantic web rules-language, combining sublanguages of OWL (OWL DL and OWL Lite) and the Rule Markup Language. SWRL allows for rule expressions involving OWL concepts enabling more powerful deductive reasoning than OWL alone. Semantically, SWRL is built on the same description logic foundation as OWL and provides similar strong formal guarantees of inference.

A SWRL rule contains an antecedent part, which is referred to as the body, and a consequent part, which is referred to as the head. Both the body and head consist of positive conjunctions of atoms, meaning that all atoms of the antecedent part must be satisfied in order for the consequent to be applied.

2.5 Temporal Representation

Dealing with information that changes over time is a critical problem for practical Knowledge Representation languages (OWL, RDF). These language are based on binary relationships between concepts.

In the following, we discuss some of the representation models along with their advantages and disadvantages. Figure 2.1 illustrates an example of a ternary relationship. Its representation using the n-ary representation model is discussed next.

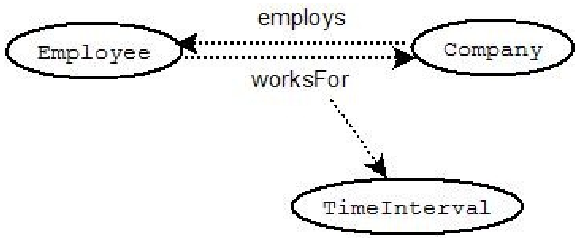

Figure 2.1: Ternary Employment.

Versioning [7] suggests that an ontology has different versions (one per instance of time). This method suffers from several disadvantages, as a simple change on an attribute of the ontology requires the creation of a new version of the ontology. This results to huge information redundancy. Moreover, searching for an event that occurred at a specific time, requires exhaustive search between the different ontology versions. Lastly, it is not clear how relations between evolving classes is represented.

Reification is a general purpose technique for representing n-ary relations using languages that only permit binary relations. An n-ary relation is represented as an object, which is the subject of n+1 triples. Those triples have as objects the participants of the n-ary relation plus one triple has as object the predicate of the property. In our example, supposing that we want to represent the statement *"John has worked for Apple from 2000 to 2005"* is expressed as *livesIn(John, Apple, t)* where t represents the interval '2000 to 2005'. Using reification, this relationship is represented as a new object with *John*, *Apple*, t and *worksFor* being objects of properties (Figure 2.2). Reification also suffers from data redundancy, because a new object is created for every reified relationship. This is a common problem to all approaches that are not based on non temporal Description Logics. A major disadvantage of reification is that it offers limited reasoning capabilities. This is a result of representing the predicate of the relation as an object of a property thus the OWL semantics over the property are no longer applicable.

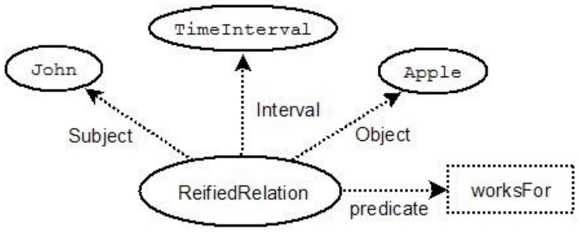

Figure 2.2: Example of Reification.

4D Fluents (Four-Dimensional Approach) [8] considers entities to exist in time the same way that material objects exist in space—they occupy spacetime. These entities have temporal parts (time slices) that represent the entity during a time interval. Therefore, according to this approach, a temporal property does not hold between the static entities but between their temporal parts. The time slices of an entity have a specific lifetime, that is the time interval of the relation that they participate in. Thus, a time slice can participate in more than one temporal relations (fluents) only if they hold for precisely the same time interval.

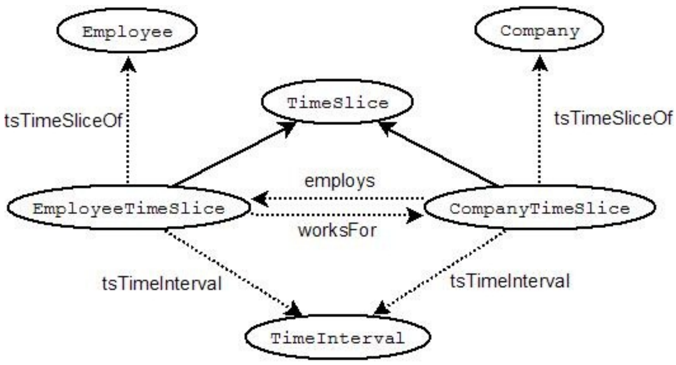

Figure 2.3: Example of the 4D Fluents approach. The dotted arrows represent object properties between classes. The solid arrows represent the 'isA' relationship.

As shown in Figure 2.3 for every time interval during which the property *worksFor* holds, two instances of the class *TimeSlice* are created. These instances are related to the time interval that defines their "lifetime", to the static entities whose they are temporal parts of and to each other with the fluent property *worksFor*.

The 4D-fluents approach suffers from data redundancy, since two individuals and four properties between them have to be added to the ontology. It also complicates the ontology. Nevertheless, it is a sufficient way to represent relations that evolve over time, maintaining the property semantics and offering reasoning capabilities.

N-ary Relations [9] is a general purpose technique for representing n-ary relations. In N-ary Relations representation model, the static entities are considered to participate in events. A temporal property property between two individuals (e.g. Employee works for Company) holds as long as that event endures. The n-ary property is represented as a class rather than as a property. Instances of such classes correspond to instances of the relation. Additional properties provide binary links to each argument of the relation. In contrast to reification, the n-ary relation is not represented as the object of a property but as two properties each related with the new object.

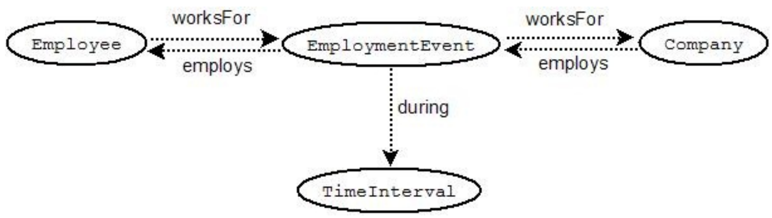

Figure 2.4: Example of the N-ary Relations representation.

As shown in Figure 2.4, for the representation of properties that change over time the property's domain and range are modified, in order to connect to the new object that is added. The new domain is the union of the old domain with the class that represents the n-ary property (*Event* class). Likewise, the new range is a union of the old one with the *Event* class.

The information redundancy using N-ary Relations is minimal in comparison to the other methods described (just one object and two properties have to be added to the ontology for each temporal triple). Property semantics are maintained and it also offers reasoning capabilities. Those reasons, along with the fact that the particular model is a W3C recommendation for representing n-ary relations, have led us to use this model in our work.

2.6 Protégé OWL Editor

Protégé [10] is a free, open-source platform that provides a suite of tools for building domain models and knowledge-based applications with ontologies. It supports the creation, visualization and manipulation of ontologies in various representation formats. Protégé can be customized to provide domain-friendly support for creating knowledge models and entering data. Further, Protégé can be extended by way of a plug-in architecture and a Java-based Application Programming Interface (API) for building knowledge-based tools and applications. The Protégé platform supports two main ways of modeling ontologies, the Protégé-Frames editor and the Protégé OWL editor.

The Protégé-OWL editor enables users to build ontologies for the Semantic Web, in particular in the W3C's Web Ontology Language (OWL) [11]. Version 4.1 of Protégé OWL provides full support of OWL 2.0 [3]. This is the version which Chronos plug-in extends.

2.7 SOWL

SOWL Ontology was developed in Intelligence Systems Laboratory of Department of Electronic and Computer Engineering of Technical University of Crete by Sotirios Batsakis. SOWL is an approach for handling spatial and temporal knowledge in ontologies. SOWL handles both, time instants and intervals(and also semi-closed intervals). It offers support for representing and reasoning over topological and directional spatial relations. With SOWL it is offered two alternative representations based on 4-d fluents and the N-ary relation models. It permits quering over spatio-temporal information with the use of two query languages,TOQL and SOWL Query Language [12]

2.8 Chronos Plugin and 4-d Fluents Plugin

The creation of a temporal ontology or the conversion of a static ontology to temporal can be very complex, time-consuming and error-prone procedure.The user must have very good knowledge of the selected representation model and all of it's peculiarities.

To handle with this problem two tools were developed in Intelligence Systems Laboratory of Department of Electronic and Computer Engineering of Technical University of Crete.

Chronos Plugin which is based on N-ary representation model and it was developed by Alexandros Preventis. [13]

4-d Fluents Plugin which is based on 4-d fluents representation model and it was developed by Xenia Makri. [14]

Both plugins are easy to use , handle with temporal ontologies as static ones allowing the user not to be familiar with the peculiarities of the underlying representation model. They both supports restrictions adding and checking on temporal properties,classes and individuals. Lastly they supports reasoning over the temporal ontologies using the standard Pellet reasoner for Protégé OWL editor.

As we selected, for modeling our ontology, the N-ary representation model we use for handling with the temporal elements of our ontology, the Chronos Plugin.

2.9 OWL API

The OWL API [15] is a Java interface and implementation for the W3C Web Ontology Language (OWL), used to represent Semantic Web ontologies. OWL API has been designed to meet the needs of people developing OWL based applications, OWL editors, such as Protégé and OWL reasoners. It is a high level API that is focused towards the OWL DL and OWL 2 specifications and supports ontology management, ontology change, ontology parsing and rendering, data structure storage and reasoner interfaces.

2.10 Related Work

Previous work on recommendation tool systems was developed by Evaggelia Maurogiannaki's Master Thesis “Time Dimension on Clinical Guidelines for the management of pathological symptoms of gynecological exams” [16] in Intelligence Systems Laboratory of Department of Electronic and Computer Engineering of Technical University of Crete. In this thesis an ontology was designed for the representation and management of the knowledge's evolution through time, for patients suffering from the HPV virus.Based on the clinical guidelines that take effect for HPV virus and using reasoning over data,recommendations and notifications were extracted and proposed to clinicians.

