Applying Quantitative Systems Pharmacology Methods to Study Psychosis in Alzheimer's Disease

by

Peihao Fan

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Master of Science, University of Pittsburgh, 2019

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This dissertation was presented

by

Peihao Fan

It was defended on

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and approved by

Levent Kirisci, Professor, Department of Pharmaceutical Sciences

Robert A. Sweet, Professor, Department of Psychiatry

Robert B. Gibbs, Professor, Department of Pharmaceutical Sciences

Junmei Wang, Associate Professor, Department of Pharmaceutical Sciences

Thesis Advisor/Dissertation Director: Lirong Wang, Assistant Professor, Department of Pharmaceutical Sciences

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Psychosis is surprisingly common in Alzheimer disease (AD) and can emerge as a part of the neurodegenerative disease process in advance of dementia during the mild cognitive impairment stage or even earlier. Approximately 50% of Alzheimer's disease patients will develop psychotic symptoms, e.g. hallucination and delusions, and these patients will experience more severe cognitive decline compared with those without psychosis. However, no medication has been approved by the Food and Drug Administration for treating psychosis in AD (AD+P) and second-generation antipsychotics are widely used in clinical practice with modest efficacy and elevated adverse events rate. It is critical to explore and propose more effective and safer treatment options to treat AD+P. Some important advances in recent years provided us opportunities in connecting and comparing the neuropsychiatric symptoms (NPS) in AD with other neurological disorders which will greatly help us understand its mechanisms and further develop appropriate treatments for AD+P. In this thesis, the journey of understanding AD+P starts at comparing it with the similar psychotic symptoms in schizophrenia. We found that the similar psychotic symptoms in AD+P and schizophrenia are supported by distinct genetic associations and pathways which also provided a possible explanation for the decreased efficacy and increased adverse events rate of antipsychotics in AD+P. Multiple approaches, classic and innovative, were applied to identify critical risk factors and possible protective roles in the advancement of AD+P. With the information we have acquired about AD+P from the previous

studies, state-of-the-art quantitative systems pharmacology (QSP) approaches are applied to explore and propose alternative treatment options for AD+P. We found out that antidepressants showed a possible beneficial effect against AD+P and they exert their effect through different pathways with antipsychotics which allowed them to form a synergetic effect that may improve therapeutic efficacy or lower the risk of side effects.

Table of Contents

List of Tables

No table of figures entries found.**List of Figures**

1.0 Introduction

1.1 Overview of Psychosis in AD

Alzheimer's Disease (AD) is the most common neurodegenerative disease affecting around 50 million people worldwide[1], and the presence of AD is responsible for a significant decrease in the quality of life[2]. It is estimated that the cost of AD is $604 billion worldwide per year and will triple by Year 2050[3].

The accumulation of extracellular amyloid beta plaques and intraneuronal neurofibrillary tangles are hallmark features of the disease[4]. For several decades, AD patients have been classified according to several clinical measurement scales that primarily determine cognitive impairment status in patients. AD patients are staged into three main clinical categories that include pre-clinical AD, mild cognitive impairment (MCI), and overt AD[5]. However, the current classification system does not consider important disease prognostic factors, such as environmental factors and the presence of coexisting disease conditions. The presence of coexisting disease conditions may ultimately have a detrimental impact on AD patients' disease management. Understanding the biological mechanisms leading to comorbid diseases in AD may provide novel routes for therapeutic interventions.

Psychosis, defined by the occurrence of delusions and/or hallucinations, is observed as a common complication of AD. Approximately 50% of patients are likely to suffer from psychotic symptoms after the onset of AD (AD with psychosis, or AD+P)[6] and this number can go as high as 97%[7]. AD+P patients have more severe cognitive impairments and a quicker cognitive decline than AD patients without psychosis (AD-P)[8]. AD+P is also associated with higher rates

of co-occurring agitation, aggression, depression, mortality, functional impairment, and increased caregiver burden compared with AD-P[8]. These non-cognitive symptoms are creating burdens not only for people with AD or other dementias but also for their caregivers, and are associated with poor outcomes in terms of function, quality of life, disease course, mortality, and economic cost in clinical circumstances[9; 10].

Psychotic symptoms may present in many neurodegenerative disorders (e.g., Lewy body dementia) as well as other psychiatric disorders (bipolar disorder with psychosis). However, the prototypical psychotic disorder is schizophrenia, and the efficacy of the vast majority of antipsychotic medications for treating psychosis was established in treating this disorder. This is why we are currently using medications indicated for schizophrenia to treat AD+P [11; 12; 13].

1.1.1 Alzheimer's Disease, Cognitive Decline and Psychotic Symptoms

1.1.1.1 Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder that impairs mental ability development and interrupts neurocognitive function. It is declared as a "global public health priority" by the WHO because there is no permanent remedy for AD[14]. So far, there are only well-stated concepts and hypotheses about the cause and drug targets of AD.

AD is the primary cause of dementia in people over the age of 60. Around 50–75% of people with dementia have Alzheimer's[15]. As per the statistical data collected worldwide, females are more prone to AD than males, and the risk increases even more with age[16]. People with certain fundamental conditions, like cardiovascular diseases, hypertension, and diabetes, are also at higher risk of developing AD later[17]. Other neurodegenerative disorders with AD like symptoms include frontotemporal dementia and lewy body dementia; inflammatory, metabolic,

and infectious conditions; vascular cognitive impairment; and a series of causes that include obstructive sleep apnea and transient epileptic amnesia[18].

Around 0.1% of the cases of AD are due to genetic inheritance, and people affected by it normally show symptoms between the ages of 30 and 50 years[19]. The genes encoding Presenillins 1 and 2, and Amyloid Precursor protein (APP) played an important role in the development of AD because mutation in any of these genes leads to APP's incorrect cleavage, forming $A\beta_{42}$ (Amyloid β protein, 40 residues) instead of $A\beta_{40}$[20]. The accumulation and aggregation of Aβ42 forms senile plaques, which is one of the major reasons behind AD. In addition, the presence of ε4 allele of Apo-lipoprotein E (APOE ε4) in heterozygotes and homozygotes increases the risk by 3% and 15%, respectively[19]. ABCA7, BIN1, CASS4, CD2AP, CELF1, CLU, CR1, EPHA1, FERMT2, HLA-DRB5, INPP5D, MEF2C, MS4A, NME8, PICALM, PTK2B, SlC24A4, SORL1, and ZCWPW1, are the 19 genes that apparently affect the risk, as reported by Genome Wide Association Studies (GWAS)[21].

1.1.1.2 Psychosis and cognitive decline

Psychosis, which is characterized by the presence of delusions and/or hallucinations, is a prevalent consequence of AD. Psychotic symptoms, which consist of hallucinations and delusions, are among the most clinically relevant NPS and are associated with hospitalization or institutionalization, cognitive and functional impairment, accelerated cognitive decline, and mortality, as well as caregiver distress[22; 23; 24; 25].

Moreover, psychotic symptoms in AD patients are correlated with disease severity and progression. Delusions and hallucinations in Alzheimer's disease are associated with different patient characteristics: in a memory clinic sample of people with probable Alzheimer's disease, delusions were associated with older age, depression, and aggression, whereas hallucinations

were associated with more severe dementia and a longer duration of illness.[26]. A more recent study focusing on National Alzheimer's Coordinating Center (NACC) data reported that delusions and hallucinations also showed differential associations with cognition and function, with hallucinations conferring greater cognitive and functional deficits than delusions[27].

Depending on the underlying dementia diagnosis, the relative incidence of psychotic symptoms varies. Psychosis is most prevalent in dementia with Lewy bodies (DLB; 75% prevalence), followed by dementia due to Parkinson disease (PD; 50% prevalence), vascular dementia (15%), and frontotemporal dementia (10%)[28]. The presence of psychosis, paired with clinicians' preexisting assumptions about psychosis and dementia, might impact a dementia diagnosis. In another study employing NACC datasets that covered 961 AD patients, the presence of psychosis in persons with AD was related to a fivefold greater chance of misinterpreting the illness as DLB[29], demonstrating that clinicians tend to favor a DLB diagnosis in the context of psychosis.

Furthermore, psychosis can co-occur with other neurological conditions, including agitation[30] and affective symptoms[31]. In 2015, the International Psychogeriatric Association (IPA) guidelines revised agitation in cognitive disorders and established three fundamental dimensions of agitation: verbal aggressiveness, physical aggression, and excessive motor activity. The classification of the domains can be used to improve the accuracy of diagnosis and develop new treatment goals. Nonetheless, there is scant evidence linking these agitation categories to psychotic symptoms. As for affective symptoms, researches have determined that psychotic and affective symptoms in dementia and MCI patients are caused by two distinct sets of variables, indicating that these symptoms are caused by different processes[31; 32].

A significant obstacle in the treatment of AD+P is the difficulty in diagnosing psychotic symptoms, especially in cognitively challenged individuals. Multiple sub-phenotypes of AD have been observed, including delusions of theft, delusions of infidelity or abandonment, beliefs that deceased individuals are alive, general suspiciousness unrelated to theft (such as being plotted against, sent to jail, or evicted), and elaborate systematized delusions[33]. It is difficult for clinicians to differentiate between delusions and amnesia or confabulation when the necessary diagnostic information is contained in patients' memories that are affected by cognitive impairment[34]. Compared to delusions, hallucinations might be more transitory or fragmented in patients[33]. Visual and aural hallucinations are the most often reported subtypes of hallucinations. To be precise, auditory hallucinations can vary from sounds to whole dialogues, while visual hallucinations typically contain people or animals but can also depict faces or deceased persons, colors, inanimate objects, or unformed images[35].

1.1.1.3 Diagnosis of AD+P

The best-known diagnosis criteria for psychosis in AD were published in 2000 by Jeste and Finkel, who described delusions and hallucinations (auditory or visual) in the context of clinically diagnosed AD[36]. Multiple instruments were reported for the measurement of AD+P including BEHAVE-AD[37], NPI-NH[38], CERAD-BRSD[39] and CUSPAD[40]. While most of them take symptomatic rather than syndromic approaches, they yield generally concordant results in assessing psychotics symptoms in AD patients with few disagreements. However, the different instruments do show minor differences in detecting symptoms[41] and changes in response to treatment[42].

Multiple studies suggest that psychosis can emerge during the prodromal or mild cognitive impairment (MCI) phase of the neurodegenerative disease continuum[43], and these

psychotic symptoms would not be included as part of the disease according to the original Jeste and Finkel criteria[36]. A revised version of the criteria, known as the new International Psychogeriatric Association (IPA) criteria, has been produced to address the issue. In this revised edition, the diagnosis of psychosis in major and moderate neurocognitive disorders now includes MCI as well as other dementia aetiologies, indicating that our knowledge of psychosis in dementia is shifting from a symptomatic to a syndromic perspective[44].

1.1.2 Mechanism Insights of AD+P

1.1.2.1 Genomics of AD+P

Major breakthroughs have been made in recent years in exploring and identifying genomic associations for AD+P. Early familial studies estimated the heritability of AD psychosis at 61%[45] emphasized the importance of genomic studies in understanding the underlying mechanisms of the development and progression of AD+P. A major international genome-wide association study (GWAS) in >12,000 individuals with AD, which was published in 2021, was the first to use single nucleotide polymorphisms (SNPs) to calculate the heritability of psychosis in AD[46]. The study explained around 18% to 31% of the heritability based on the different methods used which is close to the level in major depressive disorder (MDD) and schizophrenia. The results of the GWAS also identified that ENPP6 and SUMF1 are significantly associated with AD+P. A marginal but statistically significant association between AD+P and the apolipoprotein E ε4 (APOE ε4) allele was reported in this study.

Moreover, the first high-quality GWAS results for AD+P presented a unique opportunity to investigate the connections and common mechanisms across diagnostic borders. It enabled the identification of genetic links between AD+P and various neurological illnesses, including

depression, schizophrenia, bipolar disorder, and others. As anticipated, significant relationships were found between AD+P and "Years of Schooling" (and almost so with the associated trait, "Intelligence") and "Depressive Symptoms"[46]. The connections between AD + P and the two additional neurodegenerative conditions, amyotrophic lateral sclerosis (ALS) and Parkinson disease, were equally non-significant. Interestingly, AD+P had a substantial positive connection with "depressive symptoms", indicating that similar genetic traits were detected in the two illnesses, hence providing unique insights and directions for the development of treatments for AD+P.

1.1.2.2 Neuroimaging of AD+P

Latest neuroimaging studies have identified several brain regions that are associated with AD+P. Delusions have been associated with left frontal atrophy, and misidentification delusions have been associated with hippocampal atrophy[47]. Delusions have also been associated with default mode network disruption, including parietal and cerebellar atrophy, but no default mode network signal was associated with a composite psychosis score[48]. Hallucinations have been associated with supramarginal atrophy within the parietal lobe[49].

The analysis of the NACC cohort reported an accelerated atrophy within the frontal and temporal lobes in individuals with delusions[50] while other studies in independent cohorts have reported links with hippocampal and parahippocampal atrophy[51; 52]. An increased frontotemporal atrophy and neocortical hypometabolism in people with AD psychosis were reported by structural and functional imaging studies examining delusions[34; 53]. Another study of Alzheimer's Disease Neuroimaging Initiative (ADNI) data found that cortical thinning in the supramarginal area of the parietal lobe was a risk factor for hallucinations. However, the

fact that only a small minority of people experience hallucinations without delusions might have been a confounding factor in this study[54].

In another longitudinal study conducted by Fischer et al. using ADNI data[55], an increased rate of grey matter atrophy in the cerebellum and parietal lobe was reported prior to the onset of delusions. It is surprising that frontal areas showed little connection with these symptoms, but the authors did highlight the possible linkages between posterior cortical atrophy and frontal circuits and the default mode network (DMN). In recent years, the DMN has been the focus of several functional imaging studies for multiple literatures stated that it is impaired in AD and other disorders characterized by psychosis[28]. However, mixed opinions have been claimed regarding to the role of DMN in AD+P because the results have been inconsistent[56; 57; 58].

The majority of research documenting regional perfusion and metabolic abnormalities in AD+P was undertaken between the 1990s and the beginning of the 2010s, and delusions are the primary focus of these cases[34; 53]. Right-sided frontal and temporal cortices exhibited hypometabolism and hypoperfusion, according to the findings of these researches. However, it is unclear whether the observed pattern is the result of an increase in perfusion and/or metabolism in the left hemisphere or a decrease in the right. To date, only one SPECT study[59] and two ^{18}F-FDG PET studies[60; 61] of AD+P specifically have been conducted since the early 2010s. Both PET investigations found right orbitofrontal hypometabolism, with one focusing on delusions and the other on hallucinations. As with the atrophy study mentioned above, a substantial proportion of participants in the ^{18}F-FDG PET hallucination study would be expected to have concomitant delusions, so the similar findings could reflect the presence of delusions among individuals with hallucinations. Therefore, the findings of these studies do not necessarily reflect

the common mechanisms behind delusions and hallucinations. In the newer SPECT study, regional hypoperfusion was largely confined to the right hemisphere (inferior temporal gyrus, parahippocampal cortex, posterior insula and amygdala) but was observed bilaterally in the temporal poles[59].

We are only aware of two nuclear imaging investigations that examined psychosis-related receptor alterations. One study involving just nine AD patients revealed no link between 5-hydroxytryptamine 2A receptor (5-HT2A) binding and NPI psychosis scores[62]. Due to the tiny sample size, however, no meaningful inferences can be drawn. The other study, which evaluated dopamine receptors in 23 AD patients, found an increase in the number of striatal D2/3 receptors in psychotic individuals[63].

1.1.2.3 Neurobiology of AD+P

Substantial evidence suggests that AD+P is associated with an increased burden of neurofibrillary tangle pathology and hyperphosphorylated tau and further reflects the dysfunction of the frontal area[34; 64; 65; 66; 67]. In addition, the tau hyperphosphorylation was observed only in female subjects rather in male subjects[68; 69] which is in accordance with the fact that a higher risk of AD+P are reported in women compared to men[8]. To conclude that tau pathology is related to AD+P, additional evidence is required; hence, no PET tracer investigation has been undertaken on AD+P patients. A 2019 longitudinal study employing the tau PET tracer 11C-PBB3 in patients with traumatic brain injury (TBI) related higher levels of binding in white matter to more severe late-onset psychosis[70]. This is the closest evidence we could find. This discovery laid the groundwork for a putative connection between tau and AD+P.

Neocortical synaptic disruption is another key factor that is closely related to cognitive decline and AD. The inhibition of long-term potentiation and consequent dendritic spine loss are

believed to be the underlying mechanisms along with the accumulation of amyloid-β (Aβ)[28; 71]. The study reported that the ratio of $A\beta_{42}$:$A\beta_{40}$ is increased and the levels of the guanine nucleotide exchange factor kalirin were reduced[71], which can mediate long-term potentiation in prefrontal cortex tissue. Generally speaking, the increased levels of synaptic proteins involved in vesicular function have been shown to confer resilience to psychosis[67]. In addition, the loss of zinc transporter 3 can further impair the synaptic function and is also associated with psychosis, tau pathology, and cognitive impairment[72; 73].

PED imaging also demonstrated an increase in D3 receptor density in the nucleus accumbens and a decrease in dopaminergic neurotransmission in the amygdala in persons with AD psychosis[63; 74]. Based on these findings, the use of amisulpride, a D2/D3 receptor antagonist, was promoted in treating AD+P for its potential in optimizing the therapeutic effects while minimizing extrapyramidal side effects[75]. In the meanwhile, one of our prior investigations also reported a positive effect of vitamin D in AD+P and provided a possible explanation for this effect[76]. The impairment of serotonergic neurotransmission in psychotic symptoms in Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) is a common finding in postmortem studies[34]. With reduced 5-HT levels in the ventral temporal cortex and prosubiculum, as well as decreased neuron counts in the dorsal raphe nucleus and area CA1 of the hippocampus. On the basis of these findings, Pimavanserin, a second-generation antipsychotic that is a highly selective 5-HT2A inverse agonist, is touted as a possible therapy option[77]. In addition to dopaminergic and serotonergic neurotransmissions, the cholinergic system could be a key therapeutic target for AD+P. In AD patients with hallucinations, acetylcholinesterase activity was observed to be diminished. These results show that cholinergic denervation is an additional mechanism contributing to psychosis in AD [78].

Since DLB is reported to have a higher prevalence of psychotic symptoms than AD, the topic of whether Lewy body disease contributes to the risk of psychosis in AD was naturally raised. Although Lewy body pathology appears to increase the incidence of psychosis in Alzheimer's disease, it does not explain all cases. Some of the main studies described before controlled adequately for -synuclein pathology[71], and it has been established that AD+P can occur in the absence of concomitant Lewy body pathology[79]. Moreover, cardiovascular comorbidities are also linked to AD+P. Two studies, both utilizing NACC datasets, found that subcortical arteriosclerotic leukoencephalopathy and severe arteriosclerosis were psychosis risk factors[80; 81]. The reported connections between leukoencephalopathy and AD+P were reinforced by a 12-year longitudinal research that included small vessel disease and cerebral amyloid angiopathy[82]. Several observational studies also supported the association between vascular risk factors and AD+P[83; 84].

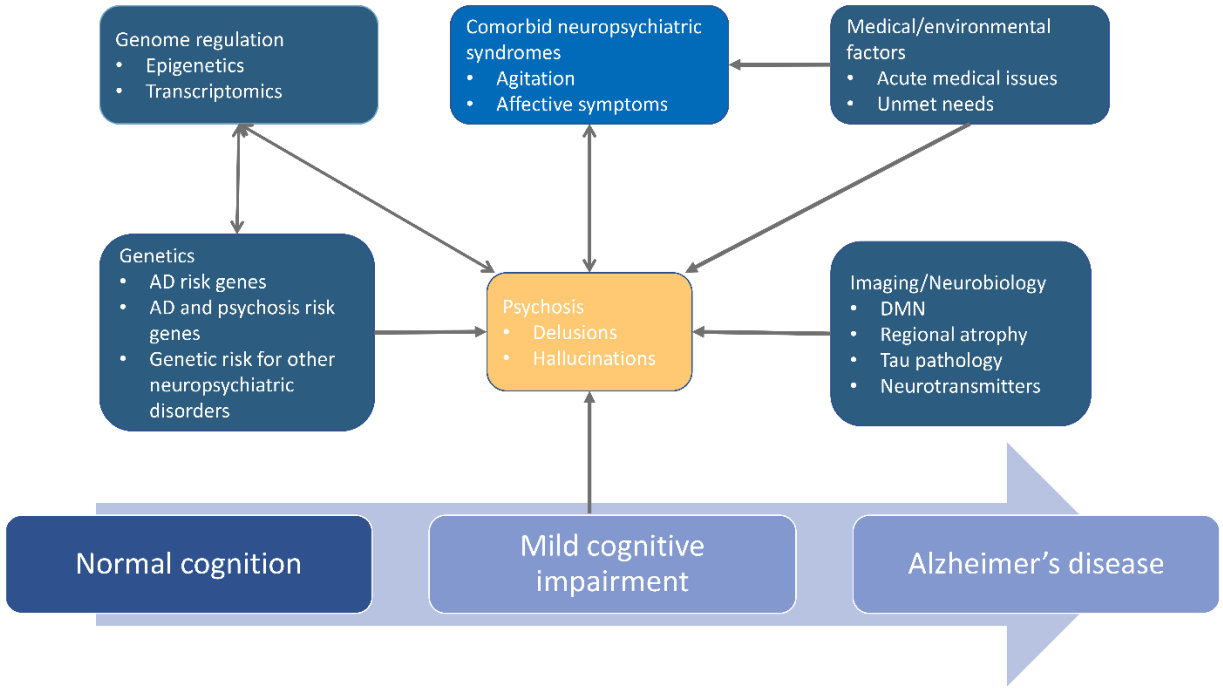

Figure 1.1 Schematic figure of mechanisms of AD+P

In conclusion, psychosis can manifest at any stage of cognitive impairment in elderly populations. Several elements, such as medical and environmental difficulties, concomitant agitation, or affective syndromes, must be addressed prior to the psychotic symptoms causing a diagnosis to be made. In AD+P, delusions and hallucinations frequently overlap despite having distinct features and natural histories. There are genetic markers connected with Alzheimer's disease, psychosis, and other neuropsychiatric illnesses. Default mode network (DMN) dysfunction, cortical atrophy, cholinergic processes, hyperphosphorylated tau, and white matter pathology are imaging and biomarker correlates.

1.1.3 Current Treatment and Management for AD+P

There are currently no medications approved by the Food and Drug Administration (FDA) for AD+P specifically. SGAs, such as Aripiprazole, Olanzapine, Quetiapine, and Risperidone, which were developed for the treatment of schizophrenia (SCZ), have been widely used and recommended by geriatric experts in the management of psychosis in AD[11; 12; 13]. Use of SGAs to treat AD+P is greatly limited by their increased rates of adverse events[85; 86], prompting the FDA to issue a "black-box" warning in 2005 to highlight the increased mortality for patients with dementia who are treated with SGAs[87]. Additionally, antipsychotics have demonstrated modest efficacy in treating psychosis, aggression, and agitation in individuals with dementia[88; 89; 90]. Therefore, safer and more efficacious medications for AD+P are needed for managing psychotic symptoms in AD.

1.1.3.1 Non-Pharmacological and Pharmacological Interventions

1.1.3.1.1 Non-Pharmacological Approaches

Due to the dearth of evidence for pharmaceutical therapies for psychotic symptoms in dementia patients, non-pharmacological techniques are chosen as an initial approach prior to medication or concurrently with medication, if not limited by immediate safety concerns[91]. The DICE technique (explain, investigate, develop, and evaluate) highlights the fundamentals of managing behavioral changes in dementia[92]. First, measurement-based care is used to describe the NPS or behavior concerns. To investigate the causes of NPS, it is necessary to conduct a medical and environmental evaluation to rule out medical issues (such as hearing loss, pain, or infection), drug side effects (such as anticholinergics or opiates), and environmental factors (such as noise, light, or disorientation) as potential contributors. Without these examinations, it is impossible to confidently diagnose syndromal psychosis as part of a neurodegenerative illness. Consequently, a plan is developed to avoid and address behavioral difficulties. The management plan is then assessed and changed as necessary[93]. Two studies, sequential drug treatment algorithm[94] and WHELD[95] (Improving Wellbeing and Health for People with Dementia), investigated combinations of non-pharmacological and pharmacological therapies for the management of neuropsychiatric symptoms (NPS) in dementia patients.

To present, only one study has particularly evaluated non-pharmacological therapies for the treatment of psychosis in dementia patients[96]. In this study, a wide variety of non-pharmacological interventions, including music therapy, orientation training, art–cognitive activities, and physical activities, were applied and was shown to reduce psychotic symptoms (NPI score −2.36, $P = 0.046$) in the 104 senior men with dementia living in two veterans' homes. Non-pharmaceutical therapies were able to alleviate dementia patients' delusions, hallucinations,

and agitation, according to the study. In summary, these findings supported the promise of non-pharmacological therapies to treat psychosis in Alzheimer's disease, while additional trials with larger and more diverse populations are required.

In clinical settings, non-pharmacological techniques for the treatment of AD+P are a best-practice supplement to the use of pharmaceuticals when psychotic symptoms are regarded as the patient's primary nonpsychotic symptom[97]. In general, we urge that caregivers avoid questioning or arguing with a person about their delusions or attempting to "give them reality," as such interaction can frequently intensify a patient's sense of fear or paranoia and increase the burden of care[98]. In addition, before prescribing medications, it is important to ascertain whether a psychotic symptom is truly distressing[99]. For instance, some hallucinations are fleeting and innocuous (such as seeing a tiny child playing), and if there is no interruption to function, a risk–benefit analysis may conclude that treatment is unnecessary.

1.1.3.1.2 Current Pharmacological Interventions: Antipsychotics

Historically, antipsychotic medications have been the mainstay of therapies for AD+P and other NPS, as they have been used to treat psychosis and agitation in individuals with other psychiatric diseases. Heated discussions were made around their usage in AD+P for their modest efficacy[88; 89; 90; 100] and significant increased adverse effect[85; 86; 101]. The use of antipsychotics in AD patients was also associated with an increase in mortality risk[102]. Among the wide collection of Antipsychotics, Aripiprazole and Risperidone were the most supported antipsychotics with a better efficacy and safety profile according to conclusions drawn from meta-analytical studies[100; 103; 104]. A recent network meta-analysis concluded that aripiprazole is the most effective and safe atypical antipsychotic for treating behavioral and psychological symptoms of dementia. This conclusion bolstered these reports.

Recent pharmacokinetic–pharmacodynamic (PKPD) investigations have shown that by modifying the dosing strategies of antipsychotics in AD patients, a balance between efficacy and safety can be optimized. This proposition is especially important given that no alternative medications for the treatment of AD+P have been approved. These results imply that dose adjustments based on age and Mini-Mental State Examination (MMSE) scores, which are hypothesized to be necessary due to the breakdown of the blood-brain barrier[105], could pave the road to a safer and more precise use of antipsychotics. As we discussed in the mechanism section above, the use of Amisulpride in late-life psychosis is also under scrutiny because it can reach higher than predicted occupancy of striatal D2/D3 receptors at a relatively low dose[75]. This strategy was effectively used in a clinical trial involving patients with very late-onset schizophrenia-like psychosis [106].

Based on the direct link between cardiovascular disease and the mechanisms of action of atypical antipsychotics, as revealed by transcriptome data[107], several researches have proposed that increased screening for cardiovascular history should guide prescribing methods. In the meantime, safety issues and the rise of adverse drug reactions (ADRs) need to be carefully considered in controlling NPS in AD+P. In the USA, no drugs are licensed for psychosis and agitation in dementia and in the European Union and Canada, only risperidone is indicated[28]. Severe dangers, including cerebrovascular accidents, extrapyramidal symptoms, falls, and fatality, were described. Though SGAs (also known as atypical antipsychotics) exhibit better safety profiles than typical antipsychotics[93; 102], a meta-analysis still found that atypical antipsychotics carried a 3.5% risk of mortality, representing a 54% relative increase in risk compared with the 2.3% risk for placebo[108].

1.1.3.1.3 Novel Treatment Options

In 2016, the Food and Drug Administration (FDA) approved Pimavanserin, the first-in-class atypical antipsychotic medication, for the treatment of Parkinson disease psychosis (PDP)[109]. This prompted the investigation of its potential for treating NPS in AD patients. Pimavanserin is a highly selective 5-HT2A inverse agonist with no dopaminergic, histaminergic, or muscarinic binding, according to its mechanism of action[110]. Some efforts have been made to systematically evaluate the safety, tolerability, and efficacy of Pimavanserin versus placebo in Alzheimer's disease patients, and it has been found to have moderate efficacy (effect size of 0.32) in reducing psychosis scores on the nursing home version of the NPI[77]. Despite the fact that favorable effects were demonstrated at 6 weeks, no substantial advantage was identified at 12 weeks when comparing Pimavanserin to placebo. Another randomized, double-blind, placebo-controlled experiment indicated a much larger therapeutic impact of Pimavanserin, with an effect size of 0.73 and a reduction in psychosis score of 30% in 88.9% of the Pimavanserin-treated group compared to 43.3% of the placebo group[111]. In another study focusing on the relapse of psychosis, 62% of open-label-treated subjects responded to the Pimavanserin treatment, and the psychosis relapse rate was 2.8-fold lower in the drug-treated group than in the placebo group ($P = 0.0023$)[112].

Pimavanserin had no adverse effect on parkinsonism, psychosis, or stroke risk, but is linked with moderate QTc prolongation (~9 ms), as well as disorientation, edema, falls, and an unsteady gait. Similar to other antipsychotic medications, Pimavanserin got a black box warning for mortality risk when it was authorized by the FDA for PD psychosis, with a necessity for post-marketing surveillance. No substantial excess deaths were found in the arms treated with Pimavanserin (five deaths versus four deaths in the placebo arms across the two trials)[77]. The

FDA has assessed that there are no new safety concerns in light of the fact that mortality rates for PD patients are consistent with expectations [113]and that there are no new safety issues. Nevertheless, a long-term, open-label safety investigation in persons with PD indicates that concomitant use of an atypical antipsychotic could have safety implications[114]. There was a fourfold increase in mortality and a threefold rise in major treatment-emergent adverse events among 66 people who received additional antipsychotics, suggesting that polypharmacy should be approached with extreme caution.

Other medications have proven efficacy for the treatment of psychosis in Alzheimer's disease that are compatible with the processes discussed above. In the CitAD research, citalopram was effective in reducing agitation, and a secondary analysis suggested a reduction in the frequency or severity of hallucinations and delusions[115]. However, QTc prolongation, primarily caused by the R-citalopram enantiomer, was also a concern with this drug, and the ongoing S-CitAD study[116] is implementing escitalopram — the safer S-enatiomer of the racemic mixture that comprises citalopram — for the treatment of AD agitation, with psychosis as a secondary outcome measure. Intriguingly, findings published in 2020 indicated a drop in CSF fluid Aβ42 levels in cognitively healthy older persons treated with escitalopram as compared to placebo[117], paving the path for the use of this medication in dementia trials.

In the 12-week Lit-AD[118] randomized trial, low-dose lithium was assessed for efficacy in treating agitation in AD. Although the experiment failed to reach its primary objective of a decrease in agitation and aggression scores on the NPI, the secondary objective of an improvement in clinical global impression was achieved. Importantly, there was no association between lithium medication and cognitive impairment. In exploratory studies, lithium was linked with a substantial reduction in delusions relative to placebo ($P = 0.04$, Cohen's $d = 0.76$), but not

hallucinations (P = 0.56, Cohen's d = –0.21). Despite limits in sample size and study power, the distinction between delusions and hallucinations is intriguing, particularly in light of the vastly different effect sizes. These results show that hallucinations and delusions have distinct etiologies and may need to be viewed as distinct entities. There is currently no unanimity on how lithium exerts its neuroprotective and therapeutic effects. Nevertheless, glycogen synthase kinase 3B (which modulates apoptosis and neuroplasticity), neurotrophic factors (such as brain-derived neurotrophic factor), neurotransmitter regulation (glutamate, dopamine, GABA, acetylcholine, and glycine), and antioxidant effects have all been implicated. These processes, particularly the neurotransmitter effects, are compatible with what is known about psychosis in AD. Lithium merits additional research in a trial using AD psychotic symptoms as the key outcome measure in light of the substantial findings to date, particularly with respect to delusions. Such an investigation could potentially generate hypotheses for the subsequent investigation of novel systems as therapy targets.

Cholinesterase inhibitors are well-established for the treatment of cognitive symptoms in Alzheimer's disease (AD), but the therapeutic effect — if any — of these drugs in persons with AD psychosis is unknown, and no randomized controlled trials have been done. Nonetheless, according to an investigation of the Swedish Dementia Registry, the use of cholinesterase inhibitors was associated with a decreased probability of initiating antipsychotic therapy in the AD subgroup[119]. Although this result does not indicate a treatment effect, these findings are consistent with the cholinergic pathways identified in AD psychosis and may represent an alternative to costly psychiatric medicines for the treatment of NPS. Once more, prospective trials are necessary.

Researchers are beginning to use the correlation between vitamin D insufficiency and neurodegenerative illnesses to investigate the potential role of vitamin D deficiency in AD psychosis. Vitamin D use was shown to be more prevalent among patients with MCI or AD who did not have psychosis and was also related to a delay in the onset of psychosis[120]. As an inexpensive and risk-free therapeutic, vitamin D merits additional research in this population.

1.1.4 Conclusion and Future Perspectives

Over the past decade, several significant advances have been made in the clinical assessment and therapy of psychosis and other NPS in dementia. These achievements include the acknowledgment of the high risk involved with antipsychotic medications, resulting in a decrease in prescriptions[121]; a greater emphasis on non-pharmacological interventions (such as DICE or WHELD); exploration of strategies to optimize existing drugs, such as aripiprazole, risperidone, amisulpride, and escitalopram, for safer precision-based treatment; development of a clinical trial program for Pimavanserin; and publication of new consensus definitions and criteria that more accurately reflect the emergence of psychosis in advance of dementia at preclinical and prodromal stages (for example, IPA, ISTAART-AA psychosis and ISTAART-AA MBI criteria). However, the significance of these milestones was restricted by the absence of a licensed pharmaceutical therapy, the relatively sparse drug research pipeline, the ongoing use of antipsychotics despite the hazards, and the lack of a specialized non-pharmacological intervention for psychosis.

In the absence of approved drugs, it is critical to develop precise risk and implementation profiles for existing antipsychotics. Aripiprazole is the antipsychotic medicine that best balances efficacy and safety, according to clinical research, statistical analysis, and computational

modeling. This research has also examined precision implementation strategies for risperidone and amisulpride for psychosis in AD, which could improve the safety profile of these drugs. These methods can be applied in a variety of settings to aid in the creation of evidence-based algorithms that incorporate both pharmacological and non-pharmacological therapies and are personalized to individual patient profiles. Non-drug treatments for psychosis need to be made and tested, and the COVID-19 epidemic shows that they should be able to be used both in person and over the internet.

Concurrent investigation of the neuroscience of psychosis could inform the creation of new or repurposed drugs. The first genome-wide important locations and evidence of DNA methylation alterations have been discovered in research into the neurobiology underlying AD psychosis; however, replication and functional validation are still required. In the meantime, neuropathology and imaging investigations have established frontal dysfunction and tau pathology as important neurobiological correlates of psychosis. Synaptic dysfunction and the protein Kalirin are fresh potential therapeutic targets deserving of further investigation. Notably, the majority of medicines in development for AD psychosis have similar modes of action to antipsychotics originally developed for schizophrenia, presumably reflecting shared underlying disease mechanisms. Evidence implicating the DMN and genetic and epigenetic risk factors for schizophrenia and depression, as well as kalirin and vitamin D in Alzheimer's disease psychosis, suggests a molecular overlap with schizophrenia. Future research could include a more systematic evaluation of the psychotic symptoms in AD and their mechanistic similarities with schizophrenia. One could expect that the presence of a schizophrenia-like phenotype would confer a greater response to antipsychotics, and alternative treatment techniques could be sought for symptom profiles that are less consistent with schizophrenia.

Enhanced phenomenology and nosology must be used for AD psychosis case identification in order to enhance symptom profile-based therapies. This attempt should be aided by the advancement of the IPA psychosis criteria and the establishment of the ISTAART psychosis and MBI criteria. In reality, these objectives guided the development of the ISTAART psychosis criteria. These criteria place late-life emergent psychosis on a spectrum, using the natural history of symptoms, symptom modality, cognitive stages, and AD biomarkers to define psychotic symptoms. The ISTAART criteria were also meant to promote genetics research by providing classification methodologies that may be adapted to the analyses being conducted (such as separating delusions and hallucinations and assuring more non-psychosis "controls" by including prior history). This approach could be used in cross-sectional and longitudinal studies to improve our understanding of the clinical, cognitive, and neurobiological underpinnings of AD psychosis and to facilitate the development and implementation of non-pharmacological therapies.

1.2 Quantitative Systems Pharmacology Approaches

Quantitative systems pharmacology (QSP) is a computational model that investigates the interface between discrete experimental data (e.g., drug or compound research) and the "system". The "system" may be any disease-related biological process, such as the physiological effects of a disease, a specific disease pathway (e.g., signal transduction or up- or down-regulation of a route, increased heart rate), or any of the "omics" (i.e., genomics, proteomics, metabolomics).

Utilizing "omics" creates significant opportunities to learn from huge data systems by searching for overlapping themes. While "omics" data on their own are unlikely to lead to

decisive directions during drug development, their combination with QSP can produce powerful insights that reduce ambiguity at key decision points during development. QSP can influence the design of a suitable study or advise on what additional trials may be required to make better-informed decisions. Similarly, QSP can significantly reduce errors that could lengthen the drug development process or possibly lead to an avoidable failure.

By merging regulatory and metabolic biological pathways with innovative drug molecule processes in order to expedite the rate of innovation through the detection of overlapping moieties, big data can be used in QSP to get powerful insights into drug development, for instance. These insights can aid in leveraging potentially additive or synergistic effects, planning around unexpected setbacks, and reorienting experimental direction at crucial periods in the early phases of drug development to prevent avoidable failures.

As previously undiscovered and crossing disease pathways are uncovered, QSP can be utilized to identify new targets, verify existing targets, comprehend the potential detrimental consequences of novel pathways, and repurpose existing medications for new targets. QSP has built upon the insights acquired through constructing physiologically-based pharmacokinetic (PBPK) models (e.g., blood flow rates, organ sizes, transporter expression, etc.) and substantially advanced our ability to comprehend drug action.

1.2.1 QSP and Its Growing Role in Drug Development

Drug development is essential to modern medicine; nevertheless, bringing medications to market is frequently hindered for a variety of reasons, including a lack of understanding of drug behavior at the level of the entire system and undesirable side effects[122]. To comprehend the mechanism of disease networks, identify novel therapeutic targets, and create successful

therapies, it is necessary to examine individual components such as genes, RNA, and proteins as dynamic systems spanning several scales[123]. The development of high-throughput technologies and the accumulation of biomedical data have revolutionized our understanding of these biological processes; however, these data types require integrative and dynamics-driven approaches to comprehend dataset repositories and accelerate novel discoveries. Consider drug-target and drug-drug interactions and their system-level repercussions as an additional source of complexity.

Systems biology aims to address these complexities by understanding biological processes at the molecular and cellular system levels. QSP stems from system biology and integrates pharmacological aspects with systems modeling to identify and design safer and more effective drug therapies. QSP was defined in 2011 in a National Institutes of Health white paper based on workshops and discussions with experts from academia, government, and industry[124; 125; 126]. One of the challenges associated with medication research is the rising cost of drug development and approval, which ranges from $1.2 to $4 billion and takes up to 10 years[127; 128; 129]. QSP tackles a portion of these obstacles by providing integrative ways to establish the mechanisms of action of novel and existing medications, maximize therapeutic effect, limit toxicity, and apply a procedure to enhance the health of individual patients[130]. QSP employs mechanistic mathematical models to characterize the dynamic interactions between a drug and physiopathology at different levels of biological organization (molecular, cellular, and organ-level networks). QSP enables innovative drug target predictions, extensive studies of mechanisms of action and safety, biomarker identification, optimization of dosages or regimens, compound selection, decision making, and responses taking into account a number of treatment variables[130; 131]. Even though QSP is relatively new, it complements other widely used

modeling methodologies for preclinical and clinical studies, including the measurement of drug behavior in the body[132]. Pharmacokinetics (PK), pharmacodynamics (PD), pharmacokinetic/pharmacodynamic (PK/PD) modeling, physiologically-based pharmacokinetic (PBPK) modeling, physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling, network biology, real-world evidence (RWE), and machine/deep learning techniques all played a part in the scope of QSP to facilitate drug discovery.

1.2.2 Network Analysis in Systems Biomedicine Research

In biology, network techniques have proven beneficial for organizing high-dimensional biological datasets and extracting relevant information. A network is a method of describing datasets that emphasizes the connections between nodes. These nodes, which can represent genes, proteins, tiny molecules, or any other entity capable of interacting in the modeled system, are connected by edges, which describe the nature of the interaction, to form a graph. Different properties and annotations can be assigned to nodes and edges. Depending on the nature of the investigation, interactions may be experimentally determined physical and chemical interactions, genetic regulatory connections, higher order links such as co-expression, or any other shared feature connecting the nodes. When information is available, edges can contain directions, weights, and other characteristics that provide information about the hierarchy of effects.

Numerous advanced techniques of computational analysis are applicable to network data structures and can reveal non-obvious aspects of nodes and their interactions. Networks enable the integration of multiple experimental data sources and biological knowledge into a framework that yields fresh insights into the system. These methods can combine genome-scale datasets with knowledge regarding particular genes and proteins. In recent years, studies of metabolic

networks, gene regulatory networks, protein–protein interaction networks, and other biological networks have shed light on the origins of overall cellular behaviors and evolutionary design principles, as well as on more specialized fields of research pertaining to specific cell biological processes or diseases. From these studies, experimentally testable hypotheses can be formulated, ranging from the prediction of novel roles for genes to genome-scale features of human cellular networks. Similarly, the study of networks for pharmacologic investigations has the potential to facilitate the identification of new drug targets for a variety of diseases, a better understanding of what makes a good drug target, and enhanced capacity to anticipate beneficial drug combinations and adverse drug events. These investigations contribute to the paradigm shift of drug action from a relatively straightforward cascade of signaling events downstream of a target to a coordinated response to various perturbations of the cellular network. Network studies in systems pharmacology can be divided into three main categories based on the type and scale of data being studied and the type of information sought: networks for global views of drug relationships, new drug target studies and studies of current drugs. **Figure 1.2** is a demonstrative figure for the three broad categories of network investigations in systems pharmacology. (A) Global drug network studies that combine information about numerous types of medications and biological datasets such as protein–protein interaction data are capable of generating network features of drug targets. These characteristics provide information on historical drug development trends and can suggest the characteristics of a druggable target. (B) Condition-specific network studies discover potential novel drug targets and therapeutic techniques using information about a specific disease. (C) Studies that incorporate information about specific diseases and pharmaceuticals can reveal novel indications for drugs, unidentified therapeutic targets, and other potentially intriguing drug features.

