Semantic Web Ontology and Data Integration: a Case Study in Aiding Psychiatric Drug Repurposing

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Abstract

Despite ongoing progress towards treating mental illness, there remain significant difficulties in selecting probable candidate drugs from the existing database. We describe an ontology – oriented approach aims to represent the nexus between genes, drugs, phenotypes, symptoms, and diseases from multiple information sources. Along with this approach, we report a case study in which we attempted to explore the candidate drugs that effective for both bipolar disorder and epilepsy. We constructed an ontology that incorporates the knowledge between the two diseases and performed semantic reasoning task on the ontology. The reasoning results suggested 48 candidate drugs that hold promise for a further breakthrough. The evaluation was performed and demonstrated the validity of the proposed ontology. The overarching goal of this research is to build a framework of ontology – based data integration underpinning psychiatric drug repurposing. This approach prioritizes the candidate drugs that have potential associations among genes, phenotypes and symptoms, and thus facilitates the data integration and drug repurposing in psychiatric disorders.

Introduction

It is reported that the cost of discovering new drugs continues to increase while the number of new therapeutic chemical and biological entities approved by US Food and Drug Administration (FDA) has been declining since the late 1990s. In psychiatric disorder, this situation may be even severe. Despite the remarkable progress in fundamental research for medication, efforts toward the discovery of new drugs for psychiatric disorders have been relatively unsuccessful. Drug repurposing aims to develop new uses for existing or abandoned drugs. It has become an active area in drug discovery and holds promise to solve the problem.

The complexity of psychiatric disorders determines the difficulty of traditional drug repurposing. The psychiatric disorder has been identified as one of the leading courses of disability in the world. Our understanding of the neurobiological mechanisms of existing psychiatric medications has been increasing through pharmaceutical studies and clinical trials. When seeking new indications (e.g., diseases, symptoms) for these drugs, the outcome may not be as satisfying as promised. One reason is that the diagnosis and the psychiatric classification system is largely based on clusters of symptoms rather than genetics, epidemiology, and etiology, due to the complexity and particularity of human central neural system (CNS). Usually, identification of psychiatric disorders involves various symptom complications and distinct pathologies, not to mention the individual difference among patients. In practice, it is difficult to identify certain psychiatric symptoms simply based on abnormalities in certain focus in CNS.

The methods used in drug repurposing comprise of a wide spectrum ranging from traditional screening methods and animal models to computational methods. The computational methods hold promise to facilitate the identification of candidate drugs with the advantage of time efficiency. As reported in a recent review on the development of computational drug repurposing, these methods can be categorized into two approaches: (1) the drug-based approach, which aims to infer useful information from pharmacological or chemical data of drugs; and (2) the disease-based approach, which takes a perspective over the associations among disease, symptom, and pathology. The drug-based methods may lead to valuable results if the data set includes rich pharmacological or chemical information. However, this approach may not result in best outcomes when it comes to psychiatric disorders. Opportunities of psychiatric drug repurposing may exist in the exploration of implicit knowledge such as relationships between the diseases, pathologies, symptoms, etc. In this regard, disease-based methods may lead better outcomes. Recent studies have already demonstrated the effectiveness of such methods in cancer therapeutics and literature-based drug repurposing. Nevertheless, it presents significant challenges to explore implicit knowledge for psychiatric drug-associated data since missing and the implicit information, such as phenotype, symptom, and gene, is
usually interconnected. To tackle this issue, we are facing two roadblocks. First, data sources are isolated with one another. In the existing data repositories, there are a few that encode information such as symptom-drug-disease associations. Mostly, gene-associated data repositories and symptom-associated data repositories are isolated from each other. For example, the Pharmacogenomics Knowledgebase (PharmGKB) encodes human genetic variation on drug responses but is limited in providing information about symptoms. Other than PharmGKB, there are three well-developed gene-disease databases: PsyGeNET (http://www.psygenet.org/web/PsyGeNET/v01/home), DisGeNET (http://www.disgenet.org/web/DisGeNET/v2.1/home), and Diseasome (http://diseasome.eu/index.html), in which PsyGeNET is particularly designed for the exploratory analysis of psychiatric diseases and the associated genes. Unfortunately, there is a lack of both an effective database and a mature integration solution to bridge all these data bases together. Second, once the data bases have been integrated, feasible data reasoning methods are needed so that one can infer candidate drugs.

