Prediction of the Evolution of Bipolar Depression using Semantic Web Technologies

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Abstract—In our study we present a design for a decision support system for patients suffering from Bipolar Disorder (BD). Bipolar Disorder is a recurrent and highly disabling psychiatric illness that evolves constantly in time and often leads to crucial incidents. We focus on Bipolar Depression and especially on a Breakthrough Depressive Episode scenario that occurs when a patient shows depressive symptoms during pharmaceutical treatment. Using Semantic Web Technologies we developed SybillaTUC, a prototype Clinical Decision Support System which combines the clinical guidelines for Bipolar Disorder with a patient's condition and his medical record. The system is able to predict the evolution of the disease for each patient, alerting the clinician on the possibility of a crucial incident suggesting optimal treatment.

Keywords—Semantic Web; Clinical Decision Support Systems; Bipolar Disorder; Breakthrough Depressive Episode

I. INTRODUCTION

The world wide use of computer technology during the last few years has generated additional interest in methods and tools aiming at 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. Clinical Decision Support Systems (CDSS) [1] are currently being applied to support health care processes. Their primary task is representation of knowledge on a specific clinical domain. They also deal with understanding, designing and implementing ways of formally coding (in the form of rules and facts concerning the clinical domain at hand) knowledge that is necessary for reasoning over existing knowledge for planning future activities and problem solving [2]. CDSS can generate reports of patient's tests, suggest when the medication a patient receives has to be recalled or, suggest changes in patient's monitoring processes. They can also notify clinicians when a patient's test result requires prompt attention. Computerized clinical guidelines can help clinicians plan diagnostic and treatment strategies according to selected guidelines, or 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 effectively [3] and by this analysis, design better treatment strategies for populations or individuals.

Diseases that evolve in time require monitoring patient's condition of the disease by the clinicians often for long periods of time. Often, clinicians have to manage crucial incidents that require direct response based on their good knowledge of the patient's medical record in accordance to the medical guidelines that are in effect for the disease under consideration. That is not an easy task in cases where when clinicians have to deal with many patients especially when their disease progresses fast or unexpectedly.

Main advantage of CDS systems is that they can provide powerful knowledge representation and management instruments whereas their main disadvantage is their incapability to handle information evolving in time. State-of-the-art information representation and reasoning methods have limited expressive power for describing real world changing processes. For example, the knowledge that a person will go through the stages of infant, adolescent, adult as a result of time, cannot be adequately described using existing methods. This is valuable information that has to be taken into account by the clinicians when dealing with chronic patients or when a patient has undergone several examinations during his/her life time for the same or different diseases. Semantic Web Technologies are being developed in nowadays to meet the challenge of knowledge management in a world of distributed and interconnected resources. They provide solutions to problems of CDSS development relating to data integration, knowledge representation and reasoning [2]. Application examples of Semantic Web Technologies in CDS systems include among others, encoding of clinical practice guidelines [4] and disease management [5-7]. None of these systems handles temporal information and deal with evolution of a disease in time.

We focus our attention on Bipolar Disorder (BD), a disease which is characterized by long periods of evolution and treatment (clinical) guidelines that change often causing certain difficulties in providing trustworthy medical care to patients. BD is a long-term and often severe psychiatric disease characterized by switching from mania or hypomania to its opposite pole of depression and *vice versa* that needs long-term care. The International Classification of Diseases of the World Health Organization (ICD-10) and the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association provide important diagnostic guidances for the classification of BD. Symptom severity measures include most frequently the 17-item or 21-item Hamilton Depression Rating (HAM-D) Scale for depression and Young Mania Rating Scale (YMRS) for mania. According to DSM-IV, BD is dividing into bipolar I (at least one manic episode) and bipolar II (hypomania and depression). Past work [22-23] deals with breakthrough depression which arises in established BD when treatment is in place, and is distinguished from *de novo* depression that arises in the absence of medication.

