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Referent Tracking for Treatment Optimisation in Schizophrenic Patients

(Extended version)

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Abstract

The IPAP Schizophrenia Algorithm was originally designed in the form of a flow chart to help physicians optimise the treatment of schizophrenic patients. We examined the current version from the perspective of recent work on terminologies and ontologies thereby drawing on the resources of Basic Formal Ontology, and this with the objective to make the algorithm appropriate for Semantic Web applications. We found that Basic Formal Ontology is a rich enough theory to represent all the entities involved and that applying the theory to the IPAP schizophrenia algorithm results in a representation that can be used by software agents to perform monitoring and control in a referent tracking environment.

Keywords

Referent tracking; IPAP; schizophrenia algorithm, realist ontology; Basic Formal Ontology, electronic health record; automated decision support

I. Introduction

Schizophrenia is one of the principal mental disorders whose treatment is still a major problem [1]. The International Psychopharmacology Algorithm Project (IPAP) is an internationally supported initiative set up in 1985 by a team of psychiatrists, psychopharmacologists and algorithm designers in an effort to improve choice of medication in psychiatry [2]. In 1995 [3], a guideline was published by IPAP, consisting of four schizophrenia treatment algorithms developed, respectively, for the first schizophrenic episode, long-term medication maintenance, schizophrenia complicated by comorbid psychiatric disorders, and schizophrenia complicated by neuroleptic malignant syndrome. In January 2005, the latest version of this IPAP guideline (v. 20041223) was released and made available on the web [4].

The algorithm is presented in the form of a flow-chart, which has one entry condition – namely an established diagnosis of schizophrenia or schizoaffective disorder – and two exit conditions, one suggesting a modification to the patient's current treatment program, the other suggesting unaltered continuation of this program. Nodes in the chart represent either questions related to the condition of the patient or instructions on how to modify the existing treatment regimen. In the electronic, hyper-linked version of the flow-chart, the former point the user to more detailed specifications of symptoms to look for, the latter to drugs which might be prescribed and to scientific papers motivating treatment suggestions. The whole is also available in a pdf format that can be printed out and consulted when the clinician is not on-line.

The on-line version provides some obvious advantages over a traditional journal or textbook publication. It can be accessed immediately through any suitable browser, and new versions become immediately accessible as soon as they are released. On the other side, however, given that the algorithm is currently implemented as a simple flow-chart in which the

included hyperlinks serve only human browsing, it still fails to exploit the real power of the computer, which is to perform reasoning automatically. An implementation could for instance draw on information already available in the patient's electronic health record (EHR) in such a way as to process relevant features of the patient's current condition in light of those criteria which play a role in the corresponding step of the algorithm. A novel approach for building such implementations is under the *referent tracking* paradigm which relies on a theory based on philosophical realism [5]. The purpose of the research reported here was to carry out the first step of the development process, namely to identify the particulars and universals (the existence of which being the corner stone of philosophical realism) that at least must be represented in a referent tracking system in order to allow software agents to carry out real-time monitoring and control activities to optimise the treatment of schizophrenic patients according to the IPAP Schizophrenia Algorithm.

II. Background

The system we here advance as a novel implementation of the IPAP schizophrenia algorithm falls under the paradigm of '*expert system for real-time monitoring and control*' [6], but is marked by some different features.

First, the IPAP schizophrenia algorithm primarily reflects phenomena observed on the side of the patient that cannot be associated with quantitative magnitudes, or for which quantitative values cannot be measured by means of any currently available device. An example is the phenomenon of *recent significant loss*, which gives rise to the two-fold problem of finding out whether a loss has in fact occurred and whether it is a *significant* loss. Thus the sudden death of a patient's mother is typically a significant loss only where the patient has previously exhibited affection for his mother. Information of this sort can only come from communicating with the patient or with members of his social circle.

The second distinguishing feature of the system we envisage concerns the issue of *when* to raise certain questions such as whether there is a loss, and if so, whether it is significant. Traditionally, questions are raised in the course of using an expert system only when the system in question has already been activated by the clinician in the course of a clinical encounter and the inference engine has encountered a node where an answer to that question would determine the next step to be taken. Under the paradigm that we advocate however, the IPAP schizophrenia algorithm would be embedded in a monitoring system that would keep track in real time of changes in those clinical records to which the monitoring system has access. The execution of the algorithm would then be triggered automatically by relevant changes in the EHR of each patient. Note that this does not need be the patient to whom the algorithm is being applied. In the case of *significant loss*, for example, the event in question will be registered initially in some other person's EHR. But the data may then trigger a software agent to initiate a process designed to establish whether the given event constitutes a significant loss for some other person. Clinicians or patients may then be called upon to provide answers to questions generated by the software, wherever these answers cannot be found automatically in the relevant EHR data. An obvious benefit of this approach is a more accurate management of risk. Since for a schizophrenic patient a significant loss is qualified as a potentially dangerous situation that might lead to suicidal ideation, one should try to anticipate such events by inviting the patient for a new consultation in order to modify his treatment as soon as possible, i.e. immediately after the significant loss, given that the time of the next scheduled visit may already be too late.

The third distinguishing feature is the origin of the data on which the algorithms operate. For most expert systems, the data derive from some single patient or from the patient's immediate environment (e.g. the temperature or air humidity in the IC unit). The IPAP schizophrenia algorithm, in contrast, rests on information that may need to be looked for elsewhere,

including in other information systems that contain EHRs, or in the wider environment of the patient. This requires the use of a *referent tracking system*.

II.A. Referent tracking

No EHR can ever be complete. Yet it is often the case that a plurality of EHRs are maintained by different institutions for the very same patient, often with considerable overlap and complementarity of data, but also with contradictory information. In addition, as argued above, data in one patient's EHR may be relevant to the care of other patients.

Unfortunately, however, the information contained in EHRs is typically stored in such a way that it is difficult to tell whether it is consistent or conflicting, or whether given data refer to the same or to different entities in reality. This is an issue that can be solved only when both software and human agents can know precisely what the statements in the EHR are about.

This problem is solved for individual patients via the mechanism of unique patient identifiers. We have proposed, however, that the same mechanism be extended to all the particular entities to which reference is made in the clinical record [5]. Systems containing data pertaining to the same particulars could then be connected automatically, in such a way that relevant changes in one system come immediately to the attention of the other systems. This will require a more dynamic type of connectivity than has been realized hitherto in the context of patient data warehouses or standard EHR messaging, connectivity of a sort which will also be able to take advantage of the ongoing trend for patients to maintain a personal health record on the Internet, thereby keeping track of their own medical history [7].