To address these problems, we proposed a semantic web ontology approach to integrating various data sources and produce semantic data reasoning. The ontology is built under the open W3C Standard of Web Ontology Language (OWL). By defining an ontology, we are able to (1) identify concepts that appear in different sources and/or in different formats, (2) encode relations between concepts in a hierarchy, and (3) perform semantic reasoning. The ontology integrates gene, drug, disease, phenotype, and symptom, and assigns properties to them. To evaluate the effectiveness of the ontology, we present a detailed ontology built across two psychiatry disorders: bipolar disorder and epilepsy as a use case. We chose these two diseases because there are clinical cases indicating shared or similar symptoms between them. Therefore, there may exist drug-repurposing opportunities between the two diseases. A semantic reasoning task was performed utilizing this ontology with the intention to explore candidate drugs activating for both diseases.

**Methods**

*Data collection and ontology construction*

We defined five top-level OWL classes to represent five data sources, disease, symptom, phenotype, gene, and drug. Figure 1 summarizes the five classes and how they link together. In addition, we defined OWL object properties so that the relations between OWL classes and OWL individuals were defined (see Table 1). For example, the property associatedWithPhenotype determines the triple ALDH7A1 associatedWithPhenotype OMIM266100.

![Figure 1](image-url)

*Figure 1. Overview of the OWL classes and the object properties in the ontology. There are five classes on the top level. They are disease, symptom, phenotype, gene, and drug. Each class may contain subclasses. A Disease has Bipolar_disorder and Epilepsy. A Drug has Bipolar_disorder_drug and Epilepsy_drug. A Phenotype has Bipolar_disorder_phenotype and Epilepsy_phenotype. A Symptom has Bipolar_disorder_symptom and Epilepsy_symptom. There are five object properties in the top-level including associatedWithDisease, associatedWithDrug, associatedWithSymptom, associatedWithPhenotype, and associatedWithGene. Under each object property, we also defined sub-level object properties. For example, associatedWithDisease has DrugRelatedToDisease, GeneRelatedToDisease, and SymptomRelatedToDisease.*
The detailed ontology includes OWL individuals that were defined under the corresponding classes. These individuals were imported mostly from open data repositories, including PharmGKB (https://www.pharmgkb.org), Human Phenotype Ontology (HPO) (http://www.human-phenotype-ontology.org), and Online Mendelian Inheritance in Man (OMIM) (http://www.omim.org). The PharmGKB contains linked data about the disease, gene, drug, and pathway. We extracted gene, drug, and disease from PharmGKB, and represented them by defining OWL individuals and object properties. OMIM provides data of human genes and genetic phenotypes. HPO was used to model human disease and phenotype with a large portion of data referring to OMIM and, the rest, medical literature. Data from HPO and OMIM were jointly used in the ontology to represent gene, disease, and phenotype as well as the relations among them. The only absent data source is the symptom, which plays a critical role in the diagnosis and treatment of psychiatric disorders. To our knowledge, there is no existing easy-to-transform database that can be used to link the symptom with the data sources we already have, for example, drug and/or phenotype. Therefore, we encoded the symptom knowledge for utilizing in the ontology.

**Table 1.** A list of examples of OWL objective properties.

| Top Objective properties | Sub Objective properties |
|--------------------------|--------------------------|
| associatedWithDisease    | DrugRelatedToDisease     |
|                          | GeneRelatedToDisease     |
|                          | SymptomRelatedToDisease  |
| associatedWithDrug       | DiseaseRelatedToDrug     |
|                          | GeneRelatedToDrug        |
| associatedWithGene       | DiseaseRelatedToGene     |
|                          | DrugRelatedToGene        |
|                          | PhenotypeRelatedToGene   |
| associatedWithPhenotype  | GeneRelatedToPhenotype   |
|                          | SymptomRelatedToPhenotype|
| associatedWithSymptom    | DiseaseRelatedToSymptom  |
|                          | PhenotypeRelatedToSymptom|

Presently, there is not a ready-to-use psychiatric disorder symptom vocabulary to provide extensive knowledge for linking disease and phenotype, where phenotype depicts “*the observable properties of an organism that are produced by the interaction of the genotype and the environment*” \(^{17}\). While symptom is mostly based on the observable properties of an organism, it may provide clearer expression of characters and traits coded by a set of genes. Therefore, we collected a subset of 34 symptoms from literature and commonly used terminologies and concepts in healthcare (e.g., Mayo Clinic) (see Table 2). We then mapped these terminologies and concepts with corresponding concepts in disease and phenotype. Table 2 shows the disease-symptom associations. To define the symptom-phenotype associations, we utilized OMIM and HPO as primary references and assigned corresponding object properties to link symptom and phenotype.