An other interesting work was presented by “CNTRO:A Semantic Web Ontology for Temporal Relation Inferencing In Clinical Narratives” [17].This work focuses in the representation of temporal information of the clinical narratives. For this purpose an ontology was designed to represent real clinical narratives that decribe patient's history, possible symptomatology, or medicines that a patient receives in the slice of time.

Chapter 3

Bipolar Disorder

3.1 Bipolar Disorder

Bipolar disorder, or as more widely known manic-depressive disorder, is a mental disorder characterized by dramatic shifts in mood, thinking, behavior, and energy that is seen in up to 5% of primary care patients. These symptoms may have great effects in the daily activities and general behavior of a person preventing him from a normal life.

In collaboration with a psychiatrist, the family or in developed countries the family physician plays a vital role in supporting the long-term stability and general health of these patients. In order to effectively treat such patients, it is important that the family or the family physician have a good grasp of the disease, its long-term management, and its impact on overall health [18].

Bipolar disorder can be distinguished in Bipolar disorder I, Bipolar disorder II.

Bipolar disorder I is characterized by the presence of one or more **manic or mixed episodes** or both manic and mixed episodes and at least **one major depressive** episode.

Bipolar Disorder II is characterized by the presence of **one or more major depressive** episodes and at least one hypomanic episode [19].

A subtype of bipolar disorder that we are interested in this thesis is **rapid cycling** and it characterizes patients who experience more than 4 episodes per year. It is associated with treatment resistance and overall poorer prognosis [18].

As Bipolar Disorder evolves in time, representing and designing every scenario of it's evolution would be too complicated for the requirements of a thesis. So we selected to deal with Bipolar disorder I as a more representative type of Bipolar Disorder that allows us to focus on specific scenario.

3.1.1 Causes of Bipolar disorder

Results of family studies and twin studies suggest a genetic bases for bipolar disorder. Because of the large variation of phenotypes seen in patients with bipolar disorder, genetic factors probably only have a small effect, and environmental and developmental factors such as **stressful events** and **life attitude** are also important on the manifestation of the disorder [19].

3.1.2 Clinical phases of bipolar disorder

Bipolar disorder includes a wide range of variations and fluctuations. It displays the following states:

Manic Episode In manic episode patients are in an euphoric state and possibly display intense irritability and agitation and profound impairments in reality testing and judgment. If the patient appears three or more of the symptoms that are presented in Figure 3.1 [20] during a week the clinician diagnoses the presence of a manic episode .About two-thirds of manic episodes are psychotic, with delusions and hallucinations. Mania usually requires psychiatric hospitalization [18].

Major Depressive Episode If the patient appears five or more of the symptoms that are presented in Figure 3.2 [20] during a two-week period the clinician diagnoses the presence of a depressive episode.

Mixed Episode During a mixed episode patients simultaneously meet full criteria for both mania and depression that co-occur for at least one week [18].

Euthymia The period of apparent clinical recovery between two episodes is called euthymia and is characterized by the patient's normal functionality and the absence of emotional symptoms [21].

3.1.3 Risk factors of Bipolar Disorder

A great risk of Bipolar Disorder is the risk of **suicide**. Especially during depressive episodes the risk of a patient admitting suicide is high. Every thought of suicide must be taken into account and receive a psychiatric treatment.

In the phase of mania the patient may not suffer from the suicide idea but may risk his life with **extreme behavior** as drug abuse, uncontrolled sexual behavior or high speed driving.

Patients with bipolar disorder have high rates of **medical, psychiatric, and substance abuse disorders**, which contribute to reduced life expectancy and lower quality of life. A majority meet criteria for at least

- Inflated self-esteem or grandiosity
- Decreased need for sleep (eg, feels rested after only three hours of sleep)
- More talkative than usual, or pressure to keep talking
- 'Flight of ideas' or subjective experience that thoughts are racing
- Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
- Increase in goal-directed activity (either socially, at work or school, or sexually, or a mental and physical restlessness)
- Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

Figure 3.1: Manic Episode symptoms.

1 other mental disorder- anxiety and substance abuse disorders are most common, with a 40% to 60% lifetime prevalence.

Compared to the general population, patients with bipolar disorder have higher rates of diabetes mellitus and liver and cardiovascular disease and experience increased disability and mortality from these illnesses. The family physician has a valuable opportunity to improve outcomes by aggressive screening for, and maintenance of, these comorbid conditions [18].

3.1.4 Fundamentals of patient management

Fundamentals of patient management concentrate in three elements: **diagnosis, access to services and safety** and **enhanced care** [22]. In order the clinicians to achieve the best medical treatment for each patient, they follow clinical guidelines.

Guidelines are systematically derived statements that are aimed at helping individual patient and clinicians decisions. For Bipolar Disorder the first guidelines were published in 2003 [22].

3.1.4.1 Diagnosis

Diagnosis of Bipolar Disorder is initially based on the study of the personal experience of the patient and the ubnormal reactions that have been noticed by the family environment.

In a second level diagnosis continues based on the symptoms the clinician observes and the estimation he does is according to defined criteria as

- Depressed mood may be indicated by:
  - subjective reports (eg, feels sad or empty)
  - observations made by others (eg, appears tearful)
- Markedly diminished interest or pleasure in activities
- Significant weight loss when not dieting, or weight gain or decrease or increase in appetite
- Insomnia or excessive sleep
- Mental and physical slowing or restlessness
- Fatigue or loss of energy
- Feelings of worthlessness, or excessive or inappropriate guilt
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt, or a specific plan for committing suicide.

Figure 3.2: Depressive Episode Symptoms.

long as the family history. **Mood Disorder Questioner (MDQ)** has been developed to guide clinicians during the diagnosis. If two or more symptoms characterized positive by the patient, should alert the clinician. In this case the clinician should explore the potential manic symptoms in more detail. The questions that compose the MDQ are presented in Figure 3.3. Once the answers of the MDQ indicates the possibility of Bipolar Disorder the clinician submits the patient in a range of functional tests (e.g. haematological, hepatic, thyroid, cardiovascular and neurological),in order to verify if the patient is actually suffering from Bipolar Disorder.

After a patient is diagnosed with a type of bipolar disorder there is a need to classify the patient. For the classification of the disorder clinicians base on Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) [23] or International Classification of Diseases and Related Health Problems -Tenth Revision (ICD-10) [24].

Also there is a need to measure the severity of the disorder. For this reason there are developed rating scales for the measurement of the Bipolar Disorder. Usually these are questioners, about the presence of specific symptoms, addressed to patients in order to refer the severity of these symptoms. The most frequently used are referenced below.

Hamilton Depression Rating(HAM-D) Scale is a scale mostly used to evaluate the severity of depression. There are two versions of the scale. **HAM-D**$_{17}$ that includes 17 items on a patients activities while **HAM-D**$_{21}$ includes 21 items. These items are scored from 0 to 4, the higher the score the more severe the depression.

Young Mania Rating Scale is a scale mostly used to evaluate the severity of mania. It is based on an 11-item questioner addressed to patients [25].

3.1.4.2 Access to services and the safety of the patient and others

When mania is diagnosed, clinicians should always consider admission to hospital or intensive community management. The particular risks to the patient and the others will be the result of poor judgement and associated actions in areas of work, personal relationships etc. Clinicians should always try to obtain third party information if in any doubt when making an assessment of clinical risk.

3.1.4.3 Enhanced care

The complete therapy and restoration of a patient suffering from Bipolar Disorder is quite difficult. Nevertheless clinicians based on the clinical guidelines can provide therapies not only to improve a patient's condition but also to be maintained in this good condition for a long time.

In order to have a successful therapy many treatment combinations are followed specialized to patient. These treatment combinations may have as basic axis one or more of the following treatments [22].

Pharmaceutical Treatment Medicines are the cornerstone in the therapy of Bipolar Disorder. Goal of pharmaceutical treatment is dealing with the crucial symptoms of mania or depression, reduce their intense and limit their duration. In a second level the goal is to conserve the good condition of the patient and prevent a possible relapse. Pharmaceutical treatment evolves. New medicines and combinations are added in clinical guidelines. As Bipolar Disorder is a complicated disorder and dealing with the one phase of the illness can trigger the other, a combination of medicines is prescribed taking into account each patient history. The main categories of the medicines that can be subscribed are refered below:

1. **Mood Stabilizers** are medicines that ensure that a patient's mood will be restored and kept in a normal level. Mood stabilizers are used in mania phase but also in the stabilization of mood and prevention of relapses and they are preferred for first-line therapies [19]. The most widely used mood stabilizer is Lithium.

2. **Antipsychotics** have been used for the treatment of mania in Europe and U.S.A for the past 50 years.New surveys are taking place over antipsychotics that broaden their new therapeutical possibilities [26].

3. **Antidepressants** are medicines that are prescribed in depression mania.They are indicated when mood stabilizers are ineffective and for "breakthrough" depressions [18].

The pharmaceutical treatment is provided not only for treating an episode but also for maintenance of euthymia with appropriate medication monitoring [18].

Psychotherapy is a modern therapeutical treatment which is used to provide patient medication compliance and acceptance of the illness, and to modify environmental risk factors. In long term treatment of bipolar disorder careful psychoeducation is an important treatment plan. The way a patient functions between episodes can be improved by working on problems associated with stigmatation by the illness, low self-esteem after the episodes etc.Maintenance of a regular pattern of daily activities, as addressed by interpersonal and social rhythm, might help with interepisodic stability therapy [19].

Hospitalization is a treatment consideration that a clinician may recommend to the patient for two reasons. The first reason is during a severe episode of mania or depression in order to have the patient a continuous monitoring of his state condition and prevent him from an episode's consequences. Hospitalization allows the patient to emerge from the crisis with the help of medication and therapy. The second reason is to stabilize the patient on medication. In a hospital setting, a clinician can adjust the medication and monitor the patients progress.

