Graph-Based Inference: A Case Study in Identifying Potential Drug Candidates for the Treatment of Schizophrenia, Major Depressive Disorder & Anxiety Disorders

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Abstract

Drug repurposing involves exploring new pharmaceutical purpose for already approved drugs. The drug development process comes with a high development risk, as it is demanding in terms of both time and cost. Drug repurposing tries to address these issues, as it focuses on drugs already on the market, thus alleviating the need for clinical trials to assess the already established safety profiles of drugs, requires less resources and is historically associated with higher success rates.

In the present work, a knowledge graph has been created with the intention to identify potential drug candidates for schizophrenia, major depressive disorder, and anxiety disorders, with the use of ontology-based reasoning.

The resulted knowledge graph involves seventy-three classes with three of them being the defined classes, designed to generate new knowledge. Twelve thousand nine hundred twenty five individuals are imported to the ontology from Kyoto Encyclopedia of Genes and Genomes and DrugBank databases containing genes and proteins, drugs, biological pathways, and the aforementioned human diseases.

To this end, two potential candidate drugs for schizophrenia were identified, as well as four for major depressive disorder – two of which are already in clinical trials, emerged. For anxiety disorders, the candidates retrieved were disproportionately high in prevalence, suggesting that further investigation is required to make the inference process more selective.

Keywords

Protégé, Knowledge Graph, Drug Repurposing, Schizophrenia, Major Depressive Disorder, Anxiety Disorders

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Introduction

Drug repurposing (or drug repositioning) is the process of revealing new medical uses, for already developed drugs. Among other reasons, less development risk, shorter timelines, and lower costs are the main factors which made pharmaceutical companies and researchers to consider drug repurposing as a more essential solution against traditional drug development activities. A drug was defined as repurposed when the active compound was used in clinical trials for another indication. Sildenafil (Viagra) is one of the most well-known examples of repurposed drugs. Originally developed as an anti-hypertensive but nowadays is used for the treatment of erectile disfunction.

There are three approaches to repurpose drugs, either experimentally, clinical based or computational based. Computational approach can be subcategorized to disease-centric or drug-centric and includes techniques like knowledge graphs, machine learning, text mining and semantic annotations, etc. Lately, knowledge graphs have made their appearance in the biomedical domain that combines information about drugs, genes, and diseases in order to predict new connections between them. A knowledge graph consists of three main components: nodes, edges, and labels. Any entity or object is a node in the graph and the edges define the relationship between the nodes. Ontologies are the foundation of knowledge graphs since they represent the data schema with respect to a Class hierarchy with suitable properties, and they are based on the Resource Description Framework (RDF) described as statements/triples - subject, predicate, object. When data are ingested properly, ontologies allow the creation of new knowledge by signifying connections that have not been realized previously.

For the scope of this project, an integrative ontology has been developed, by combining three mental and behavioral disorders -*schizophrenia, major depressive disorder (MDD) and anxiety disorder*, aiming to not only reveal potential drug candidates, but also help researchers of the biomedical domain to identify disease characteristics.

Literature Review

Background Knowledge

The term gene was originated in 1905 by Danish botanist, Wilhelm Ludvig Johannsen, which derives from the ancient Greek word γόνος [gonos] for child and race[1]. Formerly, it was called a factor and it was identified as such, by Gregor Mendel in 1866, based on his examination on the procreation of pea plants[2]. The scientific community identifies a gene as the fundamental unit of heredity which contains information for particular physical or biological characteristics, that is transferred from parent to offspring[3]. A gene is comprised of segments of Deoxyribonucleic Acid, also known as DNA, that encodes for proteins[4]. However, DNA does not produce proteins directly. The Ribonucleic Acid, also called RNA, carries that information from DNA and transforms it into proteins.
Within the genome, each gene has coding sequences called exons[5], as well as introns[6], the non-coding sequences. During the transcribe of genes, exons and introns exist in the precursor messenger RNA, otherwise pre-mRNA, outcome. As a result of splicing, the introns are eliminated and exons are inserted into the mature messenger RNA, thus indicating what proteins are generated.
To monitor and register all genes in the human body, researchers have allocated short combinations of letters in the form of abbreviations for each gene, in order to avoid using long names. For instance, Brain Derived Neurotrophic Factor is symbolized as BDNF[7]. This gene is associated with Spinal Cord Injury, Mental Retardation Syndrome, etc. and the expression of it, is reduced in Alzheimer's, Parkinson's, and Huntington's disease patients[8].

Proteins are extensive, multiplex molecules composed of thousand units of amino acids attached together in lengthy linear chains and they are essential for all the bodily functions an organism needs. They are accountable for creating cells and tissue, they allow chemical reactions -like digestion and coagulation, they maintain suitable pH levels to the blood and other body fluids, etc. Hence either the redundancy or absence of a protein, can lead to metabolic problems, disease state and organ failures[9].
There are seven types of proteins in the human body: *enzymes, hormones, antibodies, structural, storage, transport and contractile*. Hormones, for example, control and regulate specific functions such as development and reproduction. Enzymes on the other hand, behave as catalysts, which means that they accelerate biochemical reactions.
While there are hundreds of amino acids in nature, the human body creates proteins from the transformation and combination of 20 amino acids. Further categorization of proteins depends on the class of the amino acids [10]. The three sets of amino acids are: *Non-Essential, Essential, and Conditionally-Essential.*

- Non-Essential amino acids can be acquired through food and also produced internally within the body.
- Essential amino acids cannot develop inside the body, thus dietary protein takes care of those.
- Conditionally-Essential amino acids are generated under normal physiological conditions, and they become essential for the human body under difficult conditions like famine.

The process in which genetic information is transcribed in the messenger RNA and translated into proteins, is called *gene expression*. Fundamentally, gene expression is affiliated with the theory of the Central Dogma pointed by Francis Crick in 1958[11]. Throughout the action of *transcription,* the information received from a gene's DNA moves to the RNA. The type of RNA responsible for this is called messenger RNA (mRNA) because it is the 'messenger' who carries the information responsible for making a protein. Protein synthesis is accomplished through the second step of gene expression, which is called *translation*. Transfer RNA (tRNA) translates the message from mRNA to a sequence of amino acids that assembles the protein[12].

By definition, a disease can be identified as an organism's irregular state that exerts influence on its normal function. Biomedical analysis related to the causes of a disease has recognized two major points of interest; the *genetic* and the *molecular* basis of a disease[13].
The majority of research around the etiology of a disease has focused on uncovering genes associated with particular diseases. The understanding of the link between a human's genes (genotype) and the observable traits (phenotype) is the foundational purpose of genetic science. During the past years, positional cloning has been used for such purposes with huge success in the field of cystic fibrosis[14], Huntington's disease[15], and breast cancer[16]. In the approach of positional cloning, genetic mutations related to a disease are trying to be identified simply through heredity[17] and can be achieved without any prior knowledge about the influence of a gene's encoded protein in the disease. Since positional cloning is considered a laboratory method, as a first step, families in which the disease phenotype is expressed are analyzed to characterize mandatory DNA zones. Most of the times the correlation between genotype and phenotype is not direct for several reasons like pleiotropy - happens when a single gene produces multiple phenotypes, influence of other genes and environmental factors like bacteria or even the psychological state of a patient. Decrypting the molecules that trigger and control different biological processes that lead to unhealthy states is an alternative way to understand pathogenesis, trying to diagnose it and find targets of therapeutic interest. Protein interaction can issue extensive molecular information about the linkage between proteins which are required in immune, metabolic and signaling networks. Mutations caused by biological diseased conditions can induce disruptions in protein-DNA interactions, protein misfolding, new undesired interactions or pathogen-host protein interactions. Protein to Protein Interaction (PPI) networks are the tools used for interpreting the molecular basis of a disease. They are practically graphs in which the nodes and the edges represent proteins and their interactions. There are vast computational and experimental techniques to characterize, predict and detect PPI networks for instance statistical, text mining and machine learning.

Drugs defined as substances used to prevent, diagnose, and treat a disease. There are over 20.000 drug products[18] and only for the year 2021, US Food & Drug Administration (FDA), approved 50 novel drugs[19] including Cabenuva, which aims to treat Human Immunodeficiency Virus type 1 (HIV1) infection in adults[20]. Examples of generic drugs categories are: antibiotics, analgesics, anticonvulsants, antiemetics, antineoplastics etc. Antibiotics, treat a disease by eliminating or pausing the spread of hostile microorganisms. Antineoplastics work by targeting and killing

cancerous cells. Further usages relate to the correction in the low levels of chemicals, such as insulin, a hormone that regulates the levels of glucose in the body.

Presently researchers are developing new drugs by studying and understanding information about biological pathways[21]. A biological pathway is a sequence of activities between molecules in a body cell, that produces a particular result or a transformation in the cell itself. By identifying what biological pathway is related to a disease and which step of it affects patients, scientists can introduce more efficient substances to cure or prevent a disease. The most common biological pathways are *metabolic pathways, genetic pathways, and signal transduction pathways*[22].

Metabolic pathways are responsible for the chemical reactions that happen in our body. An example of metabolic pathway is the metabolism of serotonin. Serotonin, otherwise known as 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter accountable for mood regulation, learning, bladder function, etc.[23] Serotonin can be metabolized either into 5-HIAA by Monoamine Oxidase (MAO) or to N-acetyl-serotonin (NAS) by arylalkylamine N-acetyltransferase (AAAT). N-acetyl-serotonin is further metabolized to melatonin by hydroxyindole-O-methyl tranferase (HIMT).

Genetic pathways are related with the functionality of different genes in various serialized steps of a biological process (gene expression). The most distinctive example of a genetic pathway is the biosynthetic pathway, in which a forerunner molecule is chemically altered over a succession of transitional stages that are catalyzed by enzymes to assemble a product[24]. For instance, glutamine amino acid, is synthesized from glutamate and ammonia (NH_3) by glutamine synthetase enzyme (GS)[25].

Signal transduction pathways are in charge of the movement of the signals within the cells. A chemical message is picked up by the receptors, which are proteins that detect and receive signals. Subsequently, the linkage molecule attaches to the receptor obtaining a cellular response activity. In the cyclic adenosine 3,5-monophosphate signaling pathway (cAMP), epinephrine is the messenger which will bind in the G-Protein receptor. Afterwards adenosine triphosphate (ATP) will convert to cAMP, which will target Protein Kinase and activate its catalytic portions in favor of breaking down glycogen to glucose within the cell[26].

Biological Pathway Analysis

In the last decades, pathway analysis has increasingly been used to extract biological pathways and their linkage to the underlying biology of complex diseases, considering the simplicity and the descriptive capabilities it provides. A biological pathway is described by a graph with nodes and edges and illustrates the interactions between genes and proteins in the cells, that reports for given processes, mechanisms, or phenomenon[27]. Even though a vast number of analytical methods related to pathway analysis exist, the purpose of this thesis is focused only on knowledge base-driven pathway analysis. The progression of knowledge base-driven pathway analysis is divided into three generations, *over-representation analysis (ORA), functional class scoring (FCS) and pathway topology-based approaches (PT)*[28].

Over-representation analysis (ORA) is a method for identifying whether a set of genes or biological pathway is more frequent in a given condition. In other words, it statistically evaluates which genes from a particular pathway are between those which convey differences in gene expression. ORA requires as input just a list of genes, without any statistics. The most common techniques to determine statistical significance for ORA output, is either by using statistical tests like chi-square, binomial and hypergeometric, or by appropriate statistic, such as Jaccard index[29]. Even though ORA is simple and computationally inexpensive, it requires an arbitrary number of genes as an input, assumes independence between genes and pathways and evaluates every input equally weighted[30].