In [5] we have given a series of arguments why all expert systems for real-time monitoring and control should co-operate with a referent tracking system. When implemented in the domain of biomedicine, the referent tracking paradigm which we have in mind would mean that each of the real world entities (called *referents* or *particulars* or *instances* in what follows) found to be of salience in the course of medical care would be individually

represented by its own explicit (alphanumeric) reference in the EHR of the relevant patient. Current EHRs consist almost exclusively of statements to the effect that a given patient has been diagnosed with such and such a disorder or has received this or that treatment from this or that physician, where only the patient and the physician involved receive unique identifiers called IUIs (Instance Unique Identifier). All other information in the EHR is conveyed through combinations of general codes from clinical terminologies and time-stamping information.

In the type of EHR we have in mind, in contrast, the particular schizophrenia itself – which is to say, this particular *case* or *instance* of this disease in this particular patient – would also receive its own unique ID, and this within a more detailed context than under the Problem Oriented Medical Record approach [8]. This ID could then be used to make statements directly about what it is on the side of the patient to which we refer when talking about this particular case or instance. Such assignment of IUIs should be systematic – thus it should be applied to instances of all varieties at the point where they become salient to the clinical record, which means not only to instances of disorders, but also to the patient's body parts (his brain, a specific region of his brain, his heart), particular episodes in his clinical history, and the particular symptoms he presents. The feelings of distress that he experiences now will receive a new ID, different from the one received by exactly similar feelings he had two years ago, although both will be associated with the same ICD10 or DSM-IV code.

The resultant *referent tracking database* might form part of the legacy EHR system of the specific institution in which the patient is managed. Better, however, would be to have the computer systems of a plurality of institutions linked together systematically in such a way that updates in one system would immediately trigger relevant actions in the others.

IUIs can be used in statements asserting that the particulars in question are instances of given universals or kinds, for example that particular #12345 is to be classified as an instance of the

universal *lung*, or that they stand to other particulars in relations defined within a formal framework for reasoning of the type outlined in [9], for example that particular #12345 is *part_of* particular #12300. IUIs can be used to track particulars whose nature changes over given periods of time, and for reasoning about particulars whose nature is unknown, for example when an underlying disorder is postulated as being responsible for a given family of symptoms even before we know enough to classify the disorder in a determinate way.

III. Hypothesis

Our basic idea is that changes in a patient's referent tracking database would trigger the automatic execution of algorithms suggesting steps which need to be taken (sometimes urgently) in patient care. In order to assess whether it would be possible to use the IPAP schizophrenia algorithm in a setting of this sort, we had to subject it to a terminological and ontological analysis to find out which obstacles must be overcome if it is to be automated along the lines described. The first such potential obstacle would be the failure to trace back all data elements mentioned in the algorithm to the particulars and universals they would be descriptions of. Our hypothesis was that this effort could be conducted successfully.

IV. Methods

For our analysis, we used version v.20041223 of the IPAP Schizophrenia Algorithm as available on the IPAP website on June 23, 2005 [2]. We studied in detail the explanations provided for each of the nodes in the flow-chart (see Table 1) on the basis of the information sources referenced by the algorithm itself. We made an inventory of the data elements needed in order to assess whether a given patient's condition fulfils the criteria advanced in the decisional nodes of the flow-chart, identifying thereby also some of the resources (including other relevant guidelines) that would help in making accurate assessments and comparisons of these data elements. We then classified the data elements collected as pertaining to the realm of particulars (e.g. this patient's headache here and now) and to the universals or kinds

which these particulars instantiate (*patient*, *headache*, *death*, *significant loss*, etc.). For the particulars, we evaluated what universals they instantiate according to the theory of Basic Formal Ontology presented in [10]. The latter enforces distinctions such as that between enduring entities (such as the patient's brain, also called *continuants*) and associated processes (e.g. the tremor of his left lower arm), and between independent (also called *occurrents*, e.g. his arm, his brain) and dependent entities (e.g. the patient's age or temperature).

For the purpose of this paper, we refer to particulars by means of unique IDs of the form "#I-" followed by a meaningless number. Only particulars that *necessarily* exist (or have existed) given that the patient under scrutiny exists, are taken into account and we focused only on those entities that are relevant for the IPAP schizophrenia algorithm. As an example: relative to a specific patient, his age is a necessarily existing entity: there are no persons without an age. This age is a particular quality (attribute of the patient), which takes on different values at different times. So, when the referent tracking paradigm is used at the time a particular patient is being evaluated according to the IPAP Schizophrenia Algorithm, it is possible to *assign* an ID to that particular if such an assignment has not been already made (in light of the fact that, according to the paradigm, ID assignment may happen only once). In the case of attributes like age (or temperature) which vary continuously through time, we need to distinguish the attribute itself from these successive *values* of the attribute.

In contrast, a particular disorder does not need to exist on the side of a patient. Thus, when the algorithm refers to "catatonia", a reference is made to a universal rather than to a particular; this is expressed by means of an ID starting with "#U". When the referent tracking paradigm is used to support evaluation by means of the IPAP Schizophrenia Algorithm, it must be determined for each such universal whether there exists on the side of the patient a particular which is an instance of the universal referred to.

To maximize the benefits to be derived from such support, we must ensure that the various entities under review are treated in appropriate ways in light of the ontological category to which they belong. To this end we specified for each particular what BFO category it is an instance of. For each universal, we similarly specified by what BFO category it is subsumed.

V. Results

In the following section, we describe the particulars and universals referred to by the various nodes (and in the associated documentation) of the IPAP Schizophrenia Algorithm. We provide a number of tables summarizing the information contained in the present version of the IPAP algorithm. For easy reference, we formed ID numbers by taking as first digit the number of the table in which the corresponding particulars and universals are listed, followed by a consecutive number. The first column of the tables contains the IDs for the identified particulars and universals. The second column contains first what the entity represents (bold), then under what BFO category it falls (printed in italics between brackets), and finally some further comments to clarify our decisions, as well as the entity's impact on the execution of the algorithm.

V.A. Algorithm Entry Conditions

The first node in the IPAP algorithm is the entry condition for those patients who will fall within its scope. According to the documentation provided, the algorithm is designed for patients "*who meet DSM-IV and ICD10 criteria for schizophrenia and schizoaffective disorder*". At the same time it is pointed out that "*the application of these criteria in clinical practice may be difficult in some cases*". Indeed, applying the relevant criteria given in DSM-IV and ICD10 is far from trivial, and it has been argued in [11] that both sets of criteria are in fact insufficient for their purpose. (Subjecting them to the same kind of analysis as performed here for the IPAP schizophrenia algorithm would be an interesting, though considerable, challenge.) As a first step, however, it would seem to be sufficient for the entry condition

node in the algorithm to simply require that a diagnosis of schizophrenia or schizoaffective disorder should have been listed in the EHR of the patient under scrutiny. According to our proposed EHR regime, a IUI would then be immediately assigned to the corresponding disorder, a particular which depends ontologically on this given patient and which has been asserted by the responsible physician to instantiate one or other of the universals *schizophrenia* or *schizoaffective disorder*. The relevant particulars and universals are listed in Table 2.