For each phase of bipolar disorder there have been developed algorithms based on clinical guidelines from many institutions handling with bipolar disorder. According to CANMAT guidelines [27] the algorithm for acute mania is presented in Figure 3.4 and for bipolar I depression is presented in Figure 3.5

According to Australian and New Zealand clinical practice guidelines [28] the algorithm for the initial assessment for manic episode is presented in Figure 3.6 and for the initial assessment for bipolar depressive episode is presented in Figure 3.7. The treatment algorithm for a manic episode is presented in Figure 3.8. The algorithms when a failure on treatment is occurred are presented in Figure 3.9 for manic episode and Figure 3.8 for depressive episode.

3.2 Breakthrough Depressive Episode Scenario

As we have described previously bipolar disorder is a lifelong illness that is complicated by high comorbidity and risk of poor health outcomes. The management of acute mood episodes should focus first on safety, should include psychiatric consultation as soon as possible, and should begin with an evidence-based treatment that may be continued during the maintenance phase.

Long-term management focuses on **maintenance of euthymia** which is the primary goal, requires ongoing medication, and may benefit from adjunctive psychotherapy. Maintenance treatment is the longest treatment of bipolar disorder. The goal of maintenance treatment is the prevention of future mood episodes. Classically the maintenance treatment follows the continuation phase, in which the goal is preventing a relapse into a same episode for which acute treatment has begun [29]. The possible goals of a clinician for maintenance treatment may be:

- Abolitions of episodes and mood swings.
- Decreased number of episodes.
- Decreases intensity of episodes.
- Decreased length of episodes.
- Greater mood stability.
- Decreased suicide rates.

Current evidence best supports the use of *lithium* as first-line treatment: it has been shown to prevent both manic and depressive relapse, as well as suicide in meta-analytic reviews of randomized controlled trials [18].

In the longitudinal management of these patients, the clinician may be particularly helpful in working to mitigate the unfortunate effects of the comorbidity that this disorder carries with it and the adverse effects inherent in even its best treatments [18].

An example of the last one is the **Breakthrough Depressive Episode** scenario where during the treatment with lithium there may be no compliance of the patient with the treatment, obligating the clinician to change the treatment. There are evidence that rapid-discontinuation of lithium will lead to a high rate of relapse(5% of patients relapse within 5 months) [28]. In this case clinicians face a challenge. They should find the best treatment in order to preserve the patient in the state of euthymia.

Studing the Breakthrough Depressive Episode Scenario our goal is to provide recommendations to clinicians for the best medical treatment.

Breakthrough Depressive Episode is an episode where the patient, who is in the state of euthymia and receives treatment with lithium, shows depressive symptoms caused by his **reaction to the pharmaceutical treatment** [30]. These depressive symptoms should receive different treatment from the known treatment for depressive episode.

Existing evidence suggests a dose-response relationship, in which higher serum concentrations of lithium provide greater protection against recurrent mood episodes.

Patients with Bipolar Disorder on long-term treatment, in our case with lithium, are typically maintained at serum lithium concentrations between **0.6m and 0.1 mEq/L**. Although there are individuals exceptions, serum lithium levels below 0.6 mEq/L have been shown in controlled clinical trials to be less effective in preventing relapses than levels within this range, whereas levels much above 1.2 mEq/L can lead to **toxicity** [30].

Thus levels above 0.8 mEq/L presumably protect better than lower levels.At the same time clinical evidence and some experimental data suggest that many patients with bipolar disorder, moderate lithium levels (e.g 0.6-0.8 mEq/L) -or in some cases even lower levels-may afford adequate protection [30].

The problem of individualized dose finding in maintenance treatment, however, is that the clinician does not know if a given level is sufficiently protective until an episode occurs [30].

We present recommendations based on **4 evidence-based treatment guidelines** with a focus on using them to improve clinical care during the breakthrough depressive episode. Additionally, recommendations for therapeutic drug monitoring are presented due to their importance for patient safety, particularly for the primary care physician, although these are based on consensus guidelines.

1. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders, Part III: Maintenance Treatment [31] [32].
2. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder [28].
3. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009 [27].
4. NICE clinical guideline 38 Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care [33].

The recommendations based on these guidelines are meant to provide a framework for clinical decision making, not to replace clinical judgment. As with any algorithm, treatment practices will evolve beyond the recommendations of this consensus conference as new evidence and additional medications become available [34].

Combining the proposed algorithm for Breakthrough Depressive Episode's treatment [28] that is presented in Figure 3.11 with elements from the rest of our selected guidelines we have developed a scenario for handling the treatment a clinician should offer during a Breakthrough Depressive Episode.

According to the referenced guidelines a Bipolar patient could be on a long term medication after existance of one, two or three episodes depending on the episodes severity and presence of family history. The algorithm the clinician follows to decide to prescribe maintenance treatment based on lithium is presented in Figure 3.12.

Algorithm The algorithm followed to extract rules is presented in Figure 3.13

[**Step 1:**]The patient receives a pharmaceutical treatment based on mood stabilizer Lithium.

[**Step 2:**] The patient is in euthymia phase.

[**Step 3:**]Serum Lithium tests results are in normal levels(0.6¡value¡0.8)

[**Step 4:**] After 70 days prodromal symptoms manifestate.

[**Step 5:**] After 20 days patient is taking his regular functional tests.

[**Step 6:**] Serum lithium tests results are not optimal(0.4¡value¡0.6)

[**Step 7:**] Recommendation to the clinician to improve the mood stabilizer's dosage.

[**Step 8:**] After a week repeat tests for serum lithium

[**Step 9:**] Serum lithium tests results are optimal(0.6$\leq$ $value \leq$ 0.8)

[**Step 10:**]

[**case 1:**] If symptoms do not continue then Recommendation to the clinician: exit scenario

[**case 2:**] If symptoms continue AND patient suffers from rapid cycling then Recommendation to the clinician: Add second mood stabilizer

[**case 3:**] If symptoms continue AND patient does not suffer from rapid cycling then Recommendation to the clinician: Add antidepressant OR second mood stabilizer

[**Step 11:**]

[**case 1:**] If symptoms continue then Recommendation to the clinician: Study again patient's case file

[**case 2:**] If symptoms do not continue AND mood stabilizer has been added then Recommendation to the clinician: Do Full Blood Count(FBC) tests After 6 months Recommendation to the clinician: Do Serum Lithium tests

[**case 3:**] If symptoms do not continue AND antidepressant has been added then After 3 months Recommendation to the clinician: Do Serum Lithium tests

[**Step 12:**] Recommendation to the clinician:Repeat serum lithium tests every 3 months and thyroid and renal tests every 6 months.

1.	Has there ever been a period of time when you were not your usual self and...	YES	NO
	...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	☐	☐
	...you were so irritable that you shouted at people or started fights or arguments?	☐	☐
	...you felt much more self-confident than usual?	☐	☐
	...you got much less sleep than usual and found you didn't really miss it?	☐	☐
	...you were much more talkative or spoke faster than usual?	☐	☐
	...thoughts raced through your head or you couldn't slow your mind down?	☐	☐
	...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	☐	☐
	...you had much more energy than usual?	☐	☐
	...you were much more active or did many more things than usual?	☐	☐
	...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	☐	☐
	...you were much more interested in sex than usual?	☐	☐
	...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	☐	☐
	...spending money got you or your family into trouble?	☐	☐
2.	If you checked YES to more than one of the above, have several of these ever happened during the same period of time? *Please circle one response only.* YES NO		
3.	How much of a problem did any of these cause you—like being unable to work: having family,money, or legal troubles: getting into arguments or fights? *Please circle one response only.* No problem Minor problem Moderate problem Serious problem		

Figure 3.3: Mood Disorder Questionnaire.

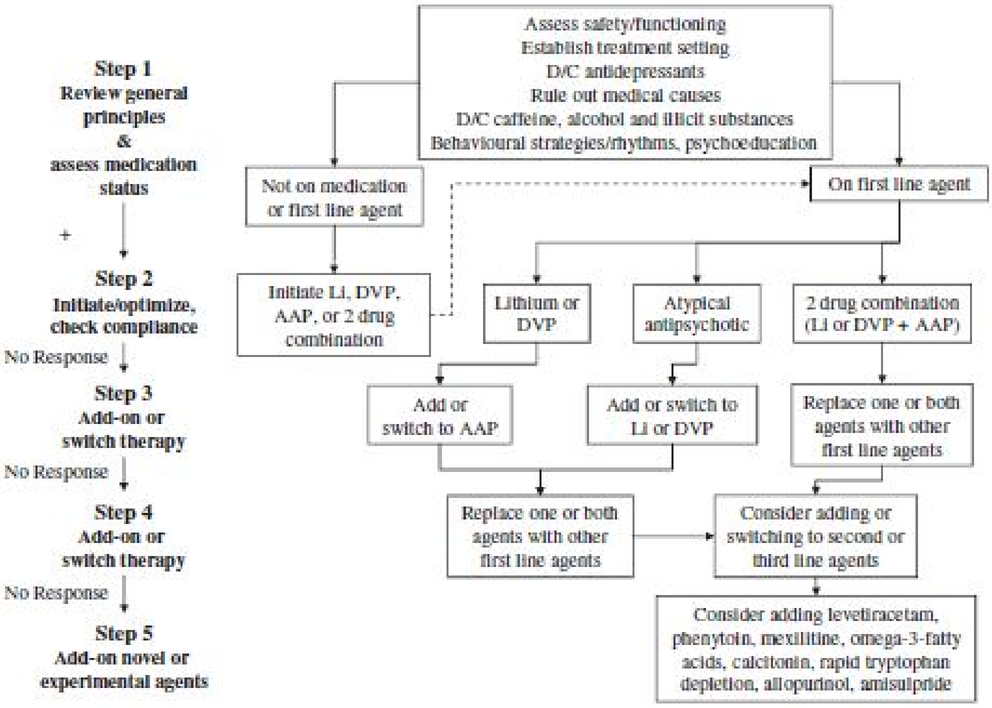

Figure 3.4: Algorithm for acute mania treatment.