**Implementation**

Based on the ontological framework described above, we enriched the ontology by importing OWL individuals and object properties. Relative OWL individuals directly or indirectly associated with the two diseases were extracted from PharmGKB, OMIM, HPO, and a symptom vocabulary created. We imported the corresponding data into the ontology, which was implemented in Protégé 4.3.0 (http://protege.stanford.edu). Below we organized the mapping procedures into these steps: (1) importing disease-gene associations from PharmGKB into the ontology; (2) for each existing gene in the ontology, searching the associated drugs from PharmGKB and imported into the ontology; (3) importing disease-symptom associations from Table 2 into the ontology; (4) searching in the HPO and OMIM for gene-phenotype associations for the two diseases and imported them into the ontology; (5) linking symptoms and phenotypes in the ontology.

Once the semantic representation was established, we used the ontology to perform consistency checking, automatic classification, and semantic reasoning \(^{18,19}\). Since the goal of the present work is to explore
candidate drugs that may share some common nexus across bipolar disorder and epilepsy, we applied semantic rules to infer OWL individuals under the class drug. Referring to Figure 1, the associations between disease and drug can be inferred by a semantic reasoner (HermiT). There is no direct association between disease and drug initially. The simplest way to reason their association is the route bridging disease, gene, and drug, in which most of the triples were imported from PharmGKB. However, as discussed in the Introduction section, information buried in symptoms and phenotypes may be neglected in this manner. For this reason, we reasoned about the candidate drugs through a new route, which passes through disease, symptom, phenotype, gene, and drug. Following this route, we generated Descriptive logic (DL) rules for delivering the reasoning results. The DL rule we utilized to find the new path between drugs and the disease can be defined as “DrugRelatedToGene some (associatedWithPhenotype some (associatedWithSymptom some ((associatedWithDisease some Bipolar_disorder) and (associatedWithDisease some Epilepsy)))))”. A candidate drug inferred by this DL must be a drug that associates with symptoms that appear in both Bipolar disorder and Epilepsy. The associations between drug and symptom were inferred through drug-gene-phenotype-symptom, where the corresponding relations had been defined as described in previous paragraphs. With this rule, we can find drugs that connect with certain symptoms.

Table 2. Encoded concepts and the reference source for symptoms.