V.B. Issues affecting management and choice of drugs

The second node describes a set of conditions that must be assessed in order to initiate or adjust drug treatment. The most elaborate condition here is that relating to absence or presence of 'major suicide risk'; though the associated documentation does not provide criteria on the basis of which such risk is to be assessed, nor does it define when that risk is supposed to be 'major'.

It would be possible, following the pattern of our treatment of the entry conditions above, to introduce just one ID representing #I-2001's risk of committing suicide. We prefer, however, to call in aid recognized external sources on suicide risk assessment. One candidate is Fenton's list of indicators compiled on the basis of a meta-study of publications on depression and suicide from 1992 to 1998. Fenton identified 12 general risk factors (GRF): 1) being male, 2) of Caucasian race, 3) being depressed, 4) self-reported hopelessness, 5) self-reported suicidal ideation, 6) prior suicide attempts, 7) poor psychosocial functioning, 8) social isolation or inadequate social support, 9) deteriorating health, 10) significant loss, 11) current or past substance abuse, and finaly, 12) a family history of suicide [12]. He identified also 7 schizophrenia-specific risk factors (SRF): 1) long-term illness with exacerbations, 2) ill and functioning poorly at discharge, 3) awareness of illness and fear of deterioration, 4) excessive dependence or loss of faith in treatment, 5) depressed mood, hopelessness, hostility

at last visit or last hospitalisation, 6) prominent positive symptoms and 7) male:female ratio attenuated.

In Table 3 we describe the universals and particulars that are referred to by the general risk factors (GRF). Table 4 covers the schizophrenia-specific risk factors (SRF). Fenton does not list the positive symptoms of schizophrenia explicitly, but they consist of hallucinations, delusions and disorganised speech and behaviour [13]. Since there is some overlap between the two sets of factors, those particulars and universals already covered in Table 3 are not repeated in Table 4.

Risk Factors not related to suicide are covered in Table 5.

V.C. Treatment related issues

The remaining nodes in the IPAP schizophrenia algorithm concern directly the drug treatment to be recommended in light of the condition of the patient at any given stage. The relevant particulars and universals are covered in Table 6. To keep the table short, we do not refer to individual drugs (such as *amisulpride*, *aripiprazole*, etc.) separately.

Discussion

To arrive at the results presented thus far, a pure ontological stance has been taken, i.e. we have tried to list what exist (or have existed) either necessarily (the entities whose ID start with '#I') or contingently (the entities whose ID start with '#U') on the side of the patient if it is to be possible to take advantage of the IPAP schizophrenia algorithm in a referent tracking environment for purposes of clinical assessment with the goal of providing optimal treatment. The central focus of the referent tracking system is the person to be monitored. Assigning unique IDs to persons – in our particular example #I-2001 – is of course common practice in many administrative contexts, although the 'uniqueness' is often restricted to the environment in which a given information system (whether electronic or manual) operates: the library from which the person loans books, the social security program in which he is registered, the

company for whom he works, the country whose citizenship he enjoys, the health facility in which he once was treated, and so forth. In the domain of healthcare, however, the fact that the very same person might be supplied with more than one unique identifier hampers the aggregation of pertinent data and increases costs [14], so that many countries have initiated programs to implement a nation-wide unique patient ID, though in some countries (as in the case of the United States), such a measure is still seen as controversial because of privacy concerns [15].

From an ontological perspective, it is important to note that we envisage assigning an ID to the patient as *person* and not as *patient* [16]. The person is an entity that starts to exist some time after conception [17], and ceases to exist when it dies. This entity is an independent continuant, and thus has to be distinguished from other entities with which it is closely associated, such as the person's *life* (a dependent occurrent), or its *corpse* (another independent continuant), which starts to exist after the person's life comes to an end, i.e. after the person ceases to exist, and which continues to exist at least for some time while undergoing a process of decay. The term *patient*, on the other hand, refers to entities which are to be classified as dependent continuants, and more precisely as *roles* which persons start to play as soon as they seek certain sorts of advice in relation to their health. The term *patient* is however also used in a second sense as signifying *person who plays the patient role*. This tells us that, while natural language can be used to establish the ontological nature of the entities referred to by its means, it should not be trusted to give reliable indications in this respect in every case.

Although English and other languages allow us to refer to a person's *body*, this does not entail that a person's body is a different entity from that person. Some, such as Liao, maintain that an organism is not the same thing as a body: *"One difference is that when a person dies, the body will continue to persist for quite some time afterwards, but the organism will no*

longer be there, since the capacity to coordinate the various life processes will no longer be there." [18]. But here the term *body* is used ambiguously, to designate also what we earlier referred to as *corpse*.

The second most important particular, from the perspective of the IPAP schizophrenia algorithm, is the disease that is being tracked – in our example #I-2002. Diseases are dependent continuants. A disease is dependent because it cannot exist without some other entity (an organism) to exist in: without human bodies there would be no human diseases. Its status as continuant is more difficult to grasp. Some consider a disease to be a process, hence an occurrent [19]. Our view is that a disease is something like a *disposition* or *power*, which comes into existence at a certain time and thereafter gives rise to a complex series of processes (such as manifestations of symptoms) together with associated continuants. The latter (tumours, redness of the skin, …) come into existence as a result of the processes in question and depend on them for their further existence [20]. The relevant disposition can be instigated by a bodily aggressor such as a virus, by biomolecular reactions that go wrong, or by processes called upon by the body to defend itself against something that is going wrong in the external environment in which the person lives.

We use the term *disease* in a narrower sense than in the medical literature, in which the words 'disease' and 'disorder' are used in a rather loose way, quite often as synonyms. We reserve the term *disease* for the disposition itself, which can evolve over time and undergo changes while preserving its identity. A *disorder* would then be anything through which the disease is manifested. This does not represent an ontological category in its own right, since manifestations can be of a very different nature: continuants such as *tumours* and *fractures*, or processes such as *tremors* and *coughing*. None of the latter examples are properly to be considered as diseases.

Whether, under these definitions, any particular *disorder* a person might exhibit is the manifestation of some *disease* is a matter furthering each case for empirical research.

For the execution of the IPAP schizophrenia algorithm, it is now mandatory that the patient's disease (#I-2002) be an instance of one or other of the universals *schizophrenia* or *schizoaffective disorder*. As explained before, we assumed thus far that such a determination has already been made. Now however we need to point out that the way the entry conditions for the algorithm are phrased poses certain problems. When we examine more closely the algorithm's documentation on this topic, two important questions arise.