Functional class scoring (FCS) accepts that both large and weak alterations in individual genes and sets of genes can have remarkable reactions in biological pathways, so FCS considers all genes as input[31]. Thus, all genes must be ranked accordingly by statistics such as ANOVA, Z-score, t-test, etc.[32] Gene-level statistics are combined into a single pathway statistic with statistical significance reported for each pathway[31]. FCS is fixing some of the limitations of ORA since it does not require an arbitrary threshold of genes and considers dependence between genes in a pathway. FCS is an improvement of the previous method, however, still analyses each biological pathway independently, even though most of the times pathways can overlap[33].

Pathway topology (PT)-based approaches provide information about gene interactions in a pathway and the way they interact. Essentially PT and FCS methods are the same, with the only difference being that PT-based methods utilize topological information such as the role and the position of the pathway genes to compute gene level statistics. Public databases with information about gene and protein interaction, have eased the usage of topology-based methods. The most established database is the Kyoto Encyclopedia of Genes and Genomes (KEGG), which displays information about thousands of biological pathways[34].

Schizophrenia

Symptoms & etiopathology

Schizophrenia is a chronic, persistent mental disorder that affects a person's perception of reality, emotions, and social behavior. About 0.32% of the worldwide population suffers from schizophrenia[35] and 20% of them have attempted suicide at least once[36]. The diagnosis of schizophrenia most of the times happens in early adulthood and it is pretty uncommon for a child or an elder to develop the disorder. New instances of schizophrenia escalate in adolescence and achieve its spike between the age of 16 and 25[37].

In the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV) schizophrenia was further categorized in five subtypes; paranoid type, disorganized type, catatonic type, undifferentiated type, and residual type. During the publication

of the 5th edition though, those subtypes were dropped because they didn't reflect the complexity of the disease. Moreover, patients could not be assigned to a particular subtype based on their symptoms and mental health providers weren't using the subtyping taxonomy anymore. This is the reason why American Psychiatric Association (APA) established a more proper term called chizophrenia Spectrum Disorder " instead of simple Schizophrenia[38].

Consecutively for the diagnosis of schizophrenia spectrum disorder, a patient must appear symptoms of delusions, hallucinations, disorganized speech, disorganized or catatonic behavior and negative symptoms like avolition or diminished emotional expression for at least six months. However, it is mandatory for a person to have appear at least one of the first three symptoms. Besides those symptoms must cause social impairment in daily life, work/school, and self-care. Symptoms based on reaction to medication, drug use or medical conditions must be excluded[39].

Even though the etiology of schizophrenia is poorly understood, factors related to the development of the disease include genetic and environmental factors. Schizophrenia is highly heritable up to the percentage of 81%[40]. As far as it concerns environmental factors, prenatal factors like the seasonality of birth (December until May), disruptions in the development of the womb, infections concerning the mother and obstetric complications are also related[41]. Abnormalities in neurotransmitter systems have also been researched. The focus has been on three hypotheses; dopamine hypothesis, glutamate hypothesis, and inflammation hypothesis, with the first being the most prominent. The dopamine hypothesis (DA) derived from the discovery that symptoms like delusions or hallucinations are related to excited action in the mesolimbic dopamine system. The glutamate hypothesis holds that various genes connected with schizophrenia, targeting glutamatergic transmission[42]. Glutamate is the main excitatory neurotransmitter in the nervous system. Glutamatergic transmission involves glia glutamate receptors, which generally identifies synaptic movement in the brain. Metabotropic glutamate receptor agonists actually decrease the excitability of the brain[43]. Finally, there has been a notable concern around the role of immune system abnormalities in schizophrenia. Since maternal infections before birth are a risk factor, association between increased inflammation and schizophrenia may be involved in the etiopathology of the disease.

Classical Treatment Approaches

Incomprehension regarding the actual causes of schizophrenia, had led physicians to use antipsychotic drugs, which are mainly focuses on easing the symptoms of the disease and make patients functional in everyday life activities. Although psychotic diseases include also other disorders like bipolar disorder or mania, so far there are no 'anti-schizophrenics' known drugs.

First generation antipsychotics are dopamine D2 antagonists, they lower dopamine neurotransmitters activity in the brain. The first drug in this category is chlorpromazine which was released in 1953[44]. The most common effects of blocking dopamine D2 receptors in the body are dyskinesia, muscle breakdown,

tremors, and akathisia. Side effects on the central nervous system include sleep disturbance, dementia, loss of memory, depression, and vertigo. Other effects on cardiovascular system are tachycardia, chest pain or arrhythmia. Side effects related to the gastrointestinal system such as weight gain, nausea, dry mouth, heartburn, anorexia, dyspepsia, constipation. From the side of the urinary and reproductive system impotence, increased or decreased libido, priapism, polyuria, delayed and premature ejaculation are also known[45,46].

Second generation drugs are blocking more serotonin 5HT2A receptors than dopamine D2. The blocking of serotonin receptors results to lesser fear and anxiety expression in orbitofrontal cortex. The first drug which led the way to the discovery of these types of compounds was clozapine. The main caveat of clozapine is the causation of agranulocytosis which may rise to death[47]. This is why the FDA indicates patients to check their number of white blood cells on a weekly basis. Other approved second generation antipsychotics are: *olanzapine, molindone, paliperidone, ziprasidone, risperidone, and quetiapine.*
Olanzapine is chemically similar to clozapine but contrary to clozapine, olanzapine is not associated with agranulocytosis. Common side effects of olanzapine are sedation and weight gain. Molindone affects dopamine transmission in the brain. The use of molindone hardly leads to sedation and in opposition to other second generation antipsychotics, infrequently affects weight gain. Quetiapine is also being used to treat bipolar disorder and major depressive disorder. Operates as a dopamine D1 and D2 and serotonin 5HT2 receptor antagonist and the side effects are usually sedation and orthostatic hypotension. Even though second generation antipsychotics present side-effects like obesity and type 2 diabetes, they are still more favorable.

Third generation drugs, includes aripiprazole, brexpiprazole and cariprazine. That group of antipsychotics are not dopamine D2 receptor antagonists but D2 partial agonists[48] and they characterized by better patient tolerability.
The side effects of aripiprazole commonly rely on akathisia, weight gain, agitation, insomnia, anxiety, headache, constipation, or nausea. However, aripiprazole participates significantly less in weight gain than clozapine, risperidone, and olanzapine[49,50,51].
Brexpiprazole was recently added to the antipsychotics drug category since it has been approved by FDA in 2015. It acts as partial agonist to dopamine D2, D3 and serotonin 1A receptors and has been[52]used pharmacologically for both schizophrenia and major depressive disorder. The side effects of using brexpiprazol are akathisia, weight gain, infections of upper respiratory tract, somnolence, headache and nasopharyngitis.

Drug repurposing and emerging treatment approaches

In a 2022 network analysis about potential medications for drug repurposing to treat the cognitive symptoms of schizophrenia, 8 drug candidates were suggested. Additionally, these symptoms could be addressed by sex-specific medical treatment

because of gene expression differences in females and males. Four out of eight drugs were chosen in male specific analysis and the rest in a female specific analysis[53].

Amoxapine, a tricyclic antidepressant (TCAs) used in the treatment of depressive disorders and psychotic depression. *Aspirin*, which is well known for pain, fever, and inflammation. *Disulfiram*, which is used to treat alcohol addiction. *Olaparid*, a poly (ADP-ribose) polymerase (PARP) inhibitor used to treat ovarian cancer, breast cancer, pancreatic cancer, and prostate cancer. *Papaverine*, an alkaloid used to treat many types of smooth muscle spasms. *Progesterone*, a hormone used for contraception, control of abnormal uterine bleeding, maintenance of pregnancy, and prevention of endometrial hyperplasia. *Sertraline*, which is known for its efficacy in Major Depressive Disorder and Anxiety Disorders and lastly *Sumatriptan*, which is known for migraines. The drugs that were identified as male specific were - amoxapine, aspirin, disulfiram and olaparib. The other four -papaverine, progesterone, sertraline and sumatriptan were identified as females specific.

A machine learning approach for the prediction of potential drugs with application to schizophrenia published in 2017[54], utilizing algorithms like support vector machines (SVM), deep neural networks (DNN), random forest, etc. Eight potential drugs were suggested -*valproate, raloxifene, nordihydroguaiaretic acid, pioglitazone, tretinoin, felodipine, aspirin and genistein.*

As mentioned above, inflammatory mechanisms may be involved in the etiology of schizophrenia. A preclinical study on male Swiss mice, led the way to research drugs that target tryptophan metabolism by testing repeated ketamine administration[55]. The authors of the study discover that melatonin, indoleamine 2,3-dioxygenase inhibitor and 1-MethylD-tryptophan were able to reverse behavioral changes caused by ketamine, suggesting that have potential as drugs for treating schizophrenia.

Major Depressive Disorder (MDD)

Symptoms & etiopathology

Major depressive disorder (MDD) or clinical depression, is a relatively common psychiatric disorder that can affect mood, behavior, and physical functions. In 2020, 14.8 million adults in the United States experienced at least one major depressive episode[56]. The prevalence of MDD ranged between 2% and 21%, with the highest percentages appearing in Europe and the lowest in Asia[57]. Women are twice likely to be diagnosed with depression. The most common sociodemographic correlation in developed countries is separation from a partner, on the other hand in developing countries is being divorced or widowed[58]. Different types of MDD include:

- *major depressive disorder*, which includes symptoms for at least two weeks and affects physical functions like sleep, eat, etc.
- *persistent depressive disorder*, which includes symptoms that last for at least two years

- *perinatal/postpartum depression*, which happens during a woman's pregnancy or after the birth
- *seasonal affective disorder*, usually occurs in late fall or early winter and goes away during summer and spring
- *disruptive mood dysregulation disorder,* which diagnosed in childhood and includes extreme anger, intense temper, and irritability
- *psychotic depression*, happens where a person experience delusions or hallucinations[59][60]

In accordance with the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), an individual must have at least five symptoms in the list below to diagnosed with MDD; depressed mood, loss of interest or pleasure, weight or gain loss, insomnia or hypersomnia, psychomotor retardation or agitation, feelings of guilt or worthlessness, decreased concentration, exhaustion, and suicidal thoughts. Plus, these five symptoms must cause social or occupational impairment. History of manic or hypomanic episodes and episodes attributable to substance effects or other medical conditions must be excluded[61][62].

The etiopathogenesis of MDD is resulted as the combination of biological, genetic, environmental, and psychological factors. Earlier MDD was considered to appear mostly because of deviations in neurotransmitters. The focus has been on three major monoamine systems -serotonin (5-hydroxytryptamine, 5HT), norepinephrine (NE), and dopamine (DA). Studies demonstrate low concentration of 5HT, NE and DA in the cerebrospinal fluid (CSF) of depressed patients as well as increased density of 5HT2 and β-Adrenergic receptors in brain postmortem tissue of patients with depression. Moreover, decreased 5HT transporter (SERT) binding and plasma concentrations of L-tryptophan, the precursor to 5HT. Increased MAO-A activity is found in the central nervous system of patients who are depressed. Brain imaging has revealed decreased dopamine transporter binding and increased postsynaptic D2/D3 receptor binding, all indicative of reduced DA neurotransmission. Stress, which triggers depression in vulnerable individuals, increases activity of the NE circuits in the brain.[63] Gamma-aminobutyric acid (GABA), glutamate and glycine neurotransmitters are found to play a role in the etiology of depression as well. Unpleasant childhood experiences, like abuse, and trauma are also associated with the development of adult depression[64].

Classical Treatment Approaches

The available treatment approaches regarding MDD consists of medication, psychotherapy, and somatic therapies. All these treatments aim to help depressive patients return to their previous levels of functionality and prevent relapses.

Medication wise, plenty of classes of antidepressants have been introduced in the scientific community over the years. Monoamine oxidase inhibitors (MAOIs) was one of the first class of antidepressant drugs and Iproniazid was the first drug defined as such. MAOIs act as irreversible inhibitors of monoamine oxidase and can cause hepatotoxicity, hypertensive crises, and intracranial bleeding[65]. Thus, MAOIs have become less popular, and their use is restricted to patients who do not behave to other treatments.