Although BD is associated with functional impairment, psychosocial disability, high suicide risk and often poses multiple relapses, little is known about the prediction of the evolution of BD and the effects of early intervention in

patients with prodromal symptoms of this disorder, especially with those of breakthrough depression. As the number of bipolar depressive episodes is recognized as an important indicator of well-functioning of bipolar patients, and as the number of past depressive episodes appears to impact the outcome of the disease to a greater extent than past manic episodes, it is important to recognize these prodromal symptoms. This may help in preventing a bipolar depressive episode and for suggesting optimal therapies. At the same time, it may become crucial for the prevention of new breakthrough depressive episodes [8]. Recent advances in clinical research related to BD, have contributed to the better understanding of the disease and its evolution in time. However, despite of technological achievements in information and Semantic Web technology during the last few years, developing computerized methods assisting to the early prevention of BD episodes is still challenging [9]. This would not only enhance the quality of medical health care but also, improve the quality of life of patients suffering from the disease.

To meet this challenge, we developed and implemented SybillaTUC, a CDSS for patients suffering from the Bipolar Disorder disease. It is designed to represent and manage information about patient's medical record and the modeling of the evolution of the disease. Combining the clinical guidelines for Bipolar Disorder with a patient's 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 clinical practice guidelines.

Sybilla TUC represents patient's and disease information as well as expert's knowledge by means of an ontology. SybillaTUC implements an ontology for modeling bipolar patients for which the breakthrough depressive symptoms are induced during lithium medication monotherapy. By using 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 that 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 record.

Dealing with the evolution of BD disease in time calls for temporal ontologies and also for tools for handling temporal information. Temporal ontologies are implemented using OWL [10] (the standard language for representing knowledge in ontologies) and the so called "N-ary relations" [11] approach for representing concepts evolving in time. SybillaTUC employees CHRONOS [12], a tool for handling temporal ontologies i.e., describing static and temporal concepts as well as the concepts that evolve in time in OWL. Hence, developers do not have to deal with the peculiarities of Semantic Web methods for dealing with temporal ontologies. Decision making relies on information stored in patient records, knowledge acquired by experts on handling the disease as well as on clinical guidelines (e.g., for, issuing alerts when patient condition changes from stable to unstable). Decision making is realized as a reasoning system which is implemented using SWRL [13] (the Semantic Web rule language for ontologies in OWL).

The rest of this paper is organized as follows: Background information such as Semantic Web technologies and tools used for implementing the BD ontology are described in Section 2. The Depressive BD scenario implemented in SybillaTUC is discussed in Section 3. Implementation of the SybillaTUC system is presented in Section 4 followed by discussion, conclusions and issues for future research in Section 5.

II. METHODS AND PROCEDURES

Semantic Web standards such as ontology construction languages (OWL), reasoning and rules (SWRL) as well as related work in the field of temporal knowledge representation using description logics are discussed in the following.

A. Description Logics

Description Logics (DLs) are a family of Knowledge Representation languages that form the basis for the Semantic Web standards [14]. The basic components of a Description Logic formalism are the concepts or classes, their properties or roles and the individuals or objects. Individuals represent objects in the domain of interest. Classes represent sets of individuals (or sets of objects) that share some common features, constraints and semantics. Properties are directed binary relations denoting class characteristics. They are distinguished into Object properties (i.e., relations between two classes) and Datatype properties (i.e., relations between instances of classes, and RDF literals or XML schema datatypes).

The OWL language [10] is based on DLs and is the standard for publishing and sharing ontologies on the World Wide Web. Accordingly, OWL is intended to provide a language that can be used to describe classes and as well as properties of classes in Web documents and applications. Semantic Web Rule Language (SWRL) [13] is the language for specifying rules applying on Semantic Web ontologies. SWRL allows for defining rule expressions involving OWL concepts enabling more powerful deductive reasoning than OWL alone.