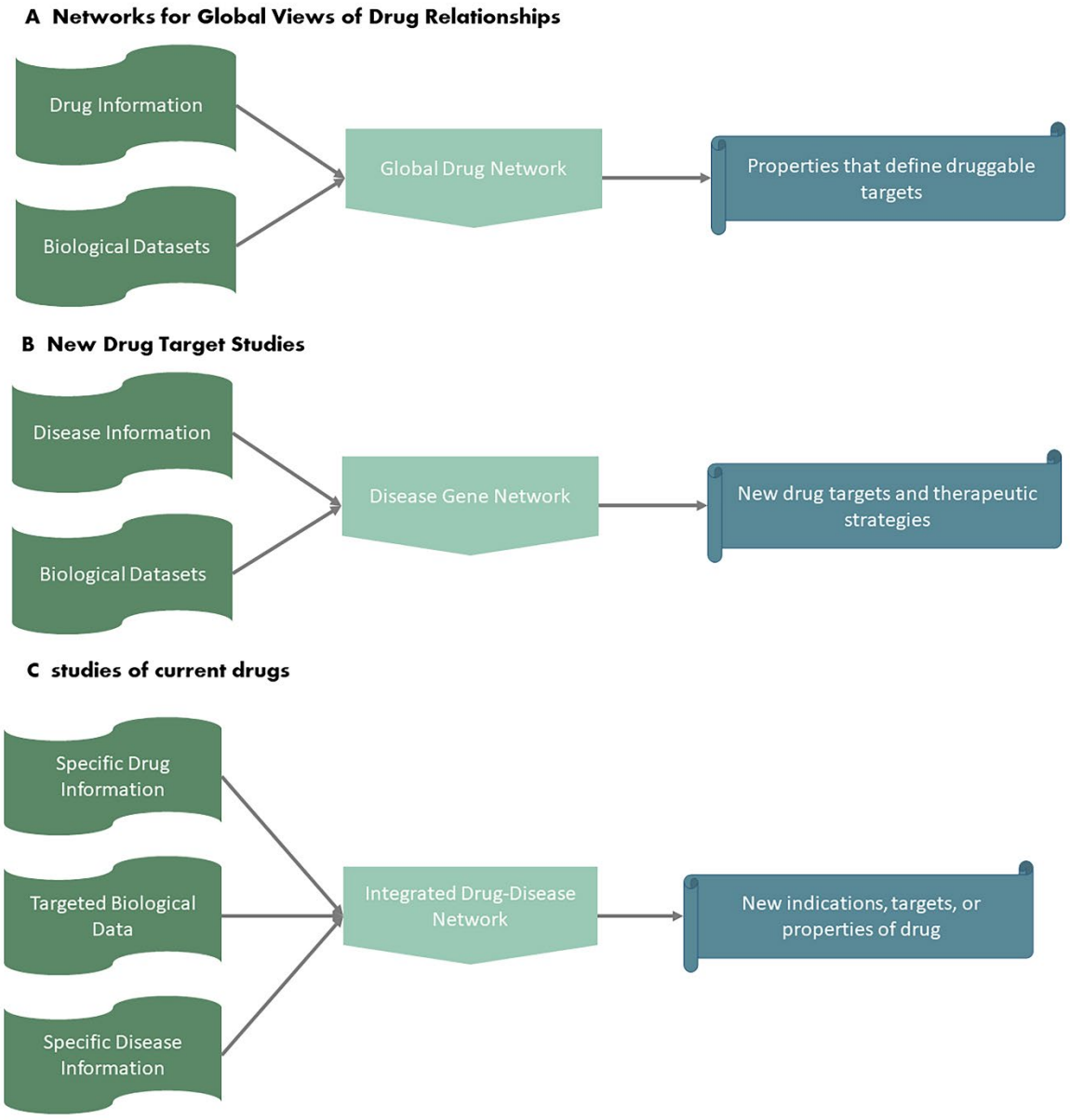

Figure 1.2 Categories of netowrk analysis in biomedical research

Nodes are the entities in a network that represent many types of items, such as genes [133], proteins[134], medications[135], and diseases[136; 137]. A network's nodes can also be utilized to define the state of a system. Such specifications can be determined using Boolean dynamics[138; 139], in which each node has a chance to exist in two states (active or inactive,

respectively), or by employing concentrations of nodes with dynamical models based on ordinary differential equations[140]. In pharmacokinetic-pharmacodynamic models, the latter method is most frequently used.

The edges of a network can be directed such that the source node has an effect on the target node, and the relationship is valid only in one way. The activation of a transcription factor by protein kinase and the transcription factor's control of a target gene are examples of directed edges[141]. The edges could also be undirected, allowing interactions in both directions. Interactions between a protein and its scaffold are instances of "undirected edges." It is also possible to provide weight to the edges based on the strength of their links. Numerous criteria, ranging from statistical correlations for distant linkages (such as gene-disease relationships) to kinetic rate constants for direct physical interactions, can be used to estimate these weights (such as hormone or drug binding to receptors). One can utilize a variety of networks based on different sorts of nodes and edges to analyze pharmacological activities. A directed edge connects a drug node to its target protein node in the simplest network[142]. The target protein node is then connected to other proteins that physically interact with the drug-target protein, and these proteins can be further connected using the same criteria[143]. All edges in this network have the same weight, indicating that they all share the same level of connectedness. This simplification assumption is not always valid, so we must be cautious when determining if the represented network accurately represents the system. These networks are referred to as "interaction networks." Interaction networks enable us to rapidly assess the potential downstream and upstream interactors of a node[144], which can be useful for finding paths for signal flow and regulatory motifs such as feed-forward and feedback loops that have the capacity to process information.

1.2.3 Machine/Deep Learning in QSP

The astounding volume of data created by contemporary technologies necessitates integrated treatments for pharmaceutical issues. The "big data" area seeks to interpret information from datasets comprising large or complicated amounts of data[145]. Observational data such as Electronic Health Records (EHR), which include patients' unique medical features such as laboratory findings, comorbidities, medications, and observed effects, is an example of big data utilized for drug discovery[146]. In drug research, machine learning (ML) has been incorporated into automated pipelines to guide and speed up preclinical wet-lab investigations, drug discovery, and clinical trials. In fact, ML approaches can be applied in practically all phases of drug discovery and development[147]. ML can be used, for instance, to identify and validate novel targets[148; 149], predict treatment responses[150], discover biomarkers[151], predict disease progression[152], degeneration[153], and risk factors[154; 155], design and optimize small-molecule components[156], and enhance analyses of high-throughput imaging in computational pathology[147; 151]. By predicting ideal physicochemical properties, pharmacokinetics, safety, and efficacy, ML can also optimize the drug candidate discovery field[157; 158; 159; 160; 161; 162; 163].

1.2.3.1 The General Concept of Machine Learning

ML approaches can be divided into two groups: supervised learning, which employs labeled data (the objective is to "predict"), and unsupervised learning, which uses unlabeled data (the objective is to "explore")[164].

Supervised machine learning techniques require input data sets to be partitioned into "training" and "test" data sets. Model training involves fitting the model to the training data set

and then validating the trained ML model using the test data set. The verified ML model may then be used to generate predictions or judgments based on the covariates of the new data set[165]. Several methods, including linear and logistic regression, ridge regression, decision trees, random forests, gradient boosting, neural networks, and evolutionary algorithms, have been developed in this field[166; 167; 168]. In supervised ML, datasets containing both covariates and outcomes are "labeled" and exploited.

Various studies approach drug discovery using supervised learning techniques such as regression analysis methods (e.g., disease and target draggability from multidimensional data[149], targets for Huntington disease[169], potential cancer biomarkers[170; 171], drug sensitivity prediction[172], and image-based diagnosis[173]) and classifier methods (e.g., tissue-specific biomarkers from gene expression signatures, target draggability based on PK properties and protein structure[173; 174]).

Moreover, supervised learning methods permit the modeling of responses for estimating the outcomes of individual patients. One way to accomplish this is by fitting a single-output model with the treatment as an input feature, making the model less flexible and offering the same result model for patients who have received treatment and those who have not. An alternative method for assessing patient outcomes is to fit two separate supervised models for different treatments[174]. This method provides greater flexibility. Unsupervised machine learning incorporates covariates but not outcomes. This method identifies patterns and relationships between data points. K-means and hierarchical clustering are examples of widely-used unsupervised ML techniques. In addition to de novo molecular design[175], unsupervised clustering algorithms have also been applied to deep feature selection for biomarkers[176], feature reduction in single-cell data to identify cell types[177], and biomarkers[178].

The estimation of the impact of a single, multiple, or time-dependent treatment on patient outcomes is made possible by causal inference strengthened by machine learning. Clinical data (e.g., age, sex, genetic information, laboratory measurement), type of treatment (e.g., binary treatment, single treatment, or multiple treatments), patient outcomes (e.g., survival probability, multiple outcomes), and treatment decisions (e.g., optimal single or combinatorial treatment, optimal dosage) can be used for training ML models to evaluate treatment effects. Consequently, causal inference approaches can aid clinicians in making therapy benefit, treatment choice, and dosage determinations[179].

1.2.3.2 Integration of QSP and ML

Developing approaches to integrate clinical data such as EHR or biological data sets (e.g., human genetic information in large populations, omics profiling of healthy and unhealthy people) with QSP models allows for further advancement in the QSP field. Here we show some innovative projects that combined QSP models and ML techniques.

Recent researches[179; 180] highlighted the benefits of merging ML techniques with mechanistic modeling in computationally expensive QSP model curation, optimization, parameter estimation, and simulations. Hartmann et al.[181] developed a predictive ML model to aid in optimizing antithrombotic treatment. During therapeutic antithrombotic medication monitoring, routine clinical data on 479 individuals was collected for this investigation. On the basis of a humoral coagulation model, a QSP model of the coagulation network was built[182] to investigate the influence of rivaroxaban, warfarin, and enoxaparin treatment on clotting factor levels. Using a nonlinear programming solver, the authors approximated the parameters (factor rate constants and production rates of coagulation factors). Model simulation uses a rigid ODE solver (a variable-step, variable-order solver based on the numerical differentiation formulas of

orders 1 to 5). The QSP model predicted the steady-state effects of rivaroxaban, warfarin, and enoxaparin on clotting factor concentrations. For instance, the model projected that rivaroxaban would have no effect on the levels of inactivated coagulation factors (such as prothrombin, protein C, and protein S). Due to the heterogeneity in how individuals respond to medications, it is essential to estimate interindividual variability[183]. Utilizing ML techniques, the significance of interindividual variability was evaluated. Sobol sensitivity analysis[184] was conducted to identify the parameters having the greatest influence on the activation of clot dissolution under various treatments. In comparison to enoxaparin and rivaroxaban, warfarin is predicted to inhibit protein C and protein S (components that govern blood clot formation) throughout treatment.

Pei et al.[185] used QSP approaches to conduct a comprehensive investigation of the cellular pathways implicated in 50 drugs of abuse, illustrating the benefits of utilizing ML to assess information from databases and forecast pharmacological targets. For this investigation, a list of 50 illicit substances and their respective pharmacological effects was compiled. Using DrugBank[186] and STITCH[187] (drug-ligand-target interaction databases), 142 known drug targets were found. Subsequently, a probabilistic matrix factorization (PMF)[188] based machine learning technique was used to select 48 additional targets. According to this study, the PMF model can perform well on large, sparse, and asymmetric datasets because it scales linearly with the number of observations. 11,681 drug-target interactions and 8,579,843 chemical-target interactions were used to train PMF models. The study analyzed and assigned a confidence level to each projected drug-target interaction and then chose predictions with high confidence, resulting in the identification of 161 unique interactions between 27 of the 50 input medicines and 89 targets. The authors also identified and classified 173 human molecular pathways from the KEGG database that were connected to the pharmacological targets. Finally, the authors

investigated the role of these targets and pathways in drug addiction prediction. This study generated fresh target predictions and identified important signaling modules that detect the impacts of drug abuse using machine learning techniques.

Another study[189] focused on the control of autophagy, an essential cellular process with roles such as cell death and survival. The scientists employed QSP models to analyze the mechanism of action of autophagy modulators by predicting novel drug-target interactions and examining the effects of the drug using pathway and network analysis methods. Two hundred twenty-five autophagy modulators, including medicines such as fostamatinib, olanzapine, melatonin, and artenimol, were collected. Using the DrugBank database for data collection, the selected modulators were manually categorized as inhibitors, activators, and dual-modulators. The PMF algorithm was then utilized to predict the drug-target interaction using ML[188]. The PMF model was trained using 14,983 interactions between 5,494 medicines and 2,807 targets in the DrugBank database. Each anticipated interaction was assigned a confidence value, and the interactions with the highest scores were chosen for each drug. This ML technique generated 368 unique drug-target interactions. Using the anticipated targets, a functional analysis was undertaken to identify the enriched pathways involved in the regulation of autophagy. The study contributes to future investigations about the mechanism of action of autophagy modulators.

Gaweda et al. published a QSP model for chronic kidney disease and mineral bone disorder (CKD-MBD)[157], in which ML techniques were used to estimate the model parameters of the differential equations representing the CKD-MBD compartments. A greater understanding of CKD-MBD and the diversity of CKD-MBD indications among individuals can aid the therapeutic goals of lowering mortality and morbidity[190]. Modifications were made to a previously published model to create the CKD-MBD model[191]. Modifications include

adding new components to the model and employing ML techniques to estimate the CKD-MBD model's characteristics (such as the parathyroid gland compartment, renal phosphate reabsorption, and smooth muscle cell compartment parameters of model). The CKD-MD model has distinct functions with estimation-required parameters. Using information from 5496 CKD patients, they estimated 23 factors related to model components. Nonlinear least-squares regression with the trust-region reflective technique was used to fit the model. A 10-fold cross-validation was used to validate the generated model (each fold included 30,106 training vectors and 3345 testing vectors).

Mathematical modeling can help you estimate risks in relation to possible benefits when you need to make a decision quickly. Several recommended medications for individuals with coronavirus illness 2019 (COVID19), for instance, were linked to cardiac adverse events[192]. This study revealed the association between cardiac risks and COVID-19 therapy by combining PK and QSP models[193]. For this purpose, the authors examined the potential effects of azithromycin, lopinavir, chloroquine, and ritonavir on cardiac electrophysiology. PK using the QSP model of ventricular myocytes has been employed in order to predict cardiac adverse events. O'Hara et al.'s model was used to predict the effects of the medicines on ventricular action potentials[194]. Then, using PK models to predict drug disposal, the drug concentrations of the QSP simulations were linked with the free plasma drug concentrations of the patients. This study expected that the combination therapy comprising these medicines would result in a higher action potential prolongation than the drugs given individually. To examine the relationship between sex and pre-existing heart failure, models for distinct patient groups were built, and virtual populations were generated to mimic the physiological variability of the individual. On the basis of population outcomes, a logistic regression analysis was conducted to determine why

specific cells were resistant or prone to arrhythmias. In the simulated population, modeled ventricular myocytes were labeled as 1 (arrhythmic dynamics) or 0 (no arrhythmic dynamics). Using the parameter values of each cell, the created logistic model predicted the likelihood of an arrhythmia. Simulations of patient groups reveal that women with a history of heart failure are especially sensitive to drug-induced arrhythmias.

2.0 Different mechanisms behind the neuropsychiatric symptoms of AD+P and schizophrenia

2.1 Network Systems Pharmacology-Based Mechanism Study on the Beneficial Effects of Vitamin D against Psychosis in Alzheimer's Disease

2.1.1 Background and Significance

In a previous study, we have compared the frequency of medication usage among AD+P and AD-P patients and conducted survival analysis on time to psychosis for AD patients to identify drugs with beneficial effects[195]. The results of our analysis revealed a significant association between Vitamin D use and delayed onset of psychotic symptoms. In addition, through the analysis of gene expression data, we found that AD- and/or psychosis-related genes were enriched in the list of genes most perturbed by Vitamin D. This observation provides us with a novel direction for the mechanism study of AD and psychosis, and may inspire the development of drugs to prevent or treat psychosis in AD.

The role of Vitamin D in neurodegenerative diseases has been reported by many researchers. Six of the nine case-control studies found significant between-group differences illustrated by lower serum concentrations of 25-hydroxyvitamin D, a metabolite of Vitamin D_3, in AD cases compared to control groups[196; 197; 198; 199; 200; 201; 202]. Thus, Vitamin D Insufficiency is considered as a risk factor for AD. However, Vitamin D's beneficial effect against AD+P was freshly discovered and its mechanism may provide a unique viewpoint in preventing and treating AD+P.

Network approaches have been used in predicting and identifying the disease genes in multiple studies and some of the results have been verified[203; 204]. It is suggested that, in the viewpoint of network biology, drug targets tend to locate at the transition area from the essential hubs, e.g. proteins interacting with more partner proteins, to redundant peripheral nodes[205], e.g. proteins interacting with fewer partner proteins. The rationale behind this is a balance of toxicity and efficacy regarding the potential influence of the targets on cellular function.

The aim of this study is to explore potential molecular mechanisms that underlie the beneficial effects of Vitamin D on reducing psychosis symptoms in AD patients and to identify potential drug targets for AD+P prevention or treatment by applying systems pharmacology approaches on analyzing their protein-protein interaction networks.

2.1.2 Methods and Materials

2.1.2.1 Gene Dataset Collection and Pathway Mapping

A network that includes both AD- and psychosis-related proteins were constructed and analyzed in order to study the crosstalk between them. AD- and psychosis-related genes were collected from multiple literatures and databases, including MetaCore from Clarivate Analytics (https://portal.genego.com/), GWAS Catalog for Genome Wide Association Studies (GWAS) (https://www.ebi.ac.uk/GWAS/home)[206] and BaseSpace Correlation Engine (https://www.illumina.com/index-d.html)[207]. These gene names were then converted to protein names by batch search function in the UniProt database. Due to the variety of information sources, genes were carefully selected from different types of data including RNA and miRNA expression, SNPs identified through GWAS, copy number variations (CNVs), and mutation data. Gene information was included in our study if 1) reported in a primary GWAS

analysis, defined as array-based genotyping and analysis of 100,000+ pre-QC SNPs selected to tag variation across the genome and without regard to gene content; 2) SNP-trait p-value <1.0 x 10^{-5} in the overall population. The threshold of 1.0 x 10^{-5} was chosen rather than the stricter one for genome-wide association of 5.0 x 10^{-8} [208; 209] to include more targets potentially related to AD and psychosis to generate a more complete structure of networks[210; 211]. Vitamin D-perturbed genes and antipsychotics-perturbed genes were collected from BaseSpace Correlation Engine (https://www.illumina.com/index-d.html)[207]. Both down- and up-regulated genes were included into our analysis.

Signaling pathways for AD and psychosis were acquired from KEGG (http://www.genome.jp/kegg/) [212] and PANTHER Classification System (http://pantherdb.org/)[213].

2.1.2.2 Triple-Focusing Network Approaches: Identification of Potential Novel Targets

In the following network analysis studies, we incorporated protein-protein interaction (PPI) data from STRING (https://string-db.org/) [214] and the Online predicted human interaction database (OPHID) (http://ophid.utoronto.ca/ophidv2.204/index.jsp)[215]. The PPI network was constructed and analyzed with python package networkx (https://networkx.github.io/)[216]. The interaction network was shown in the molecular action view with the medium confidence level (> 0.4)[217]. The network containing AD-related proteins (**AD network**) and the network containing psychosis-related proteins (**Psychosis network**) were joined to form a combined network (**AD-psychosis combined network**) for further study. PPI networks containing Vitamin D-perturbed proteins (**Vitamin D network**) and antipsychotics-perturbed proteins (**Antipsychotics network**) are also generated respectively.

Networks were processed and plotted with python package networkx[216] and Gephi[218]. The centrality of nodes in the network was calculated based on the built-in algorithm of networkx[216]. In detail, the degree centrality values were normalized by dividing by the maximum possible degree in a simple graph n-1 where n is the number of nodes in a network. The Betweenness centrality algorithm is from Ulkrik Brandes[219; 220; 221; 222]. In order to minimize the bias caused by the number of studies associated with different proteins, we use Betweenness centrality as our primary indicator in this study to lean more on the nodes' position in the network's structure, rather than the degree centrality of the nodes in the network.

To find sub-networks (communities) having different biological functions, community detection was further conducted in the combined network. The algorithm used for community detection was based on the Greedy Modularity Maximization method[223; 224]. It begins with each node in its own community and joins the pair of communities that most increases modularity until no such pair exists.

Network analysis was further used to study a joint AD-psychosis-Vitamin D network in order to find potential drug targets for AD+P. The rationale of this approach was that the ideal potential targets should be in the overlapping part of PPI networks of AD, psychosis and Vitamin D because the function of the potential targets can modulate the crosstalk between AD and psychosis and can also be regulated by Vitamin D through the Vitamin D receptor which is a transcriptional factor modulating gene expression. Thus, after constructing the AD-psychosis combined network and Vitamin D network, we overlapped them to explore the connectivity of these three parts and the roles of the triple-overlapped proteins. This approach can help us reduce the artificial bias caused by the different number of studies of those proteins, and also limit the

potential side effects caused by those very well-studied proteins which are usually located at the essential hubs.

Centrality measures of the nodes were introduced in network analysis to describe how the information will spread through the network. Two different kinds of centralities were included: Degree Centrality and Betweenness Centrality. Degree Centrality, as the most simple and direct, describes the number of connections of a particular node regardless of the direction and weight of the edges. Betweenness Centrality, as the centrality of control, represents the frequency at which a point occurs on the geodesic (shortest paths) that connect pairs of nodes. In another word, it quantifies how many times a particular node acts as a bridge linking two ends of the network.

Network analysis methods with centrality measures will first be examined with psychosis-related genes and known antipsychotics-perturbed targets. In order to do that, a combined network of psychosis network and antipsychotic network is constructed, and the centrality measures are calculated as mentioned above. The connectivity parameters of known antipsychotic targets are examined to determine if they possess a significant higher value.

2.1.3 Results

2.1.3.1 Method verification with psychosis-related PPI network and antipsychotics-perturbed genes

Psychosis-related and antipsychotics-perturbed PPI networks are used to validate the network analysis methods we proposed. Characteristics of these two PPI networks and the combined network are shown below (**Table 2.1**). Five genes, DRD2, DRD3, HTR2A, OPRD1 and HTR7, are found shared by psychosis network and antipsychotics network.

Table 2.1 Characteristics of Antipsychotics- and Psychosis-related PPI networks

Network Name	Node Number	Edge Number	Average Degree Centrality	Average Betweenness Centrality
Antipsychotics	89	419	0.106	0.0157
Psychosis	486	1409	0.0119	0.00642
Psychosis-antipsychotics Combined Network	570	1825	0.0112	0.00563

The centrality measures of nodes in the psychosis and antipsychotics are calculated and the top ten nodes sorted by Betweenness values were shown in **Table 2.2.** As we expected**,** DRD2 and HTR2A, two major targets for current antipsychotics, were ranked as the first two proteins in our combined network when measured by Betweenness Centrality. If ranked by Degree centrality, ALB and FOS, two well-studied proteins, will have higher priority than HTR2A. The result revealed the great potential for proteins with a high Betweenness centrality being drug targets and provided a solid support for the method we proposed. Thus, the network analysis methods were applied to AD- and psychosis-related PPI networks.

Table 2.2 Overview of net-influencers for top ten proteins (named by their genes) in combined network of psychosis and antipsychotics sorted by betweenness centrality

Gene Name	Degree Centrality	Betweenness Centrality
DRD2	0.0703	0.1433
HTR2A	0.058	0.0731
GRIA1	0.0615	0.0698
ALB	0.0633	0.0677
CACNA1C	0.0545	0.0513
FOS	0.0615	0.05
SYNE1	0.0246	0.0488
GRIN2A	0.0545	0.0485
FYN	0.0545	0.0432
KIT	0.0422	0.0368

2.1.3.2 The AD-psychosis combined PPI network

In order to acquire a better understanding of the connection between AD and psychosis, and to further explore the potential drug targets suggested by the previous analysis, a combined PPI network of AD and psychosis was generated. One thousand and sixty-one AD-related genes and 15,691 PPIs of their protein products together with 483 psychosis-related genes and 1,361 psychosis-related PPIs were collected as the basis of our network. Among all the proteins collected, 90 proteins were shared by both AD and psychosis, including proteins encoded by SEMA3A, TUSC3, RPN2, AMBRA1, BECN1, CACNA1C, SGK1, ADAM10, GRIN2A, FYN, ANK3, TBXAS1, EFNA5, POLN, CHRNA3, NOTCH4, GRIA1, NTRK3, IQGAP2, RELN, NOS1, GPC6, TCF7L2, TCF4, MGLL, DRD3, CHRNA2, PAK2, CTNNA2, COL25A1, COL12A1, AGER, KIF26B, PPP2R2B, TEK, KALRN, PRKG1, KSR2, COLGALT2, MEIS1, SHISA9, ZKSCAN4, PTPRG, NKAPL, CTNNA3, PDE4B, HFE, MSR1, CSMD1, COMT, APBA1, IMMP2L, ELAVL4, LRRTM4, CDH13, ZNF804A, PBRM1, LRRN2, TEP1, STXBP5L, FHIT, SYNGAP1, ZSCAN31, TENM4, ABCB1, PLCL1, RBFOX1, FSTL5, SORCS3, NKAIN2, GLIS3, NXN, MAGI2, MEGF10, MPP6, TSPAN18, FRMD4B, MTHFD1L, TMTC1, LIN28B, UXS1, BICC1, ATXN7L1, EYS, GRAMD1B, TSPAN2, ENOX1, TMEM132D, CR1 and PCNX. The AD-psychosis combined network has 1,454 nodes and 16,948 PPIs. Characteristics of the combined network were most similar to those of AD network due to the disparity of the node numbers in AD- and psychosis-related PPI networks (**Table 2.3**).

Top 10 net-influencers in the combined network are shown in **Table 2.4** based on their Degree and Betweenness centralities respectively. It is not surprising that the 3 centralities overlapped with each other substantially, since they all measure the importance of the nodes in

the whole network from different angles, and it is apparent that the top 10 nodes do have very higher values when compared with the average value, 10-fold ratio at least. A better view is provided in **Figure 2.1** showing that only a few nodes take position at the upper-right corner. This phenomenon suggests that though there are 1,454 of nodes in the network, a small group of nodes, such as the top 10 nodes shown in the table, are extremely connected and play a critical role in the signaling process and information flow within the network.

Table 2.3 Characteristics of AD- and Psychosis-related PPI networks

Network Name	Node Number	Edge Number	Average Degree Centrality	Average Betweenness Centrality
AD	1061	15691	0.0279	0.00167
Psychosis	486	1409	0.0119	0.00642
AD-psychosis Combined Network	1456	16989	0.0160	0.00158

Table 2.4 Overview of top net-influencers in the AD-psychosis combined PPI network

Gene (Degree Centrality)	Gene (Betweenness Centrality)
INS(0.200)	APP(0.0552)
AKT1(0.199)	AKT1(0.0528)
GAPDH(0.191)	INS(0.0497)
APP(0.186)	TP53(0.0451)
ALB(0.184)	FYN(0.0382)
TP53(0.175)	GRIA1(0.0348)
IL6(0.162)	GAPDH(0.0345)
MAPK3(0.153)	ALB(0.0247)
TNF(0.149)	CACNA1C(0.0245)
VEGFA(0.142)	RBFOX1(0.0209)

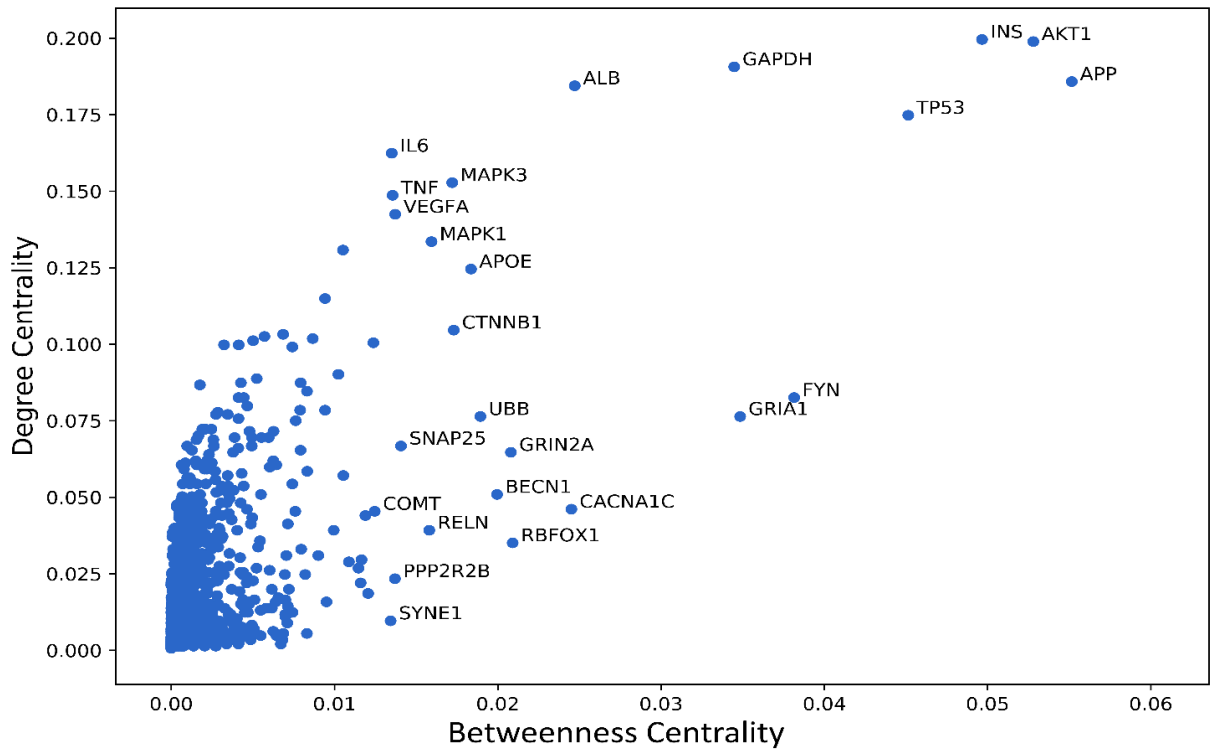

Figure 2.1 Distribution of Degree centrality and Betweenness centrality of nodes in the combined AD-psychosis PPI network. Most of the nodes have very low Degree centrality and Betweenness centrality while a very small group of nodes, like the top 10 nodes, possess very high centrality compared to others. This phenomenon suggests that the information flow within the network is controlled and regulated by the small group of nodes to a great extent.

After identifying the critical proteins in the network, the function of these proteins is our interest. We conducted pathway enrichment analysis to identify the underlying pathways participated by those proteins and therefore to establish a connection between proteins and their biological functions. Firstly, ten communities were detected as relatively separated components of the network (**Figure 2.2**). Among the 10 detected communities, 7 communities, excluding 7, 8 and 9, contain enough nodes to be biologically meaningful. When sorting the network based on the community and the nodes' Betweenness, every community has one or a few nodes that possess a much higher Betweenness value and those nodes serve as the portal connecting the community to the other parts of the network (**Figure 2.3**). Among the top 10 proteins we

mentioned above (**Table 3.4**), APP, FYN, and INS are distributed into different communities as the leading nodes, which further illustrates the importance of these nodes in the combined network. These detected communities represent different biological pathways participating in the development of psychosis in AD. Secondly, protein-pathway mapping was conducted by comparing the proteins in the same community against the proteins in the pathways from online databases like KEGG.

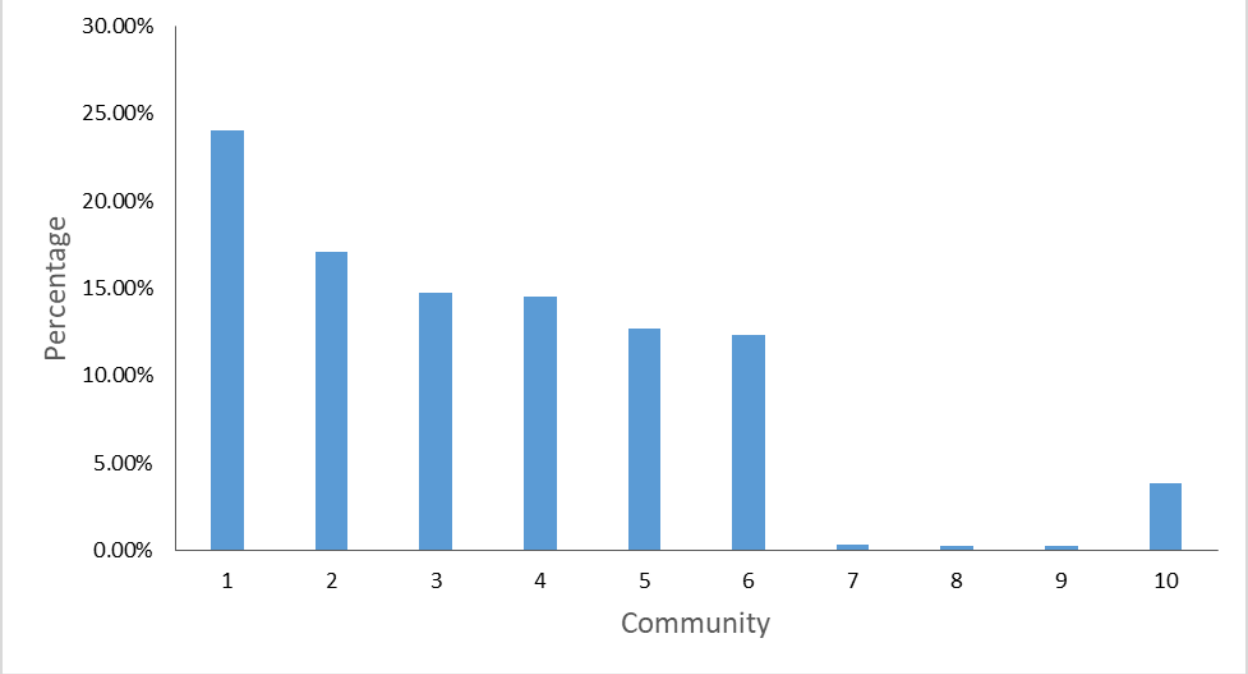

Figure 2.2. Overview of community detection. Seven meaningful communities are detected, and targets distributions are shown in the figure. These communities are constructed with similar targets amounts and can be the representatives for different biological functions involved.

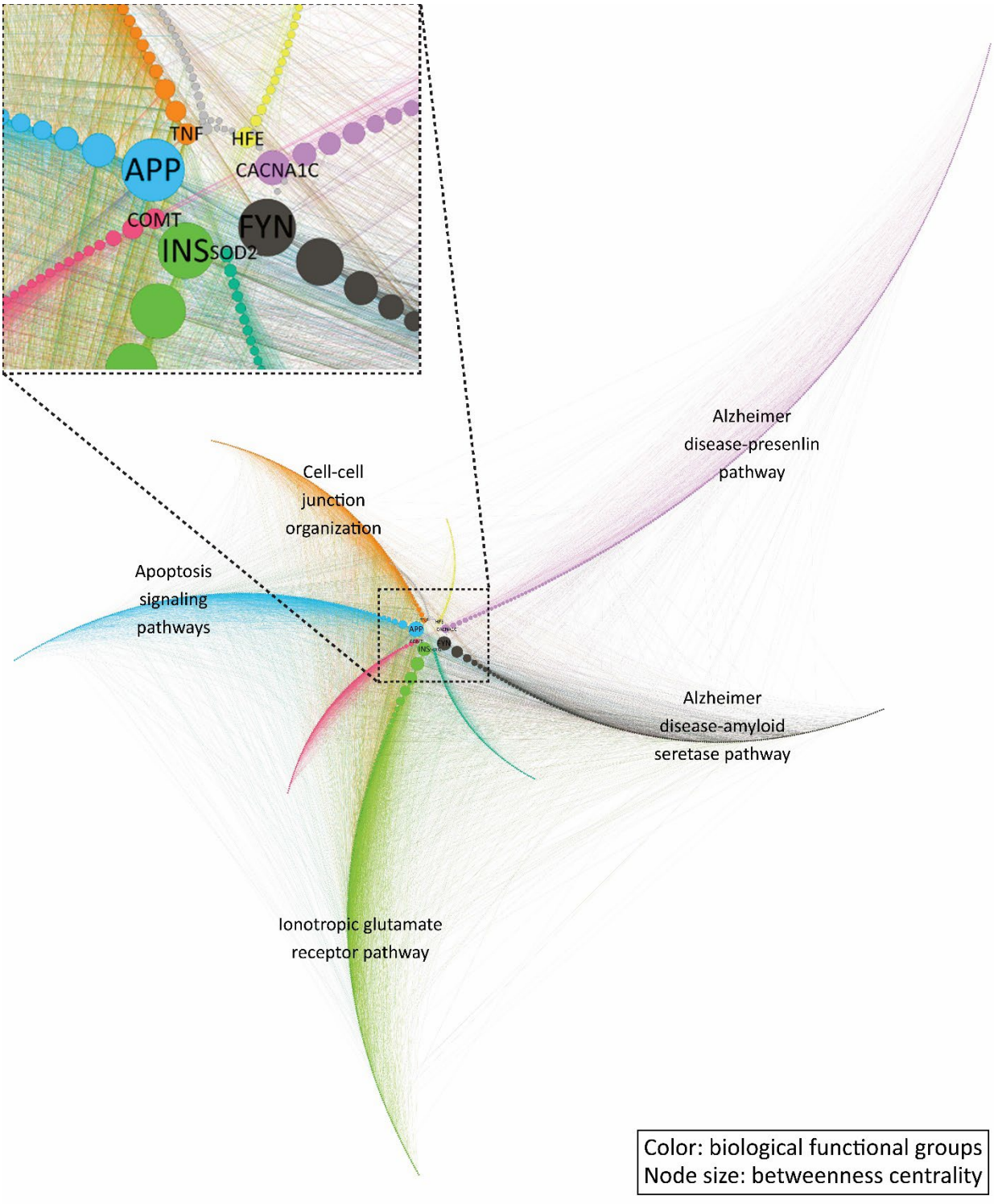

Figure 2.3 Overview of community interaction. Community interactions incorporated with the Betweenness centrality data of nodes and the functional annotations of the communities. The node size represents the Betweenness centrality of nodes. The high impact nodes, nodes with high Betweenness centrality, are evenly

distributed to communities and function as the main gateway for information exchange and interactions. The architecture of the combined network is a big system formed by several sub-networks (communities) that connect with each other through a small hub, and most of the proteins in the network work mostly with the proteins within their communities.

The protein-pathway mapping returned a list of pathways associated with these 7 communities evidenced with very low False Discovery Rate (FDR) adjusted p-values, meaning that the proteins in these communities are highly accordant with proteins in these pathways recorded in the database. Pathways closely related to AD and neurological disorders (**Table 2.5**) were enriched in the list, including the Huntington disease pathway, Alzheimer's disease-presenilin pathway, p53 pathway and Alzheimer's disease-amyloid secretase pathway.

Table 2.5 Results of protein-pathway mapping in the communities

Community	Pathways (Pathway ID)	P-value
Community 1	FAS signaling pathway (P00020)	< 0.001
Community 1	Ras Pathway (P04393)	< 0.001
Community 1	PDGF signaling pathway (P00047)	< 0.001
Community 1	Angiotensin II-stimulated signaling through G proteins and beta-arrestin (P05911)	< 0.001
Community 1	Interleukin signaling pathway (P00036)	0.00236
Community 1	Wnt signaling pathway (P00057)	0.00121
Community 1	Huntington disease (P00029)	0.00367
Community 1	p53 pathway (P00059)	0.00459
Community 1	Alzheimer disease-presenilin pathway (P00004)	0.00138
Community 1	p38 MAPK pathway (P05918)	0.0132
Community 1	Parkinson disease (P00049)	0.0135
Community 1	Integrin signaling pathway (P00034)	0.0294
Community 2	Ionotropic glutamate receptor pathway (P00037)	< 0.001
Community 2	Muscarinic acetylcholine receptor 1 and 3 signaling pathway (P00042)	< 0.001
Community 2	5HT1 type receptor-mediated signaling pathway (P04373)	< 0.001
Community 2	Enkephalin release (P05913)	< 0.001
Community 2	Synaptic vesicle trafficking (P05734)	< 0.001
Community 2	Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway (P00027)	< 0.001

Community 2	Metabotropic glutamate receptor group II pathway (P00040)	< 0.001
Community 2	Endothelin signaling pathway (P00019)	0.00296
Community 2	Opioid proopiomelanocortin pathway (P05917)	0.00136
Community 3	Alzheimer disease-amyloid secretase pathway (P00003)	< 0.001
Community 4	Apoptosis signaling pathway (P00006)	< 0.001
Community 5	Plasminogen activating cascade (P00050)	< 0.001
Community 5	Cholesterol biosynthesis (P00014)	0.0223
Community 6	Cadherin signaling pathway (P00012)	0.0494
Community 10	Cell-cell junction organization (R-HSA-421270)	0.00992
Community 10	Nectin/Necl trans heterodimerization (R-HSA-420597)	0.0177
Community 10	Cell junction organization (R-HSA-446728)	0.0275

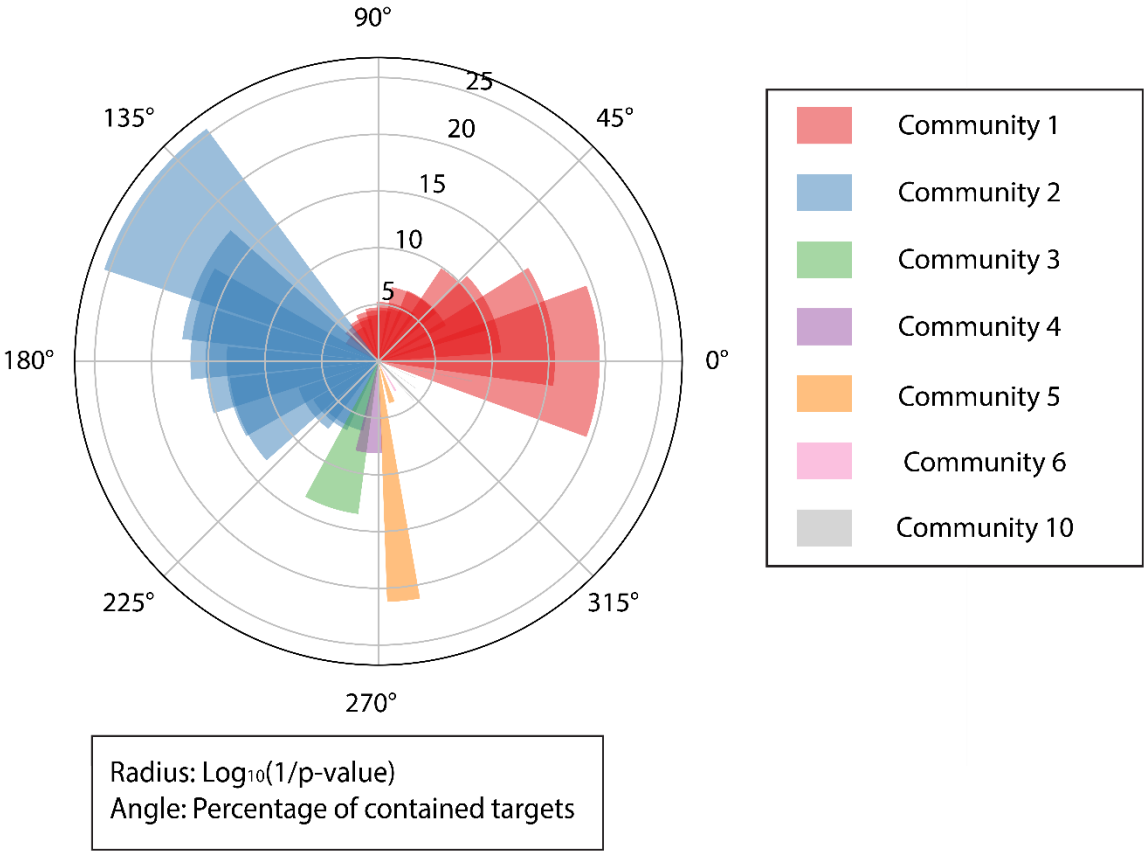

Figure 2.4 Distribution of proteins in the communities and p-values for protein-pathway mapping results. The radius represents the log10 (1/p-value) of a mapping, and a higher bar has a smaller p-value. The angle of the bar represents the percentage of proteins contained in the mapped community. Shades in same color indicate multiple pathway-matchings of one community. P-value is calculated by Fisher's exact test and all

terms are adjusted by Benjamini-Hochberg FDR. Figure generated with matplotlib (https://matplotlib.org/) version 3.1.3[225].

Figure 4 provided a more direct overview of the results of protein-pathway mapping. Community 1 and community 2 were mapped to multiple pathways with high credibility. It is fairly understandable because these two communities contain the largest amounts of targets and may result in mismatches.