| Bipolar disorder | Reference | Epilepsy | Reference |
|------------------|-----------|----------|-----------|
| Irritability     | Helpguide.org | Irritability | Immitators of Epilepsy. 2nd edition |
| Euphoria         | Helpguide.org | Euphoria | Immitators of Epilepsy. 2nd edition |
| Amnestic         | Helpguide.org | Amnestic | Immitators of Epilepsy. 2nd edition |
| Acting recklessly| Helpguide.org | Acting recklessly | WebMD |
| Delusions        | Helpguide.org | Delusions | WebMD |
| Hallucinations   | Helpguide.org | Hallucinations | WebMD |
| Sleep problems   | Helpguide.org | Sleep problems | Immitators of Epilepsy. 2nd edition |
| Feeling hopeless | Helpguide.org | - | - |
| Fatigue          | Helpguide.org | - | - |
| Physical and mental sluggishness | Helpguide.org | - | - |
| Appetite or weight changes | Helpguide.org | - | - |
| Worthlessness or guilt | Helpguide.org | - | - |
| Thoughts of death or suicide | Helpguide.org | - | - |
| Unrealistic      | Helpguide.org | - | - |
| Rapid talking    | Helpguide.org | - | - |
| Racing thoughts  | Helpguide.org | - | - |
| Distractible     | Helpguide.org | - | - |
| Impulsiveness    | Helpguide.org | - | - |
| Impaired judgment| Helpguide.org | - | - |
| -                | Unconsciousness | Mayo clinic |
| -                | Lip smacking | Mayo clinic |
| -                | Repeated swallowing or chewing | Mayo clinic |
| -                | Unusual finger movements | Mayo clinic |
| -                | Deja vu experience | Mayo clinic |
| -                | Unprovoked fear | Mayo clinic |
| -                | Strange odor or taste | Mayo clinic |
| -                | Rising sensation in the abdomen | Mayo clinic |
| -                | Confusion | Mayo clinic |
| -                | Difficulty speaking | Mayo clinic |
| -                | Laugh | Immitators of Epilepsy. 2nd edition |
| -                | Cry | Immitators of Epilepsy. 2nd edition |
| -                | Aggressiveness | Immitators of Epilepsy. 2nd edition |
| -                | Suspicious | Immitators of Epilepsy. 2nd edition |
| -                | Fright | Immitators of Epilepsy. 2nd edition |
Evaluation
To validate the inferred candidate drugs and the effectiveness of the ontology, we utilized data from PharmGKB, ClinicalTrials.gov (https://clinicaltrials.gov), and PubMed (http://www.ncbi.nlm.nih.gov/pubmed) to perform the evaluation. Though the PharmGKB serves as one data source in our ontology, it does not provide any direct association linking symptoms and/or phenotypes with candidate drugs and diseases. Therefore, we searched in PharmGKB for direct associations between drugs and the corresponding diseases and utilized the results as the baseline to compare with other searching results in ClinicalTrial.gov and PubMed.

The occurrences of associations indicate strong drug-disease connections so that they can be utilized to assess whether there is a good candidate drug. ClinicalTrials.gov provides clinical studies on a wide range of diseases. We utilized the drug names queried from the ontology as the keywords for searching on specific topics (i.e., ‘bipolar disorder’, ‘epilepsy’, and ‘mental disorder’) on ClinicalTrial.gov. In the end, we searched online publications in the PubMed with the queried drug names and the corresponding diseases. The searching results from these data sources were combined to provide evidence for validating candidate drugs.

Results
Semantic reasoning
Please note that the OWL individuals in the symptom class do not have a direct connection to the OWL individuals in the drug class without semantic reasoning. Therefore, the information imported from OMIM and HPO was critical in linking symptom-phenotype-gene. As a result, the ontology inferred 48 drugs that are relevant to the two diseases. Table 3 summarizes the results of semantic reasoning.

Evaluation
We evaluated whether symptoms contain important information in guiding drug selection. Thereupon, we examined whether these drugs could be retrieved simply from a disease-gene-drug association, which is the routine solution in PharmGKB. The evaluation results in Table 3 demonstrate that only one out of the 48 candidate drugs has direct disease-gene-drug associations. The searching in ClinicalTrial.org and PubMed provides a different angle into the associations between drugs and diseases. Eleven candidate drugs have been investigated in the clinical trials for both bipolar disorder and epilepsy. Additionally, there were 18 candidate drugs that revealed joint occurrences of the drug name and the two disease names in PubMed database, in which only four drugs revealed weak evidence (returned a number of one occurrence). Eleven candidate drugs were identified from both ClinicalTrial.org and PubMed. See Table 3 for details.

Discussion
By utilizing semantic web ontology, we constructed an ontology that integrates information from disease, gene, symptom, and phenotype with intrinsic relations among them. A use case that intends to discover candidate drugs shared in both bipolar disorder and epilepsy was performed utilizing this ontology. We encoded and imported data from different sources into the ontology and performed semantic reasoning task to predict candidate drugs. The results were validated through a set of evaluation procedures in which we investigated direct evidence from ClinicalTrial.org, PubMed, and PharmGKB to demonstrate the candidate drugs. The evaluation result reveals the effectiveness of our proposed work.