B. Temporal Representation

Representing information evolving in time in ontologies is a difficult problem to deal with. The syntactic restriction of OWL to binary relations complicates representation of temporal properties, since a property holding for a specific time instant or interval is a relation involving three objects (an object, a subject and a time instant or interval). Binary relations simply connect two instances (e.g., the therapy with the medicine) without any temporal information. Temporal relations are in fact ternary (i.e., properties of objects that change in time involve also a temporal value in addition to the object and the subject) and cannot be handled directly by OWL. Nevertheless, a representation using OWL is feasible, although complicated. In addition, reasoning over temporal information in OWL, as well as maintaining property and data semantics (e.g., cardinality restrictions) are also issues that need to be handled. SOWL (Spatiotemporal OWL) [15] handles all these issues.

Representation of dynamic features calls for mechanisms that allow uniform representation of the notions of time (and of properties varying in time) within a single ontology.
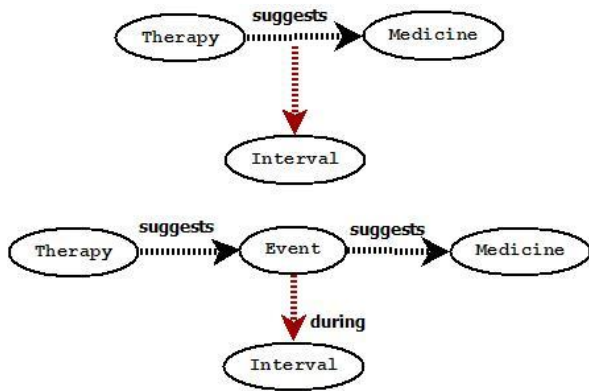
Fig. 1. N-ary Representation Model: individual of class Medicine and subject of class Therapy (above) are now related to the new object Event (below).

Existing methods for achieving this include, among others, versioning [16], N-ary relations [11] and the 4D-fluents (perdurantist) approach [17]. All result in complicated ontologies compared with their static counterparts where all relations do not change in time.

The N-ary relations approach suggests representing an n-ary relation as two properties each related with a new object. This approach requires only one additional object for every temporal relation. A temporal property between two individuals (e.g. "Therapy suggests Medicine") 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 introduce additional binary links to each argument of the relation. For properties that change in time, their domains and ranges have to be adjusted taking into account the classes of intermediate objects representing the relation. Fig.1 illustrates the static relation between concepts "Therapy" and "Medicine" and its temporal representation based on the N-ary Representation Model.

In this work, we start the design with a static ontology representing the main concepts of the Bipolar Disorder disease scenario (described in Sec. 3). This initial ontology is developed using a common ontology editor such as Protégé OWL Editor [18] and it is converted to temporal afterwards using the CHRONOS Plugin of Protégé. CHRONOS is available on the Web[1].

C. SOWL

SOWL [15] is an ontology framework for representing and reasoning over spatio-temporal information in OWL. Building-upon well established standards of the semantic Web (OWL 2.0, SWRL) SOWL enables representation of static as well as of dynamic spatio-temporal information. Reasoning in SOWL is realized by introducing a set of SWRL rules operating on temporal relations. A temporal relation can be one of the 13 pairwise disjoint Allen's relations between time points or temporal intervals such as "before", "after", "during", "equals" etc.

III. SYBILLATUC

A. BD: Breakthrough Depressive Episode Scenario

Bipolar disorder is a lifelong illness that is characterized by high comorbidity risk and poor health outcomes. The management of acute mood episodes should focus on safety, include psychiatric consultation as soon as possible and also be handled according to an evidence-based treatment that may be continued during the maintenance phase.

Long-term management focuses on maintenance of eythymia which is the primary goal, requires ongoing medication, and may benefit from adjunctive psychotherapy. Maintenance treatment is the suggested treatment of bipolar disorder during eythymia state. The goal of maintenance treatment is the prevention of future mood episodes. Typically, maintenance treatment follows the continuation phase, in which the goal is preventing a relapse into a same episode for which acute treatment has begun [19]. The possible goals of a clinician for maintenance treatment may be:

- Abolitions of episodes and mood swings,
- Decreased number of episodes,
- Decreased 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 [20]. 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 conveys with it and the adverse implications inherent in treatments [15].