2.1.3.3 Overlapping proteins between AD network and Psychosis network

Since the objective of this study is to study the development of psychosis in AD, we focused on the overlapping proteins between AD and psychosis. The net-influence parameters of the 90 overlapped proteins are shown in **Table 2.6**. Most proteins in the overlapping part possess Betweenness values above average which further supports their bridging role in the networks.

Table 2.6 Overview of net-influencers for overlapping proteins (named by their genes) between AD network and Psychosis network

Gene Name	Degree Centrality	Betweenness Centrality
SEMA3A	0.0220	0.0046
TUSC3	0.0048	0.0025
RPN2	0.0048	0.0019
AMBRA1	0.0055	0.0002
BECN1	0.0509	0.020
CACNA1C	0.0461	0.0245
SGK1	0.033	0.008
ADAM10	0.0571	0.0105
GRIN2A	0.0647	0.0208
FYN	0.0826	0.0382
ANK3	0.0268	0.0115
TBXAS1	0.0083	0.0021
EFNA5	0.0255	0.0042
POLN	0.0055	0.0026

CHRNA3	0.0117	0.0012
NOTCH4	0.020	0.0072
GRIA1	0.0764	0.0348
NTRK3	0.0248	0.007
IQGAP2	0.0055	0.0038
RELN	0.0392	0.0158
NOS1	0.044	0.0119
GPC6	0.0145	0.0071
TCF7L2	0.0296	0.0117
TCF4	0.020	0.0062
MGLL	0.0172	0.0066
DRD3	0.0482	0.0043
CHRNA2	0.0145	0.0007
PAK2	0.0241	0.0046
CTNNA2	0.022	0.0116
COL25A1	0.0124	0.0035
COL12A1	0.011	0.0015
AGER	0.0303	0.0042
KIF26B	0.0055	0.0007
PPP2R2B	0.0234	0.0137
TEK	0.0262	0.0060
KALRN	0.0289	0.0109
PRKG1	0.0310	0.0070
KSR2	0.0103	0.0022
COLGALT2	0.0076	0.0009
MEIS1	0.0117	0.0020
SHISA9	0.0096	0.0006
ZKSCAN4	0.0055	0.0069
PTPRG	0.0151	0.0021
NKAPL	0.0055	0.0043
CTNNA3	0.0124	0.0024
PDE4B	0.02	0.0037
HFE	0.0186	0.0121
MSR1	0.0248	0.0082
CSMD1	0.0138	0.0058
COMT	0.0454	0.0125
APBA1	0.0248	0.0044
IMMP2L	0.0124	0.0047
ELAVL4	0.0165	0.0051
LRRTM4	0.0062	0.0006
CDH13	0.0110	0.0023

ZNF804A	0.0151	0.0048
PBRM1	0.0096	0.0026
LRRN2	0.0028	0.0009
TEP1	0.0062	0.0050
STXBP5L	0.0124	0.0074
FHIT	0.0165	0.0044
SYNGAP1	0.0193	0.0013
ZSCAN31	0.0034	0.0003
TENM4	0.0076	0.0017
ABCB1	0.0310	0.009
PLCL1	0.0028	0.0002
RBFOX1	0.0351	0.0209
FSTL5	0.0048	0.0019
SORCS3	0.0055	0.0045
NKAIN2	0.0041	0.0003
GLIS3	0.0069	0.0031
NXN	0.0083	0.0017
MAGI2	0.0145	0.0044
MEGF10	0.0034	0.0003
MPP6	0.0055	0.0003
TSPAN18	0.0028	0.0004
FRMD4B	0.0021	0.0002
MTHFD1L	0.0103	0.0006
TMTC1	0.0034	0.0001
LIN28B	0.0034	0.0012
UXS1	0.0048	0.0064
BICC1	0.0055	0.0083
ATXN7L1	0.0048	0.0019
EYS	0.0069	0.0024
GRAMD1B	0.0028	0.0027
TSPAN2	0.0048	0.0018
ENOX1	0.0014	0
TMEM132D	0.0048	0.0055
CR1	0.0124	0.0004
PCNX	0.0014	0.0001

Figure 2.5 shows the distribution of connectivity parameters of overlapping proteins. Even in the overlapping part of the network, the average Betweenness centrality remains relatively low and only a few nodes, like FYN and GRIA1, possess a much higher connectivity

than other nodes. The distribution of Betweenness follows the same pattern as the whole network suggesting that even though 90 targets are found overlapped between psychosis and AD, only a few of them are the "bridges" for the transferring of information.

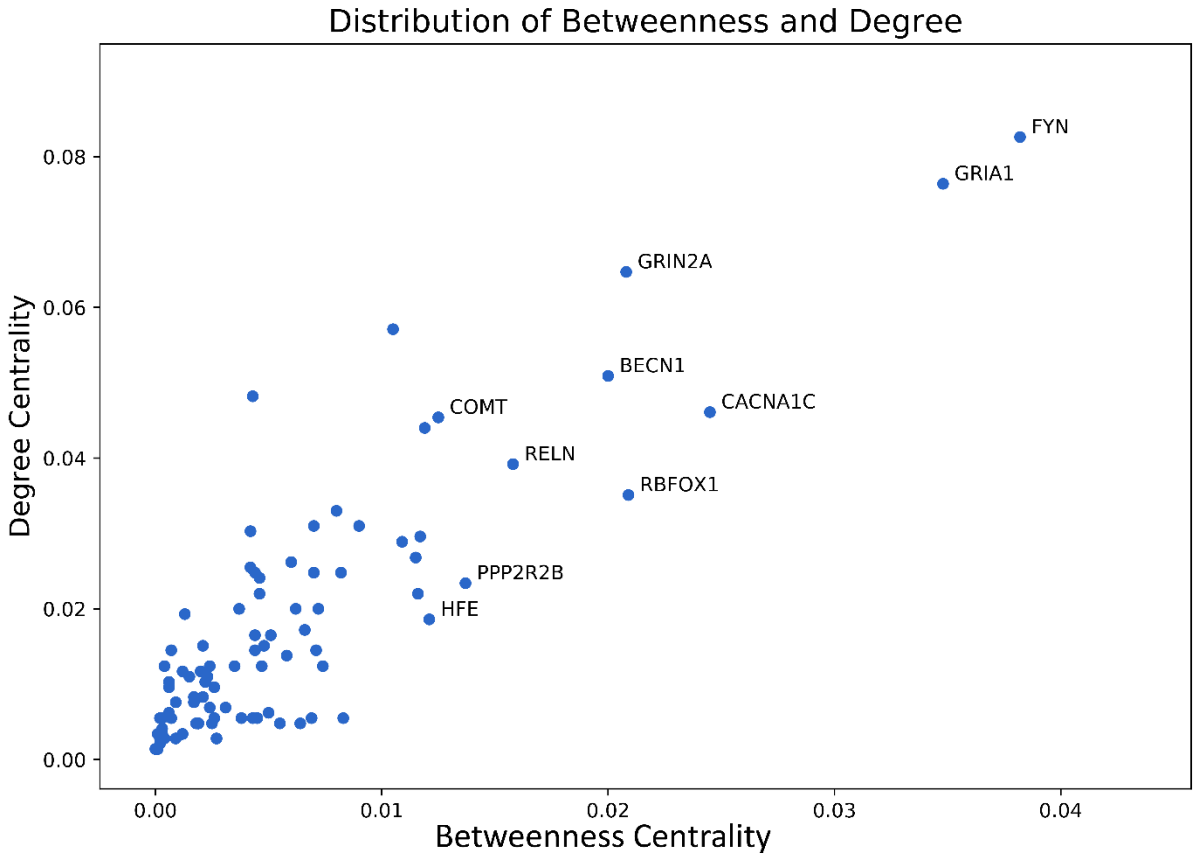

Figure 2.5 Distribution of Degree centrality and Betweenness centrality of overlapping proteins between AD network and psychosis network. FYN and GRIA1, as members of the top 10 targets, possess a far larger Degree centrality and Betweenness centrality among the overlapping proteins. Figure generated with matplotlib (https://matplotlib.org/) version 3.1.3[225].

2.1.3.4 Exploration of Vitamin D's beneficial effect through a triple-focusing approach

In our previously published paper, Vitamin D was identified as a promising medication with a significant association with decreased occurrences and delayed onset of AD+P[195]. Therefore, we examined the relationship between the Vitamin D network and the AD-psychosis

combined network. In total, 89 targets and 344 PPIs were collected in the Vitamin D network (**Table 2.7**). Among the 89 proteins, twenty-one are shared with the AD-psychosis combined network. Net influence parameters are calculated for these 21 targets and sorted by their Betweenness centrality values (**Table 2.8**).

Table 2.7 Characteristics of Vitamin D network

Network Name	Node Number	Edge Number	Average Degree Centrality	Average Betweenness Centrality
Vitamin D	89	344	0.0869	0.018

Table 2.8 Overview of top net-influencers ranked by betweenness values for overlapping proteins (named by their genes) between AD-psychosis combined network and Vitamin D network

Gene Name	Degree Centrality	Betweenness Centrality
CACNA1C	0.0461	0.0245
COMT	0.0454	0.0125
NOTCH4	0.02	0.0072
DRD3	0.0482	0.0043
CD36	0.022	0.0024
EGR1	0.0619	0.0022
CCL2	0.0867	0.0018
DLX5	0.0062	0.0010
CYP1A1	0.0227	0.0008
A2M	0.0358	0.0006
VDR	0.0282	0.0006
TGFB2	0.0296	0.0006
TIMP3	0.0268	0.0006
CD14	0.0227	0.0006
CYP19A1	0.0296	0.0004
NME1	0.0227	0.0003
HSD11B1	0.0131	0.0002
MMP12	0.0227	0.0002
AMBRA1	0.0055	0.0002
ALOX15	0.0117	0.0001
GIG25	0.0145	0.0001

After sorting by the Betweenness centrality, CACNA1C, COMT, NOTCH4 and DRD3 are ranked as the top four proteins. Their positions in the overlapping part of the combined network allow them to function more as a bridge to link different components of the network, which also suggests a therapeutic potential for AD+P. Therefore, these four proteins gained our special interest. One interesting thing is, when we look back at **Figure 2.1**, these four targets fell into the middle distribution of values for Degree centrality and Betweenness centrality, which matched the conclusion that drug targets tend to be positioned at the transition area in a biological network[205].

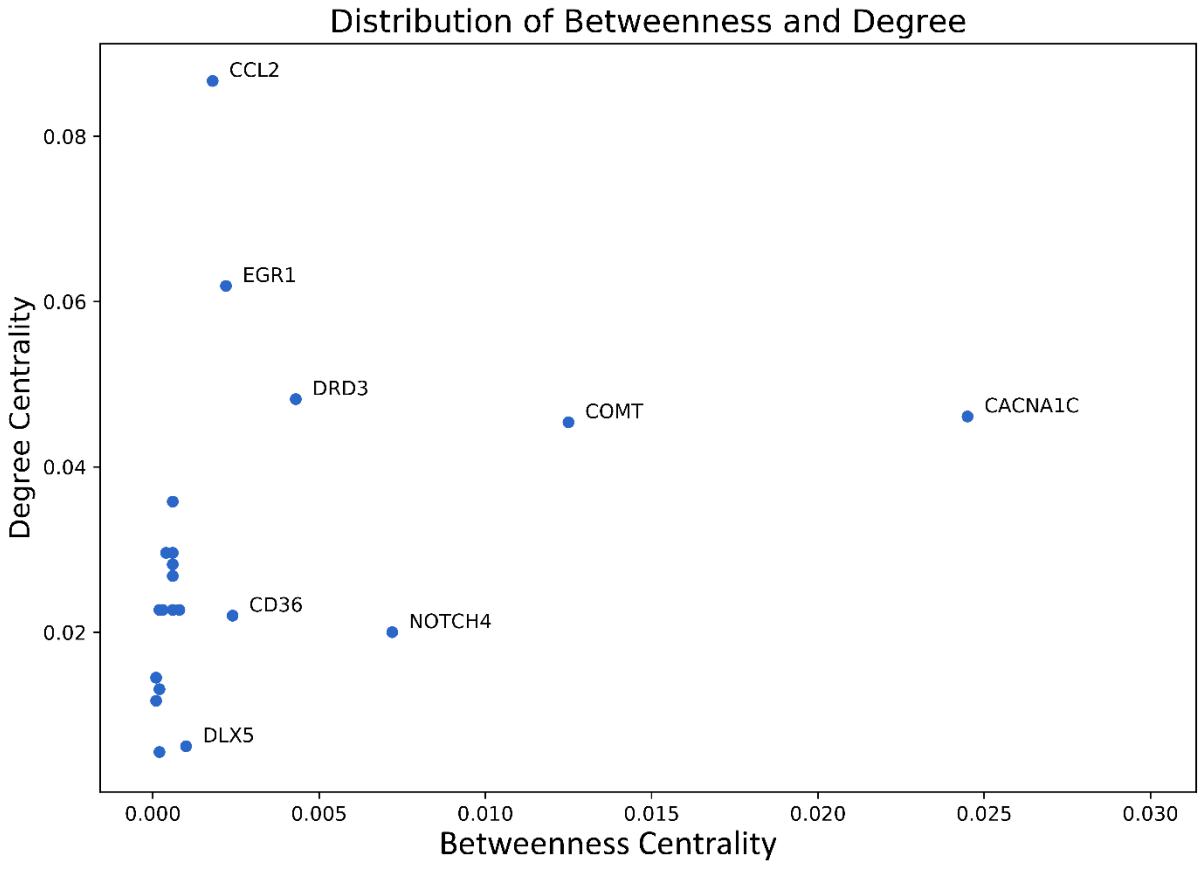

Figure 2.6 Distribution of Degree centrality and Betweenness centrality of overlapping proteins between AD-psychosis combined network and Vitamin D network. Overlapping proteins between AD-psychosis combined network and Vitamin D network follows the same pattern as the whole networks. Some nodes like

CACNA1C, COMT, NOTCH4 and DRD3 possess much higher Betweenness centrality values than the average value of the network. Figure generated with matplotlib (https://matplotlib.org/) version 3.1.3[225].

Figure 6 shows the distribution of connectivity parameters of overlapping proteins between AD-psychosis combined network and Vitamin D network. The 21 overlapped nodes followed the distribution of the whole combined network and revealed several proteins with outstanding Betweenness centrality values. These proteins will tend to act as the "bridges" in communicating AD-, psychosis-related network and Vitamin D perturbed network and thus the potential explanation of the beneficial effects of Vitamin D against AD+P.

2.1.4 4. Conclusion and Discussion

The network analysis based on the protein-protein interaction data have presented us four potential targets encoded by genes *CACNA1C, NOTCH4, COMT and DRD3* that may account for the beneficial effects of Vitamin D against AD+P. These four potential targets all possess high enough connectivity to alter the crosstalk between AD and psychosis. In addition, variants in *CACNA1C, NOTCH4* and *COMT* had been reported to be associated with schizophrenia in GWAS studies[226; 227; 228]. Among them, the function of *CACNA1C, NOTCH4* and *COMT* were reported to be closely associated with calcium homeostasis [229; 230; 231; 232; 233; 234; 235] which can be further associated with Vitamin D's effect. Similarly, after the activation of DRD3 by dopamine, the Gβγ complex is released and can interact directly with voltage-gated calcium channels[236; 237]. Except for NOTCH4, all are targeted by marketed drugs for different indications. Interestingly, DRD3 is one of the primary targets for antipsychotics in treating psychotic symptoms in schizophrenia or other neurological disorders[238; 239]. Alternative splicing of DRD3 in the transcription process may result in encoding different

isoforms that are functionally impaired[240]. Although limited, there is some support for targeting DRD3 in the treatment of AD+P[241; 242]. However, verification of DRD3 or the other of these four potential targets for AD+P will require additional studies.

The beneficial effect of Vitamin D against AD have been widely reported. The protective effect of Vitamin D can be executed by reducing the oxidative and nitrosative damage caused by elevated levels of nitric oxide (NO) and inducible nitric oxide synthase (iNOS) in nerve cells[243]. There is also evidence suggesting an overlap between the disruptions of vitamin D pathways with amyloid pathology which can partially explain the protective role of Vitamin D in AD[244]. However, this study is the first study to explore the mechanism of Vitamin D's beneficial effect against AD+P. In this study, the triple-focusing approach we use can help minimize the bias caused by the amount of studies and restrain our scope at Vitamin D related potential targets.

There are limitations in this study. The PPI networks were constructed based on the protein-protein interaction data extracted from databases, thus they are limited by the amount and availability of data in the databases. Also, there is no direction information attached with most PPIs which means our PPI networks are undirected. Therefore, centrality measures can be biased by the direction information in actual situations.

In this study, various approaches of network analysis are incorporated with systems pharmacology to provide a systematic overview on the crosstalk among AD, psychosis and Vitamin D at the molecular level. The triple-focusing network method helps us explore the designated mechanisms for Vitamin D's effects on AD+P and a potential explanation is provided: Vitamin D regulates several genes encoding proteins that play critical roles in the overlapping part of the AD-psychosis combined network, which allow them maximally influence

the signaling and information transfer process. In other words, proteins with high net-influence that localize at the triple-overlapped part of the AD, psychosis and Vitamin D network, like *CACNA1C*, *COMT*, *NOTCH4* and *DRD3*, possess the ability to play an important role in the crosstalk among AD and psychosis by delivering Vitamin D's effect to the transiting hub connecting the AD network and psychosis network. Thus, the four identified potential targets can be crucial in explaining Vitamin D's beneficial effect against AD+P. To conclude, the results from this study provided a possible explanation of the beneficial effect of Vitamin D against AD+P and presented a new direction for drug development with four potential novel targets.

2.2 Efficacy Difference of Antipsychotics in Alzheimer's Disease and Schizophrenia: Explained with Network Efficiency Analysis

2.2.1 Background and Significance

Psychotics symptoms may present in in many neurodegenerative disorders (e.g., Lewy body dementia), as well as other psychiatric disorders (Bipolar with psychosis). However, the prototypic psychotic disorder is schizophrenia, and the efficacy of the vast majority of antipsychotic medications for treating psychosis was established in treating this disorder. This is why we are currently using medications indicated for schizophrenia to treat AD+P[11; 12; 13].

However, recent studies using polygenic risk scores (PRS) — a score for an individual that is calculated by summing risk alleles carried weighted by their effect size — to evaluate shared genetic liability with schizophrenia (albeit with overlapping samples) produced variable

results, and it promoted that the associations for delusions and hallucinations might be different in schizophrenia and AD+P[245].

Therefore, a more systematic examination of the psychotic symptoms in AD and their mechanistic similarities with schizophrenia symptoms is required. One could expect that the presence of a schizophrenia-like phenotype would confer a greater response to antipsychotics, and alternative treatment techniques could be sought for symptom profiles that are less consistent with schizophrenia.

In 2021, Dr. Robert Sweet and his group published the first GWAS results for AD+P[46]. The results were generated from a Discovery Cohort of 2876 AD subjects with (N=1761) or without psychosis (N=1115) and replicated in another cohort of 2194 AD subjects with (N=734) or without psychosis (N=1460). Curiously, this study showed that increasing schizophrenia polygenic risk score was associated with reduced risk of psychosis in AD (coefficient = -0.159, p value = 5.5e−18).

Studies of familial aggregation of AD+P have established that the risk for AD+P is, in part, genetically mediated[246]. However, despite some symptomatic overlap, AD+P is not genetically correlated with schizophrenia risk[247]. Therefore, identifying the similarities and differences between their associated genetic mechanisms may provide a mechanism for understanding the reduced benefit for antipsychotics in AD+P. In this study, we applied network analytic approaches incorporating transcriptomic and genomic data from AD+P and schizophrenia subjects to accomplish this goal.

2.2.2 Material and Methods

2.2.2.1 Dataset collection

Differentially expressed genes (DEGs) and Genome Wide Association Studies (GWAS) data for AD+P were used to construct the protein-protein interaction (PPI) networks[247; 248]. GWAS data for schizophrenia was collected from GWAS Catalog (https://www.ebi.ac.uk/GWAS/home), and DEGs were collected from the CommondMind Consortium[249] and the psychENCODE cohorts[250]. Genes from GWAS and DEGs are pooled together to create an inclusive gene set that will represent the genetic characteristics of the disease as accurate as possible and these genes were used to construct the networks, respectively. These gene names were then converted to protein names by batch search function in the UniProt database[229].

Information about antipsychotics and their targets was extracted from DrugBank (https://www.drugbank.ca/)[186]. The pharmacological action label of a drug provides information about whether binding to a target contributes to the pharmacological effects. For example, Olanzapine can bind to multiple neuronal receptors, including the dopamine receptors D1, D2, D3 and D4, the serotonin receptors 5HT2A, 5HT2C, 5HT3 and 5HT6, the alpha-1 adrenergic receptor, the histamine receptor H1 and multiple muscarinic receptors. However, Olanzapine's antagonistic effect towards the DRD2 receptor in the mesolimbic pathway and serotonin receptor 5HT2A in the frontal cortex are considered as keys in achieving its pharmacological effects[251]. Thus DRD2 receptor and 5HT2A are labeled with known pharmacological action while other receptors are labeled as unknown pharmacological action. Antipsychotics are evaluated as two sub-groups: first generation antipsychotics (FGAs) and

second generation antipsychotics (SGAs). First generation antipsychotics are D2 antagonists and second generation antipsychotics are 5HT2A/D2 antagonists [252].

PPI data was collected from STRING (https://string-db.org/)[214]. The PPI networks were constructed and analyzed with python package networkx (https://networkx.github.io/)[216]. The interaction network was shown in the molecular action view with the medium confidence level (> 0.4) which is commonly used in other literatures[217]. AD+P-related proteins and schizophrenia-related proteins were joined with targets of antipsychotics to construct two disease-targets networks, i.e., AD+P-targets PPI network (**AD+P network**) and schizophrenia-targets PPI network (**SCZ network**). We also included the proteins which served to bridge between disease module proteins and target module proteins in our disease-targets networks, even if these bridging proteins were not included in the disease or target protein sets originally.

In addition, pathway enrichment analysis was conducted through the ingenuity pathway analysis (IPA, QIAGEN Inc., https://www.qiagenbioinformatics.com/products/ingenuitypathway-analysis).

2.2.2.2 Network Analysis

Network analysis approaches are incorporated to explain the modest efficacy of antipsychotics in AD+P. We hypothesized that the structure differences between protein-protein interaction (PPI) networks of AD+P and schizophrenia might result in different signaling transduction initiated by the antipsychotics and thus affect the drug efficacy. Network approaches have been used in predicting and identifying the disease genes in multiple studies and some of the results have been verified[203; 204]. While the drug actions depend on the complex signaling transduction networks of cells or the complicated profile of drug potency and selectivity, the effect of a drug can be evaluated by the impact of the drug's targets toward a PPI

network representing as a disease[253]. Therefore, we built two PPI networks for AD+P and schizophrenia respectively with targets of antipsychotics added to evaluate the effects of antipsychotics in these two diseases in a quantitative manner.

The efficiency of nodes in the network was calculated based on the built-in algorithm of networkx[216; 254]. Efficiency is a measurement of how efficiently a node can exchange information with other parts of the network[254], which has been widely used in neurology research. We calculated several graph-based metrics to characterize their topological organization at different levels, including global small-world network efficiency (global efficiency, local efficiency) and nodal efficiency. The definition and calculation methods are briefly introduced below in the context of an undirected network *G* with *N* nodes and *K* edges.

2.2.2.3 Small-world Efficiency

Efficiency is a biologically relevant metric to describe biological signaling networks from the perspective of parallel information propagation and exchange[255]. It can be calculated at both global and local levels. Mathematically, global efficiency is defined in equation 2-1:

Equation 2-1

$$E_{glob}(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{d_{ij}}$$

where *N* is the total node number of the connected network *G*, d_{ij} is the shortest distance between *i* and *j* in *G* which is the smallest sum of edge lengths throughout all possible paths from node *i* to node *j* in this study. Global efficiency mainly measures the ability of parallel information transmission over the network[256].

The local efficiency of *G* is defined in equation 2-2:

Equation 2-2

$$E_{loc}(G) = \frac{1}{N}\sum_{i \in G} E_{glob}(G_i)$$

where N is the total node number of the connected network G, $E_{glob(G_i)}$ is the global efficiency of G_i, the subgraph contained all the neighbors of node i (i.e., nodes linked directly to node i). The result of local efficiency measures the fault tolerance of the network, indicating the capability of information exchange for each subgraph when the index node is eliminated[256].

A small-world network is a type of mathematical graph in which most nodes are not neighbors of one another, but the neighbors of any given node are likely to be neighbors of each other and most nodes can be reached from every other node by a small number of hops or steps[257]. Small-world coefficient (sigma) is proposed to be used to accurately distinguish small-world network (sigma >1)[258; 259; 260]. The calculation of sigma is defined as follows[261]:

Equation 2-3

$$\mathrm{C} = \frac{1}{N}\sum_{i \in G} Ci$$

$$\sigma = \frac{C}{Cr} \Big/ \frac{L}{Lr}$$

where N is the total node number of the connected network G, C and L are respectively the average clustering coefficient and average shortest path length of G, Cr and Lr are respectively the average clustering coefficient and average shortest path length of an equivalent random graph.

2.2.2.4 Nodal Efficiency

To measure the efficiency of a certain node, two major factors should be taken into consideration: 1) the number of nodes that can be connected to this node through edges in the

network(N); 2) the distance between other connected nodes and the node of interest(d_{ij}). Therefore, nodal efficiency of a node (i) is calculated as follow:

Equation 2-4

$$\mathrm{E(i)} = \frac{1}{N-1}\sum_{i \neq j \in G} \frac{1}{d_{ij}}$$

where N is the total node number of the connected network G, d_{ij} is the shortest distance between i and j in G. Nodal efficiency measures the ability of information propagation between a node and the remaining nodes in the network. A node with high nodal efficiency indicates high capability of information transmission with other nodes and can therefore be categorized as a hub.

2.2.2.5 Method Validation

Before we apply network analysis methods to antipsychotics in AD+P and SCZ networks, we want to validate its ability to detect the efficiency differences of drugs in diseases. To accomplish that, we use first generation antipsychotics (FGAs), second generation antipsychotics (SGAs) and benzodiazepines as example to test their efficacy differences in schizophrenia. Abundant studies have shown that in schizophrenia, SGAs have slightly higher efficacy than FGAs[262], and both FGAs and SGAs are significantly more efficacious than benzodiazepines[263]. Therefore, SGAs and FGAs will serve as positive examples and benzodiazepines will serve as negative example.

We use these 3 categories of medications to evaluated 6 network metrics: Degree centrality[264], Closeness centrality[264], Betweenness centrality[264], Clustering coefficient[265] and Integrated Value of Influence (IVI)[266]. Networks were processed and analyzed with python package networkx[216].

2.2.2.6 Statistical Analysis

Nodal efficiency values are calculated as described above for antipsychotics' targets in AD+P network and SCZ network respectively. Therefore, the efficiency of targets in two networks can be compared in pairs to evaluate the difference of drug effects in two diseases. After testing, the distribution of efficiency values do not follow normal distribution, as such Wilcoxon signed-rank test[267] is used to determine whether two dependent samples were selected from populations having the same distribution.

2.2.2.7 Binding Affinity-Based Weight Calculation

Binding affinity values, including Ki, EC50, IC50 and AC50, for drugs against their targets were extracted from ChEMBL (https://www.ebi.ac.uk/chembl/)[268] with provided web service. Those values were used as the measurement for the strength of drug-target interactions.

To align the effect of different binding affinity measurements, a relative strength (RS) for each target is calculated for different measurements as follow:

Equation 2-5

$$\mathrm{RS} = Binding_{reference} / Binding_{drug-target}$$

where $\mathrm{Binding}_{\mathrm{reference}}$ is the minimum binding values for achieved by any antipsychotics with a certain target and $\mathrm{Binding}_{\mathrm{drug\text{-}target}}$ is the binding value for a certain antipsychotics and target pair.

2.2.2.8 Standard Protocol Approvals, Registrations, and Patient Consents

The genetic data used in this study is contributed by Dr. Robert Sweet's lab[247] and the collection of clinical data and genetic samples were approved by each source programs' local Institutional Review Board or Medical Ethics Committee, as appropriate.

2.2.3 Results

2.2.3.1 Network Analysis Method Validation

To validate the network analysis methods, a schizophrenia network with FGAs' targets and a schizophrenia network with SGAs' targets were constructed. In addition, to account for psychoactive effects not specifically targeting psychosis, a schizophrenia network with benzodiazepines' targets was constructed. To present a baseline for the network metrics, we constructed a random network with same node number with the largest networks among the three networks (1462 nodes). Six network metrics for drug targets in these 3 networks were calculated by implemented methods in networkx[269]. The efficiency value of each medication was considered equal to the sum of all its targets' efficiency values. Kruskal-Wallis H-test was performed to test if there are statistical differences among the 3 categories in 3 networks because the distributions of calculated metrics do not follow normal distribution[270]. As shown in **Table 2.9**, all metrics showed significant among the 3 groups and the distributions are showed in the box plot (**Figure 2.7**).

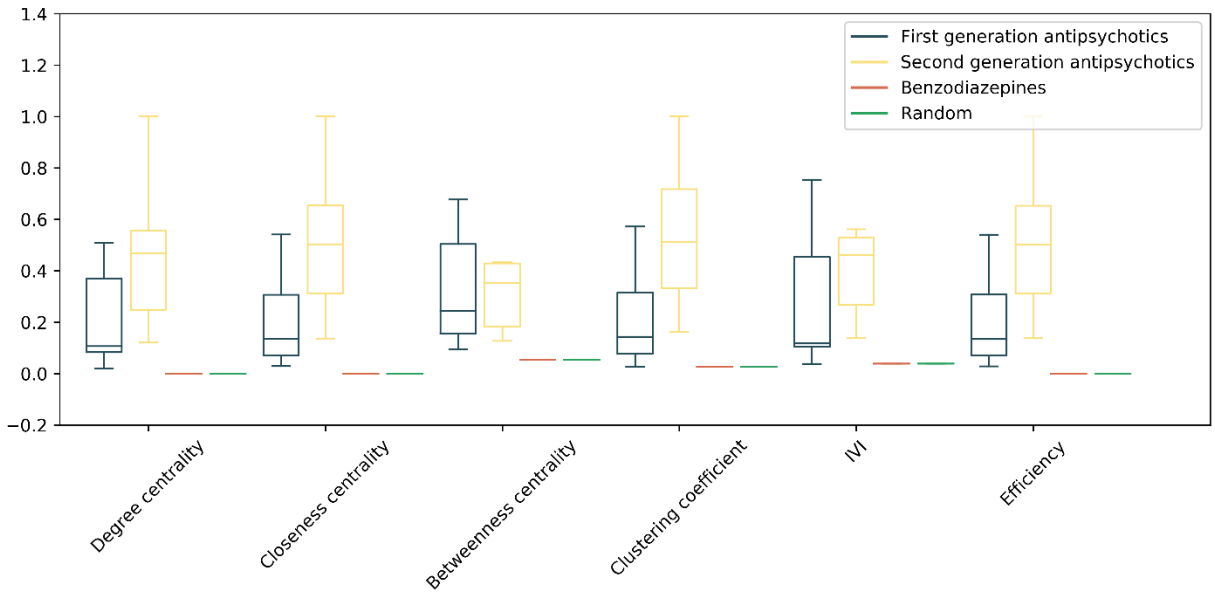

Figure 2.7 Network metrics values distribution of 3 categories of medications in 3 networks with random network. The box plot showed that first and second generation antipsychotics showed comparable values in the schizophrenia network while benzodiazepines showed values close to 0. This result is in accordance with literature reports.

Table 2.9 Statistical tests results for 6 network metrics

Network Metrics	H	P value
Degree centrality	51.5	1.36×10-09
Closeness centrality	55.1	2.90×10-10
Betweenness centrality	49.3	1.38×10-09
Clustering coefficient	50.4	2.37×10-09
IVI	45.6	3.64×10-08
Efficiency	55.1	2.90×10-10

H: Test statistic for Kruskal-Wallis H-test[270].

As shown in the box plot (**Figure 2.9**), FGAs and SGAs showed comparable values in 3 networks while SGAs are slightly higher than FGAs. On the other hand, benzodiazepines'

network metrics values are close to 0 indicating they may not possess any potential beneficial effect against schizophrenia, in accordance with the conclusion drawn by extensive evidence-based research[263]. The random network showed close to 0 topological features compared to FGAs and SGAs while benzodiazepines showed similar metrics with random networks.

Based on the results discussed above, the network analysis method is not only capable of distinguishing effective and non-effective treatments (antipsychotics and benzodiazepines), but is also able to differentiate the minor difference between sub-class of medications (FGAs and SGAs).

2.2.3.2 Overview of Genetic Variations Associated with AD+P and Schizophrenia

From the sources mentioned above, 975 genome wide associated variations and 1077 differentially expressed genes were identified for AD+P relative to AD-P, and 1668 genome wide associated variations and 464 differentially expressed genes were identified for schizophrenia based on their significance. In total, 2013 and 2123 unique genes were identified associated with AD+P and schizophrenia, respectively. Meanwhile, 75 targets were collected form DrugBank for 21 antipsychotics that are commonly used in clinical settings, including 10 first generation antipsychotics (FGAs) and 11 second generation antipsychotics (SGAs) (Full list of drugs in supplementary material ST1).

Consistent with prior observations that AD+P and schizophrenia have limited shared genetic risk[247], only 148 genes overlapped between these disorders. Antipsychotics' pharmacological targets are also jointly presented in **Figure 2.8**, 17 antipsychotics target genes overlap with AD+P and 9 overlap with schizophrenia.

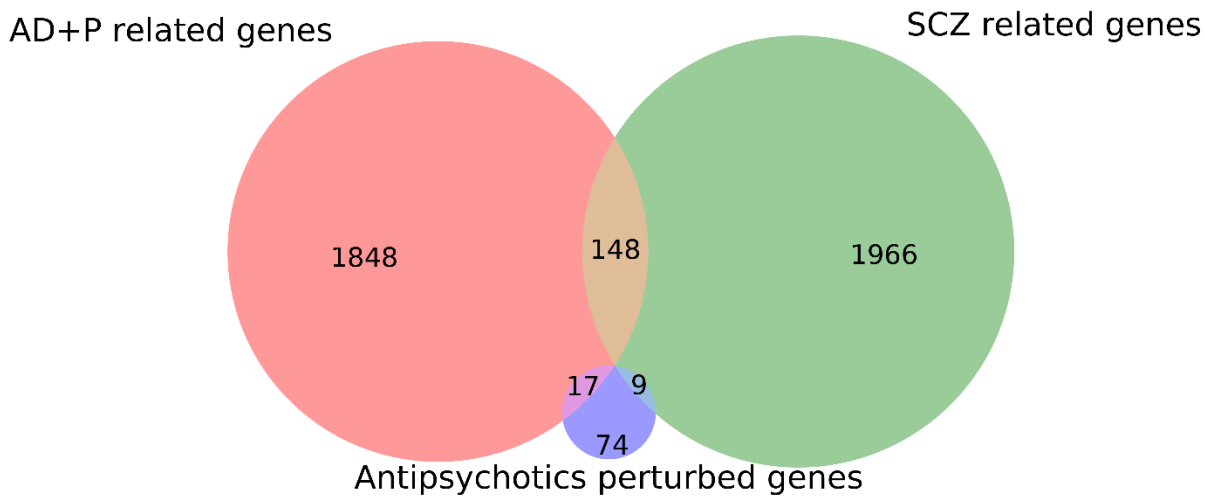

Figure 2.8 The Venn diagram of AD+P and schizophrenia-related genes and antipsychotics' targets genes.

2.2.3.3 Parameter Descriptions of AD+P Network and SCZ Network

Target-disease networks for AD+P and schizophrenia are constructed based on the previously identified genes and target proteins for antipsychotics. Only genes having interactions with other genes within the network are included. The basic information for the two networks can be found in **Table 2.10**. Both networks are confirmed as small-world networks, with small-world coefficient (sigma) > 1 as we described in method section. The AD+P network showed higher global and local efficiency reflecting its larger network size.

Table 2.10 General network parameters for AD+P and SCZ networks

	Node Number	Global Efficiency	Local Efficiency	Small-world Coefficient (sigma)
AD+P network	1512	0.289	0.262	5.825
SCZ network	1249	0.297	0.270	7.518

2.2.3.4 Decreased Drug Efficacy in AD+P Compared to Schizophrenia

2.2.3.4.1 Decreased Efficacy for Major Antipsychotics' Targets in AD+P Compared to Schizophrenia

Nodal efficiency values were calculated for antipsychotics' targets to evaluate for differences between AD+P and schizophrenia. Efficiency values for the major targets of antipsychotics are shown in **Table 2.11.** Antipsychotic targets in the AD+P network showed a significantly lower efficiency than those in SCZ network (P = 0.0039).

Table 2.11 Efficiency of major antipsychotics' targets in AD+P and schizophrenia

Targets	Efficiency in AD+P network	Efficiency in SCZ network
DRD2	0.363	0.381
HTR2A	0.337	0.371
DRD1	0.332	0.347
ADRA1A	0.29	0.319
DRD3	0.315	0.33
HRH1	0.309	0.311
HTR1A	0.304	0.355
DRD4	0.307	0.337
Paired Wilcoxon Test	W = 36, P = 0.0039	

DRD2: Dopamine Receptor D2; DRD3: Dopamine Receptor D3; DRD4: Dopamine Receptor D4; HTR1A: 5-Hydroxytryptamine Receptor 1A; HTR2A: 5-Hydroxytryptamine Receptor 2A; ADRA1A: Adrenoceptor Alpha 1A; HRH1: Histamine Receptor H1.

The results in **Table 2.11** indicate that these targets have less impact in AD+P compared with schizophrenia when perturbed with the same strength and can be interpreted as the antipsychotics targeting these proteins may therefore be less efficacious in AD+P than in schizophrenia.

2.2.3.4.2 Decreased Efficiency for Antipsychotics in AD+P Compared to Schizophrenia

To acquire a more direct measure, efficiencies of antipsychotics were calculated in the networks. The efficiency value of each antipsychotic was considered equal to the sum of all its targets' efficiency. FGAs and SGAs were calculated separately in two sets of networks. As **Table 2.12** showed, all SGAs have lower efficiency values in AD+P network compared to schizophrenia network ($P < 0.001$). This might indicate that these SGAs would have lower activity in AD+P than in schizophrenia.

Table 2.12 Network efficiency of second generation antipsychotics calculated from AD+P network and schizophrenia network

Drugs	Efficiency in AD+P network	Efficiency in SCZ network
Paliperidone	1.694	1.831
Brexpiprazole	1.643	1.799
Sertindole	1.337	1.45
Aripiprazole	0.726	0.779
Clozapine	0.726	0.779
Iloperidone	0.726	0.779
Olanzapine	0.726	0.779
Quetiapine	0.726	0.779
Risperidone	0.726	0.779
Ziprasidone	0.726	0.779
Lurasidone	0.352	0.386
Pimavanserin	0.352	0.386
Paired Wilcoxon Test	$W = 78, P < 0.001$	

As for FGAs, their efficiency values were also calculated in AD+P network and SCZ network. Similar to SGAs, FGAs showed significantly lower values in AD+P than in schizophrenia (**Table 2.13**) ($P < 0.001$). In addition, some FGAs, like Chlorpromazine and Thioridazine, showed higher or comparable efficiency values with the top SGAs. These results can be interpreted in two ways: 1) the results are biased by the amount of study because more studies are done on FGAs so they have more known targets included in the database; 2) Since the

network analysis method can only evaluate drug efficiency, it is possible that Chlorpromazine may have comparable or better efficacy than some SGAs. As a matter of effect, Chlorpromazine is reliable for its efficacy and one of the most tested first-generation antipsychotic drugs. It has been used as a 'gold standard' to compare the efficacy of older and newer antipsychotic drugs. According to randomized controlled trials (RCTs) that compared chlorpromazine with any other atypical antipsychotic drugs for schizophrenia, it showed comparable efficiency with olanzapine, risperidone, and quetiapine[271]. Therefore, it is reasonable that Chlorpromazine showed comparable efficiency values with the SGAs.

Table 2.13 Efficiency of FGAs in AD+P and schizophrenia

Drugs	Efficiency in AD+P network	Efficiency in SCZ network
Chlorpromazine	2.311	2.489
Thioridazine	1.675	1.798
Thiothixene	1.068	1.138
Trifluoperazine	0.961	1.037
Loxapine	0.726	0.779
Mesoridazine	0.726	0.779
Fluphenazine	0.716	0.752
Perphenazine	0.716	0.752
Haloperidol	0.699	0.755
Molindone	0.374	0.393
Paired Wilcoxon Test	$W = 55, P < 0.001$	

2.2.3.4.3 Weighted Efficiency Based on Binding Affinity Values for Antipsychotics in AD+P and Schizophrenia

In the above sections, the efficiency values for antipsychotics were calculated as a simple sum of efficiency values from all its targets. A simple sum method is accurate under the assumption that all antipsychotics can impact their targets at the same strength. In order to

acquire a more accurate result, binding affinity-weighted efficiency values were calculated for 12 antipsychotics for which data was available and 21 drug-target pairs were included. All the targets included in this section have been validated for pharmacological effects. Weights and weighted efficiencies were calculated as:

$$\mathrm{W}_{drug-target} = 10 \times S \quad (7)$$

$$\mathrm{E}_{weighted}(\mathrm{i}) = \mathrm{W}_{drug-target} * \mathrm{E}(\mathrm{i}) \quad (8)$$

where $W_{drug\text{-}target}$ is the weight for a drug-target pair, S is the relative strength of the binding affinity between drug and target. Therefore, weighted efficiency for an antipsychotic can be calculated by the sum of all $E_{weighted}$ from its targets. As we can see in **Table 2.14**, the values of weighted efficiency for antipsychotics are significantly lower in AD+P network (P=0.0016) than in the SCZ network.

Table 2.14 Weighted efficiency of selected antipsychotics in AD+P and schizophrenia

Drugs	Weighted efficiency in AD+P network	Weighted efficiency in SCZ network
Sertindole	8.535	9.357
Fluphenazine	4.016	4.206
Ziprasidone	3.619	3.964
Risperidone	0.967	1.058
Lurasidone	0.799	0.877
Loxapine	0.681	0.746
Clozapine	0.194	0.212
Olanzapine	0.177	0.193
Pimavanserin	0.092	0.101
Aripiprazole	0.025	0.026
Haloperidol	0.014	0.014
Quetiapine	0.008	0.009
Paired Wilcoxon Test	W = 66, P = 0.0016	

2.2.3.5 Different Pathways Involved in AD+P and Schizophrenia Networks

To get a more detailed look at how AD+P network and SCZ network react toward antipsychotics, several of the most commonly used SGAs (Aripiprazole, Olanzapine, Quetiapine, and Risperidone) were selected as examples to explore the pathways that are affected when administrated. All SGAs share DRD2 and HTR2A as major targets. The signaling pathways represented by first and second neighbors of these two targets are of great value since information flow attenuates quickly in networks[272]. As illustrated in **Figure 2.9**, DRD2 and HTR2A share some common target genes but there is a significant portion of their down-stream genes that do not overlap with each other. Taken together the pathways represented by these different genes can be the keys to answer why SGAs are less efficient in AD+P than in schizophrenia.

