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CHAPTER 1

Introduction

The idea of schizophrenia is rapidly moving out of style. Psychiatry, the field that helped create it, is now supporting it and may be abandoning it after a serious re-examination. It seems unlikely that anyone would mourn its decline. These days, being diagnosed with schizophrenia is linked to a roughly 20-year drop in life expectancy, and according to some metrics, just one in seven people recover. Despite advancements in treatment, recovery rates have not risen over time, which is worrying. This suggests a significant flaw in our understanding of the condition, as there is growing evidence that the concept of schizophrenia itself plays a role.

The long-held belief that schizophrenia is a separate, independent disorder has been completely debunked. Psychosis, which is typified by unsettling hallucinations, delusions, and abnormal thinking, is increasingly recognized as occurring on a continuum, much like autism is now thought to be. The extreme end of this range is schizophrenia. According to Jim van Os, a professor at Maastricht University, fresh terminology is necessary for a real paradigm shift. He suggests that the name "schizophrenia" be completely dropped in favor of "psychosis spectrum disorder[1]." The way schizophrenia is frequently portrayed as a chronic, hopeless mental illness is another important concern. Some people and families have apparently been informed that a cancer diagnosis would be preferable because it is curable, demonstrating how depressing this viewpoint can be. People who do recover—who are usually written off as having received the wrong diagnosis—are not included in these narratives. According to Van Os, schizophrenia simply "does not exist" when it is described as a degenerative and incurable illness.

In the end, schizophrenia could turn out to be a group of distinct diseases and causes rather than a single illness. The renowned psychiatrist Sir Robin Murray has stated, "I anticipate that the idea of schizophrenia will soon come to an end[2]. For instance, the condition is already starting to differentiate among instances brought on by drug misuse, social trauma, genetic copy number abnormalities, etc. Similar to the outmoded term "dropsy," he believes that this tendency will continue to pick up speed and that the term "schizophrenia" will finally become obsolete[2].

Current studies are looking into the several ways that people might experience symptoms including hallucinations, delusions, disordered thinking and behaviour, emotional flatness, and lack of desire that are commonly linked to schizophrenia. Treating a single roadway as the only

one that may exist—or, more frequently, confusing a minor road for a highway—has been a significant previous error. For example, scientists E. Fuller Torrey and Robert Yolken have proposed that “the most important etiological agent (cause of schizophrenia) may turn out to be a contagious cat” based on their studies of the parasite *Toxoplasma gondii*, which people may catch through cats. Recovery rates have not increased despite medical breakthroughs, underscoring the underlying problem—schizophrenia itself. It is essentially a discarded idea that it is a single, unique sickness. With symptoms including hallucinations, delusions, and disordered ideas, psychosis is increasingly seen as being along a continuum, just like autism is now understood to be a spectrum[3]. The most severe end of this range is schizophrenia. A change in terminology is necessary to embrace this new knowledge, according to Jim van Os, a professor at Maastricht University. In order to adequately represent the variety and complexity of experiences involved, he has suggested doing away with the name “schizophrenia” completely and substituting it with “psychosis spectrum disorder.” Schizophrenia is a terrible illness that starts early in life and lasts for a long time. The illness affects every aspect of perception, emotion, and thought. and act in ways that have an impact on the infected person, their family, and society[4].

One percent of people globally suffer from schizophrenia, making it a global condition. One An estimated three million men and women (equal numbers) in the US suffer from schizophrenia[5]. 2 and, regrettably, the finest half of receiving treatment 3. Even if the numbers are really small, the financial impact is substantial. It is becoming more well recognized that schizophrenia is a complex illness that is impacted by a number of environmental influences, personal vulnerabilities, and hereditary factors. Some people with schizophrenia may appear quite normal—until they start talking about their innermost thoughts, which shows symptoms of the disorder. Prominent symptoms including paranoia, delusions, and hallucinations frequently set off relapses. There are still disputes over the biological mechanisms, underlying causes, and diagnostic standards for schizophrenia because of the great variation in how the disorder manifests[6]. These noticeable or “positive” symptoms may usually be effectively managed with the help of current antipsychotic drugs. Treatments for cognitive deficits and “negative” symptoms, including decreased motivation or emotional expressiveness, are still few[7]. The majority of research on the biochemical underpinnings of schizophrenia has been on anomalies in neurotransmission. Numerous ideas propose that the illness is associated with either high or

low levels of certain neurotransmitters, particularly glutamate, serotonin, and dopamine. Other hypotheses suggest that the complex neurochemical imbalances linked to schizophrenia are caused by other neurotransmitters, including gamma-aminobutyric acid (GABA), aspartate, and glycine.[8]

CHAPTER 2

History

The word "schizophrenia," which denotes fragmented or confused thinking, has been taken up from the Greek language schizo, meaning divided, and phrene, means mind. Contrary to popular belief, it does not relate to numerous or divided personalities. Swiss psychiatrist Eugen Bleuler used the phrase in 1911 in an attempt to replace the previous term "dementia praecox," acknowledging that the illness does not necessarily lead to cognitive loss[9]. As scientists and mental health professionals work to better define, diagnose, and treat schizophrenia, our knowledge of the condition keeps growing. Schizophrenia-like symptoms were first described in ancient Egypt in the second millennium BCE, when the Book of Hearts and other writings mentioned mental and emotional disorders, such as sadness. Mental illness was frequently seen as a kind of divine retribution in ancient Greece, and this idea persisted until the Roman Empire. A shift toward medical research was indicated by the Greek physician Hippocrates, who started to examine mental disease from a scientific standpoint between 460 and 377 BCE. Early therapies, which reflected the inadequate understanding of the mind at the time, were crude and sometimes erroneous despite this change[10].