Tricyclic antidepressants (TCAs) increase the levels of norepinephrine and serotonin neurotransmitters and block the action of acetylcholine neurotransmitter. The first TCA drug was Tofranil and was introduced in 1957. The Food and Drug Administration (FDA) has approved amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, trimipramine, and amoxapine TCAs to treat MDD. Side effects dependent on the dosage, and include blurred vision, drowsiness, constipation, weight loss, excessive sweating, tremor, and sexual problems[66].

Selective serotonin reuptake inhibitors (SSRIs) are effective as TCAs but with less side effects. In 1987, fluoxetine was released in the market and in 1994 it was the second most selling drug in the world[67]. After the quick expansion of SSRIs, more similar drugs were becoming available like sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram with sexual side effects together with headaches, insomnia, and anxiety[68].

To secure patients against SSRIs side effects, Norepinephrine reuptake inhibitors (SNIs) made known during 1990s. Available SNRIs are venlafaxine, desvenlafaxine, and duloxetine and considered as effective as SSRIs[69].

In injection form ketamine which is a general anesthetic, has also been introduced as an antidepressant drug, but the effect fades out after some days. Side effects of ketamine include dizziness, neurotoxicity, cognitive dysfunction, blurred vision, psychosis, dissociation, urological dysfunction, restlessness, headache, nausea, vomiting, and cardiovascular symptoms and because the risk of addiction is high it is not recommended on daily basis[70,71].

Psychotherapy is considered the first step to treat MDD. The suggested methods are cognitive behavioral therapy (CBT), interpersonal therapy (IPT), supportive therapy (ST) and psychoeducational intervention (PEI) with the first two being more promising. After the suspension of symptoms CBT and PEI are used to maintain or entirely prevent depression. In cases of chronic depression, the European Psychiatric Association suggests cognitive behavioral analysis system of psychotherapy (CBASP)[69].

Somatic therapies are also proven to be effective treatments against MDD. The most acknowledged technique is Electroconvulsive Therapy (ECT) and involves electrical stimulation of the brain while the patient is under anesthesia. Typically used when medication and psychotherapy have not worked and also for people with suicidal tendencies[72]. Extensive research has found ETC very effective and safe, but it cannot prevent a depressive episode from happening again. Other similar methods are repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), vague nerve stimulation (VNS), deep brain stimulation (DBS), magnetic seizure therapy, and luxtherapy (phototherapy)[69].

Drug repurposing and emerging treatment approaches

There is a plethora of repurposed drugs for MDD, which range from GABA receptor modulators to dopamine agonists, second generation antipsychotics, etc. In total thirty

eight repurposed drugs have been introduced like aripiprazole, ketamine, brexpiprazole and cannabidiol and most of them have been studied in clinical trials about their efficacy in the disorder[73].

A machine learning approach with application to depression/anxiety disorders, manage to suggest repurposed drug candidates. Various machine learning algorithms were used for prediction, including deep neural networks, support vector machines, elastic net, random forest, and gradient boosted machines. The performance of the five methods was similar, but support vector machines managed to outperform the others. The top seven derived results were -cyproheptadine, chlorcyclizine, pizotifen, tetrandrine, vorinostat, apigenin, and metformin[54], proven the succession of machine learning to predict repurposed candidates for psychiatric disorders.

A medical study about drug repositioning for treatment resistant depression (TRD), a state in which the subject is unable to react in two different antidepressant compounds, identified the antagonist of muscarinic receptors, the modulation of DNA methylation and calcium channels as possible structures. Additionally, the inhibition of HSP90, can treat MDD patients with anxious distress[74].

Anxiety Disorders

Symptoms & etiopathology

Anxiety disorders are the most frequent mental health conditions and affects 19.1% of the United States population. Even though they are highly curable, only 36.9% of the patients suffering from anxiety disorders receive treatment[75]. Encountering anxiety is a normal phenomenon for every human's life and lately appears to be a very popular opinion. In 1621, Robert Burton in his book 'The Anatomy of Melancholy' describes the symptoms of anxious people with words as tremble, sweat, sudden changes in the temperature of the body and increased heart rates[76]. Anxiety disorders show intense and excessive worry and fear about daily activities and can last for a long time. Even in the 21st century, anxiety disorders are receiving insufficient acknowledgement and patients suffering from them receive less attention than patients experiencing major depressive disorder or schizophrenia. According to an article published in the British Journal of Psychiatry by Cambridge University Press in 2018 the poor handling of anxiety disorders has led to lessened productivity, greater mortality rates and increased alcohol and drugs consumption[77][78]. Thus, defining the limits between normal and psychopathological anxiety is an important distinction that needs to be made by all the psychiatry community.

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), the different types of anxiety disorders are:

- *generalized anxiety disorder*, which includes excessive anxiety and worry about daily activities. The level of anxiety is beyond the normal proportion and is difficult to control it
- *panic disorder (PD)* involves frequent episodes of unexpected fear and terror (panic attacks). Symptoms like shortness of breath, chest pain, or a rapid heartbeat appear

- *agoraphobia,* in which the patient wants to avoid overcrowded places that might cause panic and creates the feeling of trapped, helplessness and embarrassment
- *social anxiety disorder* is related with extreme levels of fear for particular social situations or events caused by a sense of embarrassment and concern about being judged
- *specific phobias,* which are characterized by high anxiety when someone is exposed to a certain object or situation
- *post-traumatic stress disorder (PTSD)*, in which the main symptom concerns the avoidance of memories associated with the traumatic event
- *separation anxiety disorder,* which is a childhood disorder described by anxiety related to separation from parents
- *obsessive-compulsive disorder (OCD), in which the patient experiences a* pattern of unwanted obsessions that lead to do repetitive compulsions
- *illness anxiety disorder, where* individuals worry about the medical diagnosis of a specific illnesses they may have

For an individual to be diagnosed with any of the above anxiety disorders, the mental health provider must proceed with a phycological evaluation first, which includes discussions about the feelings and the thoughts of the individual. At that point the mental health provider must compare symptoms to the DSM-5 ones. In accordance with this textbook published from the American Psychiatric Association (APA), each of the disorders above have its own diagnosis criteria. For instance, generalized anxiety disorder characterized by persisting anxiety and uncontrolled worry for at least 6 months about numerous routine activities or events. Those feelings are associated with three or more of the symptoms listed below; restlessness or feeling on edge, muscle tension, sleep disturbance, lack of concentration, irritability, exhaustion. Anxiety and worry must also cause impairment in social functioning and cannot be justified by another mental disorder [79]. Nevertheless, there are some common symptoms for all anxiety disorders[80]:

- panic, fear, danger
- sleep problems
- cold, sweaty, or numb limbs
- shortness of breath or hyperventilation
- heart palpitation
- nausea
- tense muscles
- rumination of problems
- lack of concentration
- avoidance of objects or places

The etiology of anxiety disorders lies on stress, genetics, first-degree relatives with generalized anxiety disorder by 25%, medical problems like diabetes or heart diseases and environmental factors. The symptoms of anxiety disorders are considered to appear because of disruptions in the central nervous system. The low activity on the serotonin system causes under activation of the noradrenergic neurotransmitter systems. Therefore, the primary focus is on selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI). Gamma-aminobutyric acid (GABA) disruptions and cholecystokinin neurotransmitter are also affecting patients with anxiety disorders. Finally, there is an increased interest in corticosteroids, a class

of steroid hormones produced in the adrenaline cortex. Corticosteroids hormones are involved in the regulation of stress, fear, behavior, etc.[81][82]

Classical Treatment Approaches

Like in Major Depressive Disorder, a combination of pharmacotherapy together with psychotherapy sessions are known to be effective for the treatment of anxiety disorders.

Selective serotonin reuptake inhibitors (SSRIs) are identified as the most common drugs for anxiety disorders. Fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, paroxetine and vilazodone are some of the drugs in this category and they are acting in a way that normalizes the function of the serotonergic pathway[83]. Serotonin norepinephrine reuptake inhibitors (SNRIs) are generally used when SSRIs failed to treat anxiety disorders. Some of these drugs are venlafaxine, desvenlafaxine, and duloxetine.
Benzodiazepines used to be very popular antianxiety medications, but they were no longer considered to be the first choices because of chronic side effects being physiological and psychological dependence, impaired cognition, lethal overdose when mixed with alcohol or opioids, and memory encoding issues. However, for some patients, small doses of benzodiazepines combined with cognitive behavioral therapy has successful results[84].

Combined efforts of SSRIs medication together with cognitive behavioral therapy (CBT) is the most common practice to treat anxiety disorders. Nonetheless due to the diversity of the anxiety disorders, CBT seems to have better effect on panic disorder patients, and on the other hand for patients with social anxiety disorder pharmacotherapy produces better results[84]. In general CBT costs more than medication, notably if medication is prescribed.

Drug repurposing and emerging drugs

In this section, a brief review for the current scene of emerging repurposed drugs for anxiety disorders is being presenting. The focus of scientific research around emerging treatments for anxiety disorders has been around serotonin and GABA systems, glutamate neurotransmitters and neuropeptides.
Vilazodone, which is a SSRI, was approved by the FDA for the treatment of MDD and is further studied in Generalized Anxiety Disorder (GAD). A 12-week double-blind, placebo-controlled trial of Vilazodone suggests promising results for social anxiety disorder (SAD) in 44 patients[85]. A relevant 2017 meta-analysis conducted three randomized control trials with duration of 10 weeks, with 844 patients under the influence of 20-40mg of vilazodone and 618 patients under placebo. Vilazodone was proven superior to placebo and an effective treatment for GAD[86]. However, in a latest network meta-analysis about pharmacological treatments of GAD which conducted in 2019, vilazodone did not appear effective in treatment[87]. Further studies are needed to reach a confident conclusion.

Vortioxetine, a 5HT3 antagonist and 5HT1A agonist, is approved by the FDA for MDD in 2013, but its effectiveness on anxiety is not clear yet. Originally promising results in GAD were published in 2012 by an 8 week randomized, double-blind, placebo controlled clinical trial in total of 301 subjects -150 to receive vortioxetine and 151 on placebo[88]. Yet the 2019 network meta-analyses[87] failed to show significant adequacy of vortioxetine over placebo in GAD. There is an ongoing study for patients with GAD coexisting with MDD with ClinicalTrials.gov identifier: NCT04220996, but no results are posted yet[89].

Tandospirone is an azapirone, which have been studied in 2018 for major depressive disorder patients with high anxiety. The results of a 6-week study in 230 subjects showed significant improvements in depressive and anxiety symptoms[90]. There is also one completed study for high doses of tandospirone in GAD patients, but no results have been posted yet[91].

Agomelatine, an antidepressant that behaves as a melatonin MT1 and MT2 receptor agonist and serotonin 5-HT2C receptor antagonist, it was also found to have antianxiety effects[92]. According to randomized controlled trials a pathway meta-analysis of treatments for GAD determined that agomelatine is potentially efficient compound [87].

Hallucinogens, like psilocybin (4-phosphoryloxy-N,N-DMT) which is a natural psychedelic compound derived from mushrooms, have potential clinical used for the treatment of anxiety disorders. Psilocybin is recorded as a Drug Enforcement Administration Schedule I controlled substance and there is a potential reduction on anxiety symptoms for patients suffering from cancer according to randomized controlled trials[93]. Another hallucinogen which is also a Schedule I controlled substance, is Lysergic acid diethylamide (LSD). There is a completed randomized, double-blind, placebo-controlled trial testing for LSD in patients with anxiety, but the results are not posted yet[94]. To avoid any misunderstanding, it is wise to explain that Schedule I drugs, are drugs or compounds with no currently accepted medical use due to high abuse levels so their clinical utilization is still questionable.

Metabotropic glutamate receptors (mGluR) have shown promising results in the areas of schizophrenia, anxiety disorders and mood disorders in animal models[95]. The mGlu receptor agonist LY354740, again has shown antianxiety properties for animal subjects, but in a placebo-controlled double-blind randomized clinical study failed to show treatment different than placebo[96].