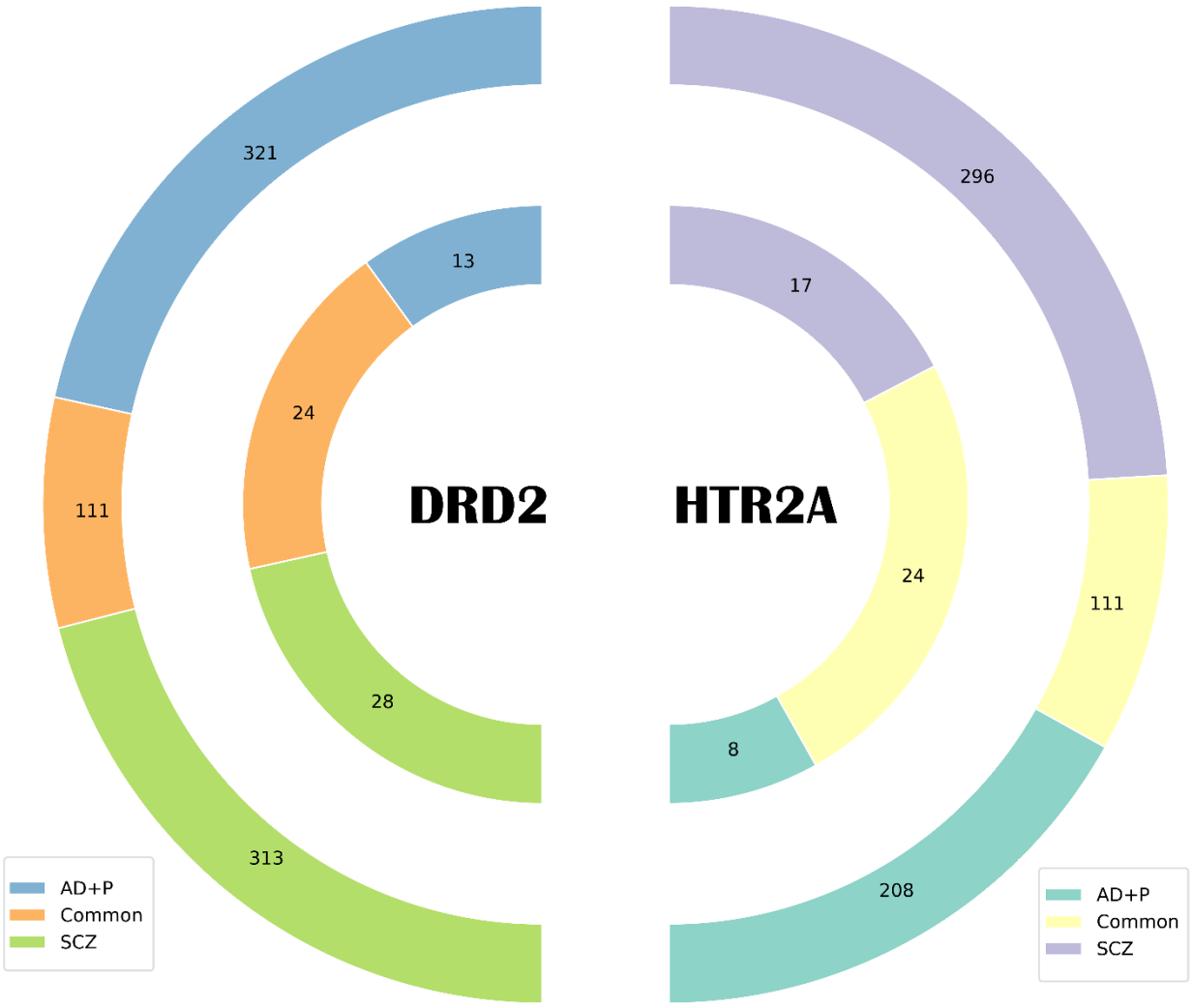

Figure 2.9 Comparison of first and second neighbors of DRD2 and HTR2A in AD+P network and SCZ network. First-neighbor proteins in the AD+P network and the SCZ networks are shown in the inner circle and second-neighbor proteins in the outer circle. If a perturbation is applied to DRD2 and HTR2A, different reactions can be expected from the AD+P and SCZ network due to these connection differences, resulting in different signaling pathways that are affected.

Furthermore, pathway enrichment analysis was conducted for the genes that are exclusively affected in the AD+P network by DRD2 and HTR2A (489 genes for DRD2, 233 for HTR2A). The ten most significant pathways are showed in **Table 2.15**. The pathways identified in **Table 2.15** are exclusive for the AD+P network. From the pathways identified in **Table 2.15,**

we can see a strong association with inflammation reactions in human tissue and can also see an association with autophagy and apoptosis. In addition, RNA synthesis and cell cycle related pathways are highlighted in our results. Since HTR2A and DRD2 are the most targeted drug targets for antipsychotics and are involved in multiple biological processes that play important roles in human neurological activities, the difference of their downstream effect can tell us a lot in how they respond differently to the medications. Just like we showed in **Table 2.15**, the results of the pathway analysis suggest a tighter bound between AD+P and neuro inflammation.

Table 2.15 Overrepresented unique pathways of AD+P

Targets	Pathways	P value*	Overlaps with dataset	Genes overlapped with datasets
DRD2	Cell Cycle: G2/M DNA Damage Checkpoint Regulation	5.62E-09	0.22	ATR,BORA,BTRC,CDK1,PPM1D,PRKDC,RPS6KA1,WEE1,YWHAB,YWHAH,YWHAZ
	tRNA Charging	1.48E-05	0.179	AARS2,DARS1,EPRS1,GARS1,LARS2,RARS2,SARS1
	Role of PKR in Interferon Induction and Antiviral Response	3.16E-05	0.0882	ATF3,CASP8,HSP90AB1,IFIH1,IFNGR1,IRF1,JAK1,MAPK3,MARCO,NLRP3,STAT1,TRAF6
	Cyclins and Cell Cycle Regulation	6.76E-05	0.107	ATR,BTRC,CDK1,HDAC4,PPP2CA,RB1,RBL2,TGFB3,WEE1
	Systemic Lupus Erythematosus In B Cell Signaling Pathway	8.71E-05	0.0614	BCL2L1,CALML5,CD40,CTNNB1,IFIH1,IFNGR1,JAK1,LYN,MAPK3,PIK3CB,PIK3R5,PTPN11,RASGRP3,SHE,STAT1,TGFB3,TRAF6
	IL-22 Signaling	1.23E-04	0.208	IL10RB,IL22RA2,JAK1,MAPK3,STAT1
	Urate Biosynthesis/Inosine 5'-phosphate Degradation	1.62E-04	0.286	IMPDH1,IMPDH2,NT5C,NT5C1A

	EIF2 Signaling	2.88E-04	0.0628	ACTA2,ATF3,IGF1R,MAPK3,PIK3CB,PIK3R5,PPP1CB,RPL13A,RPL21,RPL32,RPL6,RPS14,RPS6,RPS8
	Phosphatidylcholine Biosynthesis I	3.02E-04	0.429	CHKA,PCYT1A,PCYT1B
	Wnt/β-Catenin Signaling	3.09E-04	0.0694	BMPR2,BTRC,CDH2,CSNK1A1,CTNNB1,PIN1,PPP2CA,SOX2,SOX9,TGFB3,TLE1,WNT8B
HTR2A	IL-22 Signaling	3.55E-06	0.208	IL10RB,IL22RA2,JAK1,MAPK3,STAT1
	Systemic Lupus Erythematosus In B Cell Signaling Pathway	2.51E-05	0.0433	CALML5,CD40,CTNNB1,FGR,IFNGR1,JAK1,LYN,MAPK3,PIK3CB,PIK3R5,PTPN11,STAT1
	Phosphatidylcholine Biosynthesis I	3.39E-05	0.429	CHKA,PCYT1A,PCYT1B
	Rac Signaling	7.76E-05	0.058	IQGAP1,ITGAL,MAPK3,PIK3CB,PIK3R5,PIP4K2A,PIP4K2C,PTK2B
	Role of JAK family kinases in IL-6-type Cytokine Signaling	1.05E-04	0.16	JAK1,MAPK3,PTPN11,STAT1
	JAK/Stat Signaling	1.78E-04	0.0732	JAK1,MAPK3,PIK3CB,PIK3R5,PTPN11,STAT1
	RhoA Signaling	2.57E-04	0.0565	ARHGEF1,GNA12,IGF1R,PIP4K2A,PIP4K2C,PPP1CB,PTK2B
	RhoGDI Signaling	3.31E-04	0.0419	ARHGEF1,GNA11,GNA12,GNB4,GRIP1,ITGAL,PIP4K2A,PIP4K2C,RHOU
	Interferon Signaling	4.47E-04	0.111	IFNGR1,IRF1,JAK1,STAT1
	Trans, trans-farnesyl Diphosphate Biosynthesis	9.77E-04	0.4	FDPS,IDI1

2.2.4 Discussion and Conclusion

In this study, we elucidated the underlying sources of efficacy differences of antipsychotics in AD+P and schizophrenia by using network efficiency and pathway analysis on the combined disease-target network. The major targets of antipsychotics are found to have lower efficiency in the AD+P network than in the SCZ network, indicating that the antipsychotics interacting with these targets may modulate AD+P less efficiently. Finally, we identified pathways that are engaged by antipsychotics are involved in AD+P, but not in schizophrenia, and which may contribute to the limited efficacy or enhanced toxicity of these medications in AD+P.

Multiple meta-analysis studies have reported the modest efficacy of antipsychotics in treating AD+P[11; 273]. In those studies, Aripiprazole, Olanzapine, Quetiapine, and Risperidone were most extensively studied. Though no broad and strong effect was reported across trials and measurements, individual agents showed some efficacy on specific outcome measures. In our results, Aripiprazole, Olanzapine, Quetiapine, and Risperidone are ranked 4^{st}, 7^{th}, 8^{th} and 9^{th} in **Table 2.12** as the leading part in SGAs, but changed to 10^{th}, 8^{th}, 12^{th} and 4^{th} when weight is applied in **Table 2.14**. The ranks of these 4 SGAs accord well with other evidence of efficacy where Risperidone > Aripiprazole > Olanzapine > Quetiapine is suggested[274]. Risperidone, as the only antipsychotics licensed for the treatment of aggression (in Europe but not in the USA), has been reported by multiple studies including clinical trials as having beneficial effects against AD+P[274; 275].

While not many antipsychotics have been tested against AD+P, the results of this study can also help nominate antipsychotics that may possess higher efficacy in treating AD+P that should be tested in the future. Three antipsychotics, Sertindole, Fluphenazine, and Ziprasidone,

showed a higher weighted efficacy than Risperidone which is the most effective and commonly used SGA in clinic. Fluphenazine is a first-generation antipsychotic, and is uncommonly used in AD+P due to extrapyramidal side effects, and thus we can rule it out from the list[276]. Sertindole and Ziprasidone provide better efficacy and safety profiles in treating psychosis[277; 278]. Previous studies also showed that Sertindole has better performance than other SGAs on cognitive functions such as processing speed and executive function while Ziprasidone has better performance on composite score, executive function and processing speed, working memory, and memory and verbal learning[279]. The benefits of Sertindole and Ziprasidone can be supported by their higher affinity for 5HT6, 5HT2C and 5HT3 receptors[280; 281]. Therefore, we believe that Sertindole and Ziprasidone are promising candidates for antipsychotics with improved efficacy in treating AD+P.

The results of pathway enrichment analysis showed that when similar perturbation is applied to major antipsychotics' targets, like DRD2 and HTR2A, AD+P patients will have different reactions compared to schizophrenia patients because the pathways influenced by the perturbation are different under the two disease conditions. The identified overrepresented pathways shown in **Table 2.15** indicate a special role of neuroinflammation and RNA synthesis in AD+P compared with schizophrenia. Furthermore, many studies have reported the role of neuroinflammation in the pathogenesis of AD[282; 283] and schizophrenia[284]. The results of our study showed that though inflammation processes are involved in both conditions, different responses can be activated in AD+P and schizophrenia patients and can be used to explain the causal relationship between activated systemic inflammation and the development of neuropsychiatric symptoms in AD[282]. The accordance between the existing reports and results of our pathway enrichment analysis provided additional supports for the rationale of our results.

The different pathways affected in AD+P and schizophrenia may also have a peripheral effect that can increase the risks of adverse events for antipsychotics in AD+P patients. Infection, for example, is a common adverse event reported by multiple studies[285; 286] and can be associated with the interruption of immune systems caused by antipsychotics[287; 288].

The size difference of the AD+P and SCZ networks may raise bias. To minimize the possible bias, multiple approaches were considered, including filtering nodes and edges with certain threshold to fix the size or density of networks. However, these approaches may introduce new bias to this study by enforcing noise in a smaller network and ignoring significant connections in a larger network. Furthermore, since these two networks are categorized as small-world networks, their connectivity parameters are not sensitive to changes in network size by definition[257]. Additionally, a study conducted by BCM Van Wijk indicated that the average path length and cluster coefficient in a small-world network are not sensitive to change of node number or to average degree[289]. Since our efficiencies are calculated based on the path lengths in different networks, we believe it's safe to say the bias caused by network size in our measurement is minimized and acceptable.

Collectively, the results of this study not only provide a possible explanation for antipsychotics' modest efficacy in AD+P but can also help nominate antipsychotics that may possess higher efficacy in treating AD+P which should be tested in further studies, Sertindole and Ziprasidone. In addition, the methodology we used in this study showed great accordance with other reported pieces of evidence by incorporating bioactivity data with network analysis approaches. This methodology can be applied to provide support and guidance in drug repurposing or treatment optimization studies.

3.0 Identification and Validation of Alternative Treatment Options for AD+P with Quantitative Systems Pharmacology Methods

3.1 Drug Repurposing Screening for Alternative Treatment for AD+P

3.1.1 Background and Significance

Repurposing medications indicated for other behavioral and psychological symptoms to treat AD+P is believed as the next most possible solution. Since every failed clinical trial of a new molecular entity (NME) consumes substantial time and resources, repurposing drugs already approved by the Food and Drug Administration (FDA) for a different indication is less expensive, involves already defined possible toxicities, and can have a higher success rate (30%) as compared to the development of an NME[290]. There are some reports about repurposing antidepressants, like citalopram and perphenazine[291; 292], as treatments for AD+P. However, without a systematic understanding of the mechanism of antidepressants' beneficial effects, it is hard to optimize the balance between efficacy and tolerability. A systemic and comprehensive review of the association between antidepressants and AD+P is needed to provide support and guidance for drug repurposing studies in AD+P.

Based on our previous studies, antipsychotics do not engage the underlying biology of AD+P, and therefore their modest effectiveness is unsurprising[293]. In order to identify safe and effective treatments for AD+P, it is essential to have a comprehensive understanding of the underlying biology of AD+P. A recent study reported that the heritability of psychosis in AD is estimated to be 61%, thus suggesting a strong association between AD+P and genetic

variations[294]. Another study performed a large genome-wide meta-analysis on 12,317 AD subjects with or without psychosis[247]. The authors reported that AD + P was not significantly genetically correlated with schizophrenia, but it was negatively correlated with bipolar disorder and positively correlated with depression.

Gene expression signature (GES) is a set of comprehensive gene expression profiles that can reveal the difference between stimulated and normal cell states[295]. This concept is initially created for distinguishing different type of diffuse large B-cell lymphoma[295] and current applications of GES analysis are still fruitful in cancer-related areas for disease genotype classification and outcome predictions[296; 297; 298; 299; 300; 301; 302; 303; 304; 305; 306; 307; 308; 309; 310; 311; 312; 313; 314; 315]. For example, Ramaswamy, S. et al. had created a GES database for diagnosing and categorizing the tumour type with an accuracy rate of 78%[296]. Wright, G. et al. developed a Bayesian rule-based algorithm to classify diffuse large B cell lymphoma into two subgroups which have a significant difference in 5-yr survival rate[297]. Chen, H.-Y. et al. selected a five-gene signature which serves as an independent predictor of relapse and survival rate in non-small-cell lung cancer[301]. On the other hand, theoretically, the GES method can reveal the association (or in another word, similarity) between cell stages under disease condition and drug intervention, so it can be utilized as a drug repositioning strategy. Indeed, in recent years some successful cases of application on drug development are also reported[316; 317; 318; 319; 320; 321; 322; 323].

3.1.2 Methods and Material

3.1.2.1 Data collection

For the systems pharmacology study, the postsynaptic density (PSD) proteome was used to build the AD+P network. This proteomic signature was generated by Dr. Sweet's team[324]. To identify medications that may possess beneficial effect against AD+P, information about medications and their targets were extracted from DrugBank (https://www.drugbank.ca/)[186] including medication names, targets of medications and their corresponding actions. Drugs are classified with Drugs' Anatomical Therapeutic Chemical (ATC) Classifications on level 3 were collected from the WHO official website (https://www.whocc.no/atc_ddd_index/). All medications in the "Neurology" category (N) were included.

The desired drug-target action should be the opposite with the DEGs and protein expressions in our dataset. For example, if a gene was upregulated within our datasets, it means that it might be responsible for many of the alterations we observed in AD+P relative to AD-P. Therefore, drugs that antagonize or otherwise inhibit its activity would be predicted to induce a signal that can reverse the expression profile we observed in AD+P, which may lead to beneficial effects.

We extracted the gene expression profile for each drug from Level 5 LINCS L1000 data [325], a collection of gene expression profiles for thousands of perturbagens at a variety of time points, doses, and cell lines (GEO database accession numbers: GSE70138 and GSE92742). The gene expression profiles were included only if they are from drug treatments on a cell line derived from the central nervous system and the drug dose was $\geq$ 1μM. To identify genes that are significantly differentially expressed, the Z scores from multiple tests for a same gene were averaged. An average $|Z|>1$ was considered a significant effect [326].

3.1.2.2 Gene Expression Signature Similarity Calculation

The association between drug and PSD data was quantitatively evaluated with Signed Jaccard Index [327]. The index ranges from +1 to −1, where +1 and −1 indicate the same, or inverse, pattern of two gene sets.

Signed Jaccard Index (SJI), which is based on the Jaccard similarity coefficient[328], was used to compute the similarity between Gene Expression Signature (GES) profiles from a drug and a disease. The Jaccard similarity coefficient is a statistic used to gauge the similarity between different sample sets. It is defined as the size of the intersection divided by the size of the union of two sample sets. The Jaccard similarity coefficient of two given gene sample sets is calculated as follow:

Equation 3-1

$$Jaccard\ Similarity\ Coefficient(G_1, G_2) = \frac{S}{A}$$

G_1 and G_2 stand for two lists of differentially expressed gene sets. And "S" represents the number of same genes between two given gene sets. "A" stands for all the unique genes appeared in the two gene sets. SJI, which combines Jaccard similarity coefficient with gene regulation direction is calculated as follow:

Equation 3-2

$$Signed\ Jaccard\ index(G_1, G_2) = \frac{J\left(G_1^{up}, G_2^{up}\right) + J\left(G_1^{down}, G_2^{down}\right) - J\left(G_1^{up}, G_2^{down}\right) - J\left(G_1^{down}, G_2^{up}\right)}{2}$$

Where J means Jaccard similarity coefficient, G^{up} and G^{down} are up- or down-regulated genes in the given gene set G, respectively. The index is ranging from +1 to -1, where +1 and -1 indicate a completely same pattern and inverse pattern of two gene sets, respectively. And 0 indicates that these two sets have no associations, or the same part is cancelled out by the inverse

part. The reason to use an un-ranked score calculation method (SJI) is to keep in accordance with the same scoring method used in the source database (CREEDS).

3.1.3 Results

132 of 354 neurological medications were found from LINC1000 database. All sub-categories except N04C, Other Anti-Parkinson drugs (only contain Istradefylline), were represented in the results.

Figure 3.1 showed the SJI values of sub-categories of neurological medications. Though parasympathomimetic medications showed the lowest average scores, but this group only contains two drugs which is not sufficient to carry statistical power. Antipsychotics, the current recommended treatment for AD+P, ranked at the fifth place while antidepressants ranked at the third place. Given that the other 3 groups in the top 5 only contains 3 or 4 drugs, antipsychotics and antidepressants are the sub-categories that may possess the most potential against AD+P that have considerable amount of data.

Besides the analysis above on the basis of drug categories, we are also interested in which medications may possess strongest beneficial effect against AD+P. Based on our previous study, the average SJI of indicated drug-disease pairs is −0.00386 with a standard deviation of 0.01794[327]. Therefore, any drugs with SJI lower than -0.004 were considered with potential therapeutic effects.

Table 3.1 Drugs with SJI values smaller than the average value of indicated drug-disease pairs

Drug	Signed Jaccard Index	Drug ATC Code	Drug Category
Amoxapine	-0.0105	N06A	Antidepressants

Sertraline	-0.0103	N06A	Antidepressants
Prochlorperazine	-0.00677	N05A	Antipsychotics
Maprotiline	-0.00676	N06A	Antidepressants
Nefazodone	-0.00645	N06A	Antidepressants
Tianeptine	-0.00609	N06A	Antidepressants
Modafinil	-0.00589	N06B	Psychostimulants, Agents Used for ADHD and Nootropics
Aripiprazole	-0.00581	N05A	Antipsychotics
Diazepam	-0.00580	N05B	Anxiolytics
Duloxetine	-0.00543	N06A	Antidepressants
Neostigmine	-0.00489	N07A	Parasympathomimetics
Mirtazapine	-0.00488	N06A	Antidepressants
Phenelzine	-0.00480	N06A	Antidepressants
Methylphenidate	-0.00456	N06B	Psychostimulants, Agents Used for ADHD and Nootropics
Bupropion	-0.00455	N06A	Antidepressants
Nortriptyline	-0.00435	N06A	Antidepressants
Zolmitriptan	-0.00433	N02C	Antimigraine Preparations
Dosulepin	-0.00427	N06A	Antidepressants

As shown in **Table 3.1**, 18 medications showed smaller SJI values than the average SJI of indicated drug-disease pairs which means that these medications can invoke an opposite gene expression change with AD+P. Among these 18 medications, 11 of them are antidepressants and

2 of them are antipsychotics. The results of this study can be used to further guide drug repurposing studies or future clinical trials.

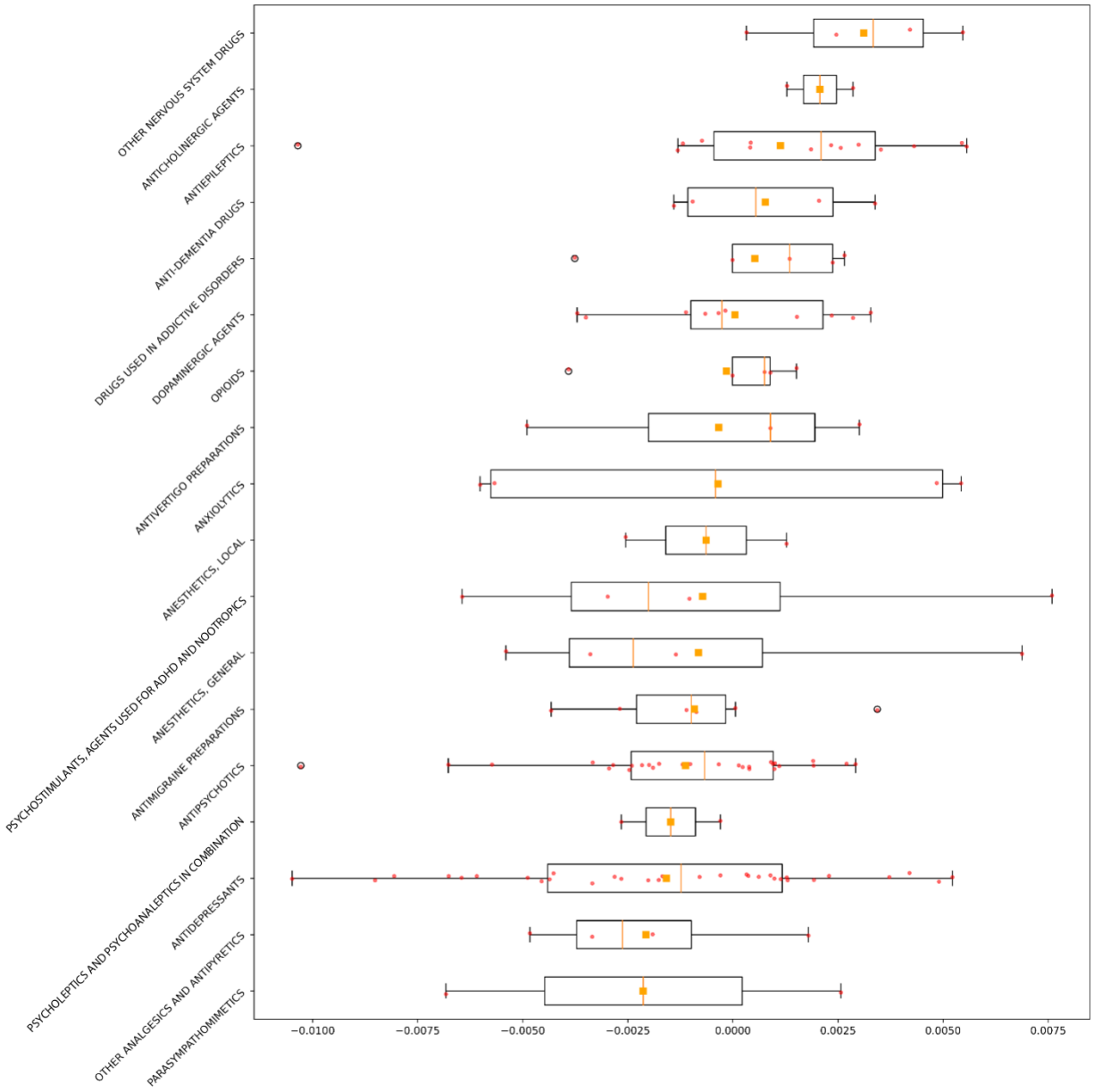

Figure 3.1 Signed Jaccard Index values of differents categories of neurological madications towards AD+P. In this figure, each red dot represent a SJI for a drug, the orange square is the mathmatical mean of this category and the orange line is the median value.

3.1.4 Conclusion and Discussion

It's well recognized that a similar gene expression pattern is supposed to reflect a similar function[329]. We conducted a systemic high throughput screening to explore neurological medications that may possess beneficial effects against AD+P. The results of this study showed high accordance with existing clinical reports and observations[330; 331; 332; 333] that antipsychotics and antidepressants are the two major categories of drugs that are under heated discussion for the treatment of AD+P. The results of this study can not only support clinical decision making on drug selections, but also lead future repurposing studies and potential clinical trials to investigate other therapy alternatives for AD+P.

Several limitations are unavoidable in this investigation. Despite the fact that we limited the DEGs data to within the CNS cell research, only a few cell types (mostly GL1) were examined, which may not reflect the expression variations in different brain areas. In addition, the test dosage is much different from the actual drug exposure in clinical settings, so modeling the actual drug exposure must take into account a great deal more variables. Furthermore, there are various forms of "therapy effect." Some medications may truly cure the disease, while others may only provide symptomatic relief, as such drugs may also create a distinct pattern of GES in comparison to the disease.

3.2 Prediction of Synergetic Effect of Antidepressants and Antipsychotics as A Novel Treatment Option for Psychosis in Alzheimer's Disease

3.2.1 Background and Significance

Based on our previous studies, antipsychotics do not engage the underlying biology of AD+P, and therefore their modest effectiveness is unsurprising[293]. In order to identify safe and effective treatments for AD+P, it is essential to have a comprehensive understanding of the underlying biology of AD+P. A recent study reported that the heritability of psychosis in AD is estimated to be 61%, thus suggesting a strong association between AD+P and genetic variations[294]. Another study performed a large genome-wide meta-analysis on 12,317 AD subjects with or without psychosis[247]. The authors reported that AD + P was not significantly genetically correlated with schizophrenia, but it was negatively correlated with bipolar disorder and positively correlated with depression. These associations provide a biologic rationale for repurposing antidepressant agents as novel treatment options for AD+P in our current study.

To answer if antidepressants are effective in managing neuropsychiatric symptoms in AD patients, nine clinical trials involving 692 patients were conducted. Five of them compared antidepressants with placebo and 4 compared with antipsychotics[291; 334; 335; 336; 337; 338; 339; 340; 341; 342; 343]. However, only two selective serotonin reuptake inhibitors (SSRIs) sertraline (Zoloft) and citalopram (Celexa) were studied and the antipsychotics in the study were typical antipsychotics (haloperidol, perphenazine) while only 1 trial studied an SGA, risperidone. Among the five studies comparing SSRIs with placebo, two of them reported a significant benefit for Citalopram against AD+P[334; 336]. Meanwhile, no significant difference was reported between the efficacy of SSRIs and risperidone. Therefore, testing more antidepressants,

especially other classes of antidepressants such as serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors, may be worthwhile to provide a better understanding of the impact of antidepressants on AD+P.

While antipsychotics and antidepressants both have shown beneficial effects against AD+P, they have different targets which in turn can modulate different biological pathways. Thus, the combination of these drugs can potentially provide multiple advantages like enhanced efficacy, decreased dosage with an equal or increased level of efficacy, and delayed development of drug resistance [344]. Due to the excessive time and cost it takes to clinically test the drug combination effects, exhaustive computational methods can be used to predict drug synergy. By integrating information from drugs and diseases we can obtain a comprehensive picture of the potential synergetic effects of these drug combinations.

To predict potential drug combinations for AD+P, we adopted the methods from Chen, S., et al. [345] and modified them by incorporating differentially expressed genes (DEGs) after drug treatment to minimize the bias caused by module sizes. Based on previous studies, for a drug pair to have a therapeutic effect on a disease, both target modules (green and yellow circles in **Figure 3.2**) of the two drugs must overlap with the disease module (pink circle in **Figure 3.2**)[345]. In addition, the two target modules need to be overlapped with the disease module independently to form a complementary exposure to have synergetic effects with each other as shown in **Figure 3.2**. To be specific, the targets of the two drugs both need to be overlapped with the disease module in the PPI network, but these two target modules can't overlap[345]. Therefore, two network approaches are applied to predict the possible drug combinations for AD+P: (1) network-based separation between targets of two drugs[346]; (2) gene signature-

based proximity between the disease (AD+P) module and the target modules of the two drugs[347].

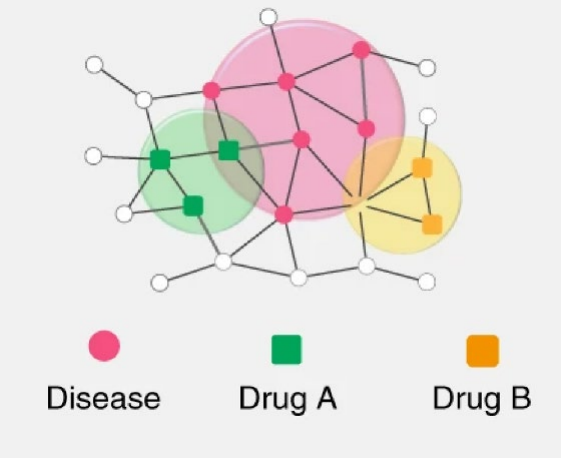

Figure 3.2 Schematic diagram for the network-based complementary exposure relationship between two drug–target modules and one disease module on a drug–drug–disease combination (adopted from Guney, E.; Menche, J.; Vidal, M.; Barábasi, A.-L., Network-based in silico drug efficacy screening. Nature communications 2016, 7 (1), 1-13. [347]). Big red circle: AD+P modules composed of AD+P related proteins/genes (small red rounds). Green and yellow circle: Drug modules composed of drug targets.

The goal of our study is to further identify key combinations of antipsychotics and antidepressants that possess potential synergetic effects against AD+P with the help of our state-of-the-art quantitative systems pharmacology approaches.

3.2.2 Methods and Material

3.2.2.1 Data collection

To systematically evaluate the potential synergetic effect between antipsychotics and antidepressants, the postsynaptic density (PSD) proteome was used to build the AD+P network. This proteomic signature was generated by Dr. Sweet's team[324]. Information about antipsychotics, antidepressants and their targets were extracted from DrugBank

(https://www.drugbank.ca/)[186]. The pharmacological action label of a drug provides information about whether binding to a target contributes to the pharmacological effects. PPI data was collected from STRING (https://string-db.org/)[214]. The PPI networks were constructed and analyzed using the python package networkx (https://networkx.github.io/)[216]. The interaction network was shown in the molecular action view with medium confidence level (> 0.4)[217]. AD+P-related proteins were joined with targets of antipsychotics and antidepressants to construct the disease-target network. In addition, we also included the proteins bridging proteins from disease module and proteins from the target module in our disease-targets networks. Gene signature data were used to calculate the proximity score for drugs and AD+P. The post-treatment gene signature data were obtained from the LINCS L1000 database[348].

3.2.2.2 Prediction of synergetic effect among antipsychotic-antidepressant pairs

3.2.2.2.1 Separation evaluation

The separation score (S_{AB}) of drug modules A and B are calculated for all possible combinations between antipsychotics and antidepressants. The separation score (S_{AB}) of drug modules A and B can be calculated as:

Equation 3-3

$$S_{AB} = < d_{AB} > - \frac{< d_{AA} > + < d_{BB} >}{2}$$

where $<d_{AA}>$, $<d_{BB}>$ and $<d_{AB}>$, are the mean shortest distance for genes within each module. It compares the mean shortest distance between the targets of each drug. For better understanding, if $S_{AB} < 0$, it means that the targets in the two drug modules are in the same

network neighborhood which is not separated; if $S_{AB} \geqslant 0$, it means that the two drug modules are topologically separated from each other. We filter the combinations based on their ability to achieve complementary exposure with the AD+P module.

3.2.2.2.2 Proximity evaluation

Level 5 LINCS L1000 data, a collection of gene expression profiles for thousands of perturbagens at a variety of time points, doses, and cell lines, were downloaded from the GEO database (accession numbers: GSE70138 and GSE92742). Gene expression profiles were included only if they are tested on a cell line of central nervous systems and their dose should be beyond 1 uM. To identify genes that are significantly differentially expressed in the data, their Z scores from multiple tests were averaged and if their $|Z|>1$, the genes are considered as significant for a drug[349].

The association between the drug and AD+P was quantitatively evaluated with Signed Jaccard Index(SJI)[327]. The index ranges from +1 to −1, where +1 and −1 indicate a same pattern and an inverse pattern of two identical gene sets, respectively. Zero indicates that the two sets have no overlap, or the positive and negative correlations cancel out. The detailed calculation methods were described in section 3.1.2.2.

3.2.3 Results

In total, 21 antipsychotics and 17 antidepressants commonly used in the clinic are included in our study along with 75 targets for antipsychotics and 32 targets for antidepressants. The PPI network was built with 240 AD+P proteins, targets for antipsychotics and antipsychotics. A PPI network with 321 nodes and 1,363 edges was generated. A total of 357

pairs of antipsychotics and antidepressants are evaluated in the network and their separation scores are calculated as shown in **supplementary figure (SF2)**.

We found that some antidepressants showed great separation (Vortioxetine, Vilazodone, Mirtazapine, Maprotiline), and most drugs pairs showed a separation score above 0 (blue). This suggests an existing difference in the mechanism which can be the key condition to the synergetic effect in the combinational therapy.

To evaluate the proximity between AD+P and medications, 148 and 78 eligible expression profiles for antipsychotics and antidepressants were collected based on the inclusion criteria described earlier. Signed Jaccard scores were calculated between them and AD+P protein expressions.

Post-treatment gene expression data for 16 antipsychotics and 13 antidepressants were exacted, and their Signed Jaccard scores were calculated accordingly and are shown in the tables below.

Table 3.2 Signed Jaccard Index values of antipsychotics and antidepressants with AD+P

Antipsychotics	Drug perturbed genes	Overlap	Same	Inverse	SJI value
Aripiprazole	3384	71	9	59	-0.01028
Thioridazine	7670	135	47	78	-0.00573
Clozapine	3801	57	13	38	-0.00334
Iloperidone	4868	78	31	39	-0.00285
Thiothixene	2109	39	23	16	-0.00247
Trifluoperazine	6286	96	21	57	-0.0024

Haloperidol	1083	22	9	12	-0.00216
Risperidone	1460	15	5	9	-0.00199
Fluphenazine	1180	20	9	11	-0.0019
Perphenazine	4758	87	23	64	-0.00176
Lurasidone	1480	17	6	9	-0.00034
Quetiapine	831	6	3	3	0.000232
Loxapine	2488	34	18	14	0.000386
Mesoridazine	2334	28	10	18	0.000986
Ziprasidone	3995	65	28	33	0.001916
Olanzapine	1013	15	11	4	0.002919
Antidepressants	**Drug gene**	**Overlap**	**Same**	**Inverse**	**Proximity Score**
Duloxetine	4710	81	17	58	-0.00851
Sertraline	5696	104	19	83	-0.00806
Maprotiline	1271	25	8	17	-0.00676
Nefazodone	1393	34	13	21	-0.00645
Mirtazapine	3105	56	26	30	-0.00488
Bupropion	600	14	5	9	-0.00455
Trazodone	3002	49	31	18	-0.00335
Paroxetine	5379	103	34	69	-0.00202
Fluoxetine	2776	47	18	24	-0.0003
Escitalopram	1977	30	14	16	0.000369

Fluvoxamine	4572	79	31	38	0.000892
Citalopram	2083	30	10	19	0.003719
Venlafaxine	1023	11	10	1	0.005222

To comprehensively evaluate the potential for these drug combinations, separation scores and proximity scores were normalized to a [-1, 1] interval and combined. A combined score was calculated for every drug pair by subtracting two proximity scores of the drugs from their separation score. The combined scores for drug pairs are shown in the heatmap below (**Figure 3.3**).

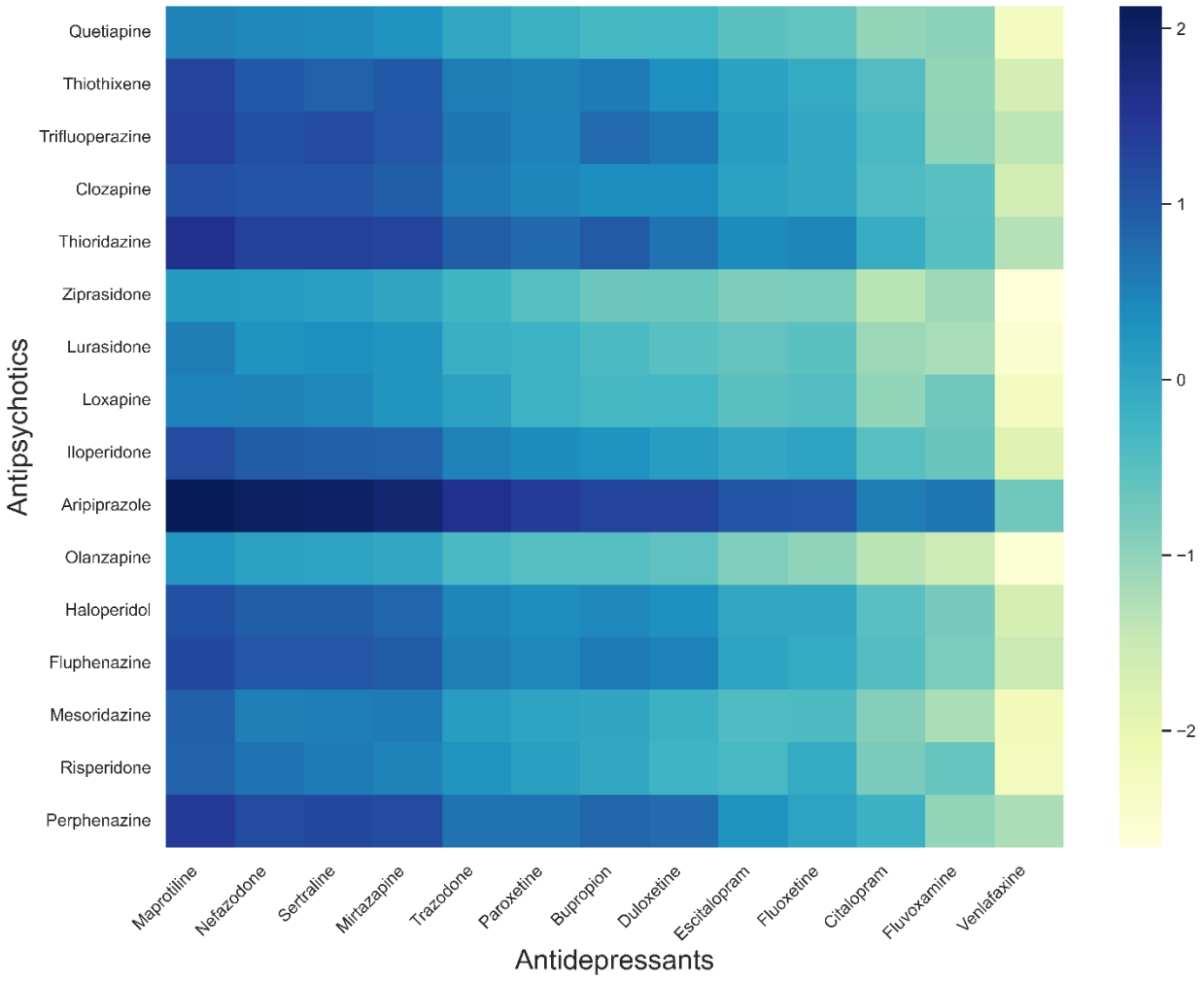

Figure 3.3 Combined scores for antipsychotics and antidepressants combinations. Though most drug pairs showed a combined score around 0, some drugs do show promising scores across the board including Aripiprazole and Thioridazine.

As shown in **Figure 3.3**, most drug pairs showed a combined score around 0 which indicate that the synergistic effect between antipsychotics and antidepressants may not be easily achieved within the two drug categories. However, some drugs showed promising results through the panel like Aripiprazole and Thioridazine. For drug combinations that may possess beneficial synergistic effect, they must meet the following criteria: 1) The separation score

between two drugs > 0; 2) The proximity scores of the two drugs <0. **Table 3.3** summarized the drug combinations that met the criteria.

Table 3.3 Antidepressants and antipsychotics combinations with highest combined scores

Antipsychotics	Antidepressants	Antipsychotics Proximity Score	Antidepressants Proximity Score	Separation score	Combined Score
Aripiprazole	Maprotiline	-1	-0.745	0.382	2.13
Aripiprazole	Nefazodone	-1	-0.7	0.345	2.05
Aripiprazole	Sertraline	-1	-0.934	0.0545	1.99
Aripiprazole	Mirtazapine	-1	-0.472	0.418	1.89
Thioridazine	Maprotiline	-0.311	-0.745	0.564	1.62
Aripiprazole	Trazodone	-1	-0.248	0.364	1.62
Aripiprazole	Paroxetine	-1	-0.0542	0.364	1.42
Thioridazine	Nefazodone	-0.311	-0.7	0.3277	1.34
Thioridazine	Sertraline	-0.311	-0.934	0.0909	1.34
Thioridazine	Mirtazapine	-0.311	-0.472	0.527	1.31
Thioridazine	Bupropion	-0.311	-0.423	0.236	0.971
Thioridazine	Trazodone	-0.311	-0.248	0.382	0.941
Thioridazine	Paroxetine	-0.311	-0.0542	0.418	0.783

Among the nominated drug combinations, Aripiprazole is the only SGAs and is also the most recommended treatment options for AD+P. As a matter of fact, the combination of Aripiprazole and Sertraline has already been tested in clinical trials and showed superior efficacy

in treating major depressive disorders (MDD) with no reports of safety concerns[350]. However, none of these drug pairs have been tested for AD+P in clinical trials. As a matter of fact, no combination drug therapy has ever been tested for AD+P at present.

3.2.4 Discussion and Conclusion

In this study, we applied a state-of-the-art systems pharmacology technique to explore the potential synergetic effect of combining antipsychotics and antidepressants in treating AD+P. This study incorporated different data types including protein expressions, post-treatment gene expressions and protein-protein interaction networks. Our results indicate that the combination of antipsychotics and antidepressants may be a more efficient treatment option for AD+P and provided informative insights for drug pairing choices for future therapies.