The first is logical in nature: does the patient's established diagnosis need to satisfy the diagnostic criteria of *both* DSM-IV and ICD-10, or is it sufficient that either one or the other be satisfied? This question is important, since there is only partial concordance between the two systems [21], concrete figures for concordance ranging from 60% (depending on the subtype of schizophrenia) [22] to 83% [23]. Thus it is possible that the #I-2002 has to be classified as schizophrenia according to one system, but that it is not allowed to be so classified by the other.

The second question is ontological in nature: to what extent do the terms ("schizophrenia" or "schizoaffective disorder") used by ICD-10 and DSM-IV represent genuine universals (or what philosophers sometimes call 'natural kinds')? Here, too, the referent tracking idea can bring certain advantages – for it is presumably reasonable to assume that, if patient records systematically include diagnoses of schizophrenia or schizoaffective disorder, then there is *something* to which these general terms refer on the side of the corresponding patients. Each such something can be given an ID, say #I-9001. We may then take advantage of the referent tracking database in carrying out a variety of different types of diagnostic tests in ways which may in the end lead to the conclusion that #I-9001 is in fact a compound of *two* or *more* disease particulars (or, in the worst case, that it is an empty ID designating no disease at all).

In this way, in the course of time, experience might prove that "schizophrenia" itself is a term that has no referent, that the corresponding universal in reality is a compound of several diseases hitherto not cleanly separated. An insight along these lines can of course not be gained on the mere application of the IPAP schizophrenia algorithm. But once obtained, modifications to the algorithm are required.

It is a matter of debate whether or not we should accept the existence of a particular which would be the patient's risk or possibility of committing suicide. Krimsky gives risk a metaphysical status as a property or quality in the physical world [24]. We think it requires further research to state convincingly what entity this property would depend on, and what kind of property it itself would actually be. One possibility is that suicide risk is something measurable that depends on the person, similar to his height or body temperature. An analogue would be the risk that the Leaning Tower of Pisa will fall down. Another analogue is to be found in debates about the nature of IQ. IQ is, some would say, *whatever intelligence tests measure*; similarly, suicide risk is *whatever standard tests for suicide risk measure*, and this would still be true even if there were no corresponding natural kind which the tests in question were giving us an insight into. In favour of this view are studies that report reliable prediction scales for suicidal intent and subsequent need for hospitalisation [25, 26, 27], although some authors question the usefulness of such tests [28].

It may even be that suicide risk is best analyzed as a property not of one single person but rather of a collection of persons. After all, a collection of persons (such as #I-3020, i.e. #I-2001's family) is a particular in its own right. Suicide risk might also be analogous for example to the risk of suffering from leptospirosis. The latter depends almost entirely on the environment [29], and can be changed even though nothing changes in the persons themselves. This view then places suicide risk in the realm of *latent variables*, which, from a mathematical point of view are defined as unobservable attributes that causally influence

observable behaviour and which are studied through the analysis of interindividual differences by statistically relating covariation between observed variables to the latent variables [30]. Borsboom *et al.* argue that, from an ontological perspective, latent variables can only be understood by taking a realist stance, although it may seem counterintuitive to accept the existence of characteristics of an aggregate (the population) that are absent at the level of the constituents of this aggregate (individuals), [31].

It was because of such problems that we chose, rather than relying upon the existence of some single risk particular, to call upon additional resources to assess whether or not a patient is at risk of committing suicide.

One recognised factor in this connection is a person's sex or gender This is relevant in the context of the IPAP schizophrenia algorithm since a patient's sex is one of the parameters determining suicide risk. First, there is the issue of the different kinds of sex, such as phenotypic sex, genotypic sex, gonadal sex or administrative sex. Clearly, any particular person has at any time only one particular and determinable phenotypic sex. In the case of #I-2001 we refer to this as #I-3001, since we assume that it is to this type of sex which Fenton refers. The same can be said for gonadal sex. By *determinable*, we mean that with the necessary technical equipment and skills it would be possible to determine the exact sex of any given person. It can be what we traditionally understand as *male* or *female*, or even *mixed*. Quite often, one can find in patient databases the value *unknown*. Clearly, however, this is not to be understood in the same sense as *male* or *female*: it is very unlikely that for a particular person whose sex has been stated as *unknown* one has taken all measures to determine the relevant value and then came to the conclusion that it is of a type never seen before. Rather, this entry reflects the fact that one did not or could not determine the give person's sex, or that, for whatever reason, the relevant checkbox has not been filled in properly in the database. To include *unknown* as a different type of sex, alongside *male* and

female, reflects a confusion between epistemology and ontology which has been shown to be pervasive in the development of biomedical terminologies [32].

For genotypic sex, the situation may be more complex, for example because of mosaicisms in which not all the cells of the body of a person exhibit the same chromosomal pattern [33]. From an ontological perspective, there is no problem in describing such a situation by using an appropriate set of foundational relationships to describe how chromosomes relate to cells, cells to a person's body, and so forth [34]. However, what names we choose to assign to conditions with different distributions of mosaicism is a matter of convention on the part of the scientific community.

Also a matter of convention is the notion of *administrative sex* which, depending on the community in which it is defined, is based not only on scientific grounds but also on political, ethical, and even religious considerations. An example is the different treatment of the right of gender self-identification which can make it possible that the same person has a different administrative sex in Australia and in the US [35]. Although Rector *et al*. claim that '*administrative sex is definitely a thing*' [36], we do not know what kind of thing it would be, though it is clear to us that it enjoys a totally different ontological relationship with the person who serves as its bearer than do biological types of sex.

Also subject to political and ethical debate is the notion of race. Although today nearly all geneticists reject the idea that biological differences are tracked by racial and ethnic distinctions, the sequencing of the human genome has identified certain genetic variants associated with different frequencies of disease susceptibility, environmental response, and drug metabolism in different ethnic and racial populations as traditionally defined [37]. This does not constitute an argument to accept race as a natural kind, or, for example, to accept *Caucasian human* as a subtype of *human* in the same sense as *human* is a subtype of *mammal*. But it does motivate the recognition of ethnic or racial subpopulations, though of

course marked by difficulties in identifying criteria that would allow any particular human to be correctly assigned to one or other of these populations. Despite these difficulties, the factor is relevant in the context of the IPAP schizophrenia algorithm since race/ethnicity is one of the parameters that influences suicide risk [38], if not directly, than at least through other observed differences within racial groups such as differences in the degree to which children are emotionally neglected [39].