Riluzole is a glutamate modulator, the efficacy of which has been tested in an 8 week, open-label, fixed-dose study for GAD. According to the results 12 out of 15 patients appeared to have positive effects of riluzole and more placebo-controlled studies were suggested[97]. Troriluzole, a similar compound to riluzole, is on a Phase III trial for GAD and the results have not been published[98].

As mentioned above, benzodiazepines which are GABA-A agonists are very efficient as a treatment for anxiety disorders. For that reason, there has been some efforts to find GABAergic antianxiety medications. There is yet no improvement on identifying GABA-A agonists with anxiolytic activity due to failure to separate from placebo treatment for patients with GAD[99,100]. SAGE-217, a GABA-A receptor positive allosteric modulator was evaluated in a double-blind, placebo-controlled, single ascending dose and multiple ascending dose study and it is under Phase II clinical programs for MDD and postpartum depression, and also is investigated for treatment of GAD[101].

Neuropeptides are small proteins that work as neuronal signaling molecules. Oxytocin is a neuropeptide that plays significant roles in modulating fear and anxiety. However, there are many studies that use oxytocin as an antipsychotic. A double-blind, placebo-controlled study of oxytocin on an exposure therapy for arachnophobia found that oxytocin compared to placebo performed better[102]. Studies on oxytocin for the treatment of anxiety have been focused on SAD. There is an ongoing study at the patient recruitment stage, which aims to evaluating oxytocin in patients with different mental illnesses[103].

Drug Repurposing: Knowledge Graph Approaches

Knowledge Graphs (KG) representing a semantic network between entities and their underlying relationships. Repurposing existing drugs can decrease the cost for pharmaceutical industries, with less risk. The idea of drug repurposing via knowledge graphs was first expressed by Ashburn & Thor in 2004[104], through the description of the links between genes, drugs, and diseases. Given the fact that a single disease cannot be interpreted as a unique gene modification, the debate has shifted to network representations for better understanding of the disease's ecosystem.

Currently with the Covid-19 pandemic, the scientific community felt the urgent need for a rapid development of potential repurposed drugs in order to treat SARS-Cov-2 virus.

A very interesting Drug Repurposing Knowledge Graph (DRKG) was built relating genes, drugs, biological pathways, side effects, and symptoms related to COVID-19 with data from different biomedical databases. DRKG consists of 97.238 entities belonging to 13 entity types and 5.874.261 triplets belonging to 107 edge types. Part of the DRKG is a pretrained embedding along with molecule embedding for small-molecule drugs using pretrained Graph Neural Networks, aiming to predict drug-disease relationships[105].

On the same page CAS Biomedical Knowledge Graph displays diseases, proteins, small-molecule inhibitors, biological pathways, and COVID-19-specific data for developing candidate small molecules drugs for COVID-19. The underlying relations are in the form of drug X targets gene/protein Y and that protein is involved in the Z biological pathway. Overall, the KG contains 6 million nodes and 18 million relationships. A sophisticated ranking algorithm was also developed to score each

compound independently and prioritize the most encouraging candidates. The research resulted in 1.350 arranged candidates and the top 50 of them were further analyzed with 11 out of the 50 results already in clinical trials [106].

Methodology

Data acquisition

For the scope of this project, an ontology has been developed which displays human diseases, genes and proteins, biological pathways, and drugs together with their underlying relationships using Protégé. Considering that drug repurposing is emerging in the biomedical domain, various databases have been designed. There are two sets of online database resources, clinical oriented and chemically oriented databases. After carefully review all of them and their different types of data, the following databases were selected.

- **KEGG: Kyoto Encyclopedia of Genes and Genomes**

  KEGG is a chemically oriented database project, which begun in 1995 under the Japanese Human Genome Project aiming to define biological mechanisms in the form of molecular pathways[107]. It essentially categorizes genes based on their biological pathways and links human diseases to the corresponding biological pathways they are associated with.

  After searching for Schizophrenia, Major Depressive Disorder, and Anxiety Disorders, information about the diseases along with the related biological pathways and drugs used for treating the diseases were presented. Biological pathways are mapped with a unique ‘hsa’ code and consequently for each pathway the involved genes were captured as well as their abbreviations. With the help of the python programming language, data was converted to excel format files, with all special characters removed and all spaces replaced with the hyphen symbol, so that the import in Protégé can be carried out without throwing any error exceptions. Eventually two excel files were created for each biological pathway -one with the genes involved, and one with the drugs affected the corresponding pathway. An example of the python script can be found in Appendix A.

- **DrugBank**

  DrugBank firstly was introduced in 2006 as a chemically oriented database, and since then is being widely used to provide information about drugs in addition to their target genes and the type of action among other things. The

latest release of DrugBank contains 15.318 drugs and over 6.716 experimental drugs[108]. It is offered as a 'free-to-access' database and in order to download the data for academic purposes a free license agreement is provided through e-mail verification[109].

After acquiring the data in xml format, the python programming language was used again to convert the file to JSON format, which is more easily manipulable. As it was mentioned above, DrugBank provides a vast amount of information about drugs, so an iteration through the objects of the JSON file was required to keep only the wanted fields, that is drug name, group of targets together with their abbreviations, the action of the drug in the target and finally the type of the drug. Repeatedly the result was converted to excel format, with all special characters removed and spaces replaced by the hyphen symbol. An example of the python script can be found in Appendix B.

Ontology Architecture

The goal of this chapter is to make the reader understand the underlying architecture of this ontology and under what criteria it was built. On a high level description, linkages between the diseases, biological pathways, drugs, and genes were trying to achieved in order to bring off the creation of inferred knowledge regarding potential repurposed drug candidates for Schizophrenia, Major Depressive Disorder and Anxiety Disorders.

Classes and Subclass

Ontologies consist of Classes which are collections of objects/individuals. The class owl:Thing is the default root class containing the set of all classes and their respective subclasses in the ontology. Inside the root class, four classes are emerging (Figure 1):

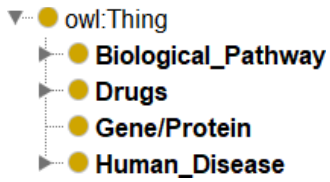

Figure 1 Classes of the Ontology

- *Biological_Pathway*, a class containing all biological pathways related to Schizophrenia, Major Depressive Disorder, and Anxiety Disorders from KEGG database
- *Drugs*, a class containing all types of drugs gathered from KEGG and DrugBank databases
- *Gene/Protein,* a class containing all concentrated genes or proteins as individuals from KEGG database

- *Human_Disease*, a class containing all human diseases as they were classified in KEGG database

After defining the Classes in the ontology, arranging them in a taxonomic hierarchy of subclasses or second level classes would be the next step. The Biological_Pathway class encloses all pathway categories (Figure 2) as they are revealed in KEGG database[110].

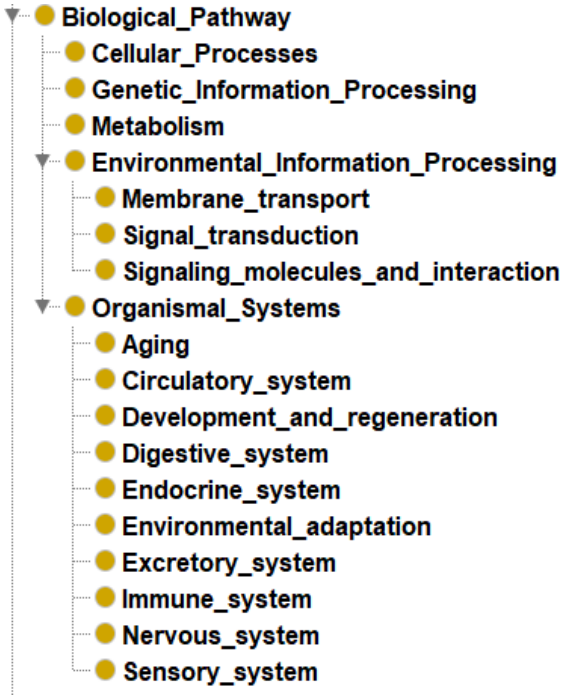

Figure 2 Biological Pathway Subclasses

Inside biological pathway categories, the biological pathways that are of interest are included as instances, which represent individual objects within this particular domain. Instances are used to represent specific individuals that belong to a class, which is a more general concept or category. Overall, instances are a key component of ontology development and reasoning, as they provide a way to represent specific knowledge about the domain being modeled. In the table below, pathway categories together with the corresponding individuals and the related disease are being displayed.

Biological Pathway Category	Biological Pathway	Disease
Signal transduction	ErbB Signaling Pathway	Schizophrenia
Signaling molecules and interaction	Neuroactive ligand receptor interaction	Schizophrenia
Nervous system	Dopaminergic synapse	Schizophrenia, Major Depressive Disorder, Anxiety Disorders
Nervous system	GABAergic synapse	Major Depressive Disorder
Nervous system	Glutamatergic synapse	Schizophrenia, Major Depressive Disorder, Anxiety Disorders
Nervous system	Serotonergic synapse	Major Depressive Disorder, Anxiety Disorders

The Drugs class encloses all drug categories (Figure 3) as they are revealed in KEGG database[111].

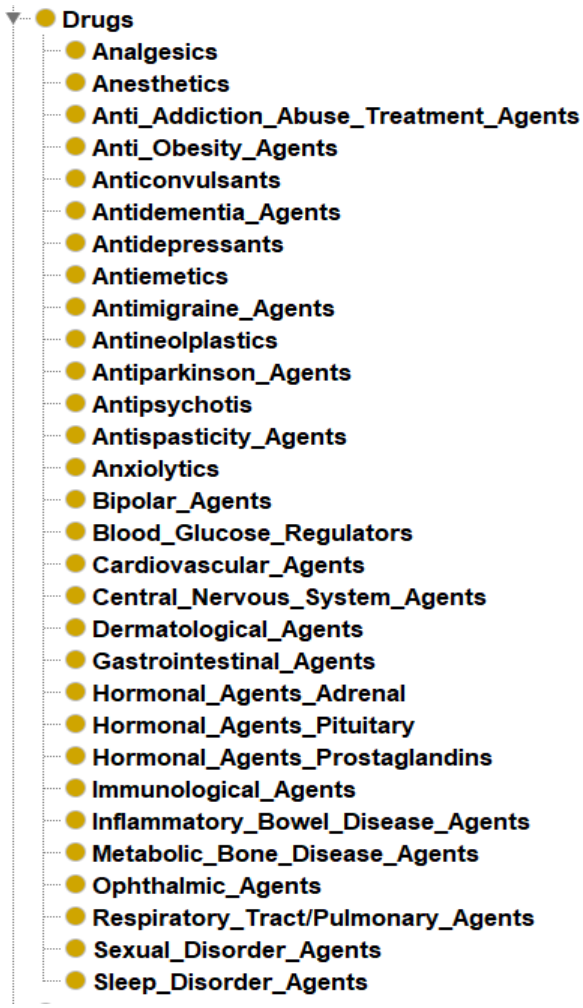

Figure 3 Drugs Subclasses

Human Disease class wraps disease categories (Figure 4) as they are revealed in KEGG database[112].