In order to provide mechanistic support for our observations and identify the most potent drug combinations for treating AD+P, we took advantage of multiple categories of data including PPI network, post-treatment gene expression profiles to quantitatively evaluate the potential synergistic effect of antipsychotics and antidepressants. Our analysis yielded several pairs of drugs that may possess better synergistic effects in treating AD+P. As shown in **Table 6**, four antipsychotics: Aripiprazole, Thioridazine, were reported, and seven antidepressants: Sertraline, Maprotiline, Nefazodone, Mirtazapine, Trazodone, Paroxetine and Bupropion were mentioned. Between the 2 antipsychotics, Thioridazine is first-generation antipsychotic and it was withdrawn worldwide in 2005 due to its association with cardiac arrythmias[351]. For Aripiprazole, it has been reported with significant better efficacy in AD patients against psychological symptoms[352] which further consolidate our conclusions. For the 7 antidepressants, Nefazodone is discontinued on 2004 because of its association with drug-

induced hepatic injuries[353]. For the rest 6 antidepressants, they belong to 4 classes. Sertraline, Trazodone, Paroxetine are selective serotonin reuptake inhibitors (SSRI) which is the most used antidepressant class[354]. Maprotiline is a tetracyclic antidepressant with similar pharmacological properties to tricyclic antidepressants (TCAs), it can inhibit neuronal norepinephrine reuptake, possesses some anticholinergic activity, and does not affect monoamine oxidase activity[355]. Mirtazapine is a tetracyclic piperazino-azepine antidepressant with its effect can be observed as early as 1 week after beginning therapy[356], it has also been reported to be efficacious in the off-label management of various other conditions. It may improve the symptoms of neurological disorders, reverse weight loss caused by medical conditions, improve sleep, and prevent nausea and vomiting after surgery[357]. Bupropion is a norepinephrine/dopamine-reuptake inhibitor (NDRI) antidepressant, and it is a unique option for the treatment of MDD as it lacks any clinically relevant serotonergic effects, typical of other mood medications, or any effects on histamine or adrenaline receptors[358; 359]. As for combination therapy consisting of antipsychotics and antidepressants, though they were never tested specifically for AD or AD+P, multiple studies have tested their safety and efficacy profile against other disorders. For example, a meta-analysis consisting of eight randomized, placebo-controlled studies reported that antidepressant-antipsychotic cotreatment was superior to monotherapy with either drug class in the acute treatment of psychotic depression[360] and another study reported that adding SGAs to antidepressants yielded highly significant superiority in treating MDD, too[361]. In that study, Aripiprazole, Olanzapine, Risperidone, and Ziprasidone were found to be more effective than other SGAs[361] .

The result of our study aims to provide a comprehensive and quantitative overview of the underlying relationship among antipsychotics, antidepressants, and AD+P. Our results supported

the efficacy of antipsychotics and suggested the most promising antidepressants such as Sertraline and Maprotiline, can be added as supplementary treatment. In addition, since they are all marketed drugs and some of their combinations are already tested by clinical trials for other indications, safety profile will not be a major concern when proposing their long-term usage as an alternative treatment option for AD patients.

4.0 Identification and Validation of Potential Alternative Treatments for AD+P with Real-World Data

4.1 Use of Antidepressants in AD Patients is Associated with Decreased Mortality

4.1.1 Background and Significance

In previous study (section 3.1), we found that antipsychotics and antidepressants are the two categories of medications that possess the highest potential in treating AD+P. In our further systematic pharmacology study (section 3.2), we found that the combination of antipsychotics and antidepressants may be able to induce a synergetic effect against AD+P. Though the beneficial effect of antidepressants in managing neuropsychiatric symptoms in AD patients have been reported in nine clinical trials involving 692 patients[291; 334; 335; 336; 337; 338; 339; 340; 341; 342; 343], only two selective serotonin reuptake inhibitors (SSRIs) sertraline (Zoloft) and citalopram (Celexa) were studied and the antipsychotics in the study were typical antipsychotics (haloperidol, perphenazine) while only 1 trial studied an SGA, risperidone. Among the five studies comparing SSRIs with placebo, two of them reported a significant benefit for Citalopram against AD+P, also no significant difference was reported between the efficacy of SSRIs and risperidone. Therefore, testing more antidepressants, especially other classes of antidepressants such as serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors, may be worthwhile to provide a better understanding of the impact of antidepressants on AD+P.

4.1.2 Methods and Material

4.1.2.1 Data source

To explore the beneficial effect of the combination therapy of antipsychotics and antidepressants, we examined the data from January 2004 to October 2019 from the Neptune system at the University of Pittsburgh Medical Center (UPMC), which manages the use of patient EMRs from the UPMC health system for research purposes (rio.pitt.edu/services)[362]. The database includes demographic information, diagnoses, encounters, medication prescriptions, prescription fill history, and laboratory tests. AD patients were identified using ICD9/10 codes (331.0, G30.0, G30.1, G30.9) and the onset of psychosis were defined by ICD9/10 codes (780.1, F06.0, R44.2, R44.1, R44.3, R44.0, 298.8, F22, F23, F28, F29, 293.82, 298.9, 290.11, 293, 290.3) based on the suggestions from UPMC clinicians.

4.1.2.2 Data preparation

We included patients who met the following inclusion criteria: 1) Patient had an AD diagnosis; 2) Patients did not take antidepressants nor antipsychotics one year prior to the diagnosis of AD. Nine comorbidities, including MDD (major depressive disorder), stroke, COPD (chronic obstructive pulmonary disease), ASCVD (atherosclerotic cardiovascular disease), T2DM (type 2 diabetes), HTN (hypertension), CKD (chronic kidney disease), HF (heart failure) and cancer, were considered as confounders in our survival analysis (ICD codes listed in supplementary material) [363; 364]. The time origin for each patient in the survival analysis is the first AD diagnosis date and time to all-cause death is the outcome. Patients are marked with the above comorbidities if they were diagnosed before the AD diagnosis. Only medications that are prescribed to the same patients more than 2 times with more than 30 days apart were

considered to eliminate short-term usage during hospitalization. The records of patients up to 5 years after the AD diagnosis were used in the analysis.

Time to all-cause death was constructed as the time between the first date of AD diagnosis and death. Patients who were alive by the end of 5 years since AD diagnosis were censored. Survival analysis was performed to evaluate the association between medications and mortality. To accommodate the change of drug usage during the follow-up, we fitted a time-dependent Cox's proportional hazards model[365; 366] with antipsychotic drug effect (yes or no) and antidepressant drug effect (yes or no) as time dependent covariates. Specifically, the 5-year follow-up period was divided into 60 months, and we assumed the drug effect from one prescription will last 2 months which covers 2 intervals in our study. As shown in **Figure 3.4**, if a patient had an antipsychotics prescription in the first month, we consider the patient under drug effect for that month and the month after. If a patient was prescribed both antipsychotics and antidepressants (boxed in **Figure 3.4**), we consider the patient under combinational therapy. The drug effect on one patient may change over time between four statuses: no drug, antipsychotics only, antidepressants only, and the combination. Baseline demographics and comorbidities were also included in the model. Contrasts between different drug groups were performed with hazard ratios and p values reported. The data were analyzed using both R (version 4.1.0) and python (version 3.7.12) packages.

Figure 4.1 Schematic diagram for identifying drug usage status of subjects. In the upper two rows of Figure 1, the sections with 1 indicate that there are antipsychotics/antidepressants prescriptions in that month while 0 means there are no prescriptions for the two kinds of medications. In the lower rows, the sections under 1 are extended for 1 month to reflect the drug effect thus these markers show the time that the subject was under drug effect.

4.1.3 Results

After applying all inclusion criteria to our dataset, 10,206 unique AD patients were included, and their baseline characteristics are shown in **Table 3.4**.

Table 4.1 Baseline characteristics for included AD subjects

Characteristic	Label	Value
Total		10206
Gender, n (%)	Female	6547 (64.1)
	Male	3659 (35.9)
Age, mean (SD)		83.0 (8.3)
Race, n (%)	Black	981 (9.6)
	Others	171 (1.7)

	White	9054 (88.7)
MDD, n (%)	0	7294 (71.5)
	1	2912 (28.5)
Stroke, n (%)	0	8349 (81.8)
	1	1857 (18.2)
COPD, n (%)	0	7838 (76.8)
	1	2368 (23.2)
ASCVD, n (%)	0	7533 (73.8)
	1	2673 (26.2)
T2DM, n (%)	0	7012 (68.7)
	1	3194 (31.3)
HTN, n (%)	0	1853 (18.2)
	1	8353 (81.8)
CKD, n (%)	0	8046 (78.8)
	1	2160 (21.2)
HF, n (%)	0	7659 (75.0)
	1	2547 (25.0)
Cancer, n (%)	0	8125 (79.6)
	1	2081 (20.4)
Psychosis, n (%)	0	9154 (89.7)
	1	1052 (10.3)
AD Medication, n (%)	0	7153 (70.1)
	1	3053 (29.9)

MDD: major depressive disorder, COPD: chronic obstructive pulmonary disease, ASCVD: atherosclerotic cardiovascular disease, T2DM: type 2 diabetes, HTN: hypertension, CKD: chronic kidney disease, HF: heart failure.

4.1.3.1 Use of antipsychotics in AD patients is associated with increased mortality

cPrior literature has reported that the use of antipsychotics is associated with increased mortality in AD patients[285; 367; 368]; we therefore first sought to replicate this finding to

validate the integrity of our methodological approach. The time varying Cox model was conducted with our data to test the significance.

Table 4.2 Multivariate Cox regression analyses of association between antipsychotics and all-cause mortality in AD patients

Covariate	Hazard ratio	Hazard ratio lower 95%	Hazard ratio upper 95%	P value
Antipsychotics vs No antipsychotics	2.47	1.978	3.084	<0.001
Age	1.051	1.047	1.055	<0.001
Gender (Female vs Male)	0.712	0.676	0.751	<0.001
Race (Other vs White)	1.622	1.427	1.841	<0.001
Race (Black vs White)	0.698	0.636	0.767	<0.001
ASCVD	1.136	1.06	1.216	<0.001
CKD	1.304	1.226	1.386	<0.001
COPD	1.175	1.107	1.247	<0.001
Cancer	1.088	1.023	1.157	0.007
HF	1.411	1.33	1.498	<0.001
HTN	1.004	0.934	1.079	0.906
MDD	1.154	1.092	1.22	<0.001
Psychosis	1.192	1.101	1.29	<0.001
Stroke	0.938	0.869	1.011	0.095
T2DM	1.131	1.07	1.195	<0.001
AD Medication	0.907	0.858	0.959	0.001

MDD: major depressive disorder, COPD: chronic obstructive pulmonary disease, ASCVD: atherosclerotic cardiovascular disease, T2DM: type 2 diabetes, HTN: hypertension, CKD: chronic kidney disease, HF: heart failure.

As indicated in **Table 3.5**, antipsychotic usage is significantly associated with increased mortality in AD patients (HR=2.47, p<0.001). The results showed in this table are in accordance with current literature which suggest that our data and methods are valid for further analysis.

4.1.3.2 Survival analysis revealed significant beneficial effect combining antidepressants and antipsychotics in AD patients

After knowing that antipsychotics may increase mortality in AD patients while antidepressants may decrease mortality[369], the effect of a combination therapy comes into play. We would like to examine the protective effects of adding antidepressants to the existing antipsychotics therapy. We performed another survival analysis to examine three mutually exclusive medication use groups: antipsychotics only, antidepressants only and combination.

The results are shown in **Table 3** and the combination group is the reference group in this model. Based on the results from **Table 3**, the combination group showed a significant beneficial effect relative to antipsychotics only group (HR=0.654, p=0.012), which means that combining antidepressants with antipsychotic treatment was associated with significantly protective effects in AD patients, reducing mortality. In addition, marginal significant difference was observed between no drug group and combination group (HR=1.294, p=0.056), which means that by using combination therapy, the increase in mortality due to using antipsychotics was mitigated to some extent in these patients.

Table 4.3 Multivariate Cox regression analyses of association among treatments and all-cause mortality in AD patients

Covariate	Hazard ratio	Hazard ratio lower 95%	Hazard ratio upper 95%	P value
Antidepressants only vs drug combination	0.518	0.382	0.703	<0.001
Antipsychotics only	1.528	1.099	2.123	0.012

vs drug combination				
No drug vs drug combination	1.294	0.993	1.684	0.056
Age	1.051	1.047	1.055	<0.001
Gender (Female vs Male)	0.712	0.676	0.751	<0.001
Race (Other vs White)	1.622	1.427	1.841	<0.001
Race (Black vs White)	0.698	0.635	0.766	<0.001
ASCVD	1.135	1.059	1.215	<0.001
CKD	1.304	1.226	1.386	<0.001
COPD	1.175	1.107	1.247	<0.001
Cancer	1.088	1.023	1.158	0.007
HF	1.411	1.33	1.497	<0.001
HTN	1.004	0.935	1.08	0.905
MDD	1.156	1.094	1.222	<0.001
Psychosis	1.193	1.102	1.292	<0.001
Stroke	0.938	0.87	1.012	0.097
T2DM	1.131	1.07	1.195	<0.001
AD Medication	0.906	0.857	0.958	0.001

MDD: major depressive disorder, COPD: chronic obstructive pulmonary disease, ASCVD: atherosclerotic cardiovascular disease, T2DM: type 2 diabetes, HTN: hypertension, CKD: chronic kidney disease, HF: heart failure.

Based on our findings shown in **Table 3.5** and **Table 3.6**, we can conclude that by combining antipsychotics and antidepressants, we can significantly mitigate the increase in mortality associated with antipsychotics. For more direct comparison between different treatment groups, a table with pair-wise comparison among groups is included in supplementary table 2 (**ST2**).

In addition to these results, we were interested to see if the effect of the treatments will change over time. Therefore, we conducted 6 analyses with follow-up times ranging from 1 to 6 years. As shown in **Figure 3.6**, we compared the effects of three different treatments (antipsychotics only, antidepressants only, no drug) to the drug combination group, their effects showed moderate fluctuation within the first 3 years and stabilized after 4 years. In comparison to co-administration of antidepressants and antipsychotics, the antidepressants only group showed a consistent lower mortality throughout the 6 years. While the antipsychotics only group had marginally increased mortality compared to the combination group at the first 3 years, subsequent worse outcomes were clearly evident in 4, 5 and 6 years of follow-up. Finally, the combination group showed comparable effects with the patients with no drug treatment throughout the 6 years period and demonstrated almost significant beneficial effects in 4, 5 and 6 years of the follow-up. Our results are attached in supplementary materials (**ST3**). **Table 3.7** shows the hazard ratios for other covariates at 1-year follow-up.

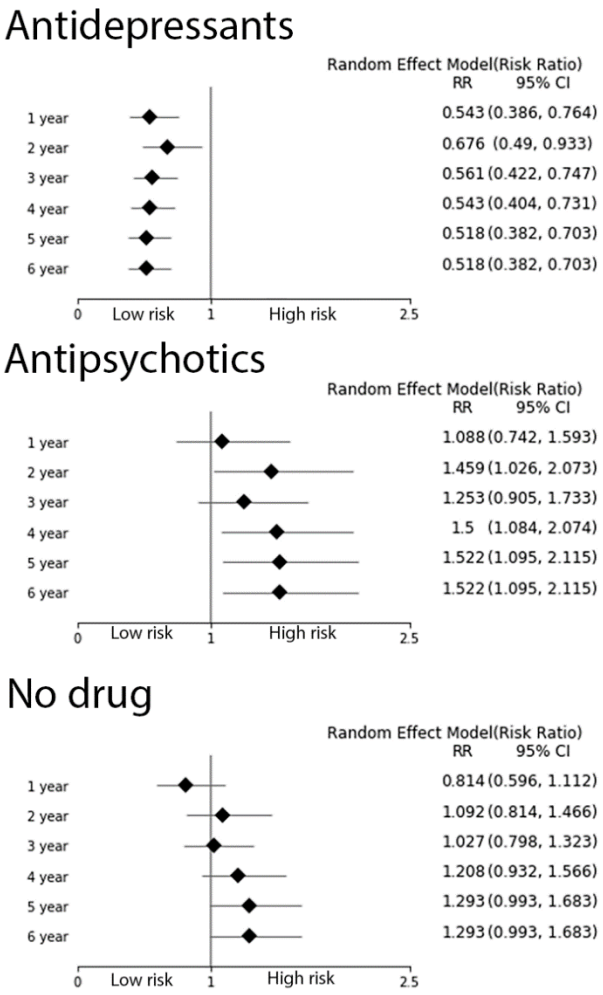

Figure 4.2 Changes of hazard ratios of 3 treatment groups versus drug combination group over 6 years of follow up. The figure how different treatment groups showed different effect through 6 years of follow up. As shown in the figure, antidepressants showed strong protective effects through all 6 years while antipsychotics, on the opposite, showed hazardous effect all the time.

Table 4.4 Multivariate Cox regression analyses of association among treatments and all-cause mortality in individuals with AD over 1 year follow-up

Covariate	Hazard ratio	Hazard ratio lower 95%	Hazard ratio upper 95%	P value
Antidepressants only vs drug combination	0.543	0.386	0.764	<0.001
Antipsychotics only vs drug combination	1.088	0.742	1.593	0.667
No drug vs drug	0.814	0.596	1.112	0.196

combination				
Age	1.051	1.048	1.055	<0.001
Gender (Female vs Male)	0.714	0.677	0.753	<0.001
Race (Other vs White)	1.525	1.37	1.702	<0.001
Race (Black vs White)	0.704	0.641	0.773	<0.001
ASCVD	1.13	1.055	1.21	<0.001
CKD	1.309	1.231	1.392	<0.001
COPD	1.168	1.101	1.24	<0.001
Cancer	1.082	1.017	1.151	0.012
HF	1.419	1.337	1.505	<0.001
HTN	1.007	0.937	1.082	0.849
MDD	1.147	1.086	1.213	<0.001
Psychosis	1.186	1.096	1.285	<0.001
Stroke	0.942	0.874	1.016	0.124
T2DM	1.136	1.075	1.2	<0.001
AD Medication	0.901	0.853	0.953	<0.001

4.1.4 Discussion and Conclusion

When dealing with real-world data, like EMRs, there is always a challenge that the compliance of patients presented in the EMR will not be as ideal as we get from a carefully performed clinical trial. In this study, by analyzing real-world EMR data through Cox model with time-dependent covariates, we were able to accommodate the complex usage patterns and allowed the maximum utilization of the data. The beneficial effect of antidepressants in AD patients were reported by multiple studies[330; 331; 332; 333], though its mechanisms remain

unclear. We also found a strong signal in our results (**Table 3.6** and **Figure 3.5**) which further substantiated our claim that antidepressants may aid in reducing mortality in AD patients. Our finding provided the fundamental support necessary for our hypothesis that by combining antipsychotics and antidepressants, we can decrease the severe side effect that is constraining the use of antipsychotics in AD therapy.

The results of our study aims to provide a comprehensive and quantitative overview of the underlying relationship among antipsychotics, antidepressants, and AD+P. Our results supported the efficacy of antipsychotics and suggested the most promising antidepressants such as Sertraline and Maprotiline, can be added as supplementary treatment. In addition, since they are all marketed drugs and some of their combinations are already tested by clinical trials for other indications, safety profile will not be a major concern when proposing their long-term usage as an alternative treatment option for AD patients.

4.2 DeepBiomarker: Identifying Important Risk Factors from Electronic Medical Records for the Prediction of Psychotic Symptoms in AD Patients

4.2.1 Background and Significance

Use of pharmacotherapy-based treatment options for Alzheimer's disease with psychotic symptoms (AD+P) tended to be limited[11; 12; 13]. These symptoms result in faster decreases in both functional abilities and may hasten placement in a nursing home[22; 23; 24; 25]. By examining the electronic medical records (EMR) of AD/MCI patients, the purpose of the proposed research is to discover drugs with the potential for preventing, delaying, or treating

AD/NPS. We anticipate that if AD/MCI drugs can reduce the risk of developing psychosis, such as aggression, psychosis, anxiety, apathy, depression, agitation, sleep problems, wandering, and so on, they will benefit the treatment of AD+P. We will develop additional deep learning algorithms and statistical analysis tools to examine EMR data from Alzheimer's and other dementia patients, and we will use systems pharmacology methodologies to interpret potential novel biological pathways. The combination of diuretics, calcium channel blockers, and renin-angiotensin-aldosterone system blockers was associated with shorter cognitive deterioration than other antihypertensive medication groups[370; 371]. In our early investigation, we utilized or developed machine learning and deep learning-based methods, such as random forest and SVM (Support Vector Machine), to reliably predict the commencement of suicide-related events among PTSD patients[372; 373]. We discovered risk factors for SREs as well as drugs with notable side effects. Using clinical trial emulations, we discovered that lurasidone users have fewer SREs than other antipsychotic users in PTSD patients.

Deep learning/data mining algorithms can translate data into information for hypothesis generation through deep hierarchical feature construction to capture long-range dependencies in EMR data. Recently, a variety of deep learning techniques and frameworks have been applied to information extraction, representation learning, outcome prediction, phenotyping, and de-identification [374; 375; 376; 377; 378] and yielded better performance than traditional methods and required less time-consuming preprocessing and feature engineering. Specifically, deep learning techniques learn optimal features directly from the data itself, without any human guidance, allowing for the automatic discovery of latent data relationships that might otherwise be unknown or hidden [379].

To enhance the prediction accuracy, we built a deep-learning based model, DeepBiomarker through modification of an established deep-learning framework, Pytorch_EHR [380]. In the DeepBiomarker, we used diagnosis, medication use and lab tests as the input, implemented data augmentation technologies to improve the model performance and also integrated a perturbation-based approach [381] for risk factor identification.

4.2.2 Methods and Materials

4.2.2.1 Data source

To explore the beneficial effect of the combination therapy of antipsychotics and antidepressants, we examined the data from January 2004 to October 2019 from the Neptune system at the University of Pittsburgh Medical Center (UPMC), which manages the use of patient EMRs from the UPMC health system for research purposes (rio.pitt.edu/services)[362]. The database includes demographic information, diagnoses, encounters, medication prescriptions, prescription fill history, and laboratory tests. AD patients and psychosis patients were identified using a series of diagnosis terms in the EMR systems (Appendix D, Supplementary list 1 & 2). In addition, to avoid the possible misdiagnosis of psychosis by short-term delirium symptoms, psychosis diagnosis that co-occur with a delirium diagnosis (Appendix D, Supplementary list 3) were excluded.

4.2.2.2 Data preparation

For each AD patient, we would like to predict whether the patient will have psychosis within next 12 months given the history of EMRs. To build the predictive model, we defined the cases and controls. At any encounter, an AD patient who had a record of psychosis within the

following 12 months is defined as a case, while no records of psychosis within the following 12 months is defined as a control. For a patient with multiple encounters satisfying the criteria of control, only the last encounter was included to mimic the latest status of these patients. We also require no records of psychosis during this period to the index date to make sure this is new onset of AD+P. And we used data augmentation to increase number of cases (see below). The date of this encounter will be the index date. We used the medication, diagnosis, lab tests 1 year preceding the index date as the input. For lab tests, we only included those abnormal ones in our modeling by searching those RESULT_FLAG labeled as "ABNORMAL", "HIGH" or "LOW". We also excluded those lab tests with low frequency and kept the 89 top frequently tested ones. The diagnosis was coded in ICD9 before year 2015 and ICD10 after year 2015. As such, we used a lookup table from https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs to convert ICD9 to ICD10 codes. The first three characters of the ICD10 which designate the category of the diagnosis were extracted, yielding 1614 diagnosis groups. Medication names were converted to DrugBank IDs by name matching, and 1407 unique DrugBank IDs were mapped. Finally, for each encounter the associated medications, diagnosis and abnormal lab test results were packed into a sequence with the indices of DrugBank IDs, categories of the diagnosis, and lab test IDs, respectively.

4.2.2.3 Data augmentation

Data augmentation is a technology used to increase the data size and to reduce overfitting. At any encounter, the chance of having psychosis within the next three months are much lower than that of having no psychosis, even within these AD patients with high risk. We included all encounters nearby the psychosis, which satisfied the inclusion criteria for positive cases, while under-sampling the encounters which satisfied the inclusion criteria for controls.

The purpose of data augmentation is to enhance the influence of factors nearby the events while reducing the effects of factors far from the events.

4.2.2.4 Dataset splitting

The dataset was split with a ratio of 8:1:1, and 8 of 10 subsets were used as the training dataset, while 1 of 10 subset was used as the validation dataset to find the optimal parameters and the left 1 subset was used as the test set to evaluate the generalization of our model.

4.2.2.5 DeepBiomarker

We adopted the Pytorch_EHR framework established by ZhiGroup where Deep learning models with Vanilla RNN, GRU, LSTM, Bidirectional RNN, Bidirectional GRU, Bidirectional LSTM, REverse Time AttentIoN model (RETAIN), Dilated RNN, Dilated GRU, Dilated LSTM, QRNN, and T-LSTM were used to analyze and predict clinical outcomes [380]. We adopted the RETAIN, T-LSTM and Logistic regression models and further modified the framework as highlighted in **Figure 4.3** by (a) data augmenting to improve the model performance; (b) including individual lab tests and medications along with the diagnosis groups as the input. So that we can assess the effects of each lab tests and medications; and (c) integrating contribution analysis [381] module for the importance estimation of key factors (see below for more details). The structure we used here is the LSTM model which stores previous illness history, infers current illness states, and predicts future medical outcomes [382]. The memory cell is gated to moderate the information flow to or from the cell. LSTMs have been adapted in many applications, such as machine translation, handwriting recognition, and speech recognition. In this study, the following parameters are used: embed dimension: 128, hidden size: 128, dropout

rate: 0.2, number of layers: 2, input size: 30000, patience: 3. The calculations were repeated ten times for each deep-learning algorithm to estimate the standard deviations of the accuracy.

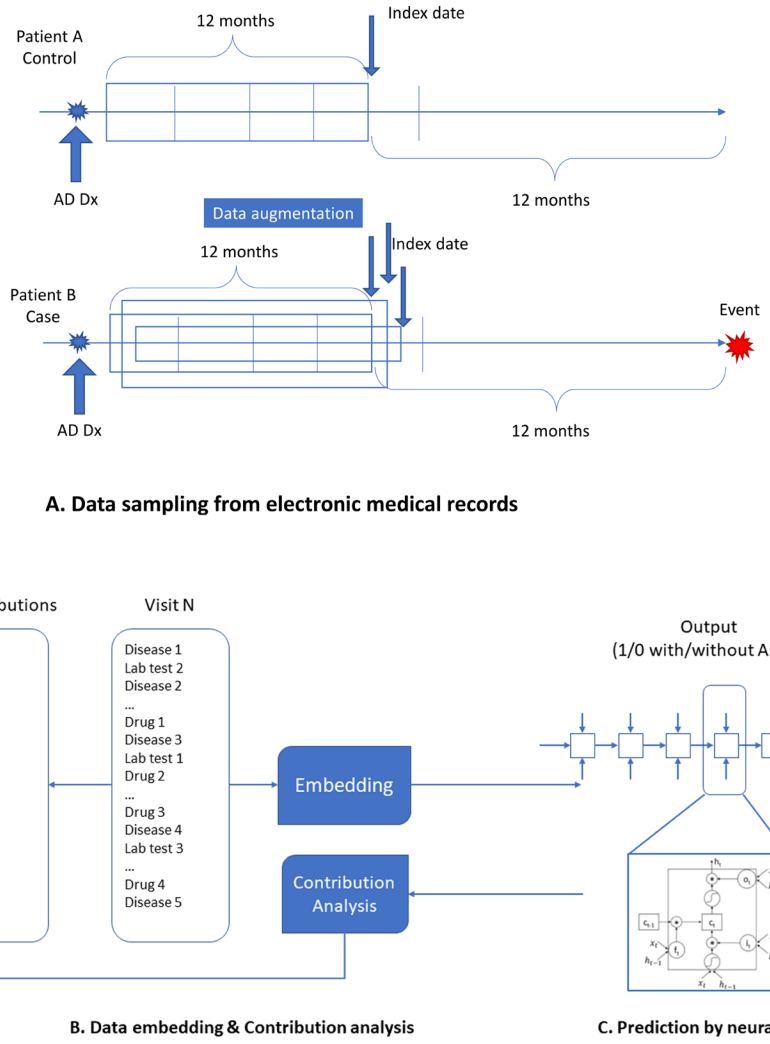

Figure 4.3 The overview of DeepBiomarker. (A) Data sampling from electronic medical records, (B) Data embedding, and (C) Prediction by neural network with LSTM as the basic prediction units. Perturbation-based contribution analysis will be used to identify important features.

4.2.2.6 Assessment of importance of the clinical factors for predicting suicide-related events

To further investigate the importance of those factors on the prediction of psychosis, we calculated the relative contribution (RC) of each feature on the psychosis [381]. The RC of a feature was calculated as the average contribution of the feature to events divided by the average contributions of this feature to no-events. The contributions were estimated by a perturbation-based approach. Such approach has been used in recent study on the important features for heart failure incidence prediction [383]. The equation is shown as follows where FC represent the feature contribution:

Equation 4-1

$$RC = \frac{mean\ FC\ in\ patients\ with\ event}{mean\ FC\ in\ patients\ without\ event}$$

FC value was the total value of the feature within the same patient if the feature appeared more than once in that patient. The natural logarithm form variance for RC was calculated as:

Equation 4-2

$$Variance(\ln(RC)) = \frac{\left(\frac{sd\ of\ FC\ of\ patients\ with\ event}{mean\ of\ FC\ of\ patients\ with\ event}\right)^2}{number\ of\ patients\ with\ event} + \frac{\left(\frac{sd\ of\ FC\ of\ patients\ without\ event}{mean\ of\ FC\ of\ patients\ without\ event}\right)^2}{number\ of\ patients\ without\ event}$$

sd: standard deviation

Thus, the 95% confidence interval (CI) of RC was given by:

Equation 4-3

$$95\%CI = e^{(\ln(RC) \pm 1.96\sqrt{Variance(Ln(RC))}}$$

And the p-value was under the assumption of z distribution[384]. Bonferroni correction[385] was used to reduce the type I error caused by multiple comparison.

4.2.2.7 Assessment of model performance

Model performance was evaluated by the area under the ROC curve (AUROC).

4.2.3 Results

4.2.3.1 The performance of DeepBiomarker in AD+P patients

We have identified 38,807 AD patients from UPMC EMR data. And we further identified 11695 cases and 11695 controls from patients with more than 1 year of EMRs before the diagnosis of AD. Those samples were split to 8:1:1 ratio for training, validation, and test sets. The performance of the DeepBiomarker can be found in **Table 4.5**.

Table 4.5 Model performance of different models on valid and test datasets.

	Validation AUC	Test AUC	Validation AUC std	Test AUC std
T-LSTM	0.921	0.903	0.006	0.005
RETAIN	0.935	0.907	0.004	0.002
LR	0.837	0.822	0.009	0.012

As shown in **Table 4.5**, the T-LSTM and RETAIN models both showed excellent performance on AD+P prediction, i.e., all yielded equal or more than 0.9 of AUROC. Deep learning models performance AUC above 0.9, better than LR (0.82).

4.2.3.2 Risk factors identified by the DeepBiomarker model with significant contributions

As we mentioned above, we used a perturbation-based estimation to calculate the relative contribution of each feature on the prediction of AD+P. Three types of features: drugs, diagnosis,

and lab tests, can be found in the results. In total, 65 features showed significant effects in our results, including 6 lab tests, 36 drugs and 23 diagnoses. We only showed the diagnose that appeared in more than 10% of the whole population to minimize the random effect and increase reliability of our test. The following 3 tables showed the details of the features that showed significant effects (**Table 4.6**, **Table 4.7,** and **Table 4.8**).

Table 4.6 Top important medication use results identified by perturbation-based contribution analysis for AD+P prediction.

Feature	RC	CI95up	CI95down	Q Value*
Memantine	0.749	0.83	0.676	<0.001
Aspirin	0.808	0.904	0.721	0.003
Losartan	0.766	0.869	0.676	0.001
Protonix	0.835	0.95	0.734	0.036
Docusate Sodium	0.78	0.907	0.671	0.011
Cephalexin	0.793	0.917	0.686	0.014
Calcium Carbonate-Vitamin D3	0.781	0.902	0.676	0.008
Tramadol	0.795	0.937	0.674	0.037
Clopidogrel	0.777	0.918	0.658	0.022
Quetiapine	0.726	0.875	0.603	0.008
Nitroglycerin	0.679	0.84	0.549	0.005
Magnesium Hydroxide	0.66	0.823	0.529	0.003
Triamcinolone Acetonide	0.751	0.923	0.612	0.038
Alprazolam	0.692	0.857	0.56	0.008
Duloxetine	0.606	0.757	0.485	<0.001
Famotidine	0.672	0.823	0.548	0.002
Isosorbide Mononitrate	0.719	0.89	0.582	0.018
Glipizide	0.732	0.923	0.581	0.046
Lactulose	0.599	0.835	0.429	0.019
Esomeprazole Magnesium	0.538	0.698	0.414	<0.001
Budesonide-Formoterol	0.578	0.763	0.437	0.002
Cyclobenzaprine	0.572	0.734	0.445	<0.001
Irbesartan	0.509	0.769	0.338	0.012
Dextromethorphan-Guaifenesin	0.439	0.757	0.255	0.022
Sucralfate	0.472	0.716	0.311	0.005
Midodrine	0.477	0.65	0.35	<0.001
Fish Oil	0.456	0.73	0.285	0.01
Ezetimibe	0.624	0.854	0.457	0.022

Glucosamine-Chondroitin	0.359	0.7	0.184	0.02
Clobetasol	2.054	3.043	1.387	0.004
Terazosin	1.842	2.633	1.288	0.009
Warfarin	1.289	1.478	1.124	0.004
Allopurinol	1.639	2.157	1.245	0.005
Cholestyramine-Aspartame	1.642	2.233	1.207	0.013
Fluconazole	1.58	2.175	1.147	0.032
Metoclopramide	1.879	2.697	1.309	0.007

*** FDR-adjusted p-value by Bonferroni correction.**

Table 4.7 Top important diagnoses use results identified by perturbation-based contribution analysis for AD+P prediction.

Feature	RC	CI95up	CI95down	Q value*
Long Term (Current) Use of Insulin	1.582	1.722	1.454	<0.001
Esophageal Reflux	1.112	1.174	1.054	0.002
Depressive Disorder	1.117	1.195	1.045	0.01
Atherosclerotic Heart	1.154	1.228	1.085	<0.001
Osteoarthritis	0.877	0.944	0.814	0.006
Type 2 Diabetes Mellitus	1.191	1.261	1.125	<0.001
Disorientation	1.148	1.268	1.039	0.039
Atrial Fibrillation	1.358	1.477	1.249	<0.001
Hypothyroidism	1.136	1.234	1.045	0.02
Abnormality of Gait	1.171	1.292	1.061	0.014
Unspecified Diabetes Mellitus	1.234	1.328	1.147	<0.001
Pain In Joint, Shoulder Region	0.764	0.898	0.651	0.01
Obstructive Sleep Apnea	1.207	1.354	1.076	0.012
Arthropathy	0.747	0.831	0.672	<0.001
Acute Kidney Failure	0.86	0.945	0.783	0.014
Activities Involving Walking, Marching and Hiking	0.782	0.876	0.699	0.001
Central Pain Syndrome	1.221	1.397	1.067	0.025
Hypocalcemia	1.417	1.689	1.189	0.002
Hypoxemia	0.718	0.85	0.606	0.002
Aortic Valve Disorders	1.274	1.506	1.077	0.03
Dependence on Renal Dialysis	1.361	1.602	1.156	0.003
Acute Venous Embolism and Thrombosis of Unspecified Deep Vessels of Lower Extremity	1.687	2.325	1.223	0.012
Primary Hypercoagulable State	1.582	1.722	1.454	<0.001

*** FDR-adjusted p-value by Bonferroni correction.**

Table 4.8 Top important lab test results identified by perturbation-based contribution analysis for AD+P prediction

Feature	RC	CI95up	CI95down	Q value*
Chloride (Cl)	0.886	0.952	0.825	0.01
Glucose	0.871	0.941	0.806	0.006
Urea Nitrogen	0.84	0.909	0.776	0.001
Anion Gap	0.863	0.944	0.789	0.012
Alkaline Phosphatase (ALP) Test	0.826	0.924	0.739	0.009
Aspartate Aminotransferase (AST) Test	0.704	0.864	0.574	0.008

*** FDR-adjusted p-value by Bonferroni correction.**

4.2.4 Discussion and Conclusion

In this retrospective study, we further applied our deep learning model DeepBiomarker1.5 to predict the risk of developing AD+P based on the history of medication prescriptions, diagnosis, and routine lab tests from the previous year. The model's AUC score was greater than 0.907, making it superior to classic machine learning models such as logistic regression. The enhancement may result from the fact that DeepBiomarker can additionally account for the temporal effects of these characteristics.

4.2.4.1 Lab tests as indicators of comorbidities and disease burdens for AD+P prediction

Through further analysis on the DeepBiomarker model, we identified several important lab tests as the biomarkers. As you may expect, these lab tests have already been reported with tight connections with AD and psychosis (**Table 4.9**). These laboratory tests might be viewed as the patients' disease burden measurement and indicators of underlying comorbidities. As a matter

of fact, the abnormality of these lab tests showed beneficial effects (RC < 1) to the occurrence of AD+P can be explained that their corresponding treatment may play a role in preventing or interfering with the development of AD+P. For example, abnormal level of glucose whole blood is an indicator of reduced risk of developing AD+P while in the EMRs, most of them are high plasma glucose. Therefore, these patients are more likely to be taking glucose-lowering medications while clinical studies have found that the use of these medications contributes to a lower risk of developing AD and better cognitive performance[386].

The lab tests identified from our model can serve as biomarkers for underlying comorbidities. We noticed that a few therapeutical areas were highlighted by the presence of multiple related biomarkers: Metabolic syndrome (Glucose-Whole Blood, Blood Urea Nitrogen), Liver function (Aspartate Aminotransferase (AST) Test, Alkaline Phosphatase (ALP) Test). We suspect that the RC values we found here are a mixture of the symptoms and the corresponding interventions that the patients received because of the abnormal lab tests, and this might cause certain abnormal lab tests to exhibit beneficial effects. For example, Glucose-Whole Blood, showed a beneficial effect in the lab test results (RC = 0.871), while the diagnosis related to it, Type 2 diabetes showed hazardous effect in the comorbidities results (RC = 1.191).

Table 4.9 Top biomarkers for prediction of AD+P in AD patients along with the effect on AD, psychosis, and realted indications

Lab Test	Effect with AD	Effect with psychosis	Disease/Conditions
Glucose Whole Blood	The impaired glucose metabolism in the brain of subject with AD is a widely recognized early feature of the disease[387]	Pooled analyses found first-episode psychosis to be related to impaired glucose tolerance[388]	Type 2 diabetes (T2D) Type 1 diabetes (T1D) Gestational diabetes
Aspartate Aminotransferase (AST) Test/	chronic liver inflammation induced outside the brain is		Test for liver damage, heart attack or muscle injury

Alkaline Phosphatase (ALP) Test	sufficient to induce neurodegeneration[389]		
Urea Nitrogen	Urea nitrogen were significantly higher in late onset AD[390]	Elevated levels of blood urea nitrogen were associated with increased severity of illness and mortality in psychiatric patients[391]	Dehydration Burns High protein diet

4.2.4.2 Medications for potential AD+P prevention and treatment

In addition to lab tests, medications that exhibited beneficial effect can also provide valuable information. It didn't surprise use when Vitamin D, Quetiapine, Memantine showed up with a significant beneficial effect since they are already reported with beneficial effect against AD+P[28; 392; 393; 394]. Furthermore, several medications identified by our model with protective effect against AD+P have close association with AD or psychosis or the related pathways and mechanisms. These findings provided side-support for the reliability and accuracy of our predictive model and suggested that the important features of our model can provided mechanistic insight for future drug repurposing and novel therapeutic development. Our analysis confirmed the beneficial effects of medications used in AD patients such as Oxybutynin, Famotidine and Memantine because their RC values are less than 1. In our previous study, we reported that vitamin D can delay the onset of psychosis[395] and in our current analysis, vitamin D also has beneficial effects, e.g., with reduced the risk of psychosis in AD patients. However, we would point out that these associations might not be causal, because the use of those medications might also indicate the disease burdens of AD patients and the indications of

those medications may be the cause of disease progression, like Warfarin, Insulin and Allopurinol.

Table 4.10 Top medications for prediction of AD+P in AD patients along with the effect on AD, psychosis, and related indications

Drugs	Effect with AD	Effect with psychosis	Indications
Aspirin	Users of high-dose aspirin had significantly lower prevalence of Alzheimer's dementia and better-maintained cognitive function than non-users[396]		Nonsteroidal anti-inflammatory drugs (NSAIDs)
Clopidogrel	Clopidogrel combats neuroinflammation and enhances learning behavior and memory in a rat model of Alzheimer's disease[397]	Psychotic patients received lower rate of prescriptions for clopidogrel[398]	Reduce the risk of heart attack and stroke. Prevention of blood clots
Quetiapine	Quetiapine produced significant improvements in behavioral disturbances and were well tolerated[399]	Quetiapine is indicated for psychotic symptoms	Schizophrenia Bipolar Disorder
Duloxetine	Duloxetine can improve cognitive function and/or have a dual or multimodal		Depression Anxiety Disorders

	mode of action[400]		
Losartan	Losartan prevents and rescues cerebrovascular, neuropathological and cognitive deficits in an Alzheimer's disease model[401]	Losartan was associated with the onset of psychosis and depression in an elderly patient[402]	Hypertension
Gabapentin	Gabapentin used as treatment of behavioral and psychological symptoms of dementia[403]	Use of gabapentin may induce psychotic and depressive symptoms[404]	Prevent and control partial seizures. Relieve nerve pain following shingles in adults. Treat moderate-too-severe primary restless legs syndrome.
Budesonide-Formoterol	Asthma in midlife and in late life increased the risk of developing any dementia and Alzheimer's disease[405]		Chronic obstructive pulmonary disease (COPD) Bronchospasm Asthma
Vitamin D	Vitamin d deficiency is associated with a substantially increased risk of all-cause dementia and Alzheimer disease[406]	Vitamin d use was significantly associated with delayed time to psychosis in Alzheimer's disease patients[28]	Hypoparathyroidism Refractory rickets (also known as Vitamin D resistant rickets) Familial Hypophosphatemia
Memantine	Cognition-enhancing medication	Memantine therapy in schizophrenic patients seems to improve mainly negative symptoms[407]	Moderate to severe dementia of the Alzheimer's type

Allopurinol	Results are inconclusive, some studies show that it has no impact on dementia in ad while some show it is protective in gout by attacking the uric acid production[408]	May help in alleviating psychosis in schizophrenic patients[409]	Management of gout, preventing tumor lysis syndrome, and preventing recurrent calcium nephrolithiasis in patients with hyperuricosuria
Glipizide	Glipizide treatment of type 2 dm patients resulted in improvement primarily in the learning of verbal material without changes in attention and complex perceptual-motor function[410]		Type 2 diabetes
Insulin		Excess insulin in plasma led to higher incidences of psychosis[411]	Treatment of type-1 and type-2 diabetes mellitus
Famotidine/ Esomeprazole Magnesium	Gastric acid suppressants such as famotidine promoted cognitive decline[412]	Famotidine is associated mental status changes, along with confusion, disorientation, and nightmares[413]	Treatment of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, and Zollinger Ellison syndrome
Magnesium Oxide	Low magnesium status is a risk factor of ad[413]	Patients with low magnesium levels experience severe psychosis[414]	Treatment of eclampsia Dysrhythmias and myocardial ischemia

Alprazolam	Benzodiazepine ever use was associated with an increased risk of Alzheimer's disease[415]	Psychosis associated with alprazolam therapy[416]	Anxiety disorders Panic disorder with or without agoraphobia.
Cholestyramine-Aspartame	High serum/plasma cholesterol levels have been suggested as a risk factor for Alzheimer's disease[417]	Lipid profile test may be considered in the assessment of suicide risk in psychosis and LDL-c an important biological marker[418]	High low-density lipoprotein (LDL) cholesterol

The presence of some medications in the results are to be expected, like Memantine, Quetiapine, Duloxetine and Alprazolam. These medications are either indicated for AD or psychosis themselves (Memantine and Quetiapine), or are popular candidates for the management of psychotic symptoms in AD (Duloxetine and Alprazolam)[419; 420]. These results provided side support for the reliability and credibility of our model and strengthened the power of the biomarkers and potential treatments that are proposed in the results.