We have classified a number of entities such as the state of being depressive and the state of feeling hopeless as *conditions*, which, according to BFO, are relational dependent continuants. In the tables we referred to these entities as universals and not particulars because we wanted to stress the fact that these universals are not necessarily instantiated on the side of #I-2001. Feelings of hopelessness and depressive moods are not entities such as a person's gender or age that necessarily exist if the person exists. But if they do exist, they depend for their existence on the person who serves as their bearer.

An issue that is still under debate is whether conditions related to feelings of hopelessness, depression and suicidal ideation are indeed continuants or processes [40, 41]. We feel that feelings of this kind – which are to be distinguished from feelings in the sense of perceptions and proprioceptions – are patterns and thus continuants.

Interestingly, the Fenton criteria require hopelessness and suicidal ideation to be self-reported by the person under scrutiny, while this is not the case for a condition of depression. From a medical perspective, there are of course good arguments for the existence of objective signs on the basis of which a skilled health professional can diagnose a depression in a patient, while that is not the case for suicidal ideas or feelings of hopelessness. Ontologically, self-reporting is a process (an act of utterance) that depends on the person reporting and that is clearly different from what is reported. (This confusion, too, is commonly encountered in contemporary biomedical terminology and messaging systems.)

The IPAP schizophrenia algorithm requires us at several points to resort to the notions of behaviour and (psychosocial) functioning, entities that we classify as aggregates of processes, rather than as individual processes, and which include #I-2001's (possible) self-reporting, or #I-2001 taking a particular drug, what would be an instance of #U-3018. Although a person's behaviour and functioning exist independently of the knowledge an observer might (or might not) have about the processes going on, there are cognitive aspects associated with such behaviour nonetheless. A person can behave between time t_1 and t_2 in exactly the same way between t_3 and t_4, yet his behaviour might be appropriate on the first occasion but not on the second. Talk of *behaviour* is neutral with respect to what a person is supposed to do, (i.e. it does not presuppose any context in which a specific mode of behaviour might be qualified as *appropriate* or *inappropriate* or qualified with respect to norms such as *aggressive* or *manic*. The reference to a person's *functioning*, however, presupposes that there is some *function* to be exercised. As an example, #I-2001's *psychosocial functioning* #I-3009 presupposes that the person in question functions in such a way as to preserve his integrity as member of a social community. It is astonishing that so many ontologies in the domain of healthcare and the life sciences do not make this important difference between a function and the execution thereof [42, 43]. Without this distinction, however, it is impossible to engage in what Hennig has termed *functional reasoning*, i.e. reasoning about what processes life forms can be expected to carry out in order to maintain their health [44].

The acceptance of behaviour as a ('neutral') aggregate of processes leads to a number of ontologically important questions. Is it for instance possible that a particular person has several stretches of behaviour going on in parallel during some period of time? How, more generally, are we to assign IDs to particular stretches of behaviour, for example if behaviour of some given type ceases for a time and then reappears? If several types of behaviour can be

instantiated at the same time, is it then possible for a specific process that contributes to of one type of behaviour to contribute simultaneously to behaviour of another type?

As mentioned earlier, precise answers to such questions would not be important if the IPAP schizophrenia algorithm were to be used in isolation, i.e. as activated by one clinician sitting in front of a single patient. But they are vital if we want to allow adequate reasoning in the context of multi-agent monitoring systems in which information about multiple particulars is collected for subsequent use for a variety of purposes in ways which add additional complexity to the type of reasoning described for example in [44]. Suppose for instance that only one relevant piece of behaviour for a particular person can exist during each relevant time frame – an assumption that we do not here endorse but merely consider for the sake of argument – and that we consider behaviour at time points t_1, t_2, t_3 and t_4. If one cognitive agent has information about #I-2001's behaviour between t_1 and t_3, and another agent carries different information about that behaviour between t_2 and t_4, then either one of the two agents has erroneous information, or they are assessing the same behaviour in relation to different norms.

The difference between individual processes and aggregates of processes, and the relation of this difference to the assessment of processes with respect to norms, is equally important when we consider #I-2001's use of medications (#U-3019). #I-2001 satisfies the condition *taking medication* as long as he is under the influence of bespoke drugs, i.e. as long as drug molecules are present in his body and are participating in biochemical reactions, which entails also that drugs are *administered* to #I-2001 through processes that are instances of #U-3018, but these processes are much shorter in duration, and there is no need for any such process to exist in any given time frame in order for an instance of #U-3019 to exist in that time frame, though there must have occurred at least one such episode in the past. When drug preparations with sustained release are used, there might indeed be very long periods between

any two processes of type #U-3019, but for short-acting drugs, three or more such processes might unfold themselves during a single day. Although in natural language we might say that such a process is '*repeated*' three times a day, each process is in fact a new and distinct particular, so that, if there is a requirement to have it explicitly registered (which typically is the case in nursing records), a new ID would need to be used for each new instance. This is also the reason why we introduced in Table the universal #U-3017, whose instances are any amount of some pharmacologically active substance in some pharmaceutical form, examples being a tablet in which there is 50 mg paroxetine, or a portion of liquid consisting of 10 drops of haloperidol in a specific concentration. Obviously, every distinct drug consumption process will involve a new instance of the corresponding chemical (drug) substance, thus another particular with its own unique ID. There are good reasons to so introduce such IDs (in addition to the fact that the corresponding particulars do indeed exist). In the context of the IPAP schizophrenia algorithm, the main reason is the need to be able to describe instances of #U-3019 (or some temporal parts thereof) as cases of *drug abuse*, rather than merely of drug *use*, or to assess whether #I-5003, i.e. #I-2001's behaviour with respect to his treatment plan, can be qualified as *compliant*.

Let us first look at a single process of type #U-3018: #I-2001, at time t_1, swallows 200 mg of paroxetine. Because of this, an instance of #U-3019 exists. Is #I-2001 now *using* or *abusing* drugs, and is his behaviour *compliant*? If he was ordered to take just 50 mg and it was checked whether he understood that order, it is clearly non-compliant, but this still leaves the further question of whether abuse is going on. Here, it matters whether taking the 200 mg was a volitional act, rather than a mistake. Taken over a longer period, referent tracking of the individual instances of processes of type #U-3018 can provide more clues useful to answering this question. When with any particular process the right dose is taken, and the number of such processes during a particular period matches the treatment plan, there is no

abuse, nor non-compliance. But if the frequency with which the processes occur is different, there is non-compliance, and when that frequency is higher from that which is prescribed, then there is also abuse, since it can safely be assumed that when a patient systematically takes higher doses than what he was ordered to take (in a way that the order was clear to him), there is no mistake involved. Of course, in this particular case there is the problem of how a referent tracking system might be able to be correctly informed about when individual instances of medication consumption have occurred. In some cases patients might register their drug use in the personal health record that they maintain digitally at home. A more advanced approach is the use of microelectronic tablet-dispensers that record the date, time and duration that the container is opened, and that could be connected directly to the referent tracking system. It has been shown that such devices guarantee a higher compliance than would be normally expected [45].