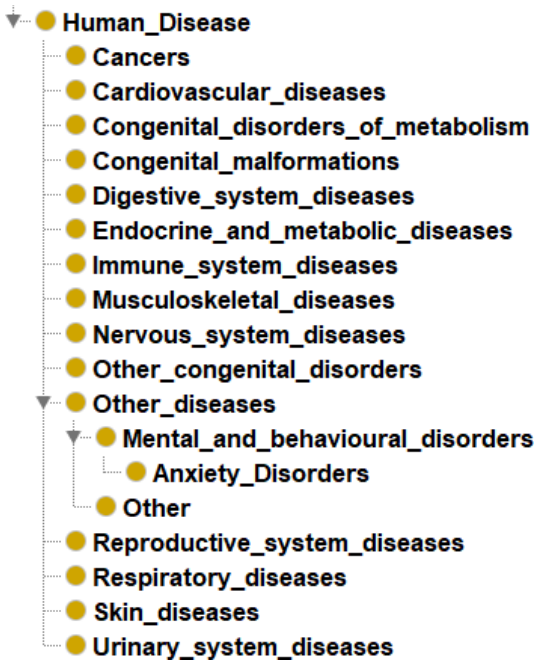

Figure 4 Human Disease Subclass

Inside human disease categories, in the Mental_and_behavioural_disorders subclass, Schizophrenia and Major Depressive Disorder are placed as individuals. Anxiety disorders consist of a subclass on their own since different disorders are included there according to bibliography but also KEGG's classification. These disorders are: *Generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), panic disorder (PD), and social anxiety disorder (SAD).*

Object Properties

Object properties are an important part of the ontology's architecture, for the simple reason that assists in the creation of relationships between two or more individuals or classes in the ontology. The semantics of object properties are based on the logical axioms that define their behavior. These axioms specify the relationships that the object property can have with classes or individuals. Object properties can have a range of different characteristics, such us transitivity, symmetry, functionality and inverse. Seven object properties were being created in a way that they can reassure the proper connection between the classes and finally result to inferred new knowledge concerning repurposed drug candidates for the needed diseases.

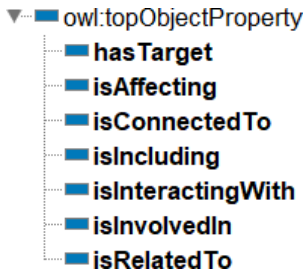

Figure 5 Object properties

In the table below (Table 1) all object properties are being displayed together with their domains and ranges. To clarify, domain refers to what or who can have a property, and range assigns the value of that property. Some object properties may have an analogous inverse property, which means that the domain of the one is range for the other. The inverse object properties are: isAffecting - isInteractingWith, isConnectedTo - isRelatedTo, isIncluding – isInvolvedIn. The object property hasTarget link individuals of the class Drugs to their appropriate gene targets. The object property isAffecting relates individuals of the class Drugs with the corresponding individuals of Biological Pathway Class. The object property isInteractingWith, is the inverse of the aforementioned property, thus the domain refers to Biological Pathway and the range to Drug individuals. isConnectedTo, connects Human Diseases to their Biological Pathways, and the inverse property of that is isRelatedTo. The object property that connects Biological Pathways together with the names of Genes/Proteins included in those pathways is isIncluding. The reverse property isInvolvedIn joins Genes/Proteins with Biological Pathways. Another characteristic for object properties is functionality. Functional object properties means that for any given individual, the property could have at most one value. Transitive is the object property which when individual A connects individual B, and individual B connects individual C, then connects individual A with individual C. In this particular case, there are neither functional object properties since a given individual can have multiple values (e.g., a drug can have multiple targets, or a disease can be connected to multiple biological pathways), nor transitive object properties.

Object Property	Domains	Ranges
hasTarget	Drugs	Gene/Protein
isAffecting	Drugs	Biological pathway
isConnectedTo	Human disease	Biological pathway
isIncluding	Biological pathway	Gene/Protein
isInteractingWith	Biological pathway	Drugs
isInvolvedIn	Gene/Protein	Biological pathway
isRelatedTo	Biological pathway	Human disease

Table 1 Object Properties

Data Properties

Data properties connect an individual (subject) with some particular characteristics. Those characteristics can have defined types like string, integers, or boolean. In a similar manner, domains can also be defined for data properties. The fromDB data property have as domain all the classes in the ontology and same goes for hasID. On the other hand, hasGenericName is applicable only for genes since their abbreviations were being imported to maintain bibliography's symbolism. Data properties can be functional, in the same way as the functional object properties. Such properties are hasGenericName and hasID since they describing individuals with a unique attribute.

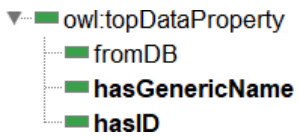

Figure 6 Data properties

Data Disjoints

In Protégé, disjoints refer to a type of relationship between classes in an ontology, ensuring that the ontology is consistent and free of contradictions. Specifically, disjoints are used to specify that two or more classes cannot have any instances in common. However, disjoints are not necessary for an ontology creation because of overlapping concepts, incomplete knowledge, and modeling preferences. In this situation no disjoints were created, since a more flexible approach for the classes was considered due to modeling preferences and avoidance of consistency issues.

Import Data

The design of the hierarchy of the ontology was based on data imported in Protégé with the use of Cellfie[113]. Cellfie is a Protégé Desktop plugin, for importing spreadsheet data into the ontology according to a set of rules in JSON format.

Underneath Drug categories, drug individuals were imported in the ontology from the excel files that were created with python from both KEGG and DrugBank databases. Here it is worth mentioning that not all drug individuals fall under one subclass, since the drug categories came from the KEGG database, and DrugBank includes more drugs (e.g., experimental, withdrawn). Additionally, because of the big amount of data from DrugBank, drugs had to be imported in batches since Protégé could not handle them with one run. In the figure below, is visible the set of rules used for importing the data in the ontology. A brief explanation is that column A from the

spreadsheet, representing individuals of types Drugs combined with an object property hasTarget from the column E, which are the gene abbreviations.

```
"Collections": [
    {
        "sheetName": "Sheet1",
        "startColumn": "A",
        "endColumn": "E",
        "startRow": "1",
        "endRow": "+",
        "comment": "",
        "rule": "Individual: @A*
                 Types: Drugs
                 Facts: hasTarget @E*"
        "active": true
    }
]
```

Figure 7 Rules for importing DrugBank data

The data for the Gene/Protein class were imported in the same way, but only for the KEGG database (Figure 8). Likewise, column B from the gene spreadsheet, representing individuals of types Gene/Protein combined with the object properties hasID from the column A, fromDB from the column D, hasGenericName from the column C and isInvolvedIn column E which referring to the biological pathway.

```
"Collections": [
    {
        "sheetName": "Sheet1",
        "startColumn": "A",
        "endColumn": "E",
        "startRow": "2",
        "endRow": "+",
        "comment": "",
        "rule": "Individual: @B*
                 Types: Gene/Protein
                 Facts: hasID @A*,
                        fromDB @D*,
                        hasGenericName @C*,
                        isInvolvedIn @E*"
        "active": true
    }
]
```

Figure 8 Rules for importing Gene/Protein data

Defined and Primitive Classes

There are two types of classes in OWL, defined and primitive[114]. A defined class is a class defined in terms of other classes and relationships using a logical expression. For a class to be defined, necessary and sufficient conditions are required for class membership. The logical expression can include OWL constructs such as class intersections, unions, complements, property restrictions and logical operators. Hence a defined class allows assumptions in both directions. It is preferably to declare a class as defined when the purpose is for the ontology to resolve the class membership and infer new knowledge. They can be useful in situations where the criteria for membership are complex or difficult to express using just the hierarchy of subclasses. Defined classes in Protégé are popularized under the equivalent class axiom and for that reason, three new classes have been created under the Drug superclass. Antipsychotics Inferred, Antidepressants Inferred, and Anxiolytics Inferred are the defined classes in this ontology, aiming to introduce new knowledge regarding to drug repurposed candidates for the corresponding diseases with the appropriate logical expressions.

For a class to be primitive, only necessary conditions are required for membership. Thus, primitive classes support only one way assumptions, and they are defined under the subclass axiom. The primitive classes are: Biological pathway, Gene/Protein and Human Disease.

Reasoner

A reasoner or a semantic reasoner is a software responsible for determining the consistency of the ontology, identifying subsumption relationship between classes, and most importantly inferring new knowledge based on a set of descriptive asserted axioms[115]. HermiT was used in this project, a reasoner for ontologies written using the Web Ontology Language (OWL). The main difference between HermiT and other widely used reasoners like Pellet and FaCT++, is the hypertableau calculus which provides more structured reasoning than any other algorithm. Hypertableau calculus allows the reasoner to partially avoid some of the nondeterministic actions indicated in the calculus beneficial to enhance performance for abrupt inferences. HermiT applies a wide range of innovative optimization approaches, such as anywhere blocking, blocking signature caching, individual reuse, and core blocking. Lastly, HermiT utilizes a unique classification method, that diminishes the number of consistency tests needed to compute the class and property hierarchies[116]. Ontologies which were previously considered to be too complex to handle and needed minutes or hours to classify hierarchies can be classified in seconds by HermiT[117].

Visualization

The tools used for the visualization of the ontology is WebVOWL[118], a web application for the interactive visualization of ontologies. Figure 9 illustrates the four primary classes of the ontology, along with their corresponding subclasses. The Drugs class, encompassing all the defined subclasses, is positioned in the bottom right corner of the visualization. The Human_Disease class is located on the left side, while Biological_Pathway and Gene/Protein classes are situated in the center. In classes that have individuals, an integer is displayed to indicate the total number of individuals in that class. Naturally, all classes are interconnected through object properties that adhere to their respective domains and ranges. A circle represents classes and subclasses, while a square denotes the object properties.

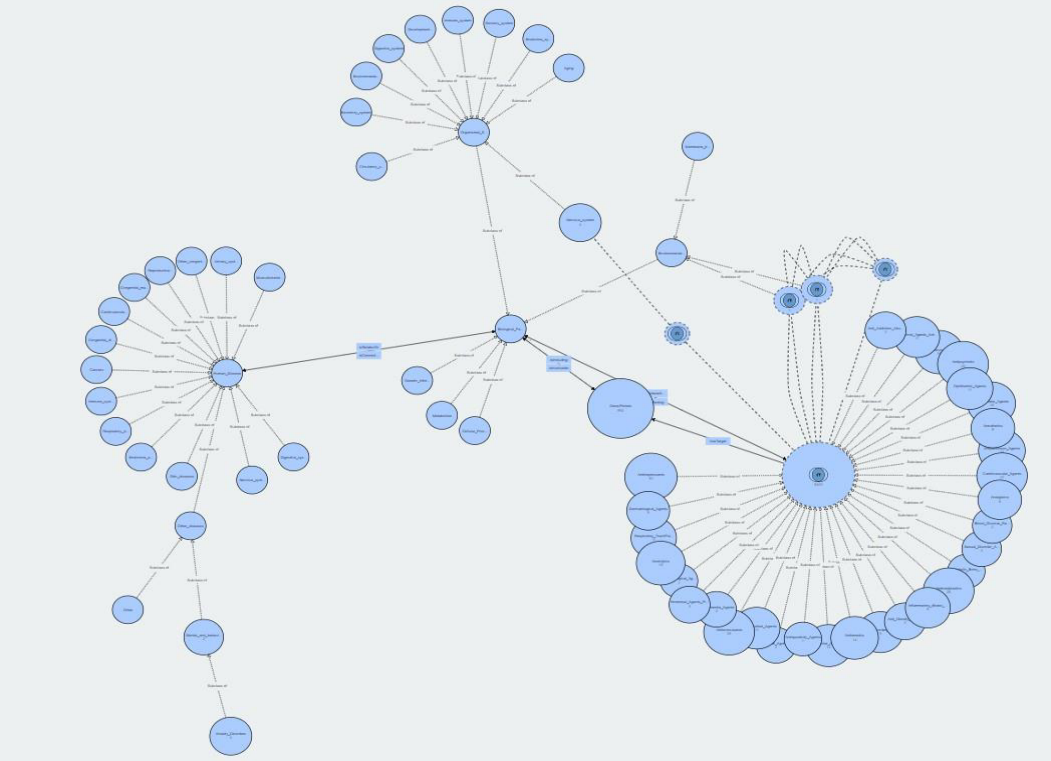

Figure 9 Visualization of the Ontology

Results

As discussed in the above section three new classes have been created to obtain all the new knowledge regarding potential repurposed drugs. The general objective was to set some descriptive logical axioms for each drug categories – namely antipsychotics, antidepressants, and anxiolytics- based on knowledge acquired from the literature, in order to not only select the appropriate drugs but also to limit the number of candidate drugs accordingly, since those three diseases they have a lot in common, from biological pathways involved to genes and symptoms. Further investigation was

carried out to determine whether any of the collected outcomes were involved in clinical trials or any research in general, as part of the validation process for the designed knowledge graph. A significant number of these hits were supported by evidence from animal and clinical studies, bolstering the credibility of the findings.