From the results shown above (**Table 4.10**), several physiology fields have been highlighted including neuroinflammatory process, cardiovascular biomarkers, and glucose metabolism. As a matter of fact, the association between these biomarkers/mechanisms and AD/psychosis have been establish by past studies[34; 421; 422; 423; 424]. Neuroinflammation and insulin resistance are regarded as important neuropathological events underpinning the start and progression of AD. Therefore, targeting this mechanism have become a novel approach in developing AD-related medications and can also provide insights for the management of AD+P. This shows that a combination of clinical support and treatment would further help alleviate

AD+P symptoms. Collectively, our study may also suggest the beneficial effects of medications like Memantine, Aspirin, Vitamin D, Clopidogrel, Magnesium, and Oxybutynin because of their potential effects in mediating the pathways/mechanisms relevant to the onset and development of AD+P. DeepBiomarker offers potentially valuable information that may augment existing tools for clinical assessment and contribute to a holistic approach to personalized medication. These results suggested the potential of our model in providing mechanism insights for the development of AD+P and propose novel research direction for potential AD+P prevention and treatment.

Table 4.11 Mechanism actions, targets, and blood brain barrier (BBB) penetration ability for the medications identified associated with the development of AD+P.

Drugs	Mechanism of action	Targets	Ability to penetrate blood brain barrier
Aspirin	Irreversibly inhibit the cyclooxygenase (COX) enzyme	COX-1 enzyme COX-2 enzyme	Yes
Clopidogrel	Irreversibly inhibit the P2Y12 receptor, which is found on the surface of platelets. Reduces the activation and aggregation of platelets.	P2Y12 receptor	Yes
Quetiapine	Antagonist of several neurotransmitter receptors in the brain, including dopamine, serotonin, and histamine receptors	DRD2 HTR1A HTR2A HRH1	Yes
Duloxetine	Inhibition of the reuptake of two neurotransmitters in the brain: serotonin and norepinephrine.	SLC6A2 SLC6A4	Yes
Gabapentin	Binding to the α2δ subunit of voltage-gated calcium channels in the brain to reduce the release of several	α2δ subunit of voltage-gated calcium channels	Yes

	neurotransmitters, including glutamate, norepinephrine, and substance p, which are involved in pain and anxiety.		
Losartan	angiotensin II receptor antagonist, blocking the binding of angiotensin II to specific receptors in the body, which inhibits its vasoconstrictive and pro-inflammatory effects	angiotensin II receptor	Yes
Budesonide-Formoterol	Binding to glucocorticoid receptors in the lungs, leading to the suppression of inflammation and immune responses	Glucocorticoid receptors Beta-2 adrenergic receptors	Yes
Vitamin D	Binding to vitamin d receptors (VDR) in cells, leading to changes in gene expression and protein synthesis	vitamin D receptor (VDR)	Yes
Memantine	Blocking of the activity of the NMDA (n-methyl-d-aspartate) subtype of glutamate receptors in the brain.	NMDA subtype of glutamate receptors	Yes
Allopurinol	Inhibiting the xanthine oxidase enzyme, which is involved in the metabolism of purines	xanthine oxidase enzyme	Yes
Glipizide	Stimulating the release of insulin from the beta cells of the pancreas.	ATP-sensitive potassium channels in pancreatic beta cells SUR1	No
Insulin	Binding to insulin receptors on target cells, which triggers a series of signaling pathways that promote glucose uptake and utilization by cells	insulin receptor (INSR)	Yes

Famotidine	Inhibiting the activity of histamine h2 receptors in the stomach	histamine H2 receptor	Yes
Esomeprazole Magnesium	Inhibiting the proton pump (h+/k+ ATPase) in the stomach	the proton pump (H+/K+ ATPase)	Yes
Magnesium Oxide	Providing magnesium ions to the body, which are essential for many biological processes		Yes
Alprazolam	Enhancing the activity of gamma-aminobutyric acid (GABA) in the brain	GABA-A receptor benzodiazepine receptor	Yes
Cholestyramine-Aspartame	Binding to bile acids in the intestine and preventing their reabsorption	bile acids	No

There two possibilities for these medications to exhibit the beneficial effects toward AD+P that were observed in this study. One is that their beneficial effects are the results of the improved overall life quality by the treatment of the indications of these medications. For example, by managing their blood glucose level or relieve their anxiety symptoms, it will elevate their life quality and thus reduce the risk of developing AD+P. Another possibility is that these medications possessed direct central nervous system (CNS) effect that are involved in the development of AD+P and is not associated with their original indications. From the summary in **Table 4.11**, most drugs are able to penetrate the BBB to exert central nervous system effects. This allowed the possibility that these medications can be the novel treatment options for AD+P.

4.2.4.3 Hypothesis on AD+P mechanisms and development

Overviewing the important features identified by the DeepBiomarker1.5 model, inflammation-, glucose metabolism-, cardiovascular- and kidney-related biomarkers/mechanisms made strong appearances in both comorbidities and lab test results. Though the beneficial effect

of glucose-lowering medications[386; 425], cardiovascular medication[426; 427; 428] and anti-inflammatory medication[429] in AD have already been reported by multiple studies, there is no clear evidence supporting their correlation with AD+P. It is possible that these medications exert their protective effects toward AD+P by treating AD, but it also provided some mechanism insight of the association between AD and AD+P. The strong beneficial effect of Memantine also supported that treating AD can be the first step of managing psychotics symptoms in AD. This theory may lead to a very different treatment plan compared to the current conventional treatments that are mainly composed of antipsychotics.

The different direction of action of the drugs with similar therapeutical effect also provided us a novel angel in drug development for AD+P. For example, we know that diabetes is a risk factor for AD+P, but if the increased risk of AD+P is a result of elevated blood glucose level, insulin and Glimepiride should possess similar effect since they can all lower the glucose level in patients. Our results suggested that the beneficial effects of Glimepiride and Clopidogrel are not exerted through their effect for their original indications, but rather through other mechanisms that are directly involved in the development of AD+P.

4.2.4.4 Limitation of our study

Our research also has several limitations: First, there may be inconsistencies in patients' biochemical test results due to enrollment bias, and some laboratory tests may be underrepresented in our database. As a result, the analysis's ability to detect the effects may be limited. In addition to diagnosis and drug use, we also investigated the influence of biomarkers; nonetheless, comorbidities had a greater impact than biomarkers. This can be explained by the fact that the diagnosis considers the historical status of the patients, whereas biomarkers only accounted for the current status of these patients.

We would also like to point out that the population used in this study is partially overlapped with the population in one of our previous studies that reported the beneficial effect of Vitamin D against AD+P[395]. We were unable to match and exclude the overlapping patients because of the deidentification process conducted by the data management team at the UPMC. However, with a total of 502 subjects included in the previous study, the overlapping sample size are too small to cause significant impact.

5.0 Conclusions and Perspectives

5.1 Key Research Findings

5.1.1 Different Mechanisms Underlying the Similar Psychotics Symptoms in AD and Schizophrenia.

In this thesis, we explored the underlying mechanisms for the psychotic symptoms in AD and schizophrenia by applying cutting-edge network analysis methods to the latest genomic data of AD+P and schizophrenia. The findings of this study not only proved that distinct mechanisms are causing the similar NPS symptoms in AD+P and schizophrenia, but also identified several promising drug targets that possess high impact in the disease conditions and provided future direction for novel drug development and drug repurposing studies.

This research uses a number of different methods of network analysis in conjunction with systems pharmacology in order to provide a comprehensive examination of the molecular level interactions that take place between Alzheimer's disease, psychosis, and vitamin D. We were able to investigate the designated mechanisms for Vitamin D's effects on AD+P with the use of the triple-focusing network approach, and a possible explanation is offered as follows: Several genes that code for proteins that play essential roles in the overlapped section of the AD-psychosis combined network are regulated by vitamin D. This allows these proteins to exert the maximum amount of influence possible on the process of signaling and information transfer. In other words, proteins with high net-influence that localize at the triple-overlapping part of the Alzheimer's disease network, the psychosis network, and the Vitamin D network, such as

CACNA1C, COMT, NOTCH4, and DRD3, have the potential to play an important role in the crosstalk between Alzheimer's disease and psychosis by delivering the effect of Vitamin D to the transiting hub connecting the Alzheimer's disease network and the psychosis network. This is accomplished by delivering Vitamin D. Therefore, the four putative targets that have been discovered could be extremely important in understanding the positive effect that Vitamin D has on AD+P. In conclusion, the findings of this study provided a possible explanation for the beneficial effect of Vitamin D against AD+P and presented a new direction for the development of drugs with four potential novel targets. In addition, the results of this study presented a novel approach to the treatment of AD+P.

In addition, we introduced the risk factors identified from our deep learning-based model, DeepBiomarker, to explore the mechanisms that are critical in the development of AD+P. Within the context of this retrospective study, we developed a deep learning model called DeepBiomarker with the goal of predicting the onset of AD+P by looking back one year at a patient's history of medication prescriptions, diagnoses, and routine laboratory tests. This model was then applied to the data from the study. The AUC score for the model was more than 0.92, which places it in a position of superiority when compared to traditional machine learning models such as decision trees and random forests. It's possible that the improvement is due to the fact that DeepBiomarker is able to additionally take into consideration the temporal effects of these traits. Our methodology identifies laboratory tests that can act as indicators for underlying comorbidities. Several therapeutic areas were highlighted by the presence of multiple related biomarkers: inflammation (Anion Gap, Mononucleosis, Eosinophil), metabolic syndrome (Glucose-Whole Blood, Sodium-Whole Blood, Blood Urea Nitrogen), kidney function (Urea Nitrogen, PH – Urine, Leukocyte Esterase), and cardiovascular function (pO2 – Arterial, Sodium

- Whole Blood, B-Type Natriuretic Peptide). It is important to note that the direction of these tests' effects vary between beneficial and harmful, and it might be misleading when an abnormal pO2 – Arterial result provides protection against AD+P. We assume that the RC values we discovered here are a combination of the symptoms and the accompanying actions that the patients received as a result of abnormal lab tests, and that this may cause certain abnormal lab tests to have good consequences. Glucose-Whole Blood, for example, demonstrated a good influence in the lab test findings (RC = 0.641), whereas Type 2 diabetes demonstrated a dangerous effect in the comorbidities test results (RC = 1.365).

5.1.2 Explained the Modest Efficacy of Antipsychotics in Treating AD+P

In this thesis, through the utilization of network efficiency and pathway analysis on the combined disease-target network, we were able to shed light on the underlying causes of efficacy disparities between antipsychotics used to treat schizophrenia and AD+P. It has been discovered that the key targets of antipsychotics have a lesser efficiency in the AD+P network than they do in the SCZ network. This finding suggests that the antipsychotics that interact with these targets may modify AD+P in a less effective manner. Finally, we discovered pathways that are activated by antipsychotics and are involved in AD+P but not in schizophrenia. These pathways may contribute to the restricted efficacy or heightened toxicity of these drugs in AD+P because they are not involved in schizophrenia.

The results of this study can also help nominate antipsychotics that may possess higher efficacy in treating AD+P as candidates for future testing. Although not many antipsychotics have been tested against AD+P, the results of this study can help nominate antipsychotics. Risperidone is the most effective and widely used second-generation antipsychotics (SGA) in

clinical settings; nevertheless, three antipsychotics, Sertindole, Fluphenazine, and Ziprasidone, exhibited a greater weighted efficacy than Risperidone did. The antipsychotic medications Sertindole and Ziprasidone have been shown to have superior effectiveness and safety profiles. Previous research also demonstrated that Sertindole performed better than other SGAs on cognitive functions such as processing speed and executive function, whereas ziprasidone performed better on the composite score, executive function, processing speed, working memory, memory, and verbal learning. Both Sertindole and Ziprasidone have a higher affinity for the 5HT6, 5HT2C, and 5HT3 receptors, which may be one of the reasons why they are beneficial. Because of this, we think that Sertindole and Ziprasidone are good choices for antipsychotics that work better for AD+P. When a similar perturbation is applied to major antipsychotics' targets, such as DRD2 and HTR2A, patients with AD+P will have different reactions compared to schizophrenia patients. This is due to the fact that the pathways that are influenced by the perturbation are different under the two disease conditions. The results of the pathway enrichment analysis showed this to be the case. When compared with schizophrenia, the overrepresented pathways point to a unique function for neuroinflammation and RNA production in Alzheimer's disease and Parkinson's disease. In addition, a number of studies have pointed to the role that neuroinflammation plays in the development of Alzheimer's disease and schizophrenia. The findings of our research showed that, although inflammatory processes are involved in both conditions, different responses can be activated in AD/PD patients and schizophrenia patients. These findings can be used to explain the causal relationship between activated systemic inflammation and the development of neuropsychiatric symptoms in Alzheimer's disease. The consistency between the previously published reports and the findings of our pathway enrichment study offered further support for the justification of our findings. The

various pathways affected by AD+P and schizophrenia may also have an unintended consequence of increasing the likelihood of antipsychotics' adverse events in AD+P patients. For instance, infection is a common side event that has been observed in several studies and has been linked to the antipsychotic-induced suppression of the immune system.

The findings of this study, taken as a whole, not only offer a possible explanation for the modest efficacy of antipsychotics in AD+P, but they also have the potential to help nominate antipsychotics that may possess higher efficacy in treating AD+P and which should be tested in further studies. These antipsychotics are Sertindole and Ziprasidone. In addition, the methodology that we used in this investigation demonstrated a high level of congruence with many other pieces of evidence that were reported by merging bioactivity data with network analysis approaches. This methodology has the potential to be utilized in drug repurposing or treatment optimization research so as to provide assistance and direction.

5.1.3 Identification of novel treatment options for AD+P

After building a solid foundation in understanding the mechanisms, risk factors and current treatment options for AD+P, we took a further step to look for novel treatment options that can provide better efficacy and improved safety profile. Large-scale drug repurposing and systems pharmacology approaches were performed to identify medications with potential beneficial effects or a cocktail therapy by combining medications from different categories.

In this thesis, cutting-edge systems pharmacology approaches were used to investigate the possible synergistic effect of combining antipsychotics and antidepressants in the treatment of AD+P. The results of this investigation showed that there was no significant synergistic effect between the two treatment modalities. This study looked at protein expressions, post-treatment

gene expressions, as well as networks of protein-protein interaction. Our findings indicate that the combination of antipsychotics and antidepressants may be a more effective treatment option for AD+P, and they provide significant information for making future decisions regarding the appropriate medication matching. For the treatment of AD+P, our research uncovered a number of different pharmaceutical combinations that have the potential to provide synergistic effects. Two antipsychotics, Aripiprazole and Thioridazine, and seven antidepressants, Sertraline, Maprotiline, Nefazodone, Mirtazapine, Trazodone, and Bupropion, were recorded as having been used. Despite the fact that antipsychotics and antidepressants have never been studied specifically for Alzheimer's disease or Alzheimer's disease plus Parkinson's disease, their safety and efficacy profile has been analyzed in a number of trials in comparison to other disorders. As a direct outcome of this analysis, the goal of our research is to provide a comprehensive and quantitative picture of the underlying link that exists between antipsychotics and antidepressants, as well as AD+P. Our research provided evidence in favor of the usefulness of antipsychotic medications, and we advised that the most promising antidepressants, such as sertraline and maprotiline, be considered for inclusion in the treatment plan. Because all of these medications are readily available over-the-counter and because several of their combinations have already been tested in clinical trials for other purposes, there is little cause for concern regarding their safety profiles when they are recommended for long-term use as an alternative treatment for Alzheimer's disease patients.

Appendix A Supplementary Material for Chapter 2.1

Inclusion criteria for genes

Due to the variety of information sources, genes were carefully selected from different types of data including RNA and miRNA expression, SNPs identified through GWAS, copy number variations (CNVs), and mutation data. 1) reported in a primary GWAS analysis, defined as array-based genotyping and analysis of 100,000+ pre-QC SNPs selected to tag variation across the genome and without regard to gene content; 2) SNP-trait p-value $<1.0 \times 10^{-5}$ in the overall population. The threshold of 1.0×10^{-5} was chosen rather than the stricter one for genome-wide association of 5.0×10^{-8} to include more targets potentially related to AD and psychosis to generate a more complete structure of networks.

Alzheimer's disease-related genes

HLADRB1	EIF4EBP1	A2M	LRP1	ABCA1	ABCA2	ABCA7
ABCC2	ABCG1	ACAD8	ACE	ACHE	CHRM2	ACTA2
ACTL8	ADAMTS1	ADAM10	ADAM12	ADAR	AGBL4	AGTR1
AGTR2	AKT1	ALDH2	ALOX12	ALOX15	ALOX5	AMBRA1
RUNX1	ANKH	ANKRD2	ANKRD6	ANO3	APEX1	APH1A
APH1B	APLP2	APOA1	APOC1	APOC1P1	APOC2	APOC4
APOD	APOE	LRP8	APOF	LPA	APOM	APP
NAE1	APPBP2	PRNP	ARHGAP30	ARPP19	SRRT	ARSB
ASAH1	ATAD2	ATF2	ATF4	ATP10B	ATP13A5	ATP8A1
ATXN7L1	ADCY2	ACAN	ADAMTS4	AGRN	SERPINA1	ACTR1A
SNCA	IAPP	AR	ANK3	ANXA13	TNFSF10	AQP1
ARSA	AXIN1	B4GALT3	B9D2	BACE1	BACE2	PBRM1
SMARCD3	ADGRB3	BAP1	DDX39B	BCAM	BCAS3	BCR
BCYRN1	BCHE	BDNF	BDNF-AS	BICC1	BIN1	PRUNE2
SLC25A14	BMP5	ASIC2	BRD3	BCL3	BCL2L2	BECN1
ADRB1	CTNNB1	BLMH	BRCA1	C10orf55	C14orf177	CLUHP3

MTHFD1L	STUM	C1R	MROH8	PP2D1	C5AR1	C6orf48
CACNA1C	CACNA2D4	CALB1	CAMK1D	CARD8	NEDD9	CBLC
CBS	CCDC83	CACNG4	CCL2	CCR3	CCR5	CD14
CR2	CD2AP	CD33	CD40	CD40LG	CD8A	CD86
CDK1	CDK5	CDK5R1	CDK5R2	CDON	CEACAM16	CEP164
CETP	CFTR	CHD6	STUB1	CHAT	CLCN6	CLEC16A
CLIC5	CLPTM1	CNGB1	CNR2	CNTN5	COG1	VPS13B
COL18A1	COMT	COPA	COX6C	PTGS1	PTGS2	COX10
CR1	CR1L	CREB1	CRHR1	LINC02210-CRHR1	CRP	CSF1
CSTF2T	CTGF	CUX2	TET1	CYP17A1	CYP19A1	CYP1A1
CYP27C1	CYP46A1	CAMK1	CAMK2A	CAMK2G	RCAN1	S100A9
S100A12	CAPN1	CAST	CSNK1D	CSNK2A2	CASP2	CASP3
CASP4	CASP8	CASP9	CNTNAP2	CTNNA3	CTSB	CTSD
CTSS	ADAP1	CP	CH25H	CHGA	CLU	F5
F8	F13A1	COL19A1	CRH	CSMD1	CUBN	CCNC
CCND1	CST3	DAPK1	DAXX	ASAP2	DEDD	DEFB122
GLUD1	DIO1	DIO2	DIP2C	DIRAS2	DISC1	PARK7
DKK1	DLD	DLGAP1	POLB	DNAJC12	DNMBP	DONSON
KCNIP3	TSC22D3	DVL1	DYNC1I1	DYRK1A	CTNND2	DRD1
DRD3	DRD4	DBN1	DNM2	E2F1	EBF3	ECE1
EDEM2	EFCAB7	EGR1	ELOVL6	ENO1	ENO2	ENTPD7
ERAP1	ERG	KCNH6	MAPK3	MAPK1	ESR1	ESR2
CELF2	EYA4	EYS	POMK	EPHA1	EPHA5	EFNA5
EPOR	ERBB4	FAAH	FAF1	OTULIN	CALHM1	MINDY1
FAM89B	UBD	FDPS	FGF1	FHIT	ENOX1	INO80D
BASP1-AS1	C5orf64	FMNL2	FMO2	FSTL5	FTO	FNTA
FASLG	FAS	FCER1G	FCGR2B	APBB1	APBB2	APBB3
AHSG	FLOT1	FYN	GNAO1	GNB3	GAPDH	GAPDHS
GCNT1	GAB2	GALNT17	GBP2	GABBR1	GCFC2	PLEKHG5
GFAP	GGA1	SLC1A3	GBA	GLUL	GLS2	GOLM1
RXFP3	ADGRG1	GRAMD1B	GRK2	GSK3A	GSK3B	GSTA4
GSTO1	GSTO2	GSTP1	GSTT1	GAL	GALP	SNCG
GSN	GHRL	GRIA1	GRIA4	GP6	GPC1	FABP3
HSD17B10	HECW1	HHEX	HLA-A	HFE	HLX-AS1	HLX
HMGCR	HMGB1	HMGCS2	ARHGAP45	HOOK3	HSD11B1	HSPB8
HSPA1B	HSPA2	CWC15	HTR1A	HTR2A	HTR2C	HTR6
ZWINT	HMOX1	ELAVL4	RNR2	HTT	IGFBP2	IGFBP3
IGFBP6	ICAM1	ICAM4	IDE	IFNG	IGF1	IGF1R

IGF2	IGF2R	IL1A	IL1B	IL10	IL18	IL2
IL33	IL6	IL1RN	IL6R	CXCR2	IMMP2L	CXCL10
ITPR1	IQCK	IREB2	TCF4	ITGAM	ITM2B	IVD
INS	INSR	IQCE	JAK2	F11R	MAPK8IP1	KLHDC9
KCNAB2	KCNH7	KCNMA1-AS1	KCNQ3	CKB	WASHC4	KANSL1
FAM214A	FAM120B	WWC1	KIF13B	KIF26B	KLC1	KIF11
KLK10	KLK6	KLK7	SLC4A1AP	KCNC4	L3MBTL4	LAMA1
LAMC1	LDLR	LHCGR	LHFPL6	LINC00466	LINC00475	LINC00836
LINC01122	LIPA	STK11	LMOD3	LOC101929570	LOC145845	RBM15-AS1
EMBP1	LPL	LRAT	LRP6	PPP1R37	LRRK2	LRRN2
LRRTM3	LRRTM4	LRTM2	LUZP2	LMNA	LCK	MAGI1
MAGI2	MAL2	MAOA	MAOB	MAPT-AS1	MAPT-IT1	MARCH10
MARK1	MAT1A	MBOAT1	SLC16A7	ABCB1	MEF2A	MEIS1
MAP2K1	MAP2K2	MEX3A	MGAT5B	MGST1	MIF	CCL3
CCL4	CCL4L1	MMP12	MMP8	MPP7	MPZL1	LRPAP1
MRE11	MROH7-TTC4	MS4A4A	MSI1	MSR1	STK24	MTHFR
ND1	MTR	STXBP1	MYH13	MYH7B	KCNMA1	MTNR1A
MS4A6A	MYOCD	MYOF	MYO10	NACA	QPRT	NALCN
ART3	NAT1	NAT2	NAV2	NCAM1	SLC8A1	NME1
NME1-NME2	NME2	NDRG2	NDUFS2	NEFH	NEFL	NGFR
TMEM147	NINJ2	NIPBL	NKAIN2	NKAPL	NOTCH1	NOTCH4
NPAS2	NPC2	NPFFR2	NPY	NQO1	GRIN1	GRIN2A
GRIN2B	SLC11A1	SLC11A2	NQO2	ITGB3BP	NTF3	NUMB
NECTIN2	NECTIN4	MME	NRG1	NCAN	NCSTN	NIT1
NKPD1	NXN	DLST	OGG1	OLIG2	OLR1	OPA1
OSGEP	OTUD7A	POU2F1	SELP	P2RY2	PADI2	SERPINE1
PARP1	PAXIP1	PCDH11X	PCGF5	PCMTD1	PCSK9	PDE4B
PDE9A	PDZD7	MPO	PFDN2	PGBD1	PTGES2	PTGDS
PICALM	PITRM1	PRKACA	PRKCA	EIF2AK2	PLA1A	PLA2G2A
PLAC4	PLAT	PLAU	PLCE1	PLXDC2	PNMT	POLN
POMC	POMT1	PON1	PON2	PON3	POTEA	PPARD
PPARG	PCK1	PPID	PPOX	PPP1R11	PPP1R1C	PPP1R3B
PPP2R2B	PRDX1	PRDX2	PRDX3	APBB1IP	PRKAR2A	PRKAR2B
PRND	PRIMA1	DLG4	PSMB9	PSMC4	PTEN	HACD1
PTPRA	PURA	GART	PVR	ALDH18A1	PAWR	PCNX1
PSENEN	HSPG2	PIN1	PLG	PSEN1	PSEN2	PCSK1N
PDYN	GRN	PREP	PRKG1	PTK2B	RSPO2	RACK1
RAD51B	AGER	GAPVD1	RASSF4	RDH13	RGS4	RPN2

ROR1	PLPPR1	RTN4R	RAB6A	RELB	RTN4	S100B
SAMSN1	SAR1A	ZFYVE9	SBSN	SCARA3	SCN2A	SERPINA3
SERPINF2	SLC6A4	SREK1IP1	SHISA9	ST6GAL1	SLC18A3	SLC1A2
SLC1A7	SLC4A2	SLC5A12	SLC6A17	SMAD3	NCOR2	SNAP25
SNCA-AS1	SNORD52	SNX10	SNX3	SOAT1	SOD1	SOD2
SORCS2	SORL1	SOS2	SP1	SGPL1	SCARB1	SIGMAR1
ZSCAN26	SSSCA1	SUPV3L1	SVIL	SYP	STH	SEC24C
CHGB	SEMA3A	SEPT1	SEPT3	SEPT7	SQSTM1	SIRT1
SST	GH1	SORCS1	SORCS3	STMN1	STXBP5L	SYN1
SYNPR	SYT1	STX8	ZNF365	TRIOBP	TARDBP	TAS2R60
TBP	TCF7L2	TDRD10	TEAD1	TEP1	TFAM	TFCP2
TFEB	TGFB1	TEK	TIMP1	TIMP2	TIMP3	TLK1
TLR4	TLR9	TM2D1	TMEM132D	TMEM147-AS1	TMEM177	TMED10
TNFRSF1A	TNFRSF1B	TNF	LTA	TNK1	TOMM40	TPH1
TPPP	THRA	TREM2	TRIM15	TRPC4AP	TSNAX-DISC1	TSPAN18
TSTD1	TTC27	TUSC3	TXNRD2	MAPT	TSPAN2	THOP1
TIAM1	KAT5	TMEM132C	TMTC1	TCN1	TCN2	TF
TTR	NTRK1	NTRK2	NTRK3	TTC4	TSC2	U2AF1L4
UBB	UBE2D1	UBE2Q1	UBXN4	UCHL1	UFC1	UGCG
UMAD1	UNC13C	USF1	USP21	USP35	UXS1	UBQLN1
UFSP1	MPP6	VDR	VEGFA	ZNF197	VSNL1	HPCAL1
MAVS	VLDLR	WDFY4	WT1	WEE1	APBA1	APBA2
XRCC1	XYLT1	TRAK2	ZBP1	ZFYVE19	ZNF155	ZNF224
ZNF225	ZKSCAN4	ZNF320	ZSCAN31	ZDHHC7	ZNF720	ZNF804A
ZC3H3	SLC30A1	SLC30A4	SLC30A6	ZYX	ABL1	RAF1
RAPGEF4	EEF2	EEF2K	EIF2S1	EIF4E	NOS3	MIR4713
MIR4761	MIR6843	MIR6886	MIR7846	NOS2	MTOR	TRNQ
CHRNA2	CHRNA3	CHRNA4	CHRNA6	CHRFAM7A	CHRNA7	CHRNB2
CHRNB4	NOS1	RELN	CDKN1B	TP53	RPS6KB1	TP73
ABCC13	AD10	AD11	AD12	AD13	AD14	AD15
AD16	AD5	AD6	AD7	AD8	AD9	ADORA2A
AGBL4-IT1	ALB	AMIGO2	APCS	APLP1	APOC4-APOC2	AQP4
ARMCX5-GPRASP2	ATP5F1A	AZIN1-AS1	BACH1	BHLHB9	CASP1	CASP6
CASP7	CCL11	CCL4L2	CCL5	CCL7	CD36	CFAP410
CHAF1B	CNR1	COL18A1-AS1	CRYAB	CXCR3	CYP2D7	CYP7B1
DAGLA	EPHA1-AS1	ERBB2	ERBB3	GCG	GHRLOS	GNAS

GPR55	GRIA2	GRIA3	HCRT	HNRNPA2B1	HP	IL12A
IL12B	KALRN	KLK8	LINC00211	LINC00972	LINC01081	LINC01266
LINC01492	LINC01501	LINC02254	LINC02516	LOC100130587	LOC100287329	LOC100379224
LOC100996288	LOC101927502	LOC101928418	LOC101928651	LOC101928961	LOC102724297	LOC414300
LOC541472	LOC643387	LOC646506	LRRC15	MELTF	MEOX2	MGLL
MMP2	MMP9	MS	MS4A4E	MUC22	NAPEPLD	OAT
P4HA3-AS1	PAK1	PDE8B	PLUT	PRDX6	PRKXP1	RABGAP1L
RNF146	SERPINF1	SLC18A2	SLC6A3	SNCB	SSSCA1-AS1	SYNPR-AS1
TNFAIP1	TRPV1	ANKRD22	LINC00624	RAD23BP2 - SEMA3A	MECOM	MCPH1-AS1
AKR7A3	IRAK1BP1	SCAPER	CEP63	SEC24B-AS1	TENM4	TMCO4
NACAP6 - LINC02150	DYSF - RPS20P10	DLC1	TMEM94	PLCL1	GPR180	LINC00626 - SUMO1P2
BAALC-AS1, BAALC	CCZ1B - OR7E39P	PCSK6	RF00438 - R3HDM2P2	CFAP74	CCDC112 - CTNNA1P1	CTNND2 - RNU6-679P
FAM240B	SLMAP	AOX1	UNC93B4	CDH1	IQGAP2	RASSF8
CEP295NL, TIMP2	FAM19A5	KLHL36 - USP10	PIFO	IGSF23	SELENOO	CDCA7L - RAPGEF5
BNIP3P13 - ZNF90	SYNGAP1	SESTD1	TAS2R5	CSNK2A1 - TCF15	C9orf152 - TXN	FAT3
RDX	ABCA8	STEAP3 - C2orf76	NEK10	ERO1A - PSMC6	RNU7-188P - SEM1	SEC24B
GTF2H3	PTPRS - ZNRF4	RASSF5	COL25A1	HMCN1	NAALADL2	RN7SKP120 - TUSC1
RNA5SP169 - LINC02273	KSR2	MDGA2 - MIR548Y	OSER1-DT - GDAP1L1	JPH3	AQP4-AS1	DNAH6
HDAC9	SHANK2	UGT1A10, UGT1A8	TBXAS1	KIFC3 - CNGB1	LINC02103 - RNU6-909P	TSNAX-DISC1, DISC1
LINC01725	PAX2	PROX1-AS1	RN7SKP168 - ZFYVE9P2	ATP8A2P3, RNF6	EDAR - RF00017	EPC2 - RNU2-9P
	APOC1 -	MTCYBP27	SIGLEC22P	BIN1 -	MRPL58 -	FBXL7

	APOC1P1	- RNU6-976P	- CD33	NIFKP9	RNU6-362P	
CACNA2D3	ADAMTS9-AS2	DCHS2	PUM3	HRK	SLC28A1	MLN - LINC01016
DYNLL1P4 - RBM19	PRRC2C	FMN2	CTNNA2	LIMS2	MOBP	STK32B
AFF1	ANKRD55	PGAM5P1	CAMK4	DMXL1	MEGF10	LINC01184
SAP30L	PLEKHG1	BZW2	CYCS	ELMO1	EXOC4	NCS1
PLPP4	SPON1	ARHGAP20	SLC4A8	CRADD	ANO4	GPC6
MYO16	CLMN	GABRG3	LIPC-AS1, ALDH1A2, LIPC	TNRC6A, LINC01567	VAT1L	SP6
CACNA1G	PPIAP59	TGM6	PARVB	RPS17P11 - MFSD4BP1	RPL3P11 - ATP5PDP3	CASC18
NDUFA12	FANCD2OS, FANCD2	RN7SL782P - RN7SKP122	IL19	NCKAP5 - RN7SKP93	CCDC85C	SDR9C7
NARS2	PKNOX2	LMOD3 - FRMD4B	SLC25A6P5 - LINC01505	LINC02098 - ETS1	OSBPL6	RNU6-248P - RNU6-261P
HNF4G - RNU2-54P	LAMP1	RBFOX1	ARVCF	UBXN11	HYI, SZT2	AHCYL1
RF00012 - NMNAT1P2	TGFB2	RNU4-77P - KCNK1	ITSN2	OTOF	MSH2	LINC01185
RAB1A - RF00090	SPRED2	LINC01965	RN7SKP141 - SMC4P1	COL4A4	RANP7 - SALL4P5	RPEP2 - HMGB3P12
C3orf67	PTPRG	RN7SL271P - UBE2Q2P9	LINC02008	TFP1	RNU6-637P - TERC	SNRPCP13 - ENPP7P11
RNU6-412P - RAC1P2	BANK1 - SLC39A8	SETD7	SH3RF1	LINC02268	RNU6-381P - FGF10	F2R - F2RL1
WDR41	MEF2C-AS1	RPS17P2 - LINC02214	RF00019 - ZCCHC10	LARS	G3BP1	KDM1B
CDKAL1	DST	COL12A1	LINC02532 - CD24	SGK1	SNX9	TULP4
PHF14	MTDHP1 - ZNF117	PQLC1P1 - EEF1A1P28	DLX5	LYPLA1P1 - IQUB	INSIG1	NKAIN3
SGK3	PPP1R42	FZD6 - CTHRC1	PDCD1LG2	LINC01243 - MTATP6P3	ATP5MFP3 - RFC5P1	LINC00476

				0		
FOXE1 - TRMO	MTND3P4 - ARL2BPP7	PNPLA7	WAC	RPL34P19 - RN7SL825P	C10orf71	RNU6-478P - MARK2P15
MICAL2	TRIM51CP	AHNAK	CCDC89	AICDA	OVCH1-AS1	RNU7-106P - OTOGL
TPTE2P3	RABEPKP1 - DACH1	ARF4P4 - LINC00377	FARP1	LINC00343	FAM181A	LINC02304 - LINC02325
HERC2	TRPM1	THSD4	AGBL1	TMC5	SDR42E2	CDH13
ALOX12-AS1	COX10-AS1	MPP3 - CD300LG	DCAF7	TCAM1P	CDH19 - RNU6-1037P	ZNF813
CST1 - CSTP2	RPS2P1 - ASIP	LINC01271 - RN7SL636P	SYNJ1	TEX33 - TST	RAB20	PDS5B
SPSB1	BDH1, BDH1	ADARB2	TOP1	LIN28B	C2orf83	TIAM2
RPL7P19 - ETF1	GOLIM4	RNF165	SLC25A48	COLGALT2	ABCB11	ARAP2
IRF2	AKAP9	DSCAML1	IL34	LINC01838 - ZNF30-AS1	SLC25A5P3 - VSTM2A	TRIQK
LINC01508	RSPO4	KAZN	CCDC134	MS4A4E - MS4A4A	PICALM - RNU6-560P	CLU - SCARA3
ZNF292	CDC42EP3	UTS2B	PAK2	ADCY8	RNF219-AS1	RORA-AS1
SLC44A5	NME9	CCRL2	MMP3 - MMP12	NFU1P1 - MYRIP	NRXN3	TLN2
BMPER	SLC8A1-AS1	SLC9A9	EFR3A	LINC02343	SLC24A4	ZFP3 - ZNF232
CEACAM22P	RF00285 - BCL3	MS4A4A - MS4A6E	BCAM - NECTIN2	TOMM40 - APOE	APOC4	APOC2
CLASRP	GEMIN7-AS1	PPP1R37	INPP5D	CD2AP - ADGRF2	ADGRF2	PILRA
AGFG2	AP4M1	CASTOR3	PMS2P1	EPHX2	GULOP	PSMC3 - RAPSN
SPI1	FERMT2	BCKDK	ZNF232	CNN2	CEACAM20	APOC4
CLPTM1 - RELB	GEMIN7	MARK4, PPP1R37	GEMIN7-AS1	EXOC3L2, MARK4	MARK4, EXOC3L2	CSTF1 - CASS4
HLA-DRB1 -	GPR141, EPDR1	CELF1	CLU	CR1; CR1	MTCO3P30	SLC2A9

HLA-DQA1						
RNU1-80P - TNRC6C	RIMBP2	RNU6-276P - EXOC1L	KRT18P16 - LINC01170	SUCLG2	GMNC - OSTN	GLIS3
PFDN1 - HBEGF	NFIC	ZAP70	PUS1	MAP2K5	ANGPT4	ARIH1
LINC01098	HIGD1AP3 - MSX2	FAM83E	RNU4ATAC8 P - LRRIQ3	KCNN3	HSPA8P9 - CLDN18	RN7SL691P
IL21-AS1	SERINC5 - KRT18P45	CDC42SE2	SH2D4B	FRMD4A	IRF6	PMS2CL
THSD7A - TMEM106B	LINC02210-CRHR1	ARL17B	WNT3	HID1-AS1 - CDR2L	MACROD2 - PPIAP17	DAPL1
PDE1A	CADM2	FBXO40	OFCC1	PEX6	SORD	LINC01684
ABI3	PLCG2	RHBDF1	ATP5F1C	BSG	C11orf65, ATM	TECTA
TREM2 - TREML2	NDUFAF6	AP2A2	IGHV2-70 - IGHV3-71	TRIP4	ZCWPW1	CASS4

Psychosis-related genes

HTR2A	DRD2	HTR7	GRB10	SLAMF1
NFKB1	ACKR1	AS1	ZNF618	COMT
GRM7	AGER	SLITRK1	ADGRL2	GSAP
TMEM26	AQP8	HS3ST3A1	SCN8A	RGS6
FAM43A	NRG3	AC087071.1	CAMKMT	SLC3A1
STX8	ZNF473	NSG1	PLA2G4A	DOCK1
FAR2P1	ST5	HS3ST4	COMT	MKNK1
KIT	TBX1	CNTN4	LIPC	AC079950.1
CCDC60	MSRA	CEACAM21	AC108734.4	TCF4
BCL9	TMEM245	COL25A1	SGCD	LINC00499
ADCK1	C3orf38	CCDC122	PHF20	ENOX1
PTPN6	EFNA5	DMAC1	AC012254.2	NFS1
PLCB1	COL26A1	IQGAP2	DLGAP2	MECR
CTNNA2	STXBP5L	TENM4	EYS	AC009468.1
BMPR1B	NRG2	TCHP	HS6ST1	CEP41
SLC14A2	COLGALT2	RGL1	CSMD1	NAV2
RICTOR	OSMR	AC009652.2	COL12A1	KHDRBS2
MPP4	TEP1	LINC01435	NFATC2	MEGF10
SPATA6L	PCDH7	CNTNAP5	TNIK	SPATA6L
NBEA	RTN1	RBFOX1	FANCA	RBKS

ZNF385B	GPM6A	TENM3	MIR583HG	ATXN7L1
FAM120A	MAD1L1	AC120114.1	CWC22	GRM3
LINC01725	CACNA1C	KLF12	AKAP6	APOPT1
AC104574.2	MSI2	ZEB2	RMND5A	FXR1
SLC39A8	BANK1	GRIA1	SLC17A3	POM121L2
ZSCAN31	CARMIL1	ABCB1	IMMP2L	AL161716.1
GLIS3	MRTFA	AKT3	FHIT	AC244033.2
SH3GL3	ZSWIM6	SHC4	AL672167.1	NTRK3
RALGAPA1	TMEM132D	CIR1	HCN1	ADCY1
NR3C2	SPATS2L	LPP	GABBR2	CNTN2
ZFHX3	AC092650.1	DST	ZDHHC2	KLF6
RPSAP52	PLCL1	EFR3B	ERCC8	XYLB
GRID1	DLG2	DNAJC11	CALN1	NOL4
MOSMO	ZDHHC8	RAB8B	PIK3C2A	SMG6
ZNF536	PRKD1	AL022476.1	EMX1	AL163541.1
GGNBP1	MPHOSPH9	SHISA6	TENM2	TBC1D29P
PCLO	ARHGAP40	INHBA	ZBTB7B	ADGRV1
NOS1	DOP1B	DNAH1	CACNA1D	LIMK2
KIF1BP	TBC1D5	TMEM182	CHRNA2	SFMBT1
MIR137HG	BCL11B	LILRP2	AL591368.1	EEFSEC
MAIP1	AC011306.1	OPCML	FRMD5	FAM86B3P
SCAPER	KYAT1	PTPRF	PSORS1C1	LIN28B
NAB2	ZNF664	NLGN1	SPG7	AC114763.1
AC008667.1	MIRLET7BHG	ROBO2	NTM	AL583808.1
NPAS3	LHFPL3	AC022784.1	DGKI	CDC25C
CYP26B1	QPCT	CACNA1I	SNAP91	SDCCAG8
ETF1	RIT1	AC091862.1	BTN3A1	AL662884.2
TSNARE1	STUM	LINC02219	EPN2	MAN2A1
LIMA1	DOP1A	SRR	LINC02267	DCC
PLCH2	FURIN	LEMD2	MAGI2	ASAP1
PTPRD	APBA1	ATP2A2	FAM214A	RUSC2
OSBPL10	TTC12	KALRN	TRPM6	MTHFD1L
OPRD1	NRGN	TSPAN2	CNNM2	ARHGEF26
ALMS1	AC021594.2	PRRG2	YPEL1	GNG7
ZBED4	MMP16	PCNX3	TCF20	AL035685.1
PPP1R16B	STK4	CLIP1	LRRTM4	HIST1H2APS4
PRKG1	SORCS3	CALB2	RHBDL3	ZNF804A
FOXP1	LINC02438	CMAHP	GUSBP2	TEK

SRPK2	DNAJA3	AP000688.2	STAG1	LINC00862
SATB2	ZFAND2B	PPP1R13B	NEU1	TMTC1
PCNX1	LINC00606	LINC01470	SLCO6A1	HFE
MSR1	EBLN3P	CACNB2	GLG1	LINC01539
ZCCHC14	PHACTR3	PTGIS	KIF21B	SCN9A
ZNF823	SP4	SOX5	GULOP	CMAHP
AL645941.2	CUX1	AC097634.4	IGSF9B	AC046136.1
MIR29B2CHG	NEGR1	TRAPPC3	CAPN2	LRRN2
ZCCHC17	VRK2	AC096570.1	SPHKAP	BCL11A
EPC2	TMEM178B	PPP2R3A	FRMD4B	KLHL29
DPYD	SLC9B2	SHISA9	AC008415.1	PTPRK
GRAMD1B	SNORC	POU6F2	FMN2	TTYH3
CHD2	AC090578.1	LINC01122	CPEB1	ANKRD23
FER	ALOX15P2	CACNB2	SKAP1	RTKN2
AL445623.2	MINDY2	DGKZ	TMCO5B	AC067752.1
CHRNA3	NFATC3	RPTOR	SPECC1	GID4
AP005203.1	PCBP3	THOC7	PSD3	THRB
ZDHHC20	PCDH9	FOXO3	AIG1	SYNGAP1
ADAMTSL3	HS6ST3	GPC6	ANKRD36	SNAPC3
SUFU	HECW2	AL391117.1	ATP2B2	PLCL2
ELAC2	YWHAE	GRIN2A	U91319.1	HCP5
ITPR3	JAM3	AP002851.1	AL138974.1	FOXO6
CENPM	PEPD	BNIP3L	PAK2	CLCN3
AC117377.1	POC1B	TACC2	LINC02551	LRP4
C12orf76	AC016866.1	NT5C2	LINC01360	AC009226.1
RN7SL100P	PCDH15	BICC1	AC024901.1	AC005906.2
AC002070.1	GPM6A	AL162726.3	KIAA0391	AL121694.1
AL358790.1	AP003174.1	MARK2	LETM2	AGO4
CRB1	NEURL1	CFAP58	MTUS2	ACTG1P22
CUL3	MGLL	GALNT10	LINC00301	GRIN2B
IQANK1	RALGPS1	GALNT2	DMTF1	EBNA1BP2
PDE4B	LINC01776	ELAVL4	AL138927.1	SLC45A1
LINC02549	CCDC192	AP003049.2	LINC01583	AC087564.1
CIB4	SLC1A1	AL390957.1	LINC01310	DNAJB5
SPOCK1	PIGO	LINC00303	AC116337.3	ZP1
AC093766.1	CNTNAP4	ZNF665	DKK3	RELN
AGBL1	ACSM1	TRAF3	PIK3C2G	HHAT
ZFYVE28	LINC01255	RORA	KIF26B	NLRC5
ARNTL	CDH13	FARSB	SGK1	RENBP