This brings us finally to the ontological status of the entities we call *drugs* or *medications*. Standards bodies and regulatory authorities have struggled for decades with the question of what it is for a chemical or biological substance to be a drug (or as it is usually called a *medicinal product*) [46]. European Directive 2001/83/EC defines ‘medicinal product’ as [47]:

> a) *Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;*
>
> *or*
>
> b) *Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.*

This definition, specifically clause b), is still very much contested, primarily by organisations favouring natural health and herbal medicine based on the argument that *modifying physiological functions* is a property that belongs not solely to medicinal products but also to a wide range of natural substances including food and water, when consumed as part of the normal diet [48]. From an ontological perspective, such a property is a power (relational dependent entity), and entities of this kind, reflecting the potential reactions the corresponding biochemical substance can induce in the human body, are often used as the main dividing criterion in building drug classification systems. Another criterion often used is the chemical structure of the individual molecules. The IPAP schizophrenia algorithm uses also the notion of pharmacological activity when it refers to certain drugs as *anti-psychotic drugs*. However, the criteria *typical* and *non-typical*, which are also used to distinguish certain drugs, do not refer to any intended action or to a specific chemical structure, but merely to the historical fact that certain drugs (the '*typical'* ones) were most often given for a specific condition, while the others only under special circumstances.

In the context of referent tracking we need to think very carefully about what precisely is to be tracked in relation to drugs. Tracking at the level of individual packages, e.g. a box containing x tablets of a certain drug, is used in some countries, and proposed in others as a mechanism for cost containment or protection against abuse [49]. Single-dose tracking has proven to reduce medication errors by 75% [50].

Conclusion

We presented a first analysis of the IPAP schizophrenia algorithm from an ontological perspective, primarily in order to find the relevant particulars and universals that must be represented in a multi-agent computer environment to allow for a new type of automatic monitoring of schizophrenic patients that will enable optimisation of their pharmacotherapeutic management. At the same time, we wanted to provide better insight into

the important differences that exist between the various entities that go to make the *what it is on the side of the patient* in virtue of which we are able to ascribe properties such as *being a person, being male, being Caucasian, being at risk for suicide,* and so forth. These expressions encode relationships of different ontological types, whose proper understanding is crucial to the building of ontologies that can be re-used in a succession of algorithms of different sorts. Rather than discussing each particular and universal thus identified, we focused on those cases that are central to the idea of referent tracking, or that are exemplary for the kind of confusion that is often exhibited in biomedical ontologies. We have shown that the various decision criteria put forward by the algorithm can be translated into a finite set of universals and particulars as proposed by Basic Formal Ontology.

This does not, of course, mean that we have solved all the problems that are of relevance to schizophrenia management. Nor does it mean that we have any special understanding of the precise nature of what we take to exist. For as we have insisted, another advantage of the referent tracking methodology is that it is in many cases possible to keep track of particulars in reality even before such precise understanding has been reached. Thus some questions that we raised in the course of our analysis do not need to be answered at this stage in order to arrive at an implementation of the IPAP schizophrenia algorithm that fulfils the objectives here outlined. It is important to mention these questions, however, because the mere awareness that they exist can serve as a safeguard against mistakes that have been made in the past in developing biomedical ontologies [51] or information models [52].

Our analysis in terms of particulars and universals is only a first, though important step. A deeper ontological analysis would involve the axiomatisation , as a basis for implementation of a reasoning system, of the foundational relations that tie the relevant entities together. Under currently prevailing paradigms, developing software programs that exhibit intelligent behaviour comes down to building a ‘conceptual model’ (a simplified digital simulacrum of

some domain) that selects from the real world relevant generic features organised in a way suitable for the task the program has to fulfil. It is in this light that in the field of knowledge representation the term '*ontology*' is used to refer to '*the specification of a conceptualisation*' [53] or to '*that part of a domain model that excludes the instances, yet describes what they can be*' [54]. To build such a model, developers use a representation language that allows them to verify whether their model is internally consistent. However, adepts of this approach consider it to be irrelevant whether or not the model represents the world faithfully, just so long as the program behaves in the way it is supposed to behave. The problem is that models built this way cannot be used for purposes other than those for which they were originally designed. Building such models is a labour-intensive process, and indeed still the main bottleneck in building knowledge-based systems [55]. Given the amount of energy expended on such models in biomedical informatics thus far, we are confronted here with a mammoth waste of resources.

On the currently dominant paradigm it is argued that to make ontologies reusable they must be 'mapped' one with another. This can occur either off-line, by having domain experts spend time finding the common elements in the ontologies to be combined [56], or dynamically, e.g. by having two agents, each equipped with his own model, interact [57] in a process of ontology negotiation. However, we know of no truly successful examples of either methodology having been applied in practice. The belief (almost never questioned) that they can be so applied rests on the prior assumption that there is an underlying common understanding, a basic agreement e.g. among all relevant domain experts, concerning what the various terms in an ontology '*mean*' [58]. But on what should these agreements on meaning be based? What could serve as benchmark? If it were on '*concepts*', a term that in the biomedical informatics community is used to denote a variety of things (including: 'units of knowledge', or 'units of thought', or 'meanings of terms') and, to make matters worse,

quite often in such a way that it is very hard to understand which meaning is precisely intended, we would be on a slippery slope [59].

On the instance-based approach, in contrast, it becomes possible for ontologies to be reused by other software programs, not least in order to support the kind of mixed initiative interaction paradigm for multi-agent systems which we referred to above. For all the agents involved are then able to keep track of the very same referents in an unproblematic way. Moreover, the instance-based approach provides the best possible measure for whether two (or more) ontologies are indeed compatible, for it allows the world itself to serve as benchmark as concerns whether two universals in an ontology are or are not identical, and it allows us to ensure that ontologies are built which are reusable.. Not the least advantage of our approach is, then, that it does not rest on agreements as concerns the meanings of terms or the associated concepts, but that it is based on the universals and particulars that populate the world [60].