Inference for Schizophrenia

Considering that the dopamine hypothesis is the most promising for schizophrenia -as mentioned in the chapter for the etiopathology of the disease, drugs that target genes in the dopaminergic synapse pathway would be treated as necessary and sufficient for the Antipsychotics_Inferred class membership. Nonetheless, because there are thousands of drugs targeting dopamine receptors, to narrow down the expected output/inference and procure more relevant to the disease drugs, signal transduction biological pathway or signaling molecules and interaction biological pathway are required as well under the equivalent class axiom (Figure 10).

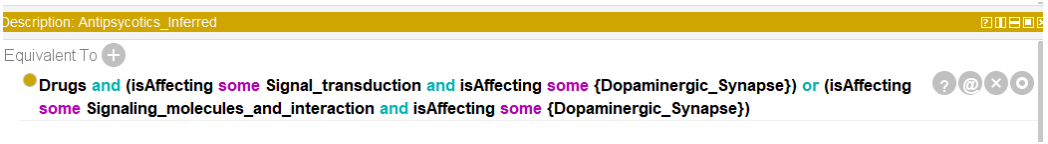

Figure 10 Equivalent axiom for Antipsychotics_Inferred

As an example, Levodopa is a drug annotated with Neuroactive ligand receptor interaction biological pathway, under Signaling molecules and interaction subclass and with Dopaminergic Synapse individual. Therefore, the above logical expression holds true and Levodopa drug becomes a member of the Antipsychotics_Inferred defined class.

After starting the reasoner, nineteen drug individuals inferred underneath Antipsychotics_Inferred class. In the table below, the name of all drug candidates, together with their classification in drug categories and their status, are being displayed.

Drug Name	Drug Category	Status
Chlorpromazine	Antipsychotic Bipolar agent	Approved Investigational
Clozapine	Antipsychotic Bipolar agent	Approved
Droperidol	Antiemetic	Approved
Haloperidol	Antipsychotic	Approved
Levodopa	Antiparkinson agent	Approved
Methotrimeprazine	Antipsychotic Bipolar agent	Approved Investigational

Olanzapine	Antipsychotic Antidepressant Bipolar agent	Approved
Pergolide mesylate	Antiparkinson agent	Approved Withdrawn
Perphenazine	Antipsychotic Antidepressant Antiemetic	Approved
Pimozide	Antipsychotic	Approved
Pramipexole dihydrochloride	Antiparkinson agent	Approved Investigational
Prochlorperazine	Antipsychotic Antiemetic	Approved
Prochlorperazine maleate	Antipsychotic Antiemetic	Approved
Quetiapine fumarate	Antipsychotic Antidepressant Bipolar agent	Approved
Risperidone	Antipsychotic Bipolar agent	Approved Investigational
Sertindole	Antipsychotic	Withdrawn
Thioridazine	Antipsychotic	Withdrawn
Thiothixene	Antipsychotic	Approved
Triflupromazine	Antipsychotic Antiemetic	Approved

Table 2 Antipsychotics_inferred class inference

Fifteen out of nineteen drugs are already tagged as antipsychotics. For example, Olanzapine is a thienobenzodiazepine classified as an atypical or second-generation antipsychotic drug used in the management of schizophrenia and bipolar disorder including mixed or manic episodes. It was discovered at Eli Lilly and approved in the US in 1996. The effect of olanzapine in the D2 receptor is reported to produce decrease in hallucinations, delusions, disorganized speech, disorganized thought, and disorganized behavior. On the other hand, its effect on the 5HT2A receptor prevents the onset of anhedonia, flat affect, alogia, avolition and poor attention[119]. Sertindole, one of the modern atypical antipsychotics, developed by a Danish pharmaceutical company Lundbeck. It was released in 1996 on the European market but after two years it has been withdrawn due to cardiac side effects. As of 2020, sertindole is reintroduced in several countries of the European Union. The rest of the drugs that popularized the Antipsychotics_Inferred class, which are already marketed as antipsychotics, are *Chlorpromazine, Clozapine, Haloperidol, Methotrimeprazine, Perphenazine, Pimozide, Prochlorperazine, Quetiapine fumarate, Risperidone, Thioridazine, Thiothixene and Triflupromazine.*

The remaining four drugs are coming from different drug categories, and they can be introduced as potential candidates for further exploration in the treatment of

schizophrenia. *Droperidol* is a butyrophenone derived pharmaceutical compound. Some of the drugs in that category are used to treat various psychiatric disorders but they are also acting as antiemetics. The most widely used antipsychotic drugs in this category are haloperidol and benperidol. Droperidol on the other hand is prescribed for nausea and vomiting during surgical procedures. The specific mechanism of action of droperidol is unknown, yet it can cause a central nervous system depression which results in low heart rate and loss of consciousness. It has strong antidopaminergic action and blocks the acetylcholine neurotransmitter. Droperidol acts like an antagonist for both alpha-1A adrenergic factor (ADRA1A) and dopamine D2 receptor (DRD2)[120,121]. Originally received FDA's approval in 1970 but in December 2001 FDA instructed the inclusion of a warning label to the packaging due to worries about high cardiac complication risks. This decision led to the disappearance of droperidol overnight and even after an independent review of the FDA's data in 2007 and an extensive literature review from 2015, the FDA refused to reverse its decision about the warning label. In February 2019, the pharmaceutical manufacturer American Regent reintroduced droperidol to the US market[122]. A 2018 systematic review compared droperidol against any other treatment for psychotic disorders, combining randomized controlled trials. Consequently, the review suggested that droperidol is nearly secure and effective for the treatment of acute psychosis in an emergency department setting, however further trials are needed which will also assess a combination therapy with droperidol with other labeled antipsychotics[123]. Until these days, droperidol is still known for the treatment of nausea and vomit without any official statement regarding antipsychotic properties.

Levodopa or L-Dopa, is commonly used to treat Parkinson's disease and other conditions associated with parkinsonism. The mechanism of action for levodopa is related with its ability to cross the blood-brain barrier and with the addition of a peripheral dopa decarboxylase inhibitor prevents the conversion of levodopa to dopamine in the periphery so that more levodopa can reach the blood-brain barrier. Once past the blood-brain barrier, levodopa is converted to dopamine by aromatic L-amino-acid decarboxylase. Essentially levodopa works as a dopamine replacement therapy, and it is the standard drug treatment of Parkinson's disease. There are no data indicating the safety and effectiveness of levodopa in children and patients over 65 years old are more likely to experience negative side effects. Levodopa acts like an agonist for dopamine D1, D5, D2, D3 and D4 receptors. [124] In 1975, FDA approved levodopa and since then is has been the mainstay of Parkinson's disease therapy[125]. Parkinson's disease co-existence with schizophrenia has been believed to be uncommon because these diseases are related to adverse modifications in the dopamine system. However, a recent study revealed an increased risk of Parkinson's disease in patients with schizophrenia spectrum disorders[126]. The majority of research around levodopa and schizophrenia has shown a negative correlation. Nonetheless a 2018 published study on 10 patients resulted that levodopa may be an effective treatment for the negative symptoms of schizophrenia[127]. Another meta-analysis on that matter suggests that for patients that are already under the influence of antipsychotic medications, levodopa can be beneficial[128].

Pergolide mesylate is a dopamine agonist used to treat again Parkinson's disease and pharmacological it was indicated as additional treatment to levodopa. Pergolide was approved in 1982 but it was later found that increased the risk of cardiac valvulopathy. The drug was withdrawn from the US and Canadian market in 2007 and even though the use of pergolide in humans is still approved in some countries, is mainly used for veterinary purposes. It acts as agonist on the dopamine D2 and D3 receptors, alpha2-adrenergic and alpha1-adrenergic group of proteins, and 5-hydroxytryptamine (5HT) receptors[129]. A clinical trial study was started in 2005 based on the hypothesis that lower activity in the dopamine system is related to the negative symptoms and cognitive dysfunction of schizophrenia, but it got suspended in the recruitment of the subjects[130]. Another clinical trial of 28 participants with the objective to study pergolide as an enhancing drug for treating cognitive dysfunction in schizophrenia started in 2010 but no results are posted yet even though the recruiting phase is completed[131].

Pramipexole is a drug used to treat the symptoms of Parkinson's Disease and Restless Legs Syndrome (RLS). It was first approved by the FDA in 1997 for Parkinson's Disease and then approved in 2006 for the treatment of RLS. The exact mechanism of action for the treatment of Parkinson's disease is yet unknown however it is believed that maybe is because of the ability of pramipexole to stimulate dopamine receptors in the striatum of the brain[132]. In August 2022 a randomized placebo control trial about the use of pramipexole for the treatment of schizophrenia in 200 subjects indicated no significant difference between pramipexole and placebo. Essentially pramipexole is not an effective antipsychotic drug for schizophrenia[133].

Inference for Major Depressive Disorder

Considering that Major Depressive Disorder is connected to serotonergic, dopaminergic, glutamatergic, and GABAergic biological pathways a class axiom needed to be found, for the sake of significantly restricting the results since the drugs involved in these pathways are plenty. Drugs that target genes in at least two individuals from the Nervous system biological pathways, would be treated as necessary and sufficient condition for the Antidepressants_Inferred class membership (Figure 11).

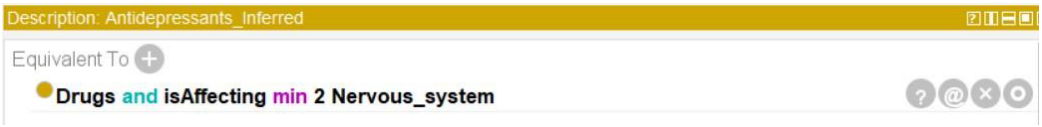

Figure 11 Equivalent axiom for Antidepressants_Inferred

After starting the reasoner, thirty eight drug individuals inferred underneath Antidepressants_Inferred class. In the table below, the name of all drug candidates, together with their classification in drug categories and their status, are being displayed.