In this context, we assume a Breakthrough Depressive Episode scenario, where a patient suffering from Bipolar Disorder I in the state of eythymia and receives treatment with lithium, displays breakthrough depressive symptoms caused by pharmaceutical treatment and may indicate an onset of bipolar depression [8, 21].

Keck (2004) reports that the pharmacological decisions for effectively treating these episodes should rely on the mood state the patient was experiencing prior to a breakthrough depressive episode, the type of drug received and the patient's history (e.g., hospitalization, number of episodes). Therefore, the best clinical approach for dealing with breakthrough depressive episodes and patients who have undergone a stage of eythymia, suggests optimizing the current medication therapy (dosage, dose frequency), or determine other treatment options (e.g., adjunctive therapy) [8]. For example, there is evidence that rapid-discontinuation of lithium will lead to a high rate of relapse (5% of patients relapse within 5 months) [22]. In this case, clinicians should find the best treatment in order to preserve the patient in the state of eythymia.

In our study, we investigate on providing recommendations to clinicians on optimal treatment of Depressive patients by leveraging information associated with a Breakthrough Depressive Episode scenario and clinical practice. As a proof of concept, we focus on a Breakthrough

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[1] http://www.intelligence.tuc.gr/prototypes.php

Depressive Episode Scenario, which is selected according to the following criteria: (a) The condition of the patient evolves in time, (b) it is relative simple regarding treatment options, compared to other potential scenarios, (c) emphasizes the importance of optimizing maintenance treatment for the prevention of mood episodes caused by treatment, (d) focuses on identifying prodromal symptoms for early intervention in BD aiming at preventing relapses or suicide attempts. The Breakthrough Depressive Episode Scenario under this setting, is being handled by a decision support system whose purpose is to provide recommendations to clinical experts for the optimal treatment of patients.

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 under long-term treatment with lithium, are typically stabilized at serum lithium concentrations between 0.6 mEq/L and 1.0 mEq/L. In certain cases (although 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 [16]. Lithium levels above 0.8 mEq/L presumably exhibit better protection than lower levels. At the same time, clinical evidence and some experimental data suggest that many patients with bipolar disorder and moderate lithium levels (e.g. 0.6-0.8 mEq/L) - or in some cases even lower levels - are assumed to be better protected [21]. The problem of individualized dose finding in maintenance treatment, however, is that the clinician cannot predict whether a given level of lithium dose is sufficiently protective until an episode occurs [21].

We focus on exploiting well established evidence-based treatment guidelines for improving the quality of treatment during a breakthrough depressive episode [22-24]. Based on these guidelines, algorithms for indications for maintenance treatment, for the breakthrough depressive episode and its treatment options were combined together in the design of the scenario. Recommendations for therapeutic drug monitoring are discussed as well due to their importance in patient safety, particularly for the primary care physician.

Recommendations based on these guidelines are meant to provide a framework for clinical decision making, not to replace clinical judgment. As new evidence and additional medications become available, it is expected that treatment practices and their supported algorithms will evolve beyond recommendations [25].

Fig. 2 outlines the procedure that a clinician typically follows in order to prescribe a maintenance treatment based on lithium.

B. Algorithm for Breakthrough Depressive Episode

In the following, we first, propose an algorithm for constant monitoring for patients and for deciding best medical treatment based on patient's condition.

STEP 1: The patient receives a pharmaceutical treatment based on mood stabilizer Lithium.
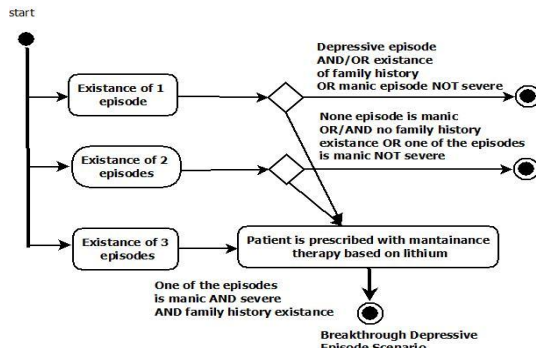
STEP 2: The patient is in eythymia phase.