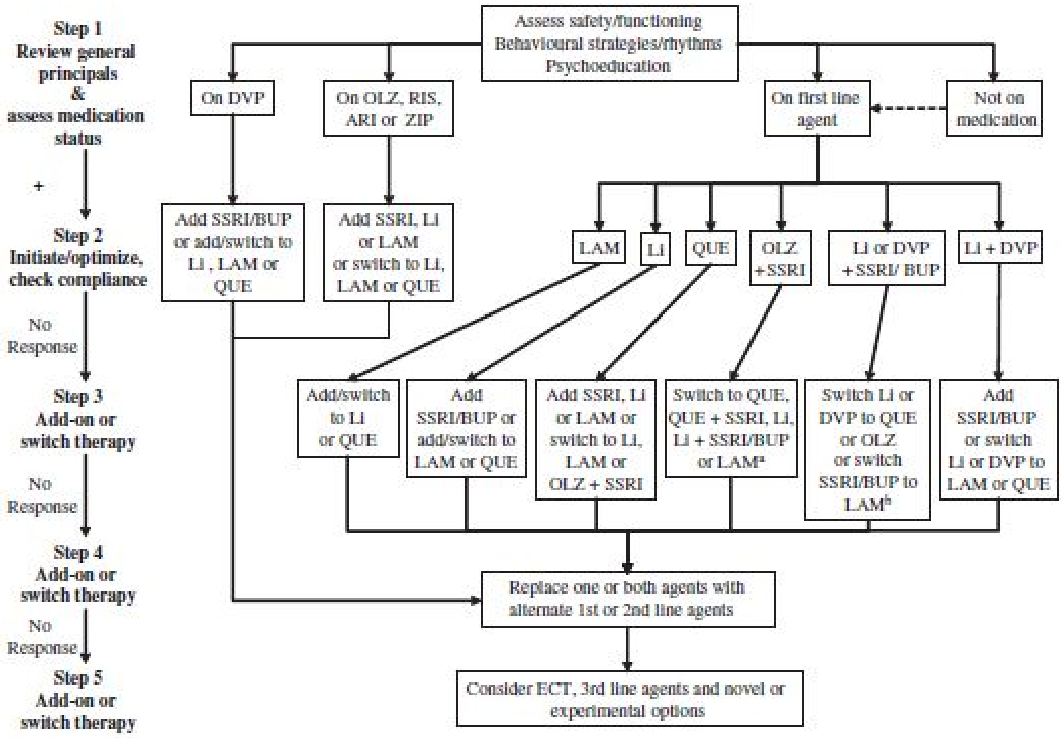

Figure 3.5: Algorithm for bipolar I depression.

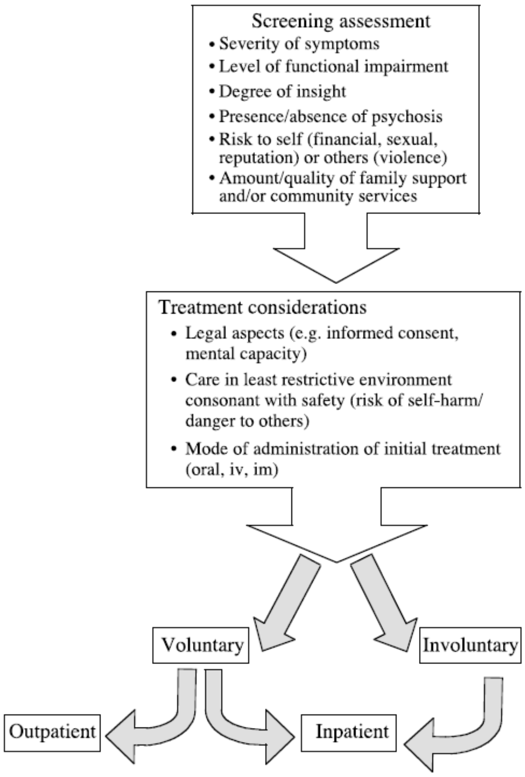

Figure 3.6: Initial Clinical Assessment for manic episode [28].

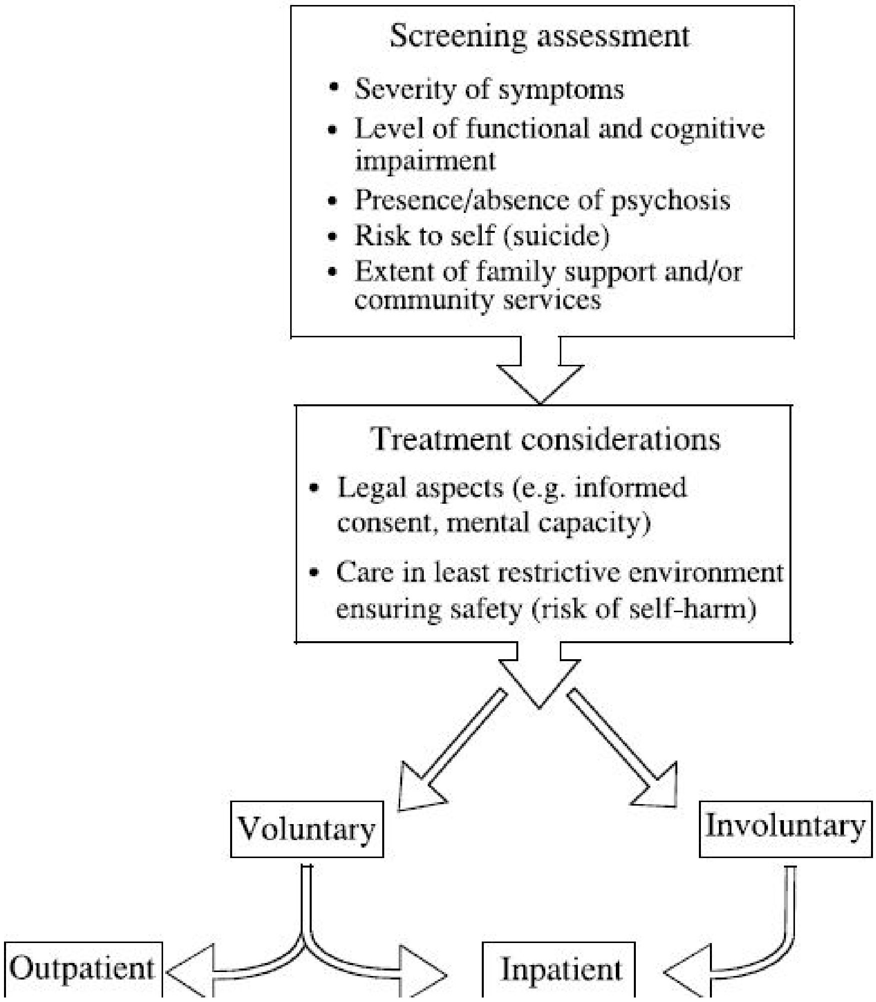

Figure 3.7: Initial Clinical Assessment for bipolar depressive episode [28].

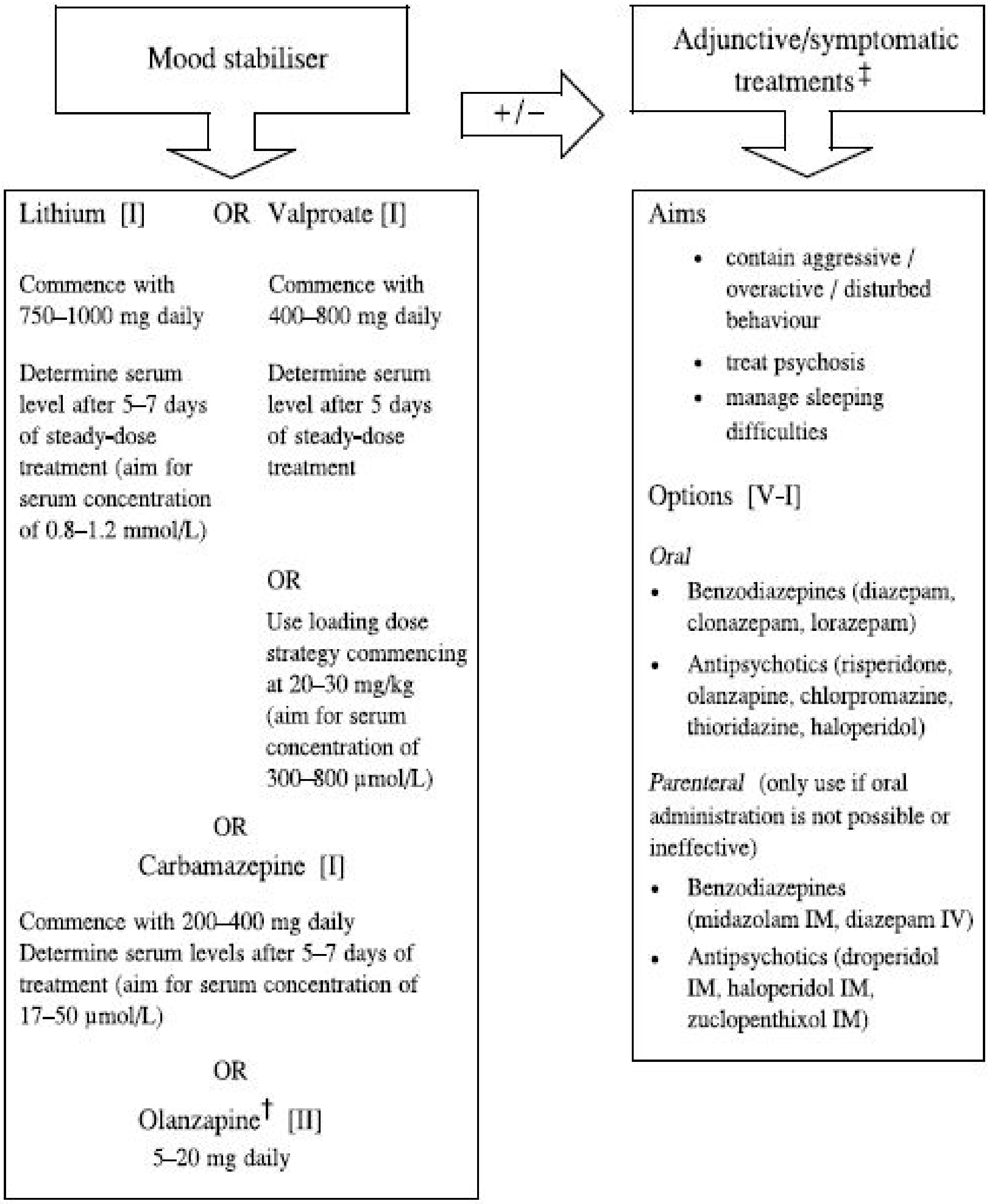

Figure 3.8: Treatment of manic episode [28].