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Table 1: Nodes in the IPAP Schizophrenia Algorithm. Decisional nodes have a number starting with 'D', therapy-related nodes start with 'T'

D1	Assess whether diagnosis of schizophrenia or schizoaffective disorder established	
D2	Consider critical initial or emergent issues affecting management and choice of drugs	
	D2A.	major suicide risk
	D2B.	catatonia or NMS
	D2C.	severe agitation or violence
	D2D.	non-compliance
	D2E.	depression or mood symptoms
	D2F.	substance abuse
	D2G.	prodromal or first episode
	D2H.	treatment-induced side effects
T3	4-6 week monotherapy trial with an atypical anti-psychotic or, if not available, with haloperidol, chlorpromazine, or other typical antipsychotic	
D4	Assess whether T3 of adequate dose and duration, and no intolerability	
D5	Assess whether psychosis persists after adjusting dose in T3.	
T6	4-6 week monotherapy trial with another atypical (if available) or typical than in T3	
D7	Assess whether T6 of adequate dose and duration, and no intolerability	
D8	Assess presence of psychosis or moderate to severe tardive dyskinesia or tardive dystonia	
T9	Six month trial with clozapine up to 900 mg/day	
D10	Assess whether symptoms (D2 or D8) persist	
T11	Optimize clozapine and/or augment electroconvulsive therapy or adjuvant medication, or alternate strategies	
T12	Enter maintenance phase	

Table 2. Entry condition entities for the IPAP Schizophrenia Algorithm

#I-2001	**The patient** (*independent continuant*). Refers to the patient as 'person', not a role played.
#I-2002	**#I-2001's disease being managed** (*dependent continuant*). It must be an instance of either **#U-1003** or **#U-1004** in order for the entry conditions to be satisfied.
#U-2003	**The disorder called '*schizoaffective disorder*' according to either ICD-10 or DSM-IV** (*dependent continuant*).
#U-2004	**The disorder called '*schizophrenia*' according to either ICD-10 or DSM-IV** (*dependent continuant*).

Table 3: Particulars and universals salient to the 'major suicide risk' node of the IPAP Schizophrenia Algorithm under the heading General Risk Factors

#I-3001	**#I-2001's gender** (*dependent continuant*). If the particular instantiates *male*, it satisfies GRF-1. Each patient has a specific and concrete gender, independent of our knowledge of what this gender is. Thus there is no gender 'unknown' of the sort that is allowed for in many current classifications.
#I-3002	**The caucasian population** (*independent continuant*). If **#I-2001** is a member of this population, GRF-2 is satisfied.
#U-3003	**The universal instantiated by a cognitive agent's state of being depressed** (*condition*). It is the *state* of being depressed, rather than a particular associated disease, which is to be understood here. GRF-3 is satisfied if, at the time of evaluation, **#I-2001** exhibits a state which is an instance of **#U-3003**.
#U-3004	**The universal instantiated by a cognitive agent's state of feeling hopeless** (*condition*). The state of feeling here is not a separate quality, one value of which might be *hopeless*. It is not the same particular feeling that at time t_1 is qualified as hopeless, and at t_2 as happy. Rather these are two distinct feelings.
#U-3005	**The universal instantiated by any act through which a cognitive agent expresses something** (*process*). GRF-4 is satisfied if at any time **#I-2001** expresses his awareness of being in a state which is an instance of **#U-3004**.
#U-3006	**The universal instantiated by a cognitive agent's state of suicidal ideation** (*condition*). GRF-5 is satisfied if at some time **#I-2001** exhibits a condition which is an instance of **#U-3006**.
#I-3007	**#I-2001's life** (*aggregate of processes*). **#I-3007** is a processual entity that unfolds through time as long as **#I-2001** exists.
#U-3008	**The universal instantiated by any volitional act** (*process*). GRF-6 is satisfied when **#I-2001** performs an instance of **#U-3008** with the goal to end **#I-3007**. What matters here is whether the act was performed to commit suicide, not whether it was successful.
#I-3009	**#I-2001's psychosocial functioning** (*aggregate of processes*). **#I-3009** is part of **#I-3007**. It has many other processes as parts. Many of them do not extend across the entire lifetime of **#I-2001**.

#U-3010	**The universal that is instantiated by behaviour that is inadequate to preserve his or her integrity as living entity in a social community** (*aggregate of processes*). When a part of **#I-3009** is an instance of **#U-3010**, GRF-7 is fulfilled.
#I-3011	**#I-2001's social environment** (*independent continuant*). Other particulars which might need to receive their own IDs in this connection are **#I-2001**'s family, or a club or social group of which he might be a member.
#I-3012	**#I-2001's ability to call upon #I-3011** (*dependent relational continuant*). Abilities belong to the same realm as powers, liabilities, dispositions and tendencies. **#I-3012** depends not only on **#I-2001** but also on **#I-3011**. A consequence of this is that **#I-3012** might change solely because of changes in **I#-3011**, and thus without any change in **#I-2001**.
#I-3013	**#I-2001's health** (*quality*). This quality is affected by the presence of particular disorders on the part of **#I-2001**. GRF-9 is satisfied when **#I-3013** is worse at time t^+ than at an earlier time t. The algorithm does not specify how much worse it should be.
#U-3014	**The universal that is instantiated by any continuant** (*continuant*).
#U-3015	**The universal instantiated by the love of a cognitive agent for any instance of #U-3014** (*relational condition*). GRF-10 requires **#I-2001** to love (or have deep affection for) a particular instance of **#U-3014** at a specific time. Once this instance is registered, the particular being loved must be assigned its own ID. Love as a relational condition is dependent upon both bearers of the relation. Love as a mental condition on the part of the agent can however persist even after the loved entity has ceased to exist.
#U-3016	**The universal instantiated by any instance of losing** (*process*). GRF-10 is satisfied if **#I-2001** is the agent of a process which is an instance of **#U-3016** and the particular related to **#I-2001** through an instance of **#U-3015** is the theme of that process.
#U-3017	**The universal that is instantiated by any drug** (*independent continuant*). Instances of this universal are for instance a tablet or a bolus of liquid in an ampoule containing a portion of a pharmacologically active substance.
#U-3018	**The universal instantiated by any process through which material is brought into an organism** (*process*).

#U-3019	**The universal instantiated by any person's drug use** (*aggregate of processes*). This universal instantiates complex entities which are composed of many smaller processes which themselves are instances of **#U-3018**. GRF-11 is satisfied if an instance of this universal (1) involves instances of **#U-3018** through which **#I-2001** receives instances of **#U-3017**, and (2) qualifies as 'abuse'.
#I-3020	**#I-2001's family** (*independent continuant*). **#I-2001**'s family necessarily exists in the sense that his parents had to exist in order for **#I-2001** to exist. Note that **#I-2001** is a member of his own family.
#I-3021	**A particular member of #I-3020, but excluding #I-2001 himself** (*independent continuant*).
#U-3022	**The universal instantiated by any act of suicide** (*process*). GRF-12 is satisfied if **#I-3021** is the agent of an instance of **#U-3022**.