Fig. 2. Algorithm for prescribing treatment based on lithium.

STEP 3: Serum Lithium tests results are in normal levels (0.6<value<0.8).

STEP 4: 70 days after Serum Lithium tests, prodromal symptoms appear.

STEP 5: 20 days after the appearance of prodromal symptoms, the patient undergoes his regular functional tests.

STEP 6: Serum lithium tests levels 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 levels are optimal (0.6 ≤value≤ 0.8).

STEP 10: *Check if despite the optimal serum lithium levels the symptoms persist. In that case, we have to provide an alternative pharmaceutical treatment:*

Case 1 If symptoms do not persist then Recommendation to the clinician: exit scenario.

Case 2 If symptoms persist AND patient suffers from rapid cycling then Recommendation to the clinician: Add second mood stabilizer.

Case 3 If symptoms persist AND patient does not suffer from rapid cycling then Recommendation to the clinician: Add antidepressant OR second mood stabilizer.

STEP 11: *Depending on the pharmaceutical treatment provided previously we recommend the appropriate clinical tests at an appropriate time:*

Case 1 If symptoms do not persist 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 2 If symptoms do not persist AND antidepressant has been added then After 3 months Recommendation to the clinician: Do Serum Lithium tests.

Case 3 If symptoms persist then Recommendation to the clinician: Study again patient's case file.

STEP 12: Optimal treatment. Recommendation to the clinician: Repeat serum lithium tests every 3 months and thyroid and renal tests every 6 months.

The proposed scenario integrates and combines episode and treatment algorithms along with patient's history and systematical assessment of prodromal symptoms, medical comorbidities and risk factors, as well as individualized pharmacological and psychosocial interventions that meet patient's needs in drug compliance, relapse prevention, for improving quality of life. In line with the most recent efforts in this field [26-27], we attempt to create a chronic care ontology model based on acquiring and utilizing personal and medical information from patients in order to provide feedback for an evidence-based intervention, the longitudinal monitoring and the best management for BD patients.

IV. IMPLEMENTATION

SybillaTUC implements a recommendation system for suggesting optimal treatment to clinicians according to the depressive episode scenario described above.

Initially, we design an ontology representing information about the patient's profile including medical history, test results and therapy followed by the clinician. Information on the patient's condition when an episode occurs is collected as well. Below are the main concepts (entities) represented in the ontology:

Static entities:

- Patient: patient's profile; first and last name, age, address, sex etc.
- EpisodeInfo: manic or depressive episode and it's severity.
- Diagnosis: type of the disorder-Type I or Type II- the patient is or is not suffering from rapid cycling.
- StandarTests: highest and lowest optimal values of each clinical test the patient is submitted.

Dynamic entities (entities which evolve in time):

- PatientCase: the patient's medical record.
- PatientState: the patient is in eythymia or in an episode.
- PatientHistory: patient's medical history; at which age the disease appeared; if he/she has been hospitalized; the number of manic or depressive episodes has occurred; if a relative also suffers from the disease; the medication a patient may have received at previous years.
- Therapy: hospitalization and other therapeutic approaches, such as psychotherapy.
- Functional Tests: serum lithium tests, thyroid tests, creatinine tests, FBC tests.
- Medicine: information about the medicine the patient receives; medicine name, category, dosage etc.
- Recommendations: the recommendation that is proposed to the clinician.

Converting the static ontology to dynamic is realized using the CHRONOS tool of Protege (by selecting the classes to be converted from static to dynamic). When necessary, temporal intervals are assigned to temporal classes. Fig. 3 illustrates the temporal ontology representing both static and dynamic concepts (evolving in time) which are important in encoding the condition and for monitoring BD patients under Breakthrough Depressive Episode scenario. Static classes and static relations are marked in Fig. 3 with a grey background.