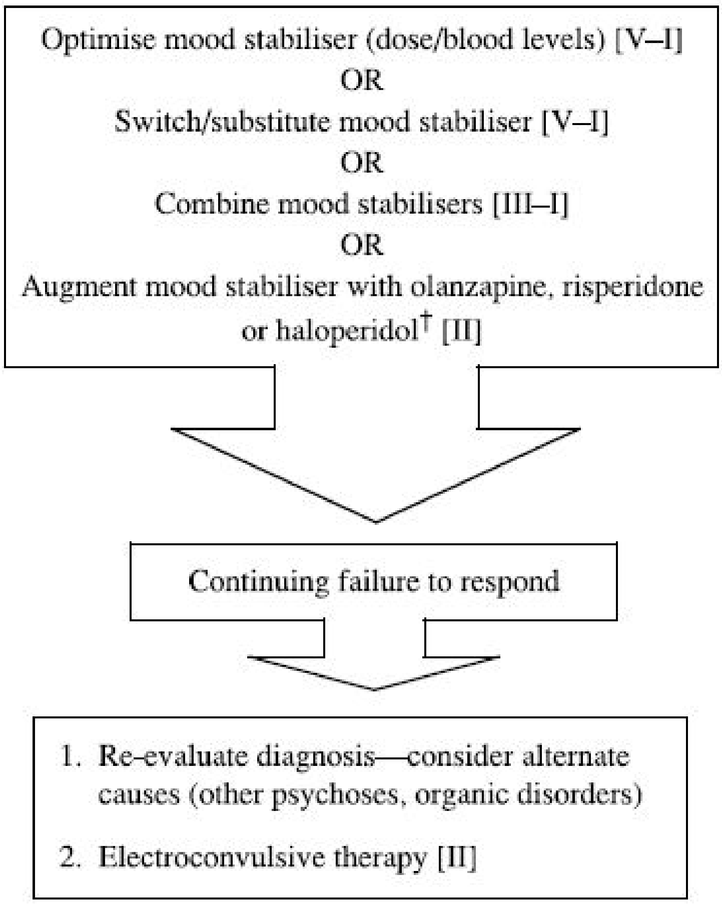

Figure 3.9: Failure to respond to treatment of mania [28].

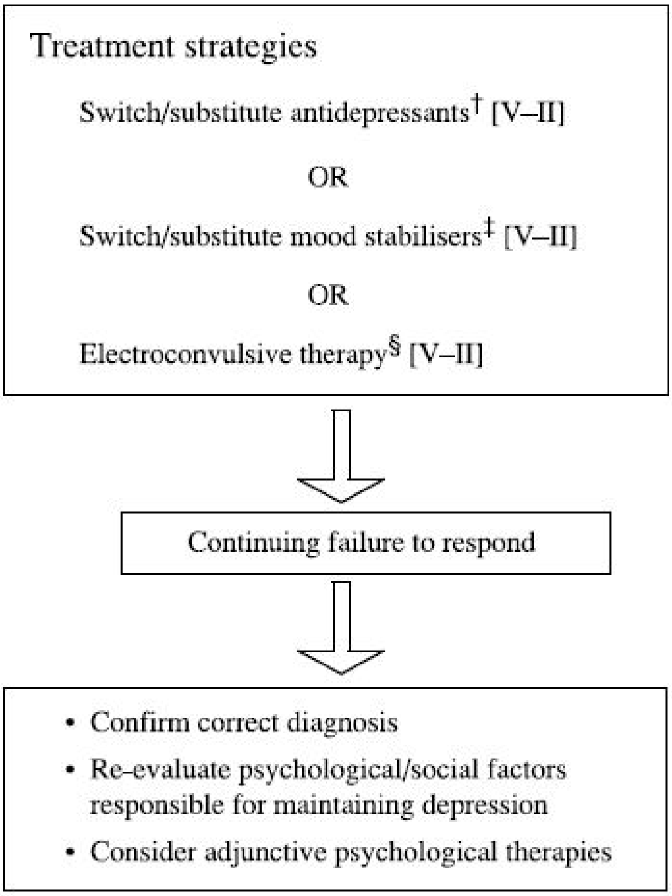

Figure 3.10: Failure to respond to treatment of bipolar depression.

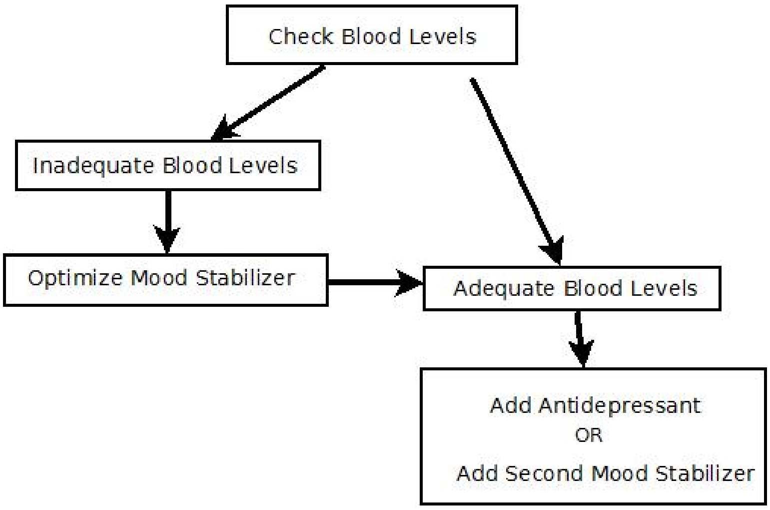

Figure 3.11: Breakthrough Depressive Episode [28].

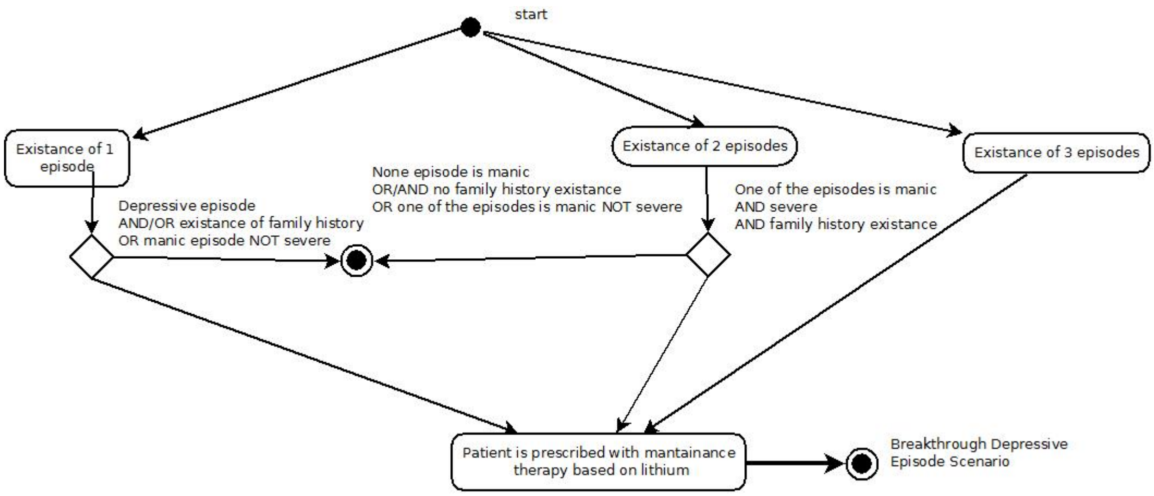

Figure 3.12: Modified Algorithm the clinician decides to prescribe maintenance treatment based on lithium .