Table 4: Particulars and universals salient to the 'major suicide risk' node of the IPAP Schizophrenia Algorithm under the heading of Specific Risk Factors

#I-4001	**#I-2002's life** (*aggregate of processes*) Just as a person has a *life*, so a disorder has a *course* or *history* during which it undergoes changes, causes symptoms to appear, etc. It is the duration of **#I-4001** which determines whether SRF-1 is satisfied.
#I-4002	**#I-2002's strength in attacking #I-3013** (*quality*). An increase in **#I-4002** reflects an exacerbation of the disease.
#U-4003	**The universal instantiated by any admission of a person to a health facility** (*process*). Any discharge requires an admission at an earlier time
#U-4004	**The universal instantiated by any discharge following an instance of #U-4003** (*process*).SRF-2 is satisfied when, at the time that an instance of **#U-4004** happens in which **#I-2001** partakes, either an instance of **#I-3010** is exhibited by **#I-2001**, or **#I-3013** is of low quality.
#U-4005	**The universal instantiated by any awareness by a cognitive agent by a phenomenon** (*condition*). SRF-3 is satisfied if **#U-4005** is instantiated by **#I-2001**'s awareness of **#I-2002**.
#U-4006	**The universal instantiated by any condition of fear on the side of a cognitive agent** (*condition*). SRF-3 is satisfied if there is an instance of **#U-4006** on the side of **#I-2001** with respect to an increase in **#I-4002**. The increase in **#I-4002** does not need to exist for SRF-3 to be satisfied.
#I-4007	**#I-2001's treatment** (*aggregate of processes*). The complex entity composed of several processes, in some of which **#I-2001** may partake directly (e.g. instances of **#U-3018**), in others indirectly, e.g. therapy planning discussions between the psychiatrists and psychologists involved in the management of **#I-2002**.
#I-4008	**#I-2001's dependence on #I-4007** (*quality*). When 'excessive', it satisfies SRF-4.
#I-4009	**#I-2001's level of faith in #I-4007** (*quality*). Where such faith is low, then the criterion corresponding to SRF-4 is satisfied.
#I-4010	**#I-2001's healthcare provider team** (*independent continuant*). This is a similar kind of particular as #I-3020.

#U-4011	**The universal instantiated by any consultation involving a health provider and a patient** (*aggregate of processes*).
#U-4012	**The universal instantiated by any hostile behaviour of a cognitive agent** (*aggregate of processes*). SRF-5 is satisfied when **#I-2001** exhibits such a behaviour at the time of that instance of **#U-4011** in which **#I-2001** partakes, or during the time interval between those instances of **#U-4003** and **#U-4004** that involve **#I-2001**. Also node D2C is satisfied when this behaviour is exhibited.
#U-4013	**The universal instantiated by any hallucination on the side of a person** (*process*). When **#I-2001** exhibits an instance of **#U-4013**, then SRF-6 is satisfied.
#U-4014	**The universal instantiated by any delusional thinking on the side of a person** (*process*). When **#I-2001** exhibits an instance of **#U-4014**, then SRF-6 is satisfied.
#U-4015	**The universal instantiated by any disorganised behaviour on the side of a person** (*aggregate of processes*). When **#I-2001** exhibits an instance of **#U-4015**, then SRF-6 is satisfied.

Table 5: Entities for the non-suicide risk-related nodes of the IPAP Algorithm

#U-5001	**The universal instantiated by a person's catatonic state** (*condition*).
#U-5002	**The disorder called *Neuroleptic Malignant Syndrome*** (*dependent continuant*). If an instance of **#U-5002** depends on **#I-2001**, then node D2B is satisfied.
#U-5003	**The universal instantiated by any inadequate execution of a plan** (*aggregate of processes*). If the part of **#I-3009** through which **#I-2001** deals with the drug treatment plan that is proposed to him by **#I-4010** is an instance of **#U-5003**, then node D2D is satisfied.
#U-5004	**The universal instantiated by any manic behaviour** (*aggregate of processes*). If a temporal part of **#I-3009** is an instance of **#U-5004**, then node D2E is satisfied.
#I-5005	**The first 'active' part of #I-4001** (*aggregate of processes*). Disorders are entities that, in the course of their existence, cause various phenomena to occur in their bearers. A disorder is often typed as 'active' during phases in its lifetime marked by manifestations of larger numbers of symptoms. **#I-5005** is the first such phase in the course of **#I-4001**.
#U-5006	**The universal instantiated by any prodromal phase of a disease** (*aggregate of processes*). For node D2G to be satisfied, a part of **#I-4001** occurring before **#I-5005** must be an instance of **#U-5006**.
#I-5007	**The collection of phenomena dependent on #I-2001** (*dependent entity*). If a member of **#I-5007** is caused unintentionally by **#I-4007**, then node D2H is satisfied.

Table 6: Entities relevant to the treatment nodes in the IPAP schizophrenia algorithm

#U-6001	**Portion of antipsychotic biochemical substance** (*portion of mass substance*).
#U-6002	**Antipsychotic drug** (*independent continuant*). Instances of this universal are a tablet or a bolus of liquid in an ampoule containing an instance of **#U-6001**.
#U-6003	**Atypical antipsychotic drug** (*independent continuant*). Instances of this universal are instances of #U-6002 that contain portions of the chemical substances amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, or ziprasidone (though not any combination thereof).
#U-6004	**Typical antipsychotic drug** (*independent continuant*). Instances hereof are instances of **#U-6002** that contain portions of the chemical substances chlorpromazine, fluphenazine, haloperidol or thiothixene (though not any combination thereof).
#U-6005	**The universal instantiated by any antipsychotic monotherapy** (*aggregate of processes*). Instances hereof unfold during a person's life which include as parts instances of **#U-3018** in which instances of **#U-6003** or **#U-6004** participate.
#I-6006	**#I-2001's capacity to tolerate an instance of #U-6005** (*dependent relational continuant*). Belongs to the same realm as powers, abilities, liabilities, and so forth. If the capacity is low, nodes D4 and D6 are not satisfied.
#U-6007	**The universal instantiated by any psychotic behaviour** (*aggregate of processes*). When this universal is instantiated on the side of **#I-2001**, D5 and D8 are satisfied.
#U-6008	**The disorder called *tardive dyskinesia*** (*dependent continuant*). When this universal is instantiated on the side of **#I-2001**, D8 is satisfied.
#U-6009	The disorder called *tardive dystonia* (dependent continuant). When this universal is instantiated on the side of #I-2001, D8 is satisfied.
#U-6010	**The universal instantiated by therapeutic sessions known as electroshock therapy** (*aggregate of processes*).
#U-6011	**The universal instantiated by the magnitudes of specific instances of #U-6001** (*quantity*). This corresponds to what is normally referred to as 'dose'. The fact that a dose can be expressed in different ways does not change the fact that it is a quantity.

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