An obvious advantage of using drug repurposing lies in the relatively low cost, low risk, and time efficiency compared to discovering new drugs since no additional safety approval is needed for existing drugs. A major advantage of the ontology-based approach is the capacity to computationally identify the hidden information among entities and their relations. The use of ontology in drug repurposing to a large extent benefits mining hierarchical and complex information such as gene, disease, drug, phenotype, and symptom. In psychiatric disorders, symptoms and phenotypes contain important information for determining the individual diseases. The expected outcome can be accrued when linking these data sources with drug and gene. However, there are a small number of complete and comprehensive knowledge bases that can be used for linking gene, drug, disease, phenotype, and symptom. This has become a barrier when attempting to locate a candidate drug for two diseases that share some aspects of similarity in symptoms, phenotypes, and genes. In this regard, the ontology plays a role in constructing a semantic web that links
data from different sources. Incorporating with DL reasoning, ontology can largely enrich the effectiveness and efficiency of discovering linked data.

Table 3. The ClinicalTriav.gov columns show a number of clinical studies that focus on the corresponding diseases. In the PharmGKB columns, we investigated whether these drugs are related to the corresponding diseases from PharmGKB database. In the PubMed columns, the numbers indicate the number of returned searching results. MD: mental disorder. BD: bipolar disorder. EP: epilepsy. ‘Both’ shows a number of searching results include both BD and EP. *: Drugs that are in the clinical trials on bipolar disorder and epilepsy. #: Drugs that jointly appear with bipolar disorder and epilepsy in PubMed.