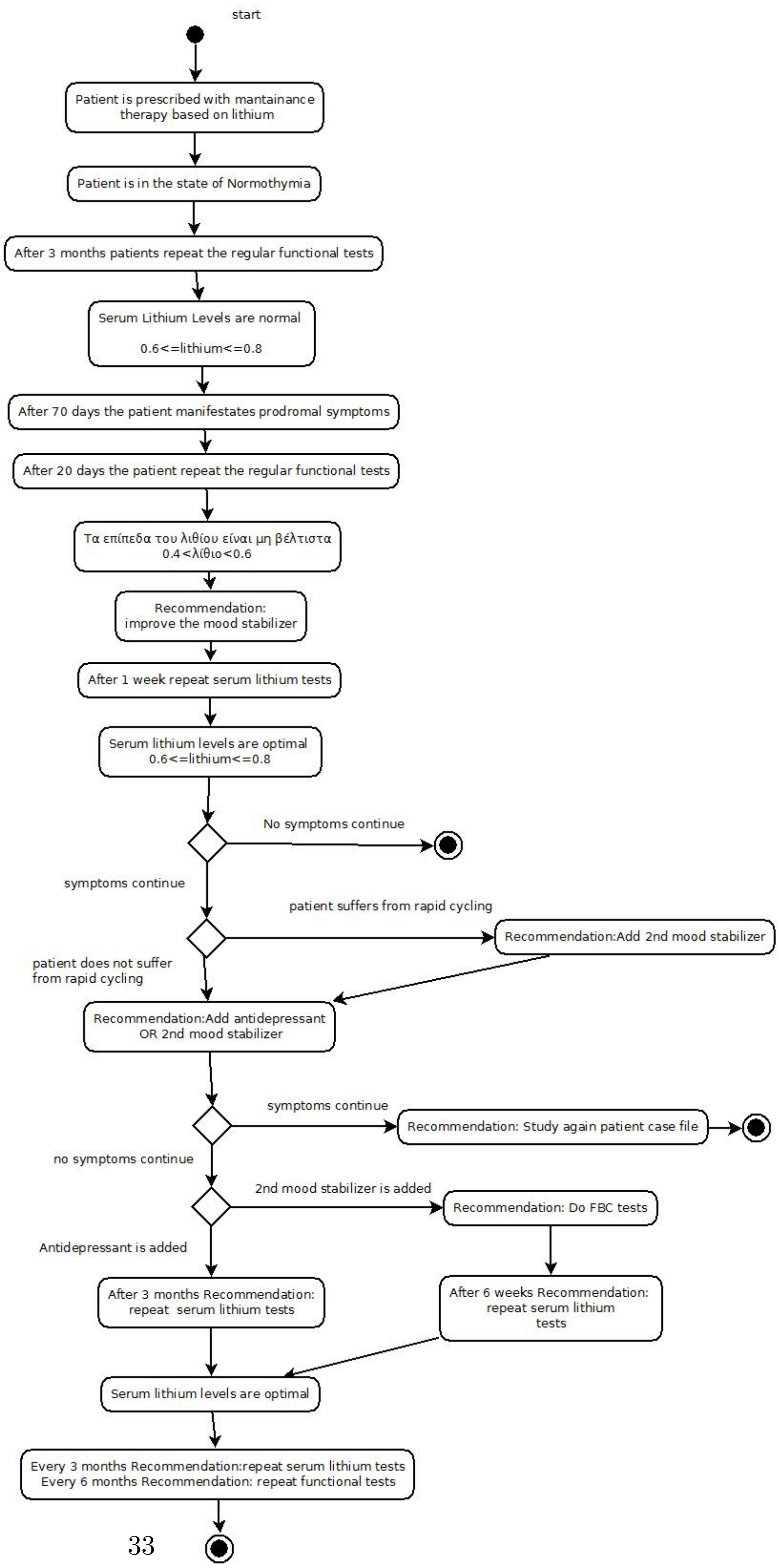

Figure 3.13: Breakthrough Depressive Scenario.

Chapter 4

SybillaTUC

SybillaTUC is a recommendation system designed to represent and manage the information about handling the evolution of patients suffering from Bipolar disorder, and more specific with patients who demonstrate the Breakthrough Depressive Episode Scenario. It also offers recommendations to clinicians following the breakthrough depressive episode algorithm we presented in Chapter 3.

Developing Sybilla TUC we designed an ontology which the information about the patient's profile is collected and represented along with his medical history, his tests results, the therapy followed by the clinician in order to handle with the disorder. Information on the patient's condition and about the episode when one occurs is collected as well. The main entities designed to code these informations are the following:

- **Patient**
- **PatientCase**
- **PatientState**
- **PatientHistory**
- **Therapy**
- **EpisodeInfo**
- **Diagnosis**

In order to implement our presented algorithm and extract recommendations we also gather information about the medicines the patient receives, the normal values the tests should have in order to compare and the recommendations. The main entities designed to code these informations are the following:

- **Medicine**
- **StandarTests**
- **Recommendations**

The object properties of the classes are presented in Figure 4.1. For each object property presented in the diagram exists it's inverse property which we don't present for space saving.

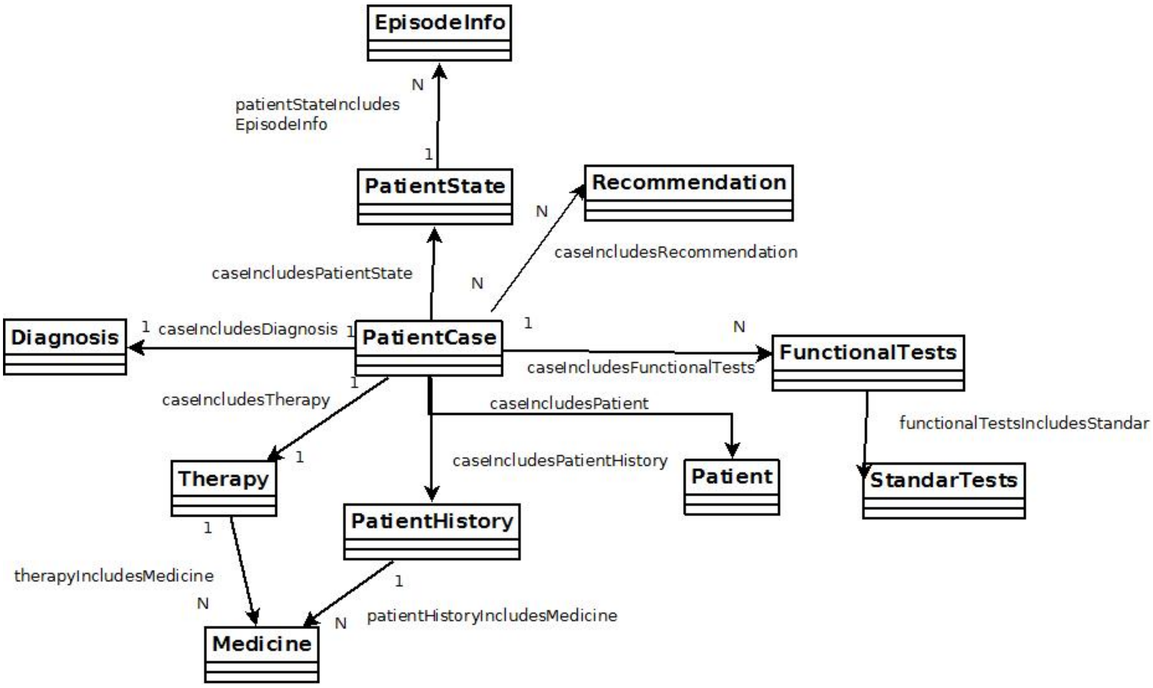

Figure 4.1: Diagram representing the object properties between the classes.

As we have described previously Bipolar Disorder evolves time. For this reason some of the classes of our ontology, their data and object properties have to represent this evolution and they can't remain static. For example the class Patient that stores the patient's profile info does not change over time, having different values from time to time. Patient is a static class. But FunctionalTests which represents the tests the patients does from time to time may have a specific value for a specific interval and a different value for a different interval. FunctionalTests is a dynamic class. In Figure 4.2 with red color we represent the classes and object properties that evolve over time.

For converting our static ontology to the dynamic one we used Chronos Plugin for Protégé OWL Editor. Selecting the class we wanted to convert, we used the functionalities that provides Chronos and we created the temporal ontology. All the convertions needed were done automatically by Chronos.

In Figure 4.3 we provide a whole view of the class diagram for the temporal ontology including the data and the object properties.

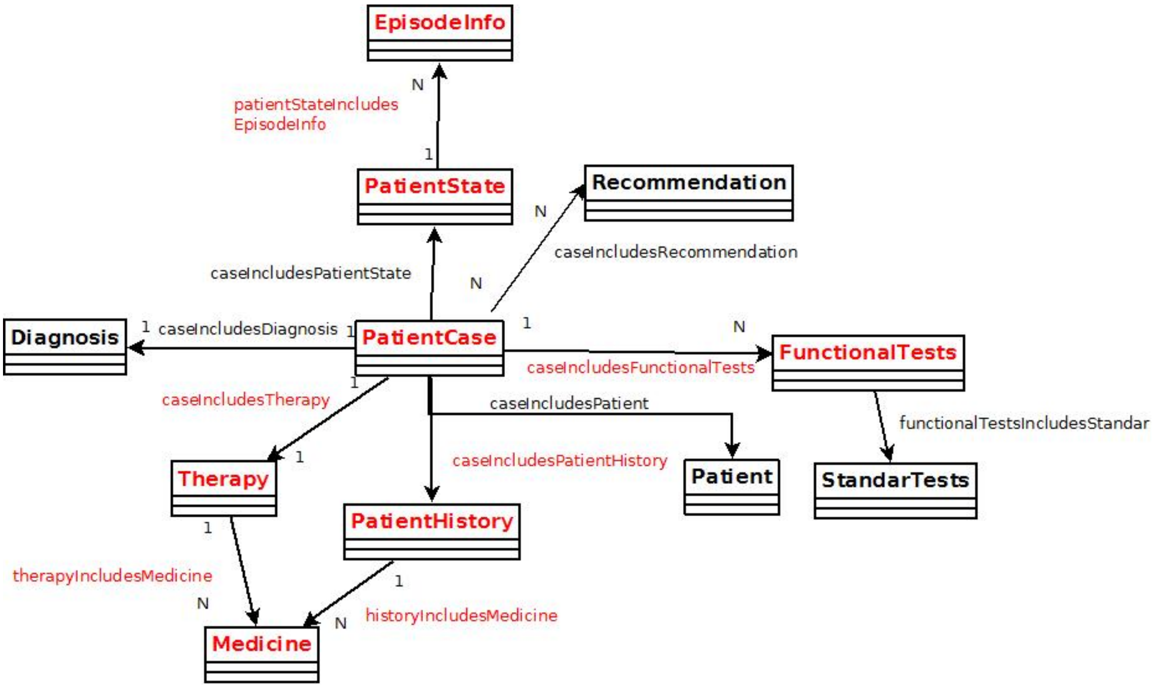

Figure 4.2: Diagram representing the object properties between the classes.With red color are presented the dynamic classes and object properties

4.1 Reasoning

We would like to offer recommendations to clinicians following the presented algorithm. For this reason we applied logical rules on the data and we extract the recommendations. We implemented the rules with SWRL for more powerful reasoning. The recommendations extracted are presented in Appendix A followed by the SWRL code.

4.2 Ontology population

For easing the process of populating the ontology, in order an average user to be able to create his own dataset, we implemented in java code a Graphical Interface, that reacts with the ontology by OWL api code.