TBXAS1	SGCZ	AGAP1	FEZ1	ANK3
PLAA	ACSM3	NOTCH4	BRD1	FBXO11
ARHGAP31	NKAIN2	PRRC2A	SNX29	AC027458.1
ANO4	AC026167.1	VIPAS39	B9D1	ZFAND6
PDE5A	SLC47A2	RASGRF2	EVL	PRMT8
PTPN13	TCERG1L	CACNA1S	AC060809.1	LINC01505
SAMD4A	PLD1	SIGLEC15	CHCHD6	PHACTR2
CR1	AC005871.2	RNF135	POMT2	CTNNA3
PIM3	EGFEM1P	USP24	SLC5A10	AL117329.1
POLN	AF127577.4	AC104041.1	AC092957.1	AC091078.1
ZBBX	ADGRE3	OXR1	EIF3F	CWH43
AC007179.2	NRP1	MIR100HG	TUSC3	XKR6
CACNA1B	AL512506.3	OSCP1	PRKN	NSMCE2
AFF3	AC091114.1	PTPRT	DPP10	FAP
AC018767.3	AC011369.1	CR1L	LINC02223	HIBCH
FSTL5	VPS45	MIR4432HG	ZNF362	TDRP
PECR	AMBP	ARHGEF28	CALD1	AC008892.1
CA12	NXN	GVQW3	PRLR	SLC17A6
TOX	ZNF611	SERPINA1	AC114689.3	C1orf167
ARL3	AC040169.4	AC069234.1	GTF2IP7	EEPD1
SIPA1L2	SPAG16	COL21A1	RASGEF1B	Z82202.2
AC078923.1	LINC01320	PPP3R1	RASSF1	LINC02232
FYN	YWHAG	KIAA1217	CLSTN3	HIP1R
AF123462.1	RYR3	AC006305.1	RERE	TRANK1
PBRM1	TNXB	UBE2Q2P1	AC022031.2	ITIH3
HYKK	CARMIL1	HIST1H1PS1	NT5C2	MDK
AMBRA1	IMMP2L	MEF2C	FAM86B3P	SFXN5
STK19	KDM4C	ZNF365	OR5V1	ZKSCAN4
TRIM27	AL662860.1	TRIM26	COX11P1	ZBED9
SFTA2	AL121936.2	HCP5	FLOT1	AL138726.1
SLC17A4	NSUN6	SLC7A6	AC092167.1	ADAM10
SLC9B1	PPP2R2B	FAM184A	PRDM14	ZFPM2
FES	TAOK2	AC012322.1	MAU2	ARHGEF10L
CABLES1	IPO8	LMO7	LTN1	PCDH12
PLCB4	RPN2	STX2	ZNF740	C11orf21
CCDC102B	GIGYF1	TMPRSS5	KSR2	UXS1
ACTL7A	ATP6V1E2	PHF2P2	LSM1	EDIL3
LRP1B	AC008474.1	NKAPL	TSPAN18	MPC2

LSM1	ITIH1	SPTLC1	MSRA	COMMD10
LINC00243	AC069228.1	AL138889.2	LINC01478	GABBR1
AC091096.1	TCF7L2	AGBL4	PSORS1C1	AL139300.2
DOCK4	TTLL6	ST3GAL1	ADAMTS16	ZZEF1
LINC01592	AC000403.1	RFESD	SNED1	ZNF93
FTCDNL1	GIGYF2	LINC00637	TMEM219	R3HDM2
SCAF1	AC104162.2	NLGN4X	NDRG4	NSD3
GSDME	RAI1	PLA2G15	SLC4A10	FAM178B
FAM177A1	LINC00461	AC007570.1	ZKSCAN3	OR5V1
DDR1	NGEF	AL662884.1	HIST1H2BN	ZSCAN9
MAD1L1	MUCL3	MIR137HG	CNOT1	F2
BTN2A2	FGFR1	CYP2D7	TWF2	RFT1
MTCO3P1	PBX2	LINC00240	CHRNA5	BTN3A2
OR11A1	KDM3B	BTN2A1	TRIM10	MUC22
C2	PBX2	HCG20	EHMT2	ATAT1
SFTA2	AL645929.2	STT3A	PLCB2	PTPRG
ITIH4	LINC02033	C12orf65	THOC7	AL807742.1
PRPF3	KIF5C	AL392086.1	AC007221.2	CLEC17A
PALB2	MPP6	GLT8D1	AC010538.1	ANKS1B
SLC35F2	SYNE1	HDAC4	ZNRD1	ZNF615
AC090993.1	SEMA3A	MRM2	GRIK1	ZMIZ1
AP001267.5	AC104009.1	NOTCH4	DRD3	CACNA1C

Vitamin D-perturbed genes

VDR	CYP27B1	CYP27A1	CYP2R1	CYP24A1
CD14	ATF3	THBD	SPP1	SERPINA1
FOS	GEM	EFTUD1	IL8	G0S2
TREM1	FN1	CLMN	THBS1	MAPK13
LCN2	EDNRA	CXCL1	FBP1	EGR1
CYP26B1	SHE	IFIT1	STAC3	VCAN
DPP4	CYP51A1	A2M	CAMP	HBEGF
EDN1	S100A8	OSR2	SULT1C2	SLC22A3
GCLC	C15orf48	HOPX	TGFB2	CYP19A1
GPNMB	DDX27	INMT	TIMP3	CD36
KCNK3	NREP	PDK4	IBSP	FGF9
MYC	CCL2	DLX5	SEMA6B	SEMA3C
HAVCR1	ALOX15	S100A4	GZMB	TGM2
HSD11B1	BTG2	CTSH	CYP1A1	CILP

BHLHE40	CCND2	AFP	IGFBP1	PPP2CA
CRISPLD2	TNC	ZFP36	NME1	CCL22
FABP4	CYP3A4	SCD	ORM1	VNN1
CA2	RGN	COL3A1	DUSP5	MED1
TNFRSF1	C20orf197	HMGCS1	PVALB	NR0B2
PHLDA1	BCAT1	MMP12	C3	ROCK2

Antipsychotics-perturbed genes

DRD2	ACE	CACNA1G	HRH1	ADRA1A
ADRA1B	HTR2A	HTR2B	DRD4	HTR1A
ADRA1D	SLC6A2	HTR3A	DRD1	HTR2C
OPRD1	SLC6A4	SLC18A2	CHRM2	CHRM3
CHRM5	DRD3	HTR7	ADRB1	CHRM4
CHRM1	HTR1D	HRH4	CALY	EGR1
FOS	ATF3	CYP1A1	CYP51A1	CDK1
HMGCS1	CTGF	SULT1A1	MEIS2	CCNA2
ALB	ONECUT1	HERPUD1	GDF15	CA3
RRM2	STAC3	DDX27	EGR2	PHLDA1
CYP2E1	CCNB2	DBP	PPP2CA	HAMP
MKI67	RGN	BHLHE40	NREP	PLAU
SCD	FAM111A	HMOX1	SLC22A8	JUN
GJB1	CDKN1A	ALDH1A1	GZMB	DDIT4
CSDC2	TAGLN	CXCL1	IFIT1	RSAD2
CHAC1	SOX11	ZNF354A	FGF9	IGFBP5
CTH	FABP1	INSIG1	HSPA1B	LTN1
EDNRA	CCL2	LOC1720	CYP1B1	ENPP2
KLF4	NR4A3	LOX	SPP1	NR1D2
PPP3CA	CEP104	LDLR	HOMER1	IDI1

Appendix B Supplementary Material for Chapter 2.2

ST1 Network metrics of the networks built with all drug targets

	Node Number	Global Efficiency	Local Efficiency	Small-world Coefficient (sigma)
AD+P network	1839	0.221	0.214	5.257
SCZ network	1578	0.234	0.220	6.978

ST2 Antipsychotics and their targets

DRUG NAME	TARGET	Target Gene	Class
Acepromazine	5-hydroxytryptamine receptor 1A	HTR1A	Non_SGA
Acepromazine	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Acepromazine	Dopamine D1 receptor	DRD1	Non_SGA
Acepromazine	Dopamine D2 receptor	DRD2	Non_SGA
Acepromazine	Serum albumin	ALB	Non_SGA
Aceprometazine	Histamine H1 receptor	HRH1	Non_SGA
Acetophenazine	Androgen receptor	AR	Non_SGA
Acetophenazine	Dopamine D1 receptor	DRD1	Non_SGA
Alimemazine	Histamine H1 receptor	HRH1	Non_SGA
Amoxapine	Sodium-dependent serotonin transporter	SLC6A4	Non_SG

			A
Amperozide	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Chlorpromazine	5-hydroxytryptamine receptor 1A	HTR1A	Non_SGA
Chlorpromazine	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Chlorpromazine	Alpha-1A adrenergic receptor	ADRA1A	Non_SGA
Chlorpromazine	Alpha-1B adrenergic receptor	ADRA1B	Non_SGA
Chlorpromazine	Dopamine D1 receptor	DRD1	Non_SGA
Chlorpromazine	Dopamine D2 receptor	DRD2	Non_SGA
Chlorpromazine	Histamine H1 receptor	HRH1	Non_SGA
Chlorprothixene	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Chlorprothixene	5-hydroxytryptamine receptor 2B	HTR2B	Non_SGA
Chlorprothixene	5-hydroxytryptamine receptor 2C	HTR2C	Non_SGA
Chlorprothixene	Dopamine D1 receptor	DRD1	Non_SGA
Chlorprothixene	Dopamine D2 receptor	DRD2	Non_SGA
Chlorprothixene	Dopamine D3 receptor	DRD3	Non_SGA
Dapiprazole	Alpha-1A adrenergic receptor	ADRA1A	Non_SGA
Dapiprazole	Alpha-1B adrenergic receptor	ADRA1B	Non_SGA
Dapiprazole	Alpha-1D adrenergic receptor	ADRA1D	Non_SGA
Droperidol	Alpha-1A adrenergic receptor	ADRA1A	Non_SGA
Droperidol	Dopamine D2 receptor	DRD2	Non_SGA
Flupentixol	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Flupentixol	Alpha-1A adrenergic receptor	ADRA1A	Non_SGA
Flupentixol	Dopamine D1 receptor	DRD1	Non_SGA

Flupentixol	Dopamine D2 receptor	DRD2	Non_SGA
Fluphenazine	Dopamine D1 receptor	DRD1	Non_SGA
Fluphenazine	Dopamine D2 receptor	DRD2	Non_SGA
Fluspirilene	Dopamine D2 receptor	DRD2	Non_SGA
Haloperidol	5-hydroxytryptamine receptor 2C	HTR2C	Non_SGA
Haloperidol	Dopamine D2 receptor	DRD2	Non_SGA
Loxapine	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Loxapine	Dopamine D2 receptor	DRD2	Non_SGA
Mesoridazine	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Mesoridazine	Dopamine D2 receptor	DRD2	Non_SGA
Methotrimeprazine	Dopamine D2 receptor	DRD2	Non_SGA
Methylene blue	Guanylate cyclase soluble subunit alpha-2	GUCY1A2	Non_SGA
Methylene blue	Nitric oxide synthase, brain	NOS1	Non_SGA
Molindone	Dopamine D2 receptor	DRD2	Non_SGA
Moricizine	Sodium channel protein type 5 subunit alpha	SCN5A	Non_SGA
Periciazine	Alpha-2A adrenergic receptor	ADRA2A	Non_SGA
Periciazine	Dopamine D1 receptor	DRD1	Non_SGA
Perphenazine	Dopamine D1 receptor	DRD1	Non_SGA
Perphenazine	Dopamine D2 receptor	DRD2	Non_SGA
Pimozide	Dopamine D2 receptor	DRD2	Non_SGA
Pimozide	Dopamine D3 receptor	DRD3	Non_SGA
Pimozide	Potassium voltage-gated channel subfamily H member 2	KCNH2	Non_SGA
Pipotiazine	5-hydroxytryptamine receptor 1A	HTR1A	Non_SGA

Pipotiazine	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Pipotiazine	Dopamine D1 receptor	DRD1	Non_SGA
Pipotiazine	Dopamine D2 receptor	DRD2	Non_SGA
Prochlorperazine	Dopamine D2 receptor	DRD2	Non_SGA
Promazine	Dopamine D2 receptor	DRD2	Non_SGA
Promethazine	Histamine H1 receptor	HRH1	Non_SGA
Remoxipride	Dopamine D2 receptor	DRD2	Non_SGA
Reserpine	Synaptic vesicular amine transporter	SLC18A2	Non_SGA
Sulpiride	Dopamine D2 receptor	DRD2	Non_SGA
Thioproperazine	5-hydroxytryptamine receptor 1A	HTR1A	Non_SGA
Thioproperazine	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Thioproperazine	Alpha-1A adrenergic receptor	ADRA1A	Non_SGA
Thioproperazine	Alpha-1B adrenergic receptor	ADRA1B	Non_SGA
Thioproperazine	Dopamine D2 receptor	DRD2	Non_SGA
Thioridazine	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Thioridazine	Alpha-1A adrenergic receptor	ADRA1A	Non_SGA
Thioridazine	Alpha-1B adrenergic receptor	ADRA1B	Non_SGA
Thioridazine	Dopamine D1 receptor	DRD1	Non_SGA
Thioridazine	Dopamine D2 receptor	DRD2	Non_SGA
Thiothixene	5-hydroxytryptamine receptor 2A	HTR2A	Non_SGA
Thiothixene	Dopamine D1 receptor	DRD1	Non_SGA
Thiothixene	Dopamine D2 receptor	DRD2	Non_SGA
Tiapride	Dopamine D2 receptor	DRD2	Non_SGA

Tiapride	Dopamine D3 receptor	DRD3	Non_SGA
Trifluoperazine	Alpha-1A adrenergic receptor	ADRA1A	Non_SGA
Trifluoperazine	Dopamine D2 receptor	DRD2	Non_SGA
Trifluoperazine	Neuron-specific vesicular protein calcyon	CALY	Non_SGA
Triflupromazine	5-hydroxytryptamine receptor 2B	HTR2B	Non_SGA
Triflupromazine	Dopamine D1 receptor	DRD1	Non_SGA
Triflupromazine	Dopamine D2 receptor	DRD2	Non_SGA
Triflupromazine	Muscarinic acetylcholine receptor M1	CHRM1	Non_SGA
Triflupromazine	Muscarinic acetylcholine receptor M2	CHRM2	Non_SGA
Zuclopenthixol	Dopamine D1 receptor	DRD1	Non_SGA
Zuclopenthixol	Dopamine D2 receptor	DRD2	Non_SGA
Zuclopenthixol	Dopamine D5 receptor	DRD5	Non_SGA
Amisulpride	5-hydroxytryptamine receptor 7	HTR7	SGA
Amisulpride	Dopamine D2 receptor	DRD2	SGA
Aripiprazole	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Aripiprazole	Dopamine D2 receptor	DRD2	SGA
Aripiprazole lauroxil	5-hydroxytryptamine receptor 1A	HTR1A	SGA
Aripiprazole lauroxil	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Aripiprazole lauroxil	Dopamine D2 receptor	DRD2	SGA
Asenapine	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Asenapine	Dopamine D2 receptor	DRD2	SGA
Blonanserin	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Blonanserin	Dopamine D2 receptor	DRD2	SGA
Blonanserin	Dopamine D3 receptor	DRD3	SGA
Brexpiprazole	5-hydroxytryptamine receptor 1A	HTR1A	SGA
Brexpiprazole	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Brexpiprazole	Alpha-1B adrenergic receptor	ADRA1B	SGA
Brexpiprazole	Alpha-2C adrenergic receptor	ADRA2C	SGA
Brexpiprazole	Dopamine D2 receptor	DRD2	SGA

Cariprazine	5-hydroxytryptamine receptor 1A	HTR1A	SGA
Cariprazine	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Cariprazine	5-hydroxytryptamine receptor 2B	HTR2B	SGA
Cariprazine	Dopamine D2 receptor	DRD2	SGA
Cariprazine	Dopamine D3 receptor	DRD3	SGA
Cariprazine	Histamine H1 receptor	HRH1	SGA
Clozapine	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Clozapine	Dopamine D2 receptor	DRD2	SGA
Iloperidone	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Iloperidone	Dopamine D2 receptor	DRD2	SGA
Lumateperone	Dopamine D2 receptor	DRD2	SGA
Lurasidone	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Melperone	Dopamine D2 receptor	DRD2	SGA
Olanzapine	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Olanzapine	Dopamine D2 receptor	DRD2	SGA
Paliperidone	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Paliperidone	5-hydroxytryptamine receptor 2C	HTR2C	SGA
Paliperidone	Dopamine D2 receptor	DRD2	SGA
Paliperidone	Dopamine D3 receptor	DRD3	SGA
Paliperidone	Dopamine D4 receptor	DRD4	SGA
Perospirone	5-hydroxytryptamine receptor 1A	HTR1A	SGA
Perospirone	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Perospirone	Dopamine D2 receptor	DRD2	SGA
Pimavanserin	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Quetiapine	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Quetiapine	Dopamine D2 receptor	DRD2	SGA
Risperidone	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Risperidone	Dopamine D2 receptor	DRD2	SGA
Sertindole	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Sertindole	5-hydroxytryptamine receptor 2C	HTR2C	SGA
Sertindole	5-hydroxytryptamine receptor 6	HTR6	SGA
Sertindole	Dopamine D2 receptor	DRD2	SGA
Ziprasidone	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Ziprasidone	Dopamine D2 receptor	DRD2	SGA
Zotepine	5-hydroxytryptamine receptor 2A	HTR2A	SGA
Zotepine	5-hydroxytryptamine receptor 7	HTR7	SGA
Zotepine	D(1) dopamine receptor	DRD1	SGA
Zotepine	Dopamine D2 receptor	DRD2	SGA
Zotepine	Sodium-dependent noradrenaline transporter	SLC6A2	SGA
Zotepine	Sodium-dependent serotonin transporter	SLC6A4	SGA

ST3 Summary of binding data between antipsychotics and their targets

Drugs	target_pref_name	Ki	EC50	IC50	AC50
Amisulpride	Dopamine D2 receptor	12.59		3.04	
Amisulpride	Dopamine D3 receptor	3.981			
Amisulpride	Serotonin 2a (5-HT2a) receptor	630.96			
Amisulpride	Serotonin 2b (5-HT2b) receptor	316.23			
Amisulpride	Serotonin 7 (5-HT7) receptor	25.12			
Amoxapine	Alpha-1d adrenergic receptor	150		306	
Amoxapine	Alpha-2a adrenergic receptor	493		1314	
Amoxapine	Alpha-2b adrenergic receptor	255		558	
Amoxapine	Alpha-2c adrenergic receptor	461		3174	
Amoxapine	Dopamine D1 receptor	196		392	
Amoxapine	Dopamine D2 receptor	67		200	
Amoxapine	Dopamine D3 receptor	46		134	
Amoxapine	Dopamine D4 receptor	34			
Amoxapine	Histamine H1 receptor	11		99	
Amoxapine	Muscarinic acetylcholine receptor M1	287		1192	
Amoxapine	Muscarinic acetylcholine receptor M2	933		2623	
Amoxapine	Muscarinic acetylcholine receptor M3	378		1781	
Amoxapine	Muscarinic acetylcholine receptor M4	242		1737	
Amoxapine	Muscarinic acetylcholine receptor M5	615		856	
Amoxapine	Norepinephrine transporter	13		13	
Amoxapine	Serotonin 1a (5-HT1a) receptor	221			
Amoxapine	Serotonin 2a (5-HT2a) receptor	1.107		1.552	
Amoxapine	Serotonin 2b (5-HT2b) receptor	6.569		10	
Amoxapine	Serotonin 2c (5-HT2c) receptor	1.984		3.787	
Amoxapine	Serotonin 6 (5-HT6) receptor	35		76	
Amoxapine	Serotonin 7 (5-HT7) receptor	500			
Amoxapine	Serotonin transporter	18		34	
Aripiprazole	Alpha-1a adrenergic receptor	63		170	
Aripiprazole	Alpha-1b adrenergic receptor	100			
Aripiprazole	Alpha-2a adrenergic receptor	100			
Aripiprazole	Alpha-2b adrenergic receptor	1000			
Aripiprazole	Alpha-2c adrenergic receptor	100			
Aripiprazole	Dopamine D1 receptor	522.5			
Aripiprazole	Dopamine D2 receptor	1.732586207	956.5654167	15.804	
Aripiprazole	Dopamine D3 receptor	5.727866667	19.75		
Aripiprazole	Dopamine D4 receptor	192.164			
Aripiprazole	Dopamine D5 receptor	1312.75			

Aripiprazole	HERG	879.3333333		2337.74	
Aripiprazole	Histamine H1 receptor	62.55		420	
Aripiprazole	Histone H1.0	28			
Aripiprazole	Muscarinic acetylcholine receptor M1	1000			
Aripiprazole	Muscarinic acetylcholine receptor M2	1000			
Aripiprazole	Muscarinic acetylcholine receptor M3	1000		100000	
Aripiprazole	Muscarinic acetylcholine receptor M4	1000			
Aripiprazole	Muscarinic acetylcholine receptor M5	1000			
Aripiprazole	Serotonin 1a (5-HT1a) receptor	9.758454545	253		
Aripiprazole	Serotonin 1b (5-HT1b) receptor	1000			
Aripiprazole	Serotonin 1d (5-HT1d) receptor	100			
Aripiprazole	Serotonin 1e (5-HT1e) receptor	1000			
Aripiprazole	Serotonin 2a (5-HT2a) receptor	12.31388889		1945	
Aripiprazole	Serotonin 2b (5-HT2b) receptor	1.006333333			
Aripiprazole	Serotonin 2c (5-HT2c) receptor	245.6866667		1380	
Aripiprazole	Serotonin 3 (5-HT3) receptor	501.19			
Aripiprazole	Serotonin 3a (5-HT3a) receptor	1000			
Aripiprazole	Serotonin 5a (5-HT5a) receptor	1000			
Aripiprazole	Serotonin 6 (5-HT6) receptor	390.506			
Aripiprazole	Serotonin 7 (5-HT7) receptor	42.9			
Aripiprazole	Serotonin transporter	362.405			
Asenapine maleate	Histamine H2 receptor	5.727			
Bifeprunox	Dopamine D2 receptor	1.390142857		2.9	
Bifeprunox	Serotonin 1a (5-HT1a) receptor	9.3	323.59		
Blonanserin	Dopamine D2 receptor	0.14			
Blonanserin	Serotonin 2a (5-HT2a) receptor	0.81			
Brexpiprazole	Dopamine D2 receptor	0.3	6.3		
Brexpiprazole	Serotonin 1a (5-HT1a) receptor	0.12			
Brexpiprazole	Serotonin 2a (5-HT2a) receptor	0.47			
Brexpiprazole	Serotonin 2b (5-HT2b) receptor	0.3981			

Brexpiprazole	Serotonin 7 (5-HT7) receptor	3.7			
Cariprazine	Dopamine D1 receptor	2100			
Cariprazine	Dopamine D2 receptor	2.501111111	32.53495714	1.68	
Cariprazine	Dopamine D3 receptor	0.18025	5.777		
Cariprazine	Dopamine D4 receptor	110			
Cariprazine	Dopamine D5 receptor	7900			
Cariprazine	Serotonin 1a (5-HT1a) receptor	2.85			
Cariprazine	Serotonin 2a (5-HT2a) receptor	21.45			
Cariprazine	Serotonin 7 (5-HT7) receptor	111			
Chlorpromazine	Aldehyde oxidase	1460		570	
Chlorpromazine	Alpha-1d adrenergic receptor	1.962		3.991	
Chlorpromazine	Alpha-2a adrenergic receptor	132		352	
Chlorpromazine	Alpha-2b adrenergic receptor	12		26	
Chlorpromazine	Alpha-2c adrenergic receptor	54		374	
Chlorpromazine	Calmodulin	19280		8520	
Chlorpromazine	Cytochrome P450 2D6	7000		1490	278.3
Chlorpromazine	Delta opioid receptor	7365		20894	
Chlorpromazine	Dopamine D1 receptor	104		225	
Chlorpromazine	Dopamine D2 receptor	6.37		14.2	
Chlorpromazine	Dopamine D3 receptor	5.9491		12	
Chlorpromazine	Dopamine D4 receptor	141.435		1365	
Chlorpromazine	Dopamine D5 receptor	172			
Chlorpromazine	Dopamine transporter	2100		2643	
Chlorpromazine	HERG	4774.3		1960.24	
Chlorpromazine	Histamine H1 receptor	3.1035		14.5	
Chlorpromazi	Histamine H2 receptor	2582		2626	

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Chlorpromazine	Histamine H3 receptor	1000			
Chlorpromazine	Kappa opioid receptor	4433		11082	
Chlorpromazine	Melanocortin receptor 3	21244		24343	
Chlorpromazine	Melanocortin receptor 4	14619		15204	
Chlorpromazine	Melanocortin receptor 5	7145		7617	
Chlorpromazine	Mu opioid receptor	5844		14397	
Chlorpromazine	Muscarinic acetylcholine receptor M1	72.945		83	
Chlorpromazine	Muscarinic acetylcholine receptor M2	232		652	
Chlorpromazine	Muscarinic acetylcholine receptor M3	44		206	
Chlorpromazine	Muscarinic acetylcholine receptor M4	89.745		149	
Chlorpromazine	Muscarinic acetylcholine receptor M5	18		25	
Chlorpromazine	Neurokinin 2 receptor	9065		27195	
Chlorpromazine	Norepinephrine transporter	19		19	
Chlorpromazine	P-glycoprotein 1	6400			
Chlorpromazine	Serotonin 1a (5-HT1a) receptor	673			
Chlorpromazine	Serotonin 2a (5-HT2a) receptor	4.7995		3.6255	
Chlorpromazine	Serotonin 2b (5-HT2b) receptor	57.27		126	
Chlorpromazine	Serotonin 2c (5-HT2c) receptor	25.9504		5.235	
Chlorpromazine	Serotonin 6 (5-HT6) receptor	41.73		57	
Chlorpromazine	Serotonin 7 (5-HT7) receptor	53.26166667			
Chlorpromazine	Serotonin transporter	42.05		79.5	
Chlorpromazine	Sigma opioid receptor	189		451	

Chlorprothixene	Dopamine D1 receptor	18			
Chlorprothixene	Dopamine D2 receptor	2.96			
Chlorprothixene	Dopamine D3 receptor	4.56			
Chlorprothixene	Dopamine D5 receptor	9			
Chlorprothixene	Histamine H1 receptor	3.75		435.98	
Chlorprothixene	Histamine H3 receptor	1000			
Chlorprothixene	Serotonin 6 (5-HT6) receptor	3			
Clozapine	Adrenergic receptor alpha-1	21.39			
Clozapine	Adrenergic receptor alpha-2	105.5			
Clozapine	Aldehyde oxidase	5100		43300	
Clozapine	Alpha-1a adrenergic receptor	16			
Clozapine	Alpha-1b adrenergic receptor	10			
Clozapine	Alpha-1d adrenergic receptor	17		35	
Clozapine	Alpha-2a adrenergic receptor	310.75		90	
Clozapine	Alpha-2b adrenergic receptor	55.5		23	
Clozapine	Alpha-2c adrenergic receptor	34.68133333		7.875	
Clozapine	Dopamine D1 receptor	209.1153846		107	
Clozapine	Dopamine D2 receptor	139.959589		193.64625	
Clozapine	Dopamine D2 receptor and serotonin 2a receptor	64565422.9			
Clozapine	Dopamine D3 receptor	501.9775		354	
Clozapine	Dopamine D4 receptor	192.1665455		79.58333333	
Clozapine	Dopamine D5 receptor	553.25			
Clozapine	HERG	9960.12		1987.4825	
Clozapine	Histamine H1 receptor	4.194555556	0.4	4.912	
Clozapine	Histamine H2 receptor	3550		3610	
Clozapine	Histamine H3 receptor	815.5			
Clozapine	Histamine H4 receptor	292.85			
Clozapine	Histone H1.0	1			
Clozapine	Muscarinic acetylcholine receptor	34			

Clozapine	Muscarinic acetylcholine receptor M1	18.894		9.6	
Clozapine	Muscarinic acetylcholine receptor M2	134.5		476	
Clozapine	Muscarinic acetylcholine receptor M3	58.5		78	
Clozapine	Muscarinic acetylcholine receptor M4	39.631		45	
Clozapine	Muscarinic acetylcholine receptor M5	54.766		13	
Clozapine	Norepinephrine transporter	1458		1470	
Clozapine	Serotonin 1a (5-HT1a) receptor	267.17 30769		150	
Clozapine	Serotonin 1b (5-HT1b) receptor	1000			
Clozapine	Serotonin 1d (5-HT1d) receptor	1000			
Clozapine	Serotonin 1e (5-HT1e) receptor	1000			
Clozapine	Serotonin 2 (5-HT2) receptor	8.506			
Clozapine	Serotonin 2a (5-HT2a) receptor	9.8644 57143		8.0975	
Clozapine	Serotonin 2b (5-HT2b) receptor	5.171	20	11	
Clozapine	Serotonin 2c (5-HT2c) receptor	19.551 5	250	8.0195	
Clozapine	Serotonin 3 (5-HT3) receptor	398.11			
Clozapine	Serotonin 3a (5-HT3a) receptor	457.47 33333			
Clozapine	Serotonin 5a (5-HT5a) receptor	1000			
Clozapine	Serotonin 6 (5-HT6) receptor	15.245 77778		16	
Clozapine	Serotonin 7 (5-HT7) receptor	398.17 77037			
Clozapine	Serotonin transporter	1730		5273	
Clozapine	Sigma opioid receptor	8500			
Dapiprazole	Alpha-1d adrenergic receptor	4.086		8.312	
Dapiprazole	Alpha-2b adrenergic receptor	526		1153	
Dapiprazole	Serotonin 2a (5-HT2a) receptor	173		606	
Dapiprazole	Serotonin 2b (5-HT2b) receptor	672		1056	
Dapiprazole	Serotonin 2c (5-HT2c) receptor	327		625	
Droperidol	Alpha-1d adrenergic receptor	41		83	
Droperidol	Alpha-2a adrenergic receptor	1112		2965	
Droperidol	Alpha-2b adrenergic receptor	101		220	
Droperidol	Alpha-2c adrenergic receptor	256		1763	
Droperidol	Dopamine D1 receptor	546		1092	
Droperidol	Dopamine D2 receptor	0.802		2.407	
Droperidol	Dopamine D3 receptor	0.939		2.765	
Droperidol	HERG	759.6		131.76 88889	
Droperidol	Histamine H1 receptor	525		4519	
Droperidol	Muscarinic acetylcholine receptor M4	537		3849	

Droperidol	Muscarinic acetylcholine receptor M5	1651		2298	
Droperidol	Serotonin 2a (5-HT2a) receptor	0.738		2.584	
Droperidol	Serotonin 2b (5-HT2b) receptor	854		1342	
Droperidol	Serotonin 2c (5-HT2c) receptor	238		454	
Fluphenazine	Adenosine A3 receptor	6746		11935	
Fluphenazine	Alpha-1d adrenergic receptor	16		33	
Fluphenazine	Alpha-2a adrenergic receptor	80		215	
Fluphenazine	Alpha-2b adrenergic receptor	13		29	
Fluphenazine	Alpha-2c adrenergic receptor	22		154	
Fluphenazine	Beta-3 adrenergic receptor	22116		29488	
Fluphenazine	Delta opioid receptor	8473		24036	
Fluphenazine	Dopamine D1 receptor	95		23	
Fluphenazine	Dopamine D2 receptor	0.9895		1.616	
Fluphenazine	Dopamine D3 receptor	1.706		0.594	
Fluphenazine	Dopamine D4 receptor	2061		5877	
Fluphenazine	Dopamine D5 receptor	21			
Fluphenazine	Dopamine transporter	1631		2053	
Fluphenazine	HERG	4674.6		5705.8	
Fluphenazine	Histamine H1 receptor	22.331		40	
Fluphenazine	Histamine H2 receptor	1205		1226	
Fluphenazine	Histamine H3 receptor	1000			
Fluphenazine	Kappa opioid receptor	9891		24727	
Fluphenazine	Melanocortin receptor 5	8929		9518	
Fluphenazine	Mu opioid receptor	8421		20745	
Fluphenazine	Muscarinic acetylcholine receptor M1	646		2683	
Fluphenazine	Muscarinic acetylcholine receptor M2	2660		7481	
Fluphenazine	Muscarinic acetylcholine receptor M3	1002		4728	
Fluphenazine	Muscarinic acetylcholine receptor M4	484		3468	
Fluphenazine	Neurokinin 2 receptor	7495		22484	
Fluphenazine	Norepinephrine transporter	1946		1962	
Fluphenazine	Serotonin 2a (5-HT2a) receptor	1.458		5.104	
Fluphenazine	Serotonin 2b (5-HT2b) receptor	25		39	
Fluphenazine	Serotonin 2c (5-HT2c) receptor	35		67	
Fluphenazine	Serotonin 6 (5-HT6) receptor	37		52	
Fluphenazine	Serotonin transporter	793		1492	
Fluphenazine	Sigma opioid receptor	8.575		20	
Fluspirilene	Nociceptin receptor	500			
Fluspirilene	Serotonin 2b (5-HT2b) receptor	151.4			
Fluspirilene	Serotonin 6 (5-HT6) receptor	1188			
Haloperidol	3-beta-hydroxysteroid-delta(8),delta(7)-isomerase	190			

Haloperidol	Adrenergic receptor alpha-1	12.35			
Haloperidol	Adrenergic receptor alpha-2	5000			
Haloperidol	Alpha-1a adrenergic receptor	11			
Haloperidol	Alpha-1d adrenergic receptor	41		84	
Haloperidol	Alpha-2a adrenergic receptor	1865		4973	
Haloperidol	Alpha-2b adrenergic receptor	618		1354	
Haloperidol	Alpha-2c adrenergic receptor	268		1845	
Haloperidol	Dopamine D1 receptor	92.685 11111		110	
Haloperidol	Dopamine D2 receptor	74.325 58587		98.131 99	
Haloperidol	Dopamine D2 receptor and serotonin 2a receptor	11748 9755.5			
Haloperidol	Dopamine D3 receptor	9.5626 73913		7.5775	
Haloperidol	Dopamine D4 receptor	12.655 39024	5008.5	116.36	
Haloperidol	Dopamine D5 receptor	101			
Haloperidol	HERG	316		263.41 125	
Haloperidol	Histamine H1 receptor	474.6		2781	
Haloperidol	Histamine H2 receptor	1147		1166	
Haloperidol	Histone H1.0	780			
Haloperidol	Mu opioid receptor	5496	10000	2443	
Haloperidol	Muscarinic acetylcholine receptor	4670			
Haloperidol	Muscarinic acetylcholine receptor M1	1600		5500	
Haloperidol	Muscarinic acetylcholine receptor M5	2795		3890	
Haloperidol	Norepinephrine transporter	3660		1836	
Haloperidol	P-glycoprotein 1	200		5300	
Haloperidol	Serotonin 1a (5-HT1a) receptor	2925.7 5		1500	
Haloperidol	Serotonin 2 (5-HT2) receptor	23.316 66667			
Haloperidol	Serotonin 2a (5-HT2a) receptor	140.23 5		181.5	
Haloperidol	Serotonin 2b (5-HT2b) receptor	1305		2050	
Haloperidol	Serotonin 2c (5-HT2c) receptor	5093.9 17273		6673.5	
Haloperidol	Serotonin 6 (5-HT6) receptor	4027.6 66667			
Haloperidol	Serotonin 7 (5-HT7) receptor	736.56 25			
Haloperidol	Serotonin transporter	1599.7 5		3386	

Haloperidol	Sigma intracellular receptor 2	16.53333333			
Haloperidol	Sigma opioid receptor	5.364723404		43.88666667	
Haloperidol	UDP-glucuronosyltransferase 1-9	344000			
Haloperidol	UDP-glucuronosyltransferase 2B7	590000			
Loxapine	Dopamine D2 receptor	21		54	
Loxapine	Dopamine D4 receptor	6.266666667		14	
Loxapine	Histamine H4 receptor	4570.88	218.78		
Loxapine	Serotonin 2a (5-HT2a) receptor	2.42			
Loxapine	Serotonin 6 (5-HT6) receptor	32.5			
Lumateperone tosylate	Alpha-1a adrenergic receptor	73			
Lumateperone tosylate	Alpha-1b adrenergic receptor	31			
Lumateperone tosylate	Dopamine D1 receptor	52			
Lumateperone tosylate	Dopamine D4 receptor	108			
Lumateperone tosylate	Histamine H1 receptor	1000			
Lumateperone tosylate	Serotonin 1a (5-HT1a) receptor	1480			
Lumateperone tosylate	Serotonin 2a (5-HT2a) receptor	0.54		7	
Lumateperone tosylate	Serotonin 2c (5-HT2c) receptor	173			
Lumateperone tosylate	Serotonin transporter	66.5			
Lurasidone	Dopamine D2 receptor	1.7			
Lurasidone	Serotonin 1a (5-HT1a) receptor	6.7			
Lurasidone	Serotonin 2a (5-HT2a) receptor	2			
Lurasidone	Serotonin 7 (5-HT7) receptor	0.5			
Molindone	Dopamine D2 receptor and serotonin 2a receptor	16595 8690.7			
Molindone	Serotonin 7 (5-HT7) receptor	265			
Olanzapine	Adrenergic receptor alpha-1	24.075			
Olanzapine	Adrenergic receptor alpha-2	211			
Olanzapine	Adrenergic receptor beta	10000			
Olanzapine	Alpha-1a adrenergic receptor	373.33			

		33333			
Olanzapine	Alpha-1b adrenergic receptor	1000			
Olanzapine	Alpha-1d adrenergic receptor	45		92	
Olanzapine	Alpha-2a adrenergic receptor	465		541	
Olanzapine	Alpha-2b adrenergic receptor	146		421	
Olanzapine	Alpha-2c adrenergic receptor	86.333 33333		531	
Olanzapine	Dopamine D1 receptor	86.125		72	
Olanzapine	Dopamine D2 receptor	35.412 30769		64	
Olanzapine	Dopamine D3 receptor	46.829 16667		78	
Olanzapine	Dopamine D4 receptor	37.743 75		173	
Olanzapine	Dopamine D5 receptor	95			
Olanzapine	GABA-A receptor; anion channel	10000			
Olanzapine	HERG	36000		11291. 41889	
Olanzapine	Histamine H1 receptor	4.1966 25		13	
Olanzapine	Histone H1.0	2			
Olanzapine	Muscarinic acetylcholine receptor	47			
Olanzapine	Muscarinic acetylcholine receptor M1	29.2			
Olanzapine	Muscarinic acetylcholine receptor M2	100			
Olanzapine	Muscarinic acetylcholine receptor M3	91.5		392	
Olanzapine	Muscarinic acetylcholine receptor M4	344.86 33333		155	
Olanzapine	Muscarinic acetylcholine receptor M5	19.5		40	
Olanzapine	Serotonin 1a (5-HT1a) receptor	2814.2 5			
Olanzapine	Serotonin 1b (5-HT1b) receptor	1000			
Olanzapine	Serotonin 1d (5-HT1d) receptor	1000			
Olanzapine	Serotonin 1e (5-HT1e) receptor	1000			
Olanzapine	Serotonin 2 (5-HT2) receptor	10			
Olanzapine	Serotonin 2a (5-HT2a) receptor	8.1427 72727		30.254	
Olanzapine	Serotonin 2b (5-HT2b) receptor	21.155		57	
Olanzapine	Serotonin 2c (5-HT2c) receptor	8.601		46	
Olanzapine	Serotonin 3 (5-HT3) receptor	199.53			
Olanzapine	Serotonin 3a (5-HT3a) receptor	1000			
Olanzapine	Serotonin 5a (5-HT5a) receptor	1000			
Olanzapine	Serotonin 6 (5-HT6) receptor	10.242 77778		13	

Olanzapine	Serotonin 7 (5-HT7) receptor	367.086			
Olanzapine	Serotonin transporter	8516.333333		1033	
Osanetant	Neurokinin 1 receptor	624.5516667			
Osanetant	Neurokinin 2 receptor	60.0575			
Osanetant	Neurokinin 3 receptor	2.148708333		0.505	
Penfluridol	Alpha-1d adrenergic receptor	602			
Penfluridol	Alpha-2b adrenergic receptor	401			
Penfluridol	Alpha-2c adrenergic receptor	445			
Penfluridol	Beta-3 adrenergic receptor	515			
Penfluridol	Delta opioid receptor	1714			
Penfluridol	Dopamine D1 receptor	147			
Penfluridol	Dopamine D2 receptor	159			
Penfluridol	Dopamine D3 receptor	136			
Penfluridol	Dopamine D4 receptor	1000			
Penfluridol	Dopamine D5 receptor	125			
Penfluridol	Dopamine transporter	1714			
Penfluridol	Histamine H1 receptor	1000			
Penfluridol	Histamine H2 receptor	1000			
Penfluridol	Kappa opioid receptor	1000			
Penfluridol	Mu opioid receptor	867			
Penfluridol	Norepinephrine transporter	588			
Penfluridol	Serotonin 1a (5-HT1a) receptor	356			
Penfluridol	Serotonin 1d (5-HT1d) receptor	3560			
Penfluridol	Serotonin 2a (5-HT2a) receptor	361			
Penfluridol	Serotonin 2b (5-HT2b) receptor	184			
Penfluridol	Serotonin 2c (5-HT2c) receptor	881			
Penfluridol	Serotonin 5a (5-HT5a) receptor	1000			
Penfluridol	Serotonin 6 (5-HT6) receptor	1000			
Penfluridol	Serotonin 7 (5-HT7) receptor	280			
Penfluridol	Serotonin transporter	1000			
Perphenazine	HERG	3454.1		4216	
Perphenazine	Serotonin 7 (5-HT7) receptor	23			
Pimozide	Dopamine D2 receptor	11.85			
Pimozide	HERG	42		151.995	
Pimozide	Histamine H4 receptor	2000			
Pimozide	Serotonin 6 (5-HT6) receptor	71			

Prochlorperazine	Alpha-1d adrenergic receptor	16		34	
Prochlorperazine	Alpha-2a adrenergic receptor	63		169	
Prochlorperazine	Alpha-2b adrenergic receptor	4.741		10	
Prochlorperazine	Alpha-2c adrenergic receptor	12		82	
Prochlorperazine	Dopamine D1 receptor	78		155	
Prochlorperazine	Dopamine D2 receptor	3.608		11	
Prochlorperazine	Dopamine D3 receptor	4.454		13	
Prochlorperazine	Dopamine D4 receptor	810		2311	
Prochlorperazine	Dopamine transporter	1379		1735	
Prochlorperazine	HERG	1514.1		1848.1	
Prochlorperazine	Histamine H1 receptor	2.794		24	
Prochlorperazine	Muscarinic acetylcholine receptor M1	244		1013	
Prochlorperazine	Muscarinic acetylcholine receptor M2	1107		3112	
Prochlorperazine	Muscarinic acetylcholine receptor M3	321		1514	
Prochlorperazine	Muscarinic acetylcholine receptor M4	190		1363	
Prochlorperazine	Muscarinic acetylcholine receptor M5	158		220	
Prochlorperazine	Norepinephrine transporter	396		400	
Prochlorperazine	Serotonin 2a (5-HT2a) receptor	2.018		7.062	
Prochlorperazine	Serotonin 2b (5-HT2b) receptor	65		102	
Prochlorperazine	Serotonin 2c (5-HT2c) receptor	41		78	
Prochlorperazine	Serotonin 6 (5-HT6) receptor	124		267	
Prochlorperazine	Serotonin transporter	621		1169	
Prochlorperazine	Sigma opioid receptor	23		54	