| Drug                               | PharmGKB ID   | ATC code  | ClinicalTriav.gov | PharmGKB | PubMed |
|------------------------------------|---------------|-----------|-------------------|----------|--------|
| 3,5-dimethyl-2-(3-pyridyl) thiazolidin-4-one | PA165958321   | missing   | 0 0 0             | 0 0 0    | 0 0 0  |
| acetaminophen                       | PA448015      | N02BE01   | 17 0 1            | 0 6 105  |        |
| anastrozole                         | PA448432      | L02BG03   | 3 0 1             | 0 1 1    |        |
| *# antiepileptics                   | PA143485705   | N03; N03A  | 409 118 531       | Yes 328  | 3353   | 34690  |
| artemisinin                         | PA165111696   | P01BE01   | 2 0 0             | 0 1 5    |        |
| artesunate                          | PA165111697   | P01BE03   | 0 0 0             | 0 1 3    |        |
| azathioprine                        | PA448515      | L04AX01   | 1 0 0             | 0 4 55   |        |
| *# caffeine                         | PA448710      | N06BC01; N02BE01 | 45 2 2  | 1 37 279 |
| *# carbamazepine                    | PA448785      | N03AF01   | 30 14 50          | Yes 106  | 1210  | 5738   |
| celecoxib                           | PA448871      | L01XX33; M01AH01 | 8 1 0  | 0 11 23  |
| cotinine                            | PA166114414   | missing   | 58 2 0            | 0 8 2    |        |
| coumarin                            | PA134521193   | missing   | 0 0 0             | 0 0 17   |        |
| cyclophosphamide                    | PA449165      | L01DB07; L01AA01 | 6 0 0  | 0 5 131  |
| dasatinib                           | PA162372878   | L01XE06   | 0 0 0             | 0 0 0    |        |
| dexlansoprazole                     | PA166110257   | missing   | 2 0 0             | 0 0 0    |        |
| # dexametomidine                    | PA449256      | N05CM18   | 36 0 1            | 1 2 33   |        |
| # dextromethorphan                  | PA449273      | R05DA09   | 18 2 0            | 1 11 80  |        |
| *# diazepam                         | PA449283      | N05BA01; N05BA17 | 19 2 9  | Yes 13 81 3111 |
| docetaxel                           | PA449383      | L01CD02   | 0 0 0             | 0 0 3    |        |
| efavirenz                           | PA449441      | J05AG03   | 2 0 0             | 0 4 13   |        |
| esomeprazole                        | PA100756      | A02BC05   | 2 0 0             | 0 0 0    |        |
| fluorouracil                        | PA128406956   | L01BC02   | 0 0 0             | 0 3 32   |        |
| *# gabapentin                       | PA449720      | N03AX12   | 42 1 14           | Yes 32 196 987 |
| hydroxchlorothiazide                | PA449899      | C03AA03   | 2 0 0             | 0 11 16  |
| irinotecan                          | PA450085      | L01XX19   | 0 0 1             | 0 0 3    |        |
| lamivudine                          | PA450163      | J05AF05   | 1 0 0             | 0 1 6    |        |
| *# lamotrigine                      | PA450164      | N03AX09   | 84 58 58          | Yes 78 763 2211 |
| letrozole                           | PA450196      | L02BG04   | 2 0 0             | 0 2 4    |        |
| *# lithium                          | PA450243      | D11AX04; N05AN01 | 159 119 1  | Yes 115 7196 751 |
| mercaptopurine                      | PA450379      | L01BB02   | 0 0 0             | 0 4 42   |        |
| methotrexal                         | PA450433      | D05AD02; D05BA02 | 0 0 0  | 0 1 2    |        |
| *# methylphenidate                  | PA450464      | N06BA04   | 232 5 2           | 3 92 119 |
| nevirapine                          | PA450616      | J05AG01   | 0 0 0             | 0 1 4    |        |
| # nicotine                          | PA450626      | A11HA01; N07BA01; C04AC01 | 377 9 0  | 1 126 297 |
| oxaliplatin                         | PA131285527   | L01AX03   | 0 0 0             | 0 0 1    |        |
| *# oxcarbazepine                    | PA450732      | N03AF02   | 7 2 26            | Yes 22 124 898 |
| # phenobarbital                     | PA450911      | N03AA02   | 7 0 14            | Yes 12 26 4654 |
| # phenytoin                         | PA450947      | N03AB02; N03AB05; N03AB04 | 9 0 31  | Yes 19 63 6616 |
| # pilocarpine                       | PA450962      | S01EB01; N07AX01 | 0 0 0  | 7 20 1859 |
| # quetiapine                        | PA451201      | N05AH04   | 358 101 0         | Yes 3 728 43 |
| quinidine                           | PA451209      | C01BA01   | 6 0 0             | 0 3 35   |        |
| S- adenosylmethionine               | PA164754994   | missing   | 8 1 0             | 0 21 18  |
| tegafur                             | PA452620      | missing   | 0 0 0             | 0 1 2    |        |
| *# topiramate                       | PA451172      | N03AX11   | 67 12 45          | Yes 27 229 1534 |
| *# valproic acid                    | PA451846      | N03AG     | 132 84 53         | Yes Yes 131 1454 4999 |
| varenicline                         | PA164781343   | N07BA03   | 87 4 0            | 0 28 6   |        |
| warfarin                            | PA451906      | B01AA03   | 7 0 1             | 0 7 64   |        |
| zidovudine                          | PA451954      | J05AF01   | 8 0 0             | 0 8 20   |        |
During the semantic reasoning, we discovered a pivotal role symptoms and phenotypes play when positioning candidate drugs between similar diseases. The etiology of the psychiatric disorder is elusive due to the phenotypic heterogeneity and symptom complexity. For example, it remains challenging to properly define genotypes to detect target genes for certain psychiatric disorders. The linkage studies provide suggestive evidence of detecting candidate genes and drugs for diseases, which has been recognized as a key to discovering effective drugs in psychiatric disorders. These studies resulted in a large portion of research outcomes documented in semantics, such as literature and gene ontology, even though the data is usually incomplete and in low quality. This situation has become a challenge for data integration and knowledge discovering. In our view, ontology is a promising approach to underpin the linked semantic data. A discussion over our evaluation results reveals rich information beyond drug-gene-disease associations. For example, there are plenty of ongoing or completed clinical trials (may contain a very few of clinical trials with unknown status) on antiepileptic and aim either bipolar disorder (118 clinical trials) or epilepsy (531 clinical trials). Meanwhile, the PubMed search result shows 328 entries that contain drug names and the two diseases simultaneously, whereas the PharmGKB only indicates the association between epilepsy and the drug. The resulted discrepancy between different data sources implies missing knowledge between individual data sources.

The present work should be interpreted within the context of its limitations. First, although we validated the results through matching information retrieved from multiple credible sources, a secondary review from clinical experts can make the evaluation, even more, convincing. Second, under the present framework, the most challenging part lies in encoding symptom information from heterogeneous data sources (e.g. literature and medical data) since they are in lack of a unified medical vocabulary and effective coding system for data alignment and disambiguation. Third, there is also a need for a commonly recognized data repository for the associations between symptom and phenotype. Fourth, there are a number of inferred drugs that are either used for the two diseases already or fail on face value. Therefore, a follow-up method to select exact drugs will benefit the goal of drug repurposing.

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