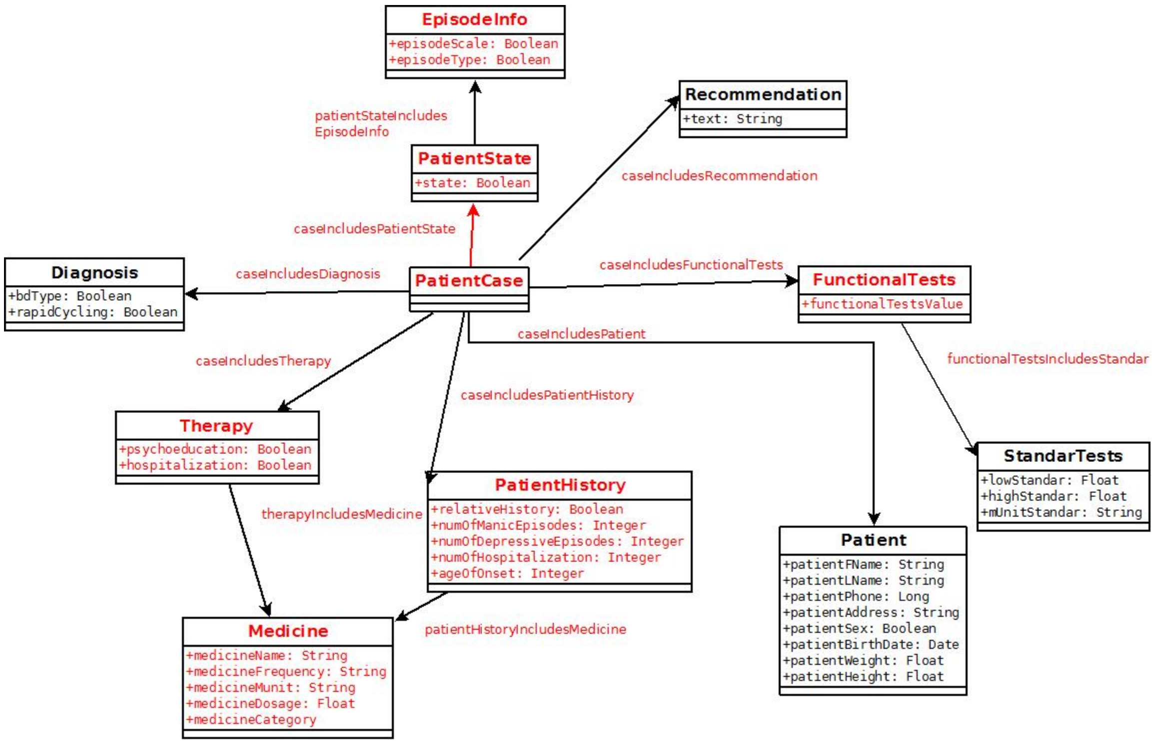

Figure 4.3: Final Class Diagram

Chapter 5

Conclusion and Future Work

In this thesis we presented SybillaTUC a system based on Semantic Web technologies that deals with the evolution of Bipolar Disorder and more specifically with Breakthrough Depressive Episode Scenario. We propose the use of semantic web technologies in order to manage with diseases that evolve in time. It is proposed using ontologies to represent the information needed for the description of the disease(e.g patient's data, the relationships between them) and moreover temporal ontologies to deal with the representation of time that is included in the data. Also reasoning over data offers us the ability to extract the information's static and temporal knowledge, allowing us to observe and predict the evolution of the disease. Sybilla TUC offers clinicians easy and direct access to a patient's medical record, individualized condition monitoring, prediction of the evolution of the disorder and treatment proposal, fast notification of the clinician.

Extensions and future work based on the concept of Sybilla TUC could be: and implement of all the possible scenarios of the disorder. to non-experts the ability to deal with changes that could take place, that have effects on the system(e.g clinical guidelines while changing would effect on our system and it's results),without the presence of informaticians. and implement a system that could predict the evolution of the disorder to the patient and his family.

Chapter 6

AppendixA

6.1 OWL code for Classes

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#Creatinine -->

<owl:Class rdf:about="&SybillaTUC;Creatinine">
<rdfs:subClassOf rdf:resource="&SybillaTUC;FunctionalTests"/>
</owl:Class>
```

Figure 6.1: Creatinine OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#Diagnosis -->

<owl:Class rdf:about="&SybillaTUC;Diagnosis"/>
```

Figure 6.2: Diagnosis OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#EpisodeInfo -->

<owl:Class rdf:about="&SybillaTUC;EpisodeInfo">
<rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.3: EpisodeInfo OWL Code

Medicine in Figure **??**
Patient in Figure 6.7

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#FBC -->

<owl:Class rdf:about="&SybillaTUC;FBC">
<rdfs:subClassOf rdf:resource="&SybillaTUC;FunctionalTests"/>
</owl:Class>
```

Figure 6.4: FBC tests OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#FunctionalTests -->

<owl:Class rdf:about="&SybillaTUC;FunctionalTests">
<rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.5: FunctionalTests OWL Code

PatientCase in Figure 6.8
PatientHistory in Figure 6.9
PatientState in Figure 6.10
Recommendation in Figure 6.11
SerumLithium in Figure 6.12
StandarTests in Figure 6.13
T3test in Figure 6.14
T4test in Figure 6.15
TSHtestin Figure 6.16
Therapy in Figure 6.17
ThyroidTests in Figure 6.18

6.2 SWRL Rules

If serum lithium level
➔ Improve mood

Event(?e1), Event(?e2),
Recommendation(?impr
Interval(?i3), Interval(?i
overlaps(?i4, ?i2), caseI
caseIncludesPatientStat
?e2), inEpisodeOP(?p, ?
?st), text(?improve_moo
mood stabilizer"), lessT
?improve_mood_stabili

Figure 6.23: If serum
symptoms

If antidepressant is
➔ Repeat serum

Event(?e1), Event(?e
Medicine(?m1), Med
Recommendation(?re
Interval(?i2), Interva
during(?e1, ?i1), dur
?i6), during(?e7, ?i7)
caseIncludesFunctio
caseIncludesPatientS
inEpisodeOP(?p, ?e2
therapyIncludesMed
therapyIncludesMed
intervalFinishes(?i2,
?med1), medicineCa
booleanNot(?inepis,
"antidepressant"), eq
?repeat_serum_lithiu

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#Medicine -->

<owl:Class rdf:about="&SybillaTUC;Medicine">
  <rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.6: Medicine OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#Patient -->

<owl:Class rdf:about="&SybillaTUC;Patient">
  <rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.7: Patient OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#PatientCase -->

<owl:Class rdf:about="&SybillaTUC;PatientCase">
  <rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.8: PatientCase OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#PatientHistory -->

<owl:Class rdf:about="&SybillaTUC;PatientHistory">
  <rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.9: PatientHistory OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#PatientState -->

<owl:Class rdf:about="&SybillaTUC;PatientState">
  <rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.10: PatientState OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#Recommendation -->

<owl:Class rdf:about="&SybillaTUC;Recommendation">
<rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.11: Recommendation OWL Code

Figure 6.12: SerumLithium OWL Code

Figure 6.13: StandarTests OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#T3test -->

<owl:Class rdf:about="&SybillaTUC;T3test">
<rdfs:subClassOf rdf:resource="&SybillaTUC;ThyroidTests"/>
</owl:Class>
```

Figure 6.14: T3 OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#T4test -->

<owl:Class rdf:about="&SybillaTUC;T4test">
<rdfs:subClassOf rdf:resource="&SybillaTUC;ThyroidTests"/>
</owl:Class>
```

Figure 6.15: T4 OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#TSHtest -->

<owl:Class rdf:about="&SybillaTUC;TSHtest">
<rdfs:subClassOf rdf:resource="&SybillaTUC;ThyroidTests"/>
</owl:Class>
```

Figure 6.16: TSH OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#Therapy -->

<owl:Class rdf:about="&SybillaTUC;Therapy">
  <rdfs:subClassOf rdf:resource="&owl;Thing"/>
</owl:Class>
```

Figure 6.17: Therapy OWL Code

```
<!-- http://www.semanticweb.org/ontologies/2012/7/SybillaTUC.owl#ThyroidTests -->

<owl:Class rdf:about="&SybillaTUC;ThyroidTests">
  <rdfs:subClassOf rdf:resource="&SybillaTUC;FunctionalTests"/>
</owl:Class>
```

Figure 6.18: ThyroidTests OWL Code

If 2nd mood stabilizer is added and 6 weeks passed since the last functional tests
➔ Repeat serum lithium tests