Drug Name	Drug Category	Status
Alpidem	Anxiolytic	Withdrawn
Amantadine hydrochloride	Antiparkinson agent	Approved
Aripiprazole	Antipsychotic Antidepressant Bipolar agent	Approved
Befloxatone	Antidepressant Anxiolytic	Unknown
Benserazide hydrochloride	Antiparkinson agent	Approved
Blonanserin	Antipsychotic	Investigational
Brofaromine	Antidepressant Anxiolytic	Experimental
Buspirone hydrochloride	Antidepressant Anxiolytic	Approved Investigational
Carbidopa	Antiparkinson agent	Approved
Chlorpromazine	Antipsychotic Antiemetics	Approved
Clozapine	Antipsychotic	Approved
Cocaine	Anesthetic	Illicit
Cocaine hydrochloride	Anesthetic	Illicit
Lazabemide hydrochloride	Antiparkinson agent	Withdrawn
Loxapine	Antipsychotic	Approved
Mazindol	Appetite suppressant	Approved
Mesoridazine besylate	Antipsychotic	Approved
Methadone hydrochloride	Opioid addiction	Approved
Methamphetamine hydrochloride	Attention Deficit Disorder with Hyperactivity (ADHD)	Illicit Withdrawn
Moclobemide	Antidepressant Bipolar agent	Approved
Olanzapine	Antidepressant Bipolar agent Antipsychotic	Approved
Opipramol hydrochloride	Anxiolytic Antidepressant	Investigational
Pargyline hydrochloride	Antihypertension Antidepressant	Approved
Phenelzine sulfate	Antidepressant	Approved
Propericiazine	Antipsychotic	Approved
Quetiapine fumarate	Antipsychotic Antidepressant Bipolar agent	Approved
Rasagiline mesylate	Antiparkinson agent	Approved
Reserpine	Antihypertension	Withdrawn
Riluzole	Central Nervous System agent	Approved

Risperidone	Antipsychotic Bipolar agent Antidepressant	Approved Investigational
Safrazine hydrochloride	Antidepressant	Approved
Selegiline hydrochloride	Antidepressant Antiparkinson agent	Approved
Sertindole	Antipsychotic	Withdrawn
Toloxatone	Antidepressant	Experimental
Topiramate	Anticonvulsant	Approved
Tranylcypromine sulfate	Antidepressant	Approved
Ziprasidone hydrochloride	Antipsychotic Bipolar agent	Approved
Zotepine	Antipsychotic	Withdrawn

Table 3 Antidepressants_Inferred class inference

Fifteen out of thirty-nine drugs are already tagged as antidepressant. For example, Aripiprazole is an atypical antipsychotic used in the treatment of mood and psychotic disorders, like schizophrenia, bipolar disorder, major depressive disorder, etc. It is an agonist of dopamine and 5HT1A receptors and antagonist of alpha adrenergic and 5HT2A receptor[134]. Aripiprazole received FDA approval in 2002 for schizophrenia, in 2006 for bipolar disorder and major depressive disorder and in 2007 for autism spectrum disorders[135]. Brofaromine is a reversible inhibitor of monoamine oxidase A used in the treatment of depression and anxiety. It also acts as a serotonin reuptake inhibitor, while result to less anticholinergic side effects in comparison with other antidepressant drugs like the tricyclic antidepressants[136]. However, brofaromine is still an experimental drug with no official FDA approval[137]. The rest of the drugs that popularized the Antidepressants_Inferred class, which are already marketed as antidepressants, *are Befloxatone, Buspirone hydrochloride, Moclobemide, Olanzapine, Opipramol hydrochloride, Pargyline hydrochloride, Phenelzine sulfate, Quetiapine fumarate, Risperidone, Safrazine hydrochloride, Selegiline hydrochloride, Toloxatone, and Tranylcypromine sulfate.*

Three illicit compounds also appeared as antidepressants, cocaine, cocaine hydrochloride and Methamphetamine hydrochloride. To avoid any misunderstandings cocaine refers to base cocaine and crack or smoked cocaine and cocaine hydrochloride is in the form of injection[138]. Medically, cocaine hydrochloride is being used as a local anesthetic particularly for the eye, nose, ear, and throat. In the short term, cocaine can increase dopamine levels and counteract the symptoms of depression. However, the comedown period of cocaine escalates depressive signs. Methamphetamine hydrochloride is used in the treatment of attention deficit hyperactivity disorder (ADHD) and obesity. Methamphetamine hydrochloride includes effects like euphoria, increased energy, and high self-esteem, yet the FDA withdrew its approval because of potential abuse in the usage[139].

The remaining drugs are coming from different drug categories, and they can be introduced as potential candidates for the treatment of major depressive disorder. *Alpidem* is a nonbenzodiazepine medication that acts at the gamma-aminobutyric acid

receptor, which was used to treat anxiety disorders, especially generalized anxiety disorder. Due to severe cases of hepatic toxicity, which lead to one death and some liver transplantation, alpidem was withdrawn from the French market in 1993 and it was never released in the US market.

Amantadine hydrochloride is treating dyskinesia on Parkinson's patients receiving levodopa. The mechanism of action of amantadine hydrochloride is quite understood, but it is probably related to the increase in dopamine release in the brain[140]. Some studies have evaluated the effects of amantadine in animal species for the treatment of MDD beneficial[141]. Amantadine is already participating in a randomized, single-blind, controlled clinical trial of 150 patients with treatment resistant depression (TRD), since 2021. The study is trying to compare how efficient is the parallel use of selective serotonin reuptake inhibitors (SSRIs) with amantadine vs pramipexole vs quetiapine[142].

Benserazide hydrochloride is a drug used again to treat Parkinson's disease in parallel with levodopa. It is not capable of crossing the blood-brain barrier like levodopa but acts to prevent the formation of dopamine in extracerebral tissues, hence is trying to diminish negative side effects like nausea and vomiting. At particular dosages, levodopa and benserazide hydrochloride can also treat restless legs syndrome[143]. So far there is no indication in the bibliography that benserazide can treat major depressive disorder, and not any clinical trials or studies are being conducting to test this hypothesis. Same as benserazide hydrochloride, *Carbidopa,* another drug used for treating Parkinson's disease in parallel with levodopa, does not appear to interest the scientific community so far in regard to the treatment of major depressive disorder. In addition, the first product with only carbidopa was approved by FDA in 2014, so it is relatively new.

Blonanserin antagonizes dopamine and serotonin receptors to reduce symptoms of schizophrenia. Is a relative new second generation antipsychotic, approved in Japan and South Korea in 2008 but not in the US[144]. A 2016 experimental animal study has proven that blonanserin has positive effect on depression symptoms and longer clinical studies were suggested[145].

Chlorpromazine was the first antipsychotic drug, marketed in 1953. It is widely used for treating nausea, vomiting, schizophrenia, bipolar disorder, and severe behavioral problems in children. Acts as an antagonist for dopamine D2, D1 receptors and 5-hydroxytryptamine receptor 1A (5HTR1A) and 5-hydroxytryptamine receptor 2A (5HTR2A), etc.[146] Nonetheless it is not so effective on treating the negative effects of schizophrenia[147].

Clozapine is the first drug discovered in the category of second generation antipsychotic drugs. The main caveat of clozapine is the causation of agranulocytosis which may rise to death, and that is the reason why is only available through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program[148]. According to FDA clozapine has two approved usages -the treatment of schizophrenia and diminishing the risk of self-harm in patients with suicidal tendencies. Off-label though it has been used for Parkinson's

disease, bipolar disorder, and there is evidence that can be proven beneficial also for major depressive disorder[149].

Lazabemide hydrochloride is a reversible, selective monoamine oxidase B (MAOB) inhibitor that was under clinical development for Parkinson's disease and Alzheimer's disease. However, the development of the drug was interrupted due to liver toxicity[150].

Loxapine is an antipsychotic used for the treatment of schizophrenia. It is acting like a dopamine antagonist, and also a serotonin 5-HT2 blocker. There are some evidences that can improve psychotic depression since it is further metabolized into two antidepressant substances - desmethylloxapine and 8-hydroxyamoxapine[151].

Mazindol is used to treat obesity. Euphoria does not occur at therapeutic doses but can occur at higher doses[152]. Mazindol causes serious side effects like anorexia, insomnia, dry mouth, nausea, constipation, vomiting, and tremor. A double bind evaluation study in thirty terminal cancer patients about the effects of mazindol on pain, depression, anxiety, appetite, and activity showed that pain was positively impacted by mazindol, but anxiety and appetite were significantly worse. Depression and activity were not impacted at all[153].

Mesoridazine besylate, belongs to the class of phenothiazine and is used to treat schizophrenia, hyperactivity, anxiety, and tension. Pharmacological studies in animal objects have established that mesoridazine besylate t acts as a tranquilizer. Is a dopamine D2 receptor (DRD2) and 5-hydroxytryptamine receptor 2A (HTR2A) antagonist. Due to its tranquilizer property, it does not appear to be an efficient candidate for major depressive disorder[154]. *Propericiazine* another drug in the phenothiazine category used to reduce pathologic arousal and aggressiveness and hostility resulted from schizophrenia[155].

Methadone hydrochloride is an opioid analgesic used for management of pain that is not responsive to alternative treatments. Also used to assist in the detoxification and of opioid drug addicts[156]. Methadone, according to studies can be used to treat depression in heroin or other opioid addicts under the supervision of a psychiatrist and an addiction center counselor[157]. No indications about the use of methadone in major depressive disorder patients since it is a highly abusive substance.

Rasagiline mesylate is a monoamine oxidase-B (MAO-B) irreversible inhibitor used as a monotherapy to treat early symptoms of Parkinson’s disease. Rasagiline’s exact mechanisms of action is unknown but is believed that because of MAO-B inhibitory activity, extracellular dopamine levels are increasing[158]. A clinical trial in phase 4 tryed to define whether or not rasagiline improves depressive symptoms compared to placebo as measured by the Beck Depression Inventory-Amended (BDI-IA) total score after 12 weeks of treatment[159]. The trial showed that the administration of Rasagiline to patients with PD who had moderate depressive symptoms did not result in significant changes in cognitive abilities or depressive symptoms when compared to those who received a placebo. However, post hoc analyses suggested some improvement in patient-rated outcomes related to depression and cognitive function,

though findings were somewhat limited by absence of correction for multiple comparisons.

Reserpine has been used as an antihypertensive and an antipsychotic. The solo use of reserpine has declined since it was first approved by the FDA in 1955 and chronic use of the drug has been reported to develop depression in some patients[160]. However combined use of reserpine and a thiazide diuretic or vasodilator is still recommended.

Riluzole is a glutamate antagonist used for the treatment of amyotrophic lateral sclerosis (ALS, Lou Gehrig's Disease)[161]. Glutamatergic modulators may have therapeutic potential in the treatment of major depressive disorder. For riluzole there is a study that prove antidepressant and anxiolytic effects in ten patients from the first week of treatment[162]. Another randomized placebo-controlled trial though in 373 patients found that riluzole did not show any antidepressant effects compared to placebo[163]. More studies are needed to clarify the potential of riluzole as an antidepressant drug.

Topiramate is used to treat seizures and decrease migraines. It was primarily approved by the FDA in 1996 and in 2004 was approved for the prevention of migraines. In 2012 a combination release of topiramate with phentermine was approved for chronic weight control in adults[164]. In a double-blind, placebo controlled clinical trial of 42 patients suffering from major depressive disorder, topiramate improved depressed symptoms combined with their prescribed antidepressants in comparison to patients under placebo medication[165]. More clinical trials will be needed to define topiramate as an antidepressant drug, however the results seem promising.

Ziprasidone is a second generation antipsychotic drug used to manage schizophrenia and bipolar mania. Is a dopamine and 5HT2A receptor antagonist with a unique receptor binding profile which may suggest antidepressant potential[166,167]. Yet in a 12-week randomized double-blind, placebo-controlled trial with 120 patients suffering from major depressive disorder, the treatment with ziprasidone was not showing any statistically significant improvement in the depressive symptoms over placebo[168]. Definitely more clinical trials are needed since ziprasidone may have an antidepressant possibility.

Zotepine was designed as an antipsychotic drug. It has been used in Japan, India, and some places in Europe since 1980, however it was never approved by the FDA. In 2016 FDA was conducting again an analysis on antipsychotic drugs but again zotepine did not manage to be further studied[169].

Inference for Anxiety Disorders

Considering that Anxiety Disorders are linked to serotonergic, dopaminergic, and glutamatergic biological pathways a class axiom needed to be found, on ground of significantly restricting the results since the drugs involved in these pathways are plenty. However, even though different class axiom options were tested combining

the aforementioned biological pathways, none of them produced outstanding results since in most of the cases all drugs affecting the particular biological pathways inferred in the Anxiolytics_Inferred class. Essentially more data is needed to assist in the creation of a consist class axiom which will limit the number of the resulted drugs, since KEGG database has restricted information about anxiety disorders. The drugs inferred were not deemed inaccurate since they have an impact on the serotonergic, dopaminergic, and glutamatergic biological pathways. Nevertheless, assessing these drugs individually can be time consuming and does not align with the objective of developing an ontology.