As presented in Fig. 3, class PatientCase is connected with classes Patient, PatientHistory, Therapy, Diagnosis, FunctionalTests, PatientState and Recommendation allowing the system to access easily the information of these classes when it accesses PatientCase. Class PatientState is connected with class EpisodeInfo allowing the system to represent knowledge on the type and the severity of an episode when a patient is in an episode state. Class FunctionalTests is connected with class StandarTests allowing the system to decide if a clinical test has optimal value or not. Class Therapy and PatientHistory are connected with class Medicine allowing the system to represent knowledge about the medicines that a patient may receive at the present or has received at the past.

In order to provide recommendations to clinicians based on the scenario of the Breakthrough Depressive Episode presented previously, we implement a reasoning system using SWRL. For example, when a patient, who is not diagnosed with rapid-cycling (four or more mood episodes within 1 year), presents depressive symptoms while his serum lithium test value is optimal, the rule should issue a recommendation to the clinician to add antidepressant or second mood stabilizer. The system issues a recommendation to the clinician based on the following rule expressed in Description Logics [14]:

$$PatientCase \cap \exists caseIncludesDiagnosis.rapidCycling = false \cap (\exists caseIncludesFunctionalTests.functionalTestsValue \geq 0.6 \cap \langle f \rangle \exists caseIncludesPatientState.state = true) \longrightarrow Recommendation \ (add \ antidepressant \ OR \ 2^{nd} \ mood \ stabilizer).$$

For communicating with the ontology (e.g, for populating, the ontology with new patients, updating patient's condition with new tests and their values) we created a Graphical User Interface.

V. CONCLUSIONS

We introduce SybillaTUC, a recommendation system for monitoring patients suffering a Breakthrough Depressive Episode. Building upon state-of-the art technologies for representing patients, their condition and its evolution in time, the Breakthrough Depressive Episode as well as patients associated with such a scenario, are represented by temporal ontologies. SybillaTUC issues recommendations to clinicians for optimal handling of patients by accommodating changes of patient's condition in the monitoring processes. Reasoning over temporal concepts as patient's condition evolved in time is unique feature of SybillaTUC.

A. Advantages and limitations

SybillaTUC offers clinicians easy and direct access to a patient's medical record achieving constant and individualized monitoring of a patient's condition. The system provides individualized prediction of the evolution of the disorder and treatment proposal, early warnings of patient's condition to the clinician.

For the evaluation of the system performance we worked on synthetic data. Similarly to the majority (approximately 90%) existing clinical decision support systems, is not yet tested on lab conditions and even less in real trial datasets [28]. We acknowledge that this is a limitation of the present study. SybillaTUC can potentially become a tool for carers and family members, who are not familiar with informatics technologies, the ability to report mood changes observed
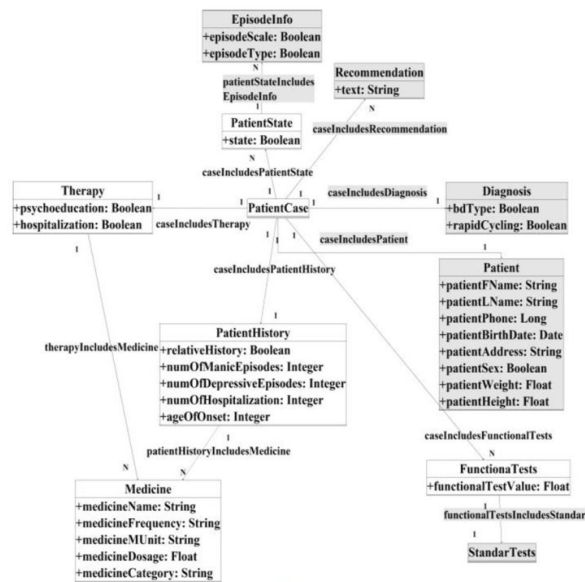
Fig. 3.   The Ontology

during this long-standing disease (e.g. prodromal symptoms); our system in turn will process this information and prevent the recurrence of a new episode (depression, mania) and suicide attempt.

B. Extensions and Future Work

Extensions and future work include among others the design and implementation of more scenarios of the BD such as the transition hazard from bipolar depressive episodes to opposite episodes of BD.

Acknowledgment

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