```
Event(?e1), Event(?e2), Event(?e3), Event(?e4), Event(?e5), Event(?e6), Event(?e7), Event(?e8),
FBC(?f), Medicine(?m1), Medicine(?m2), PatientCase(?x), PatientState(?p),
Recommendation(?do_FBC_tests), Therapy(?t), Interval(?i1), Interval(?i2), Interval(?i3),
Interval(?i4), Interval(?i5), Interval(?i6), Interval(?i7), during(?e1, ?i1), during(?e2, ?i2),
during(?e3, ?i3), during(?e4, ?i4), during(?e5, ?i5), during(?e6, ?i6), during(?e7, ?i7), during(?e8,
?i8), caseIncludesFunctionalTests(?e8, ?f), caseIncludesFunctionalTests(?x, ?e8),
caseIncludesPatientState(?e1, ?p), caseIncludesPatientState(?x, ?e1), caseIncludesTherapy(?e3,
?t), caseIncludesTherapy(?x, ?e3), inEpisodeOP(?p, ?e2), medicineCategoryOP(?m1, ?e5),
medicineCategoryOP(?m2, ?e7), therapyIncludesMedicine(?e4, ?m1),
therapyIncludesMedicine(?e6, ?m2), therapyIncludesMedicine(?t, ?e4),
therapyIncludesMedicine(?t, ?e6), intervalFinishes(?i2, ?i4), intervalFinishes(?i2, ?i6),
durationFBC(?f, ?d), inEpisode(?e2, ?inepis), medicineCategory(?e5, ?med1),
medicineCategory(?e7, ?med2), text(?do_FBC_tests, ?txt), booleanNot(?inepis, ?true), equal(?d,
42), equal(?med1, "mood stabilizer"), equal(?med2, "mood stabilizer"), equal(?txt, "do FBC
tests") -> caseIncludesRecommendation(?x, ?repeat_serum_lithium_tests)
```

Figure 6.19: If 2nd mood stabilizer is added and 6 weeks passed since the last functional tests

If 3 months passed since the last serum lithium tests

➔ **Repeat serum lithium tests**

PatientCase(?x), Recommendation(?repeat_serum_lithium_tests), SerumLithium(?s), caseIncludesFunctionalTests(?e1, ?s), caseIncludesFunctionalTests(?x, ?e1), durationFBC(?s, ?d), text(?repeat_serum_lithium_tests, ?txt), equal(?d, 90), equal(?txt, "repeat serum lithium tests") -> caseIncludesRecommendation(?x, ?repeat_serum_lithium_tests)

Figure 6.20: If 3 months passed since the last serum lithium tests

If 2nd mood stabilizer is added and there are no depressive symptoms

➔ **Do functional tests**

Event(?e1), Event(?e2), Event(?e3), Event(?e4), Event(?e5), Event(?e6), Event(?e7), Medicine(?m1), Medicine(?m2), PatientCase(?x), PatientState(?p), Recommendation(?do_FBC_tests), Therapy(?t), Interval(?i1), Interval(?i2), Interval(?i3), Interval(?i4), Interval(?i5), Interval(?i6), Interval(?i7), during(?e1, ?i1), during(?e2, ?i2), during(?e3, ?i3), during(?e4, ?i4), during(?e5, ?i5), during(?e6, ?i6), during(?e7, ?i7), caseIncludesPatientState(?e1, ?p), caseIncludesPatientState(?x, ?e1), caseIncludesTherapy(?e3, ?t), caseIncludesTherapy(?x, ?e3), inEpisodeOP(?p, ?e2), medicineCategoryOP(?m1, ?e5), medicineCategoryOP(?m2, ?e7), therapyIncludesMedicine(?e4, ?m1), therapyIncludesMedicine(?e6, ?m2), therapyIncludesMedicine(?t, ?e4), therapyIncludesMedicine(?t, ?e6), intervalFinishes(?i2, ?i4), intervalFinishes(?i2, ?i6), inEpisode(?e2, ?inepis), medicineCategory(?e5, ?med1), medicineCategory(?e7, ?med2), text(?do_FBC_tests, ?txt), booleanNot(?inepis, ?true), equal(?med1, "mood stabilizer"), equal(?med2, "mood stabilizer"), equal(?txt, "do FBC tests") -> caseIncludesRecommendation(?x, ?do_FBC_tests)

Figure 6.21: If 2nd mood stabilizer is added and there are no depressive symptoms

Bibliography

[1] Sujansky W: *"The Benefits and Challenges of an Electronic Medical Record:Much More than a "World Processed" Patient Chart."*VJM,169(3):176-183,Sept,1998.

[2] Antezana E,Kuiper M,Mironov V: *"Biological knowledge management:the emerging role of the Semantic Web technologies."*Briefings in Bioinformatics,10(4):392-407,May,2009.

[3] http://www.w3.org/TR/owl2-overview/

[4] Berners-Lee T, HendlerJ ,Lassila O: *"The Semantic Web."* Scientific American,May,2001
http://semanticweb.org/wiki/Semantic$_WebJepsenT$:
"Just What Is an Ontology, Anyway?."$ITPro, Sept - Oct$, 2009.

[5] Johannes Pretorius A: *"Ontologies - Introduction and Overview."* Adapted from: PRETORIUS, A.J., Lexon Visualisation: Visualising Binary Fact Types in Ontology Bases, Chapter 2, MSc Thesis, Brussels, Vrije Universiteit Brussel, 2004.

[6] Horrocks I, Patel-Schneider P.F., Boley H., Tabet S., Grosof B. and Dean M: *"SWRL: A Semantic Web Rule Language Combining OWL and RuleML."* W3C Member submission, 2004.
http://www.w3.org/Submission/SWRL/

[7] Klein M, Fensel D: *"Ontology Versioning for the Semantic Web."* In International Semantic Web Working Symposium, 75-92, California, USA, Jul-Aug 2001.

[8] Welty C and Fikes R: *"A Reusable Ontology for Fluents in OWL."* Frontiers in Artificial Intelligence and Applications, 150:226-236,2006.

[9] Noy N, Rector A: *"Defining N-ary Relations on the Semantic Web."* W3C Working Group Note Apr,2006.
http://www.w3.org/TR/swbp-n-aryRelations/

[10] http://protege.stanford.edu/

[11] M K. Smith, C Welty, D L. McGuinness: *"OWL Web Ontology Language Guide."* W3C Recommendation, Feb 2004.
http://www.w3.org/TR/owl-guide/

[12] Batsakis S, Petrakis E G.M: *"SOWL: Spatio-temporal Representation, Reasoning and Querying over the Semantic Web."* 6th International Conference on Semantic Systems (I-SEMANTICS' 2010), Sept 2010.

[13] Preventis A: *"Chronos: A Tool for Handling Temporal Ontologies in Protégé."* Diploma Thesis, Department of Electonic and Computer Engineering, Technical University of Crete, Feb, 2012.

[14] Makri P: *"4D-Fluents Plug-In: A Tool for Handling Temporal Ontologies in Protégé."* Diploma Thesis, Department of Electonic and Computer Engineering, Technical University of Crete, May,2011.

[15] Horridge M, Bechhofer S: *"The OWL API: A Java API for Working with OWL 2 Ontologies."* The University of Manchester, UK.

[16] Mavrogiannaki E: *"The time dimension in Clinical Guidelines for the management of abnormal gynaecological exam results."* Master's thesis, Department of Electronic and Computer Engineering, Technical University of Crete, Greece, Jun 2011.

[17] Tao C,Wei W.Q,Solbrig H..R,Savova.G,Chute C.G: *"A Semantic Web Ontology for Temporal Relation Inferencing in Clinical Narratives."* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3041418/

[18] Connolly K,Thase M: *"The Clinical Management of Bipolar Disorder: A Review of Evidence-Based Guidelines."* Primary Care Companion CNS Disord, 13(4), 2011.

[19] Mller-Oerlinghausen B,Berghfer A,Bauer M: *"Bipolar Disorder."* The Lancet, 359(9302):241 - 247,Jan,2002.

[20] Mitchel P,Malhi G,Redwood B,Ball J: *"Bipolar Disorder Australian treatment guide for consumers and carers"*. The Royal Australian and New Zealand College of Psychiatrics,Jun,2005.

[21] Olley A, Malhi GS, Mitchell PB, Batchelor J, Lagopoulos J, Austin MP. **"When euthymia is just not good enough: the neuropsychology of bipolar disorder."** J Nerv Ment Dis,193(5):323-30, May,2005.

[22] Goodwin GM,Consensus Group Of The British Association For Psychopharmacology: *"Evidence based guidelines for treating bipolar disorder: revised second edition-recommendations from the British Association for Psychopharmacology."* Journal of Psychopharmacology ,23(4):346-388,2009.

[23] http://allpsych.com/disorders/dsm.html

[24] http://www.who.int/classifications/icd/en/

[25] http://www.cnsforum.com/clinicalresources/ratingscales/ratingpsychiatry/

[26] Editorial Group of Scottish Intercollegiate Guidelines Network(SIGN). *"Bipolar affective disorder, A national clinical guideline.",82,May, 2005.*

[27] *Yatham LN,Kennedy SH,Schaffer A,Parikh SV,Beaulieu S,OĎonovan C,MacQueen G,McIntyre RS,Sharma SV,Ravindran A,Young LT,Young AH,Alda M,Milev R,Vieta E,Calebrese JR,Berk M,Ha K,Kapczinski F:* "Canadian Network for Mood and Anxiety Treatment(CANMAT) and International Society for Bipolar Disorder(ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder:update 2009." *Bipolar Disorder, 225-255,Noe,2009.*

[28] *The Royal Australian and New Zealand College of Psychiatrics Clinical Practice Guidelines Team for Bipoalar Disorder:* " Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder." *Australian and New Zealand Journal of Psychiatry,38:280-305,2004."*

[29] Gitlin M, Frye MA: *"Maintenance therapies in bipolar disorders."* Bipolar Disorder, 14(2):51-65,May,2012, May.

[30] Hopkins HS,Gelemberg AJ: *"Serum Lithium Levels and the outcome of maintenance therapy of bipolar disorder."*. Bipolar Disorders, 2,174-179,2000.

[31] Grunze H,Kasper S,Goodwin G. **" World Federation of Societies of Biological Psychiatry(WFSBP) Guidelines for Biological treatment of biological disorder. Part I. Treatment of bipolar depression."** World Journal of Biological Psyciatry, 3:115-124,2002.

[32] Grunze H,Kasper S,Goodwin G. **" World Federation of Societies of Biological Psychiatry(WFSBP) Guidelines for Biological treatment of biological disorder. Part II. Treatment of mania."** World Journal of Biological Psyciatry, 4:5-13,2003.

[33] National Collaborating Centre of Mental Health. **" Bipolar Disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care."** NICE Clinical Guideline 38,Jul 2006.

[34] Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, Bowden CL, Calabrese JR, Crismon ML, Ketter TA, Sachs GS, Swann AC: *"Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder."* J Clin Psychiatry, 66(7):870-86, Jul,, 2005.

[35] Gardner RM, Overhage JM, Steen EB, Munger BS, Holmes JH, Williamson JJ, Detmer DE: *"Core Content for the Subspecialty of Clinical Informatics."* J Am Med Inform Assoc,6(2):153-7,Mar-Apr,2009.

[36] Vdovjac R,Fransicar F,Houben G,Barna P : *"Engineering Semantic Web Information Systems."* http://people.few.eur.nl/frasincar/papers/PACIS2003/pacis2003.pdf