Discussion

The initial scope of this project was to provide the reader with some potential candidate drugs for the treatment of schizophrenia, major depressive disorder (MDD), and anxiety disorders. From a generalized social perspective, mental disorders are still a strict taboo and stigma. The culture of social labeling encourages judgment and discrimination, which leads to insufficient acknowledgement and patients suffering from them are feeling isolation and suffocation. Throughout the research phase, it was profound that schizophrenia, major depressive disorder, and anxiety disorders share similarities in the way patients conceive the symptoms, in the genes and biological pathways included in the diseases and last but not least in the medications used for their treatment. Schizophrenia is poorly understood by the scientific world, since the etiopathology is still vague. MDD and Anxiety Disorders are very similar and sometimes even medical practitioners are struggling to make the separation for the correct diagnosis. The knowledge graph presented attempts to utilize bibliographic understanding to create some logical descriptive axioms in exchange for inferred information.

After carefully importing all available data, the final ontology consists of four main classes with sixty nine subclasses, connected with seven object properties and three data properties. Twelve thousand nine hundred twenty five individuals are imported to the ontology from KEGG and DrugBank databases comprising genes and proteins, drugs, biological pathways, and the forenamed human diseases. The complete number of triplets in the present knowledge graph is fifty thousand three hundred sixty-three and out of total seventy three classes, three of them are defined classes designed to generate new knowledge, suggesting potential drug candidates for schizophrenia, major depressive disorder, and anxiety disorders.

Relative to schizophrenia, four aspirant drugs were introduced – *droperidol, levodopa, pergolide, and pramipexole*. Droperidol is being used in emergency departments as an antipsychotic but still the official FDA labeling referring to it as an antiemetic drug. Interestingly enough, the rest of the drugs are antiparkinson agents, even though Parkinson's disease and schizophrenia are related to adverse modifications in the dopamine system. The last three years the scientific community appears to be more interested in understanding Parkinson's disease and the

relationship with schizophrenia in favor of new drug treatments. For pramipexole a recent study reached the conclusion that is not a sufficient treatment for schizophrenia, but for levodopa and pergolide the results are promising.

In accordance with major depressive disorder twenty drugs were introduced, but not all of them showing encouraging results. The most prominent ones are *amantadine hydrochloride, blonanserin, rasagiline, and topiramate.* Amantadine is in recruitment status for a clinical trial since 2021 designed to compare how efficient is the parallel use of selective serotonin reuptake inhibitors (SSRIs) with amantadine *vs* pramipexole *vs* quetiapine. Blonanserin is an experimental drug with proven positive effect on depression symptoms. Even though more clinical trials are required, blonanserin seems to be a positive candidate for MDD. Rasagiline is already in a phase 4 clinical trial designed to define whether or not improves depressive symptoms compared to placebo as measured by BDI-IA scoring. Lastly for topiramate even though larger clinical trials are required to confirm any antidepressant properties, some doctors are choosing to prescribe it off label if some antidepressants are failing. In general, a lot of antipsychotic drugs appeared in the Antidepressants_Inferred class. It is well known that many psychiatric disorders show symptoms of depression. A drug which can treat both at the same time seems appealing, but antipsychotics should be carefully prescribed at the lowest possible dose in patients with MDD, and patients need close monitoring for adverse side effects.

Below is the summary table (Table 4) with all potential drug candidates along with the suggested treatable diseases.

Potential Drug Candidates	Disease
Levodopa	Schizophrenia
Pergolide	Schizophrenia
Amantadine hydrochloride	Major Depressive Disorder
Blonanserin	Major Depressive Disorder
Rasagiline	Major Depressive Disorder
Topiramate	Major Depressive Disorder

Table 4 Potential Drug Candidates

The current study has several limitations, including its small size, the absence of an adequately arithmetic metric for computing a ranked result in reference to potential drug repurposed candidates for schizophrenia, major depressive disorder and anxiety disorders, and limited data from only two medical database resources. This study does have the advantage, however, of being reproducible for all known human diseases as long as the corresponding data are imported correctly to the ontology and some knowledge from literature review to make appropriate rules for defined classes.

Future Work

Many different approaches, techniques, and experiments need to be addressed in order to make future improvements in the present work.

In terms of data acquisition, future research should be devoted to the development of a more consistent and enriched ontology. This could be achieved by importing data from more database resources. By way of illustration, SIDER contains information about marketed drugs together with a list of their side effects. On top of that, supplementary information from DrugBank could be useful, such as molecular details of each drug e.g., weight, chemical structure. This could also assist to create a ranking algorithm to prioritize the inferred drugs according to scoring.

Future research should also examine strategically a revamp of the ontology's architecture. For instance, the class Gene/Protein could be further subcategorized into different classes instead of plain individuals. The PANTHER Classification System (Protein ANalysis THrough Evolutionary Relationships) classifies proteins and their genes to assist on deeper analysis. According to PANTHER a subclass of the Gene/Protein class could be G protein-coupled receptors (GPCRs), which contains fourteen genes for homo sapiens including D1, D2 dopamine receptors. Then it could be possible to extract inferred knowledge based on this class instead of biological pathways. Moreover, the ontology can be expanded by incorporating new object properties that specify the effect of drugs on genes, particularly in terms of indicating agonist and antagonist action, which would enable the documentation of both positive and negative impacts on the biological pathways.

One of the caveats of this research was the difficulty to propose potential drug candidates for anxiety disorders due to lack of data related to biological pathways from KEGG database, which made it more difficult to form fitting class axioms. The struggle was to restrict the number of produced results based on a more proper axiom. To address that, further investigation is required, to gather more information about anxiety disorders and related genes and biological pathways.

Knowledge graphs refers to a semantic network representation of different entities and their relationships. For the last years, artificial intelligence field is becoming more interesting in knowledge graphs. Graph neural networks (GNNs) utilize deep learning to integrate and learn topological information and attributes derived from graph data to provide holistic end-to-end solutions like link prediction and knowledge graph reasoning.

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Appendix A – Python Script for processing KEGG data

```
import pandas as pd

kegg_id = []
abbrev = []
name_final = []

with open('GABAergic.txt') as f:
    lines = f.readlines()
    for line in lines:
        first = line.split(';')[0]
        res = first.split(maxsplit=1)
        kegg_id.append(res[0])
        abbrev.append(res[1])
        name = line.split(';')[1]
        name_final.append(name.split('[')[0])

df = pd.DataFrame(list(zip(kegg_id, abbrev, name_final)), columns=['kegg_id', 'abbrev', 'name'])
df.to_excel(r'GABAergic.xlsx', index=False)
```

Appendix B – Python Script for parsing DrugBank

```
import json
import xmltodict
import pandas as pd
import csv
import re


def write_row_to_csv(row):
    with open('drug_data.csv', 'a', newline='', encoding="utf8", errors='ignore') as f:
        csv_writer = csv.writer(f)
        csv_writer.writerow(row)
        f.close()


def save_drug_data_to_csv_many_lines(drug_dictionary):
    d_name = drug_dictionary['drug_name']
    final_name = re.sub(r'\s+', '-', d_name)
    final_name = final_name.replace('[', '(')
    final_name = final_name.replace(']', ')')
    final_name = final_name.replace('{', '(')
    final_name = final_name.replace('}', ')')
    initial_target_row = [final_name, drug_dictionary['group']]
    for ele in drug_dictionary['targets_enzymes']:
        target_name = re.sub(r'\s+', '-', ele['target_name'])
        initial_target_row.append(target_name)
        if 'action' in ele:
            initial_target_row.append(ele['action'])
        else:
            initial_target_row.append('unknown')
        initial_target_row.append(ele['abbr'])
        write_row_to_csv(initial_target_row)
        initial_target_row = [final_name, drug_dictionary['group']]


with open("full database.xml", encoding="utf8") as xml_file:
    data_dict = xmltodict.parse(xml_file.read())
    json_data = json.dumps(data_dict)
    with open("full_data.json", "w", encoding="utf8") as json_file:
        json_file.write(json_data)
json_file.close()
```

```
df = pd.read_json("full_data.json")
a = pd.DataFrame(df['drugbank']["drug"])

for ind in a.index:
    drug_fields = dict()
    drug_name = a["name"][ind]
    drug_fields['drug_name'] = drug_name
    if 'groups' in a:
        drug_group = a["groups"][ind].get("group")
        if type(drug_group) is list:
            drug_fields['group'] = drug_group
        else:
            drug_fields['group'] = [drug_group]
    else:
        drug_fields['group'] = []
    targets_enzymes = []
    if type(a["targets"][ind]) is not None and type(a["targets"][ind]) is dict:
        res_target = a["targets"][ind].get('target')
        if type(res_target) is dict:
            target = {}
            target['target_name'] = res_target.get("name")
            if res_target.get("actions") is not None:
                target['action'] = res_target.get("actions").get('action')
            else:
                target['action'] = 'unknown'
            if res_target.get("polypeptide") is not None and type(res_target.get("polypeptide")) is dict:
                target['abbr'] = res_target.get("polypeptide").get('gene-name')
            elif res_target.get("polypeptide") is not None and type(res_target.get("polypeptide")) is list:
                for dic in res_target.get("polypeptide"):
                    if 'gene-name' in dic.keys():
                        target['abbr'] = dic.get('gene-name')
            else:
                target['abbr'] = 'unknown'
            targets_enzymes.append(target)
        else:
            for i in range(len(res_target)):
                target = {}
                target['target_name'] = res_target[i]['name']
                if 'actions' in res_target[i] and res_target[i]['actions'] is not None \
                        and 'action' in res_target[i]['actions']:
```

```
                    target['action'] = res_target[i]['actions']['action']
                else:
                    target['action'] = 'unknown'
                if 'polypeptide' in res_target[i] and 'polypeptide' in res_target[i]:
                    if type(res_target[i]['polypeptide']) is list:
                        target['abbr'] = res_target[i]['polypeptide'][0]['gene-name']
                    else:
                        target['abbr'] = res_target[i]['polypeptide']['gene-name']
                else:
                    target['abbr'] = 'unknown'
                targets_enzymes.append(target)
    if type(a["enzymes"][ind]) is not None and type(a["enzymes"][ind]) is dict:
        res_enzymes = a["enzymes"][ind].get('enzyme')
        if type(res_enzymes) is dict:
            target = {}
            target['target_name'] = res_enzymes.get("name")
            if res_enzymes.get("actions") is not None:
                target['action'] = res_enzymes.get("actions").get('action')
            if res_enzymes.get("polypeptide") is not None and type(res_enzymes.get("polypeptide")) is dict:
                target['abbr'] = res_enzymes.get("polypeptide").get('gene-name')
            elif res_enzymes.get("polypeptide") is not None and type(res_enzymes.get("polypeptide")) is list:
                for dic in res_enzymes.get("polypeptide"):
                    if 'gene-name' in dic.keys():
                        target['abbr'] = dic.get('gene-name')
            else:
                target['abbr'] = 'unknown'
            targets_enzymes.append(target)
        else:
            for i in range(len(res_enzymes)):
                target = {}
                target['target_name'] = res_enzymes[i]['name']
                if 'actions' in res_enzymes[i] and res_enzymes[i]['actions'] is not None \
                        and 'action' in res_enzymes[i]['actions']:
                    target['action'] = res_enzymes[i]['actions']['action']
                else:
                    target['action'] = 'unknown'
                if 'polypeptide' in res_enzymes[i] and 'polypeptide' in res_enzymes[i]:
                    if type(res_enzymes[i]['polypeptide']) is list:
                        target['abbr'] = res_enzymes[i]['polypeptide'][0]['gene-name']
```

```
                    else:
                        target['abbr'] = res_enzymes[i]['polypeptide']['gene-name']
                else:
                    target['abbr'] = 'unknown'
                targets_enzymes.append(target)
    drug_fields['targets_enzymes'] = targets_enzymes
    print(drug_fields)
    save_drug_data_to_csv_many_lines(drug_fields)

read_file = pd.read_csv('drug_data.csv')
read_file.to_excel('drug_data_final.xlsx', index=None, header=None)
```