Promazine	Alpha-1d adrenergic receptor	6.18		13	
Promazine	Alpha-2a adrenergic receptor	126		337	
Promazine	Alpha-2b adrenergic receptor	8.418		18	
Promazine	Alpha-2c adrenergic receptor	37		253	
Promazine	Dopamine D1 receptor	1232		2464	
Promazine	Dopamine D2 receptor	168		505	
Promazine	Dopamine D3 receptor	69		205	
Promazine	Histamine H1 receptor	0.399		1229.0725	
Promazine	Histamine H2 receptor	2810		2858	
Promazine	Muscarinic acetylcholine receptor M1	117		487	
Promazine	Muscarinic acetylcholine receptor M2	387		1089	
Promazine	Muscarinic acetylcholine receptor M3	88		416	
Promazine	Muscarinic acetylcholine receptor M4	42		299	
Promazine	Muscarinic acetylcholine receptor M5	46		64	
Promazine	Norepinephrine transporter	13		13	
Promazine	Serotonin 2a (5-HT2a) receptor	6.695		23	
Promazine	Serotonin 2b (5-HT2b) receptor	221		347	
Promazine	Serotonin 2c (5-HT2c) receptor	52		99	
Promazine	Serotonin 6 (5-HT6) receptor	127		274	
Promazine	Serotonin transporter	46		86	
Promazine	Sigma opioid receptor	114		271	
Promethazine	Alpha-1d adrenergic receptor	90		183	
Promethazine	Alpha-2a adrenergic receptor	256		681	
Promethazine	Alpha-2b adrenergic receptor	24		53	
Promethazine	Alpha-2c adrenergic receptor	353		2431	
Promethazine	Dopamine D1 receptor	1372		2744	
Promethazine	Dopamine D2 receptor	260		439.5	
Promethazine	Dopamine D3 receptor	190		559	
Promethazine	Histamine H1 receptor	0.334		4.1355	
Promethazine	Histamine H2 receptor	1146		1165	
Promethazine	Muscarinic acetylcholine receptor M1	3.321		14	
Promethazine	Muscarinic acetylcholine receptor M2	12		35	
Promethazine	Muscarinic acetylcholine receptor M3	4.149		20	
Promethazine	Muscarinic acetylcholine receptor M4	1.057		7.576	
Promethazine	Muscarinic acetylcholine receptor M5	3.307		4.603	
Promethazine	Norepinephrine transporter	4203		4238	
Promethazine	Serotonin 2a (5-HT2a) receptor	19		45	
Promethazine	Serotonin 2b (5-HT2b) receptor	43		68	
Promethazine	Serotonin 2c (5-HT2c) receptor	6.477		12	
Promethazine	Serotonin 6 (5-HT6) receptor	1128		2429	

Promethazine	Serotonin transporter	2130		5800	
Promethazine	Sigma opioid receptor	120		287	
Quetiapine	Adrenergic receptor alpha-1	31.25			
Quetiapine	Adrenergic receptor alpha-2	593.5			
Quetiapine	Alpha-1a adrenergic receptor	60			
Quetiapine	Alpha-1b adrenergic receptor	100			
Quetiapine	Alpha-1d adrenergic receptor	47.5		96.6	
Quetiapine	Alpha-2a adrenergic receptor	967.15		2491.4	
Quetiapine	Alpha-2b adrenergic receptor	522.9		100.3	
Quetiapine	Alpha-2c adrenergic receptor	80.55		420.8	
Quetiapine	Dopamine D1 receptor	1428.92		429.3	
Quetiapine	Dopamine D2 receptor	352.2		1329.9	
Quetiapine	Dopamine D3 receptor	492.715		1163.2	
Quetiapine	Dopamine D4 receptor	1480			
Quetiapine	Dopamine D5 receptor	1000			
Quetiapine	Histamine H1 receptor	12.6598		39.6	
Quetiapine	Histone H1.0	10			
Quetiapine	Muscarinic acetylcholine receptor	1020			
Quetiapine	Muscarinic acetylcholine receptor M1	436.782		2615	
Quetiapine	Muscarinic acetylcholine receptor M2	1094.6		3344.7	
Quetiapine	Muscarinic acetylcholine receptor M3	1000			
Quetiapine	Muscarinic acetylcholine receptor M4	448.6966667		1578.7	
Quetiapine	Muscarinic acetylcholine receptor M5	1577.95		3000.7	
Quetiapine	Serotonin 1a (5-HT1a) receptor	427.405			
Quetiapine	Serotonin 1b (5-HT1b) receptor	1000			
Quetiapine	Serotonin 1d (5-HT1d) receptor	1000			
Quetiapine	Serotonin 1e (5-HT1e) receptor	1000			
Quetiapine	Serotonin 2 (5-HT2) receptor	220			
Quetiapine	Serotonin 2a (5-HT2a) receptor	205.8555556		117.8	
Quetiapine	Serotonin 2b (5-HT2b) receptor	193.545		213.5	
Quetiapine	Serotonin 2c (5-HT2c) receptor	1908.166667		3300.8	
Quetiapine	Serotonin 3a (5-HT3a) receptor	1000			
Quetiapine	Serotonin 5a (5-HT5a) receptor	1000			

Quetiapine	Serotonin 6 (5-HT6) receptor	1200			
Quetiapine	Serotonin 7 (5-HT7) receptor	531.55			
Quetiapine	Serotonin transporter	9500			
Quetiapine	Sigma opioid receptor	963.9		2293.5	
Raclopride	Dopamine D2 receptor	14.922		51.9625	
Raclopride	Dopamine D3 receptor	11.375			
Raclopride	Dopamine D4 receptor	3100			
Raclopride	Dopamine receptor	6.9			
Remoxipride	Dopamine D2 receptor	217		440.601	
Remoxipride	Dopamine D4 receptor	3872		3872	
Remoxipride	Sigma opioid receptor	55			
Reserpine	Canalicular multispecific organic anion transporter 1	295000		68400	
Reserpine	Mu opioid receptor	1686		4152	
Reserpine	P-glycoprotein 1	5416		6896162690	
Reserpine	Serotonin 2a (5-HT2a) receptor	1000			
Reserpine	Synaptic vesicular amine transporter	348.42		13.2	
Risperidone	Adrenergic receptor alpha-1	1.33			
Risperidone	Adrenergic receptor alpha-2	4.65			
Risperidone	Alpha-1a adrenergic receptor	5.033333333		10.54	
Risperidone	Alpha-1b adrenergic receptor	10			
Risperidone	Alpha-1d adrenergic receptor	4.913		9.995	
Risperidone	Alpha-2a adrenergic receptor	337.876		9.674	
Risperidone	Alpha-2b adrenergic receptor	506		26	
Risperidone	Alpha-2c adrenergic receptor	4.863		9.557	
Risperidone	Dopamine D1 receptor	434.8183333		479	
Risperidone	Dopamine D2 receptor	4.4495625		13.545	
Risperidone	Dopamine D3 receptor	21.02327273		24	
Risperidone	Dopamine D4 receptor	23.38571429			
Risperidone	Dopamine D5 receptor	1000			
Risperidone	HERG	2176.4		690.0105556	
Risperidone	Histamine H1 receptor	40.91166667		451.5	
Risperidone	Histamine H2 receptor	1458		1483	

Risperidone	Histone H1.0	14			
Risperidone	Muscarinic acetylcholine receptor	5650			
Risperidone	Muscarinic acetylcholine receptor M1	2933.333333			
Risperidone	Muscarinic acetylcholine receptor M2	1000			
Risperidone	Muscarinic acetylcholine receptor M3	1000		55000	
Risperidone	Muscarinic acetylcholine receptor M4	1000			
Risperidone	Muscarinic acetylcholine receptor M5	1000			
Risperidone	Serotonin 1a (5-HT1a) receptor	442.0271429	10000		
Risperidone	Serotonin 1b (5-HT1b) receptor	10			
Risperidone	Serotonin 1d (5-HT1d) receptor	1000			
Risperidone	Serotonin 1e (5-HT1e) receptor	1000			
Risperidone	Serotonin 2a (5-HT2a) receptor	0.516176471		1.610975	
Risperidone	Serotonin 2b (5-HT2b) receptor	17.475		23	
Risperidone	Serotonin 2c (5-HT2c) receptor	33.528		5.738333333	
Risperidone	Serotonin 3a (5-HT3a) receptor	1000			
Risperidone	Serotonin 5a (5-HT5a) receptor	1000			
Risperidone	Serotonin 6 (5-HT6) receptor	1141.833333			
Risperidone	Serotonin 7 (5-HT7) receptor	3.925			
Risperidone	Serotonin transporter	1200			
Risperidone	Sigma opioid receptor	4300			
Ritanserin	Serotonin 2a (5-HT2a) receptor	0.45			
Ritanserin	Serotonin 2c (5-HT2c) receptor	1.5525			
Ritanserin	Serotonin 7 (5-HT7) receptor	30.425			
Sertindole	Adrenergic receptor alpha-1	1.8			
Sertindole	Adrenergic receptor alpha-2	1680			
Sertindole	Dopamine D1 receptor	210			
Sertindole	Dopamine D2 receptor	2.766666667			
Sertindole	Dopamine D3 receptor	5.4			
Sertindole	Dopamine D4 receptor	16			
Sertindole	Histamine H1 receptor	285.255			
Sertindole	Muscarinic acetylcholine receptor	5000			
Sertindole	Serotonin 1a (5-HT1a) receptor	33			
Sertindole	Serotonin 1b (5-HT1b) receptor	56			
Sertindole	Serotonin 2a (5-HT2a) receptor	0.725			
Sertindole	Serotonin 2c (5-HT2c) receptor	0.833333333			

Sertindole	Serotonin 6 (5-HT6) receptor	5			
Sulpiride	Alpha-2a adrenergic receptor	757		2019	
Sulpiride	Carbonic anhydrase I	4237.5		1200	
Sulpiride	Carbonic anhydrase II	40		40	
Sulpiride	Carbonic anhydrase III	10600			
Sulpiride	Carbonic anhydrase IX	43			
Sulpiride	Carbonic anhydrase VA	174			
Sulpiride	Carbonic anhydrase VB	18			
Sulpiride	Carbonic anhydrase VI	0.8			
Sulpiride	Carbonic anhydrase VII	2421.2			
Sulpiride	Carbonic anhydrase XII	3.9			
Sulpiride	Dopamine D2 receptor	65.2		85.76	
Sulpiride	Dopamine D3 receptor	61.666 66667		265.07 33333	
Sulpiride	Dopamine D4 receptor	2100			
Tetrahydropa lmatine	Dopamine D1 receptor	192		1630	
Tetrahydropa lmatine	Dopamine D2 receptor	3062.5		450	
Tetrahydropa lmatine	Dopamine D3 receptor	1371			
Tetrahydropa lmatine	Dopamine D4 receptor	1000			
Tetrahydropa lmatine	Dopamine D5 receptor	305			
Tetrahydropa lmatine	Serotonin 1a (5-HT1a) receptor	5000			
Thioridazine	Alpha-1d adrenergic receptor	2.895		5.891	
Thioridazine	Alpha-2a adrenergic receptor	50		133	
Thioridazine	Alpha-2b adrenergic receptor	174		380	
Thioridazine	Alpha-2c adrenergic receptor	25		171	
Thioridazine	Dopamine D1 receptor	97		194	
Thioridazine	Dopamine D2 receptor	19.5		35	
Thioridazine	Dopamine D3 receptor	3.36		9.892	
Thioridazine	Dopamine D4 receptor	515		1468	
Thioridazine	Dopamine transporter	1888		2376	
Thioridazine	HERG	1085		249.77 25	
Thioridazine	Histamine H1 receptor	8.412		72	
Thioridazine	Histamine H2 receptor	934		950	
Thioridazine	Kappa opioid receptor	996		2490	
Thioridazine	Muscarinic acetylcholine receptor M1	1.69		7.019	
Thioridazine	Muscarinic acetylcholine receptor M2	38		106	

Thioridazine	Muscarinic acetylcholine receptor M3	19		90	
Thioridazine	Muscarinic acetylcholine receptor M4	11		80	
Thioridazine	Muscarinic acetylcholine receptor M5	6.643		9.246	
Thioridazine	Norepinephrine transporter	1538		1551	
Thioridazine	Serotonin 2a (5-HT2a) receptor	1.247		4.366	
Thioridazine	Serotonin 2b (5-HT2b) receptor	82		129	
Thioridazine	Serotonin 2c (5-HT2c) receptor	23		44	
Thioridazine	Serotonin 6 (5-HT6) receptor	33		71	
Thioridazine	Serotonin 7 (5-HT7) receptor	70			
Thioridazine	Serotonin transporter	399		751	
Thioridazine	Sigma opioid receptor	153		363	
Tiapride	Alpha-2a adrenergic receptor	779		2078	
Tiapride	Dopamine D2 receptor	411		1232	
Tiapride	Dopamine D3 receptor	390		1149	
Trifluoperazine	3-beta-hydroxysteroid-delta(8),delta(7)-isomerase	8			
Trifluoperazine	Emopamil-binding protein-like	3.9			
Trifluoperazine	HERG	5100.8		6226	
Trifluoperazine	P-glycoprotein 1	6500		8133.333333	
Trifluoperazine	Sigma opioid receptor	15			
Triflupromazine	P-glycoprotein 1	15700			
Ziprasidone	Adrenergic receptor alpha-1	8.3		11	
Ziprasidone	Adrenergic receptor alpha-2	390			
Ziprasidone	Alpha-1a adrenergic receptor	6			
Ziprasidone	Dopamine D1 receptor	156.5			
Ziprasidone	Dopamine D2 receptor	4.224364286		5	
Ziprasidone	Dopamine D3 receptor	7.642			
Ziprasidone	Dopamine D4 receptor	40.03			
Ziprasidone	Histamine H1 receptor	187.4333333			
Ziprasidone	Histone H1.0	15			
Ziprasidone	Muscarinic acetylcholine receptor	5000			
Ziprasidone	Muscarinic acetylcholine receptor M1	7550			
Ziprasidone	Serotonin 1a (5-HT1a) receptor	9.417			
Ziprasidone	Serotonin 2a (5-HT2a) receptor	0.503875		0.42	
Ziprasidone	Serotonin 2b (5-HT2b) receptor	1.585			

Ziprasidone	Serotonin 2c (5-HT2c) receptor	5.6898 57143			
Ziprasidone	Serotonin 3 (5-HT3) receptor	398.11			
Ziprasidone	Serotonin 6 (5-HT6) receptor	56.22			
Ziprasidone	Serotonin 7 (5-HT7) receptor	5.3373 33333			
Ziprasidone	Serotonin transporter	311.10 75			
Zotepine	Adrenergic receptor alpha-1	3.4			
Zotepine	Adrenergic receptor alpha-2	570			
Zotepine	Dopamine D1 receptor	56.5			
Zotepine	Dopamine D2 receptor	12			
Zotepine	Dopamine D3 receptor	11.2			
Zotepine	Dopamine D4 receptor	39			
Zotepine	Histamine H1 receptor	2.01			
Zotepine	Muscarinic acetylcholine receptor M4	550			
Zotepine	Serotonin 1a (5-HT1a) receptor	330			
Zotepine	Serotonin 2a (5-HT2a) receptor	1.37			
Zotepine	Serotonin 2c (5-HT2c) receptor	2.9			
Zuclopenthixol	Serotonin 6 (5-HT6) receptor	169			
Methylpromazine	Bile salt export pump			73720	
Methylpromazine	HepG2			61659.5	
Amisulpride	Bile salt export pump			133000	
Amisulpride	Canalicular multispecific organic anion transporter 1			133000	
Amisulpride	Canalicular multispecific organic anion transporter 2			133000	
Amisulpride	Multidrug resistance-associated protein 4			133000	
Amoxapine	Bile salt export pump			181550	
Amoxapine	Canalicular multispecific organic anion transporter 1			133000	
Amoxapine	Canalicular multispecific organic anion transporter 2			133000	
Amoxapine	Cytochrome P450 2D6			10000	3981.07
Amoxapine	Multidrug resistance-associated protein 4			133000	
Amperozide	Anandamide amidohydrolase			897.5	

Amperozide	HepG2			95000	
Aripiprazole	Bile salt export pump			133000	
Aripiprazole	Canalicular multispecific organic anion transporter 1			133000	
Aripiprazole	Canalicular multispecific organic anion transporter 2			133000	
Aripiprazole	Multidrug and toxin extrusion protein 1			130000	
Aripiprazole	Multidrug and toxin extrusion protein 2			500000	
Aripiprazole	Multidrug resistance-associated protein 4			133000	
Aripiprazole	P-glycoprotein 1			780	
Aripiprazole	Solute carrier family 22 member 2			239000	
Brexpiprazole	HEK293			19.1	
Cariprazine	HERG			20720	
Chlorpromazine	Bile salt export pump			95161.66667	
Chlorpromazine	Canalicular multispecific organic anion transporter 1			133000	
Chlorpromazine	Canalicular multispecific organic anion transporter 2			133000	
Chlorpromazine	Cytochrome P450 1A2			4140	2490.535
Chlorpromazine	Cytochrome P450 2C19			34100	
Chlorpromazine	Cytochrome P450 2C9			50000	
Chlorpromazine	Cytochrome P450 2J2			24400	
Chlorpromazine	Cytochrome P450 3A4			23300	1000
Chlorpromazine	Epidermal growth factor receptor erbB1			28868	
Chlorpromazine	Glutamate [NMDA] receptor			850	
Chlorpromazine	HaCaT			36100	
Chlorpromazine	Homo sapiens			155700	
Chlorpromazine	Multidrug resistance-associated protein 4			133000	

Chlorpromazine	NADPH oxidase 1			17000	
Chlorpromazine	NHDF			25500	
Chlorpromazine	Potassium channel subfamily K member 2			2700	
Chlorpromazine	Receptor protein-tyrosine kinase erbB-2			19366	
Chlorpromazine	Sodium channel alpha subunit			4300	
Chlorpromazine	Sodium channel alpha subunits; brain (Types I, II, III)			4300	
Chlorpromazine	Solute carrier family 22 member 1			15650	
Chlorpromazine	Sphingomyelin phosphodiesterase			11000	
Chlorpromazine	Tyrosine-protein kinase FYN			8680	
Chlorpromazine	Voltage-gated L-type calcium channel			3400	
Chlorprothixene	Bile salt export pump			27470	
Chlorprothixene	Sodium channel alpha subunits; brain (Types I, II, III)			10000	
Chlorprothixene	Solute carrier family 22 member 1			77800	
Clozapine	Bile salt export pump			117310	
Clozapine	Calmodulin			80000	
Clozapine	Canalicular multispecific organic anion transporter 1			133000	
Clozapine	Canalicular multispecific organic anion transporter 2			133000	
Clozapine	Cytochrome P450 1A2			50000	14219.09
Clozapine	Cytochrome P450 2C19			45300	25118.86
Clozapine	Cytochrome P450 2C9			21200	39810.72
Clozapine	Cytochrome P450 2D6			18000	11896.105
Clozapine	Cytochrome P450 2J2			14100	
Clozapine	Cytochrome P450 3A4			46300	31622.78
Clozapine	HepG2			47863.	

				01	
Clozapine	Multidrug resistance-associated protein 4			133000	
Clozapine	Voltage-gated L-type calcium channel			3600	
Droperidol	Bile salt export pump			10000	
Droperidol	Sodium channel alpha subunits; brain (Types I, II, III)			740	
Droperidol	Voltage-gated L-type calcium channel			7600	
Flupentixol	Potassium channel subfamily K member 2			2000	
Flupentixol	Sigma opioid receptor			2.239	
Flupentixol	Solute carrier family 22 member 1			89500	
Flupentixol	Ubiquitin carboxyl-terminal hydrolase 1/WD repeat-containing protein 48			7000	
Fluphenazine	Bile salt export pump			25820	
Fluphenazine	Epidermal growth factor receptor erbB1			40107	
Fluphenazine	HepG2			4382.58	
Fluphenazine	NADPH oxidase 1			17000	
Fluphenazine	P-glycoprotein 1			7533.333333	
Fluphenazine	Potassium channel subfamily K member 2			4700	
Fluphenazine	Receptor protein-tyrosine kinase erbB-2			19570	
Fluphenazine	Sodium channel alpha subunits; brain (Types I, II, III)			3700	
Fluphenazine	Solute carrier family 22 member 1			110000	
Fluphenazine	Tyrosine-protein kinase FYN			7990	
Fluspirilene	HERG			2300	
Fluspirilene	X-box-binding protein 1			10000	
Haloperidol	5637			11150	
Haloperidol	A-427			9866.666667	
Haloperidol	Bile salt export pump			96920	
Haloperidol	Canalicular multispecific organic anion transporter 1			133000	
Haloperidol	Canalicular multispecific organic anion transporter 2			133000	
Haloperidol	Cytochrome P450 1A2			40000	31622.78
Haloperidol	Cytochrome P450 2C19			26435	
Haloperidol	Cytochrome P450 2C8			30000	
Haloperidol	Cytochrome P450 2C9			40000	
Haloperidol	Cytochrome P450 2D6			16820	5660.72

Haloperidol	Cytochrome P450 2J2			4690	
Haloperidol	Cytochrome P450 3A4			20650	
Haloperidol	DAN-G			20000	
Haloperidol	Dopamine receptor			5	
Haloperidol	MCF7			21267.5	
Haloperidol	Multidrug resistance-associated protein 4			133000	
Haloperidol	Potassium channel subfamily K member 2			5500	
Haloperidol	RT-4			20000	
Haloperidol	Sodium channel alpha subunit			7000	
Haloperidol	Sodium channel alpha subunits; brain (Types I, II, III)			1200	
Haloperidol	Solute carrier family 22 member 1			141900	
Haloperidol	Voltage-gated L-type calcium channel			1500	
Iloperidone	Bile salt export pump			23400	
Iloperidone	Canalicular multispecific organic anion transporter 1			133000	
Iloperidone	Canalicular multispecific organic anion transporter 2			133000	
Iloperidone	Dopamine D2 receptor			110	
Iloperidone	Multidrug resistance-associated protein 4			133000	
Iloperidone	Sigma opioid receptor			64	
Lithium ion	Glycogen synthase kinase-3			2000000	
Lithium ion	Glycogen synthase kinase-3 beta			2000000	
Loxapine	Dopamine D3 receptor			22	
Loxapine	Muscarinic acetylcholine receptor M1			5500	
Loxapine	Potassium channel subfamily K member 2			20000	
Melperone	Bile salt export pump			133000	
Melperone	Canalicular multispecific organic anion transporter 1			133000	
Melperone	Canalicular multispecific organic anion transporter 2			133000	
Melperone	Multidrug resistance-associated protein 4			133000	
Mesoridazine	HERG			358.825	
Levomepromazine	Bile salt export pump			127000	

Methylthionium chloride	Apoptotic protease-activating factor 1			57750	
Methylthionium chloride	Beta amyloid A4 protein			500	
Methylthionium chloride	Fibrinogen beta chain			46265.5	
Methylthionium chloride	Glutathione reductase			16200	
Methylthionium chloride	HT-29			9600	
Methylthionium chloride	Microtubule-associated protein tau		360	2233.333333	
Methylthionium chloride	Monoamine oxidase A			70	
Methylthionium chloride	Thioredoxin reductase 1			30000	
Olanzapine	Bile salt export pump			93785	
Olanzapine	Canalicular multispecific organic anion transporter 1			133000	
Olanzapine	Canalicular multispecific organic anion transporter 2			133000	
Olanzapine	Multidrug resistance-associated protein 4			133000	
Osanetant	Cytochrome P450 1A2			100000	
Osanetant	Cytochrome P450 2C19			7000	
Osanetant	Cytochrome P450 2C9			11000	
Osanetant	Cytochrome P450 2D6			55000	
Osanetant	Cytochrome P450 3A4			1000	
Paliperidone	Dopamine D2 receptor			8.28	
Paliperidone	HERG			1234.351667	
Paliperidone	Serotonin 2a (5-HT2a) receptor			5.2	
Paliperidone	Sodium channel protein type V alpha subunit			91804.09	
Paliperidone	Voltage-gated L-type calcium channel			193900	

Paliperidone	Voltage-gated L-type calcium channel alpha-1C subunit			699053.585	
Paliperidone	Voltage-gated potassium channel subunit Kv4.3			63095.73	
Paliperidone	Voltage-gated potassium channel, IKs; KCNQ1(Kv7.1)/KCNE1(MinK)			2511898.64	
Penfluridol	MDA-MB-231			5400	
Perphenazine	AN3-CA			25400	
Perphenazine	Aldehyde oxidase			33	
Perphenazine	Bile salt export pump			100946.6667	
Perphenazine	Canalicular multispecific organic anion transporter 1			133000	
Perphenazine	Canalicular multispecific organic anion transporter 2			133000	
Perphenazine	Cytochrome P450 1A2			4490	316.23
Perphenazine	Cytochrome P450 2C19			18500	
Perphenazine	Cytochrome P450 2C9			21300	
Perphenazine	Cytochrome P450 2D6			120	31.62
Perphenazine	Cytochrome P450 2J2			10600	
Perphenazine	Cytochrome P450 3A4			13900	
Perphenazine	Dopamine D2 receptor			0.3	
Perphenazine	HEC-1-A			23300	
Perphenazine	HEC-1B cell line			29800	
Perphenazine	HepG2			16218.1	
Perphenazine	Ishikawa			19400	
Perphenazine	KLE			30800	
Perphenazine	Multidrug resistance-associated protein 4			133000	
Perphenazine	NADPH oxidase 1			17000	
Perphenazine	Ubiquitin-conjugating enzyme E2 N			14790	
Pimavanserin	Serotonin 2a (5-HT2a) receptor			15.5	
Pimozide	Bile salt export pump			10000	
Pimozide	Cytochrome P450 1A2			30000	23735.855
Pimozide	Cytochrome P450 2C19			30000	15848.93
Pimozide	Cytochrome P450 2C8			30000	
Pimozide	Cytochrome P450 2C9			30000	
Pimozide	Cytochrome P450 2D6			30000	3162.28
Pimozide	Cytochrome P450 2J2			30000	

Pimozide	Cytochrome P450 3A4			19850	
Pimozide	Delta opioid receptor			3760	
Pimozide	K562			5000	10000
Pimozide	Kappa opioid receptor			990	
Pimozide	Mu opioid receptor			372	
Pimozide	Multidrug and toxin extrusion protein 1			500000	
Pimozide	Multidrug and toxin extrusion protein 2			500000	
Pimozide	P-glycoprotein 1			2200	
Pimozide	Potassium channel subfamily K member 2			1800	
Pimozide	Sodium channel alpha subunit			54	
Pimozide	Solute carrier family 22 member 2			34200	
Pimozide	Ubiquitin carboxyl-terminal hydrolase 1			2000	
Pimozide	Ubiquitin carboxyl-terminal hydrolase 1/WD repeat-containing protein 48			2000	
Pimozide	Voltage-gated L-type calcium channel			201	
Pimozide	X-box-binding protein 1			10000	
Prochlorperazine	Bile salt export pump			92666.66667	
Prochlorperazine	Canalicular multispecific organic anion transporter 1			133000	
Prochlorperazine	Canalicular multispecific organic anion transporter 2			133000	
Prochlorperazine	Cytochrome P450 1A2			2000	1755.945
Prochlorperazine	Cytochrome P450 2D6			300	596.22
Prochlorperazine	Induced myeloid leukemia cell differentiation protein Mcl-1			3773.28	
Prochlorperazine	Multidrug resistance-associated protein 4			133000	
Prochlorperazine	Solute carrier family 22 member 1			49600	
Prochlorperazine	Tyrosine-protein kinase FYN			5684	
Promazine	Cytochrome P450 2D6			300	150.655
Promazine	Sodium channel alpha subunits; brain (Types I, II, III)			5400	
Promazine	Solute carrier family 22 member 1			17200	
Promethazine	Bile salt export pump			134000	
Promethazine	Calmodulin			60000	

Promethazine	Canalicular multispecific organic anion transporter 1			133000	
Promethazine	Canalicular multispecific organic anion transporter 2			133000	
Promethazine	Multidrug resistance-associated protein 4			133000	
Promethazine	Sodium channel alpha subunits; brain (Types I, II, III)			6900	
Promethazine	Solute carrier family 22 member 1			35100	
Quetiapine	HERG			5777.2	
Quetiapine	Sodium channel protein type V alpha subunit			16900	
Remoxipride	Bile salt export pump			92666.66667	
Remoxipride	Canalicular multispecific organic anion transporter 1			133000	
Remoxipride	Canalicular multispecific organic anion transporter 2			133000	
Remoxipride	Multidrug resistance-associated protein 4			133000	
Reserpine	ATP-binding cassette sub-family G member 2			19451.34	
Reserpine	Bile salt export pump			9237.5	
Reserpine	Canalicular multispecific organic anion transporter 2			133000	
Reserpine	DNA topoisomerase I			160000	
Reserpine	HL-60			67000	
Reserpine	MCF7			0.116666667	
Reserpine	Multidrug resistance-associated protein 4			133000	
Reserpine	Sodium channel alpha subunits; brain (Types I, II, III)			1600	
Risperidone	Bile salt export pump			92750	
Risperidone	Canalicular multispecific organic anion transporter 1			133000	
Risperidone	Canalicular multispecific organic anion transporter 2			133000	
Risperidone	Cytochrome P450 2D6			5273.4	5552.78
Risperidone	HEK293			600	
Risperidone	Multidrug and toxin extrusion protein 1			1600	
Risperidone	Multidrug and toxin extrusion protein 2			291000	

Risperidone	Multidrug resistance-associated protein 4			133000	
Risperidone	Sodium channel protein type V alpha subunit			102000	
Risperidone	Solute carrier family 22 member 2			11000	
Risperidone	Voltage-gated L-type calcium channel			34200	
Risperidone	Voltage-gated L-type calcium channel alpha-1C subunit			125000	
Ritanserin	Diacylglycerol kinase alpha			12850	
Ritanserin	U-251			5000	
Ritanserin	Ubiquitin-conjugating enzyme E2 N			20000	
Ritanserin	VMM39			10000	
Sertindole	Bile salt export pump			82700	
Sertindole	Canalicular multispecific organic anion transporter 1			133000	
Sertindole	Canalicular multispecific organic anion transporter 2			133000	
Sertindole	HERG			10.41	
Sertindole	Multidrug resistance-associated protein 4			133000	
Sertindole	P-glycoprotein 1			6500	
Sertindole	Sodium channel alpha subunit			2300	
Sertindole	Voltage-gated L-type calcium channel			7600	
Sertindole	Voltage-gated potassium channel subunit Kv1.5			2000	
Sulpiride	Bile salt export pump			638100	
Sulpiride	Cytochrome P450 2J2			50000	
Sulpiride	Sigma opioid receptor			10000	
Tetrahydropalmatine	Coagulation factor III			22.78	
Thioridazine	Bile salt export pump			24330	
Thioridazine	Cytochrome P450 1A2			9332.3	
Thioridazine	Cytochrome P450 2C19			6377.8	
Thioridazine	Cytochrome P450 2D6			1772.6	
Thioridazine	Epidermal growth factor receptor erbB1			2947	
Thioridazine	KG-1a			6010	
Thioridazine	MCF7			12950	
Thioridazine	MDA-MB-231			14190	
Thioridazine	MRC5			8.2	
Thioridazine	PBMC			13780	
Thioridazine	SK-BR-3			18230	
Thioridazine	SUM-159-PT			14510	

Thioridazine	Serine/threonine-protein kinase PIM1			6890	
Thioridazine	Sodium channel alpha subunits; brain (Types I, II, III)			6500	
Thioridazine	Sodium channel protein type V alpha subunit			1830	
Thioridazine	Tyrosine-protein kinase FYN			5050	
Thioridazine	Voltage-gated L-type calcium channel			3500	
Thioridazine	Voltage-gated L-type calcium channel alpha-1C subunit			1320	
Thiothixene	Bile salt export pump			30400	
Thiothixene	Ubiquitin-conjugating enzyme E2 N			20000	
Tiapride	Bile salt export pump			133000	
Tiapride	Canalicular multispecific organic anion transporter 1			133000	
Tiapride	Canalicular multispecific organic anion transporter 2			133000	
Tiapride	Multidrug resistance-associated protein 4			133000	
Trifluoperazine	Bile salt export pump			10000	
Trifluoperazine	DNA-dependent protein kinase			100000	
Trifluoperazine	Homo sapiens			201800	
Trifluoperazine	KG-1a			4580	
Trifluoperazine	MCF7			11330	
Trifluoperazine	MDA-MB-231			21580	
Trifluoperazine	NADPH oxidase 1			17000	
Trifluoperazine	SK-BR-3			15890	
Trifluoperazine	SUM-159-PT			17030	
Trifluoperazine	Sodium channel alpha subunits; brain (Types I, II, III)			5000	
Trifluoperazine	U-87 MG		13500	9900	
Trifluoperazine	Ubiquitin carboxyl-terminal hydrolase 1/WD repeat-containing protein 48			8000	
Triflupromazine	Bile salt export pump			39010	

Ziprasidone	HERG			230.1188889	
Amoxapine	Cytochrome P450 1A2				3981.07
Amoxapine	Cytochrome P450 3A4				15848.93
Amperozide	Cytochrome P450 2D6				12589.25
Chlorpromazine	HepG2				7620
Droperidol	Cytochrome P450 2D6				3162.28
Droperidol	Cytochrome P450 3A4				6309.57
Fluphenazine	Cytochrome P450 1A2				1755.945
Fluphenazine	Cytochrome P450 2D6				944.945
Fluphenazine	Cytochrome P450 3A4				18854.055
Fluspirilene	Cytochrome P450 1A2				12589.25
Fluspirilene	Cytochrome P450 2C19				11896.105
Fluspirilene	Cytochrome P450 2C9				39810.72
Fluspirilene	Cytochrome P450 2D6				5792.445
Fluspirilene	Cytochrome P450 3A4				6309.57
Methylthionium chloride	Caspase-6				1600
Methylthionium chloride	DNA repair protein RAD52 homolog				936
Moricizine	Cytochrome P450 2C9				1000000000
Moricizine	Cytochrome P450 3A4				5011.87
Olanzapine	FAD-linked sulfhydryl oxidase ALR				369
Perphenazine	DNA repair protein RAD52 homolog				13940
Prochlorperazine	Cytochrome P450 2C19				8922.095
Prochlorpera	Cytochrome P450 3A4				10430

zine					.4
Promazine	Cytochrome P450 1A2				3784.25
Promazine	Cytochrome P450 2C19				7943.28
Raclopride	Cytochrome P450 1A2				31622.78
Raclopride	Cytochrome P450 2C19				1258.93
Raclopride	Cytochrome P450 2C9				7943.28
Raclopride	Cytochrome P450 2D6				12589.25
Remoxipride	Cytochrome P450 2C19				39810.72
Remoxipride	Cytochrome P450 2D6				199.53
Risperidone	Cytochrome P450 2C19				1584.89
Tiapride	Cytochrome P450 2D6				19783.03
Trifluoperazine	Cytochrome P450 1A2				815.48
Trifluoperazine	Cytochrome P450 2C19				10266.265
Trifluoperazine	Cytochrome P450 2D6				1497.63
Trifluoperazine	Cytochrome P450 3A4				12924.465
Trifluoperazine	DNA repair protein RAD52 homolog				13000
Triflupromazine	Cytochrome P450 1A2				1189.61
Triflupromazine	Cytochrome P450 2D6				596.22
Zuclopenthixol	Cytochrome P450 1A2				15848.93
Zuclopenthixol	Cytochrome P450 2C19				2511.89
Zuclopenthixol	Cytochrome P450 2D6				10000
Zuclopenthixol	Cytochrome P450 3A4				12589.25
Aripiprazole	Mu opioid receptor		92469		
Chlorpromazi	Prion protein		2000		

ne					
Clozapine	Homo sapiens		6.4		
Fluspirilene	Glycine receptor subunit alpha-1		1200		
Fluspirilene	H4		2400		
Haloperidol	Prion protein		10000		
Methylthionium chloride	Peroxisome proliferator-activated receptor gamma/Nuclear receptor coactivator 1		958		
Methylthionium chloride	Peroxisome proliferator-activated receptor gamma/Nuclear receptor coactivator 2		742		
Methylthionium chloride	Peroxisome proliferator-activated receptor gamma/Nuclear receptor coactivator 3		3056		
Paliperidone	Serotonin 1a (5-HT1a) receptor		10000		
Penfluridol	H4		3200		
Pimozide	Glycine receptor subunit alpha-1		1700		
Promazine	Prion protein		5000		
Promethazine	Prion protein		8000		
Risperidone	Glycine receptor subunit alpha-1		320		
Triflupromazine	HCC1954		10000		
Triflupromazine	T47D		7000		

ST4 Binding reference for antipsychotics and their targets

	Ki	EC50	IC50	AC50
TXNRD1			30000	
HTR2B	0.3981	20	10	
MAOA			70	
SCN1A			54	
RAD52				936
UGT1A9	344000			
PRNP		2000		
AOX1	1460		33	
CYP2D6	7000		120	31.62
CYP1A2			2000	316.23
ADRA1D	1.962		3.991	
ADRA1A	1.33		10.54	
TACR1	624.5517			
KCNK2			1800	

ADRA2B	4.741		10	
EBPL	3.9			
MC4R	14619		15204	
EGFR			2947	
Human		6.4	155700	
GSR			16200	
CA9	43			
HTR7	0.5			
CA5A	174			
GABRG1	10000			
HTR1A	0.12	253	34	
KCNE1			251188.6	
CYP3A4			1000	1000
DRD3	0.18025	5.777	0.594	
SLC47A2			291000	
ABCG2			19451.34	
OPRM1	867	10000	372	
XBP1			10000	
DHCR24	8			
CACNA1C			201	
MCL1			3773.28	
UBE2N			14790	
SCN5A			1830	
HRH1	0.334	0.4	4.1355	
H1-0	1			
OPRD1	1714		3760	
CYP2C19			6377.8	1258.93
FGB			46265.5	
Cell			4382.58	7620
HTR6	3		13	
CA7	2421.2			
CYP2C9			11000	7943.28
KCNH2	42		10.41	
SLC22A2			11000	
HTR2C	0.833333	250	3.787	
ADORA3	6746		11935	
CA6	0.8			
ADRA2A	4.65		9.674	
DRD	1379		1735	
ADRB3	515		29488	
ABCC4			133000	

MC5R	7145		7617	
ERBB2			19366	
KCNA5			2000	
CAMKK2	19280		8520	
ABCC2	295000		68400	
HTR2A	0.45		0.42	
CHRM3	4.149		20	
SLC6A2	13		13	
HTR3A	199.53			
HTR1B	10			
SLC47A1			1600	
CASP6				1600
GSK3A			2000000	
DRD1	18		23	
ADRA1B	10			
HRH3	815.5			
CA3	10600			
ADRA2C	4.863		7.875	
GLRA1		320		
MDR1	200		780	
HTR5A	1000			
ADRB1	10000			
NOX1			17000	
UCHL1			2000	
OPRK1	996		990	
CA1	4237.5		1200	
KCND3			63095.73	
MAPT		360	2233.333	
HTR1D	100			
HTR1E	1000			
HRH2	5.727		950	
GFER				369
GRIN2B			850	
TOPBP1			160000	
CA5B	18			
OPRL1	500			
SLC22A1			15650	
PPARG		742		
APAF1			57750	
CA12	3.9			
MC3R	21244		24343	

CHRM4	1.057		7.576	
FYN			5050	
CA2	40		40	
CYP2J2			4690	
UGT2B7	590000			
TACR3	2.148708		0.505	
HRH4	292.85	218.78		
CYP2C8			30000	
DRD5	9			
F3			22.78	
GSK3B			2000000	
ABCB11			9237.5	
CHRM2	12		35	
TACR2	60.0575		22484	
PIM1			6890	
CHRM5	3.307		4.603	
CHRM1	1.69		7.019	
OGFR	5.364723		2.239	
TMEM97	16.53333			
DRD4	6.266667	5008.5	14	
FAAH			897.5	
PRKDC			100000	
SCN3A			740	
DRD2	0.14	6.3	0.3	

ST5 Network Efficiency of second generation antipsychotics calculated from AD+P network and schizophrenia network built with GWAS data only.

Drugs	Efficiency in AD+P network	Efficiency in SCZ network
Paliperidone	1.378	1.432
Brexpiprazole	1.184	1.297
Sertindole	1.093	1.132
Aripiprazole	0.554	0.63
Clozapine	0. 554	0. 63
Iloperidone	0. 554	0. 63
Olanzapine	0. 554	0. 63
Quetiapine	0. 554	0. 63
Risperidone	0. 554	0. 63

Ziprasidone	0. 554	0. 63
Lurasidone	0.146	0.242
Pimavanserin	0.146	0.242
Paired Wilcoxon Test	W = 34, P = 0.003	

ST6 Network Efficiency of second generation antipsychotics calculated from AD+P network and schizophrenia network built with DEGs data only.

Drugs	Efficiency in AD+P network	Efficiency in SCZ network
Paliperidone	1.198	1.287
Brexpiprazole	1.143	1.231
Sertindole	1.056	1.074
Aripiprazole	0.485	0.536
Clozapine	0.485	0.536
Iloperidone	0.485	0.536
Olanzapine	0.485	0.536
Quetiapine	0.485	0.536
Risperidone	0.485	0.536
Ziprasidone	0.485	0.536
Lurasidone	0.113	0.156
Pimavanserin	0.113	0.156
Paired Wilcoxon Test	W = 26, P = 0.02	

Appendix C Supplementary Material for Chapter 4.1

ST1 Drug combination count in EMR

Antipsychotics	Antidepressants	count
Quetiapine	Sertraline	408
Quetiapine	Citalopram	372
Haloperidol	Sertraline	367
Haloperidol	Citalopram	355
Risperidone	Citalopram	346
Risperidone	Sertraline	342
Haloperidol	Mirtazapine	299
Haloperidol	Trazodone	280
Quetiapine	Trazodone	274
Quetiapine	Escitalopram	269
Quetiapine	Mirtazapine	242
Risperidone	Trazodone	224
Haloperidol	Escitalopram	221
Risperidone	Mirtazapine	210
Risperidone	Escitalopram	200
Olanzapine	Citalopram	169
Olanzapine	Sertraline	157
Olanzapine	Mirtazapine	146
Olanzapine	Trazodone	138
Quetiapine	Venlafaxine	109
Aripiprazole	Sertraline	38

Appendix D Supplementary Material for Chapter 4.2

List 1. Diagnosis used for the identification of Alzheimer's disease.

1. Alzheimer's disease
2. early-onset Alzheimer's disease
3. late-onset Alzheimer's disease
4. Alzheimer's disease, unspecified

List 2. Diagnosis used for the identification of psychosis.

1. Unspecified psychosis
2. Senile dementia with delusional features
3. Hallucinations
4. Presenile dementia with delusional features
5. Delusional disorder
6. Depressive type psychosis
7. Other and unspecified reactive psychosis
8. Psychotic disorder with delusions in conditions classified elsewhere
9. Psychotic disorder with hallucinations in conditions classified elsewhere
10. Vascular dementia with delusions
11. Delusional disorders
12. Excitative type psychosis
13. Unspecified psychosis not due to a substance or known physiological condition

14. Hallucinations unspecified
15. Visual hallucinations
16. Psychotic disorder with hallucinations due to known physiological condition
17. Auditory hallucinations
18. Other hallucinations
19. Psychotic disorder with delusions due to known physiological condition
20. Psychogenic paranoid psychosis

List 3. Diagnosis used for the identification of delirium disorder.

1. Delirium due to conditions classified elsewhere
2. Vascular dementia with delirium
3. Senile dementia with delirium
4. Subacute delirium
5. Delirium due to known physiological condition

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