Symptoms

A person with active schizophrenia frequently has episodes in which they are unable to discriminate between reality and delusion[11]. The intensity, length, and frequency of symptoms might differ from person to person, as is the case with many disorders. On the other hand, severe psychotic symptoms in people with schizophrenia tend to decrease with age. Symptoms can be made worse by things like substance abuse (including alcohol and illegal substances), excessive amounts of stress, and not taking prescription prescriptions as directed. Generally speaking, these symptoms fall into three major groups. Positive symptoms, which are experiences or actions that are uncommon in healthy people, are one of them. These include paranoia, exaggerated or

distorted ideas, beliefs, and actions, and hallucinations (such hearing voices or seeing things that aren't there). The lack or diminution of typical functioning is referred to as negative symptoms. These may include a reduced capacity for speaking, initiating activities, expressing feelings, or enjoying pleasure[12]. Disordered thought and conduct, such as nonsensical speech, trouble with logical reasoning, and even odd or unpredictable motions, are indications of disorganization. Cognitive functioning is also impacted by schizophrenia, which can result in problems with focus, memory, attention, and academic achievement. These mental difficulties might have a big influence on day-to-day living. Early adulthood is usually when symptoms first appear, and they must be lasting for minimum six months in order to be officially detected. Men often start exhibiting symptoms in their late teens or early 20s, but women are more likely to start exhibiting symptoms in their 20s to early 30s. Widespread misconceptions about schizophrenia contribute to the stigma and social avoidance that people with the condition frequently experience. It seems sense, though, that some of the social issues that people with schizophrenia have also make it harder for them to engage with other people. These difficulties may eventually result in a rise in negativity, social distancing, and rejection.

In a study by Nisenson, Berenbaum, and Good (2001), this relationship was illustrated by asking student research assistants, who were selected for their amiable personalities, to make short-term connections with individuals who had schizophrenia[13]. The students' conduct altered significantly over the course of the two-week trial, with a noticeable rise in hostility against the patients.

But do people's reluctance to marry, associate, or work with someone who has schizophrenia have anything to do with inadequate social skills? According to research, they are important. Clinically stable outpatients with schizophrenia were recorded having a three-minute role-play conversation with a confederate in a research by Penn, Kohlmaier, and Corrigan (2000)[14]. Eye contact, speech patterns, and disruptions like pauses or stutters were used by trained observers to score the patients' social abilities.

Structure of Dopamine 2 Receptor

Dopamine receptors are classified into two primary groups, D1 and D2, and are members of the G-protein-coupled receptor (GPCR) superfamily. Adenylyl cyclase is activated by stimulatory Gs proteins that are connected to the D1 family, which comprises D1 and D5 receptors[15]. On the other hand, the D2 family, which includes the D2, D3, and D4 receptors, lowers adenylyl cyclase activity by binding to inhibitory Gi/o proteins. Alternative signalling routes for dopamine receptors have been discovered in addition to these traditional pathways. Dopamine D2 receptors (D2Rs) are located both pre- and post-synaptically in the central nervous system (CNS). They are primarily expressed in the striatum, nucleus accumbens, and olfactory tubercle, while being expressed at lower levels in the substantia nigra, ventral tegmental area, hypothalamus, cortex, amygdala, and hippocampus. Only post-synaptic, dopamine D1 receptors (D1Rs) are most widely expressed in the striatum, amygdala, olfactory bulb, and frontal brain.

G-protein-coupled receptors (GPCRs) include D2 receptors. The structure of GPCRs is defined by seven transmembrane domains, with the carboxyl (C) terminus on the intracellular side and the amino (N) terminus on the extracellular side[16]. One of the intracellular loops, which is noticeably bigger than the others, interacts with the related G-protein. Alpha (α), beta (β), and gamma (γ) are the three subunits that make up G-proteins; the $\beta\gamma$ complex is essential for attaching the G-protein to the cell membrane. G-proteins can be classified into several categories based on their functions, such as G α s (stimulatory) and G α i (inhibitory)[17].

Due to their accessibility on the cell surface and their significance in controlling a variety of physiological processes, G-protein-coupled receptors (GPCRs) are among the most researched therapeutic targets in the pharmaceutical business[18]. GPCRs are principally responsible for the actions of around 34% of FDA-approved medications. Nevertheless, a large number of currently available pharmacological treatments and GPCR-targeting medications are not selective and frequently interact with other proteins or unexpected GPCR subtypes.

Based on pharmacological traits and sequence homology, dopamine receptors, which belong to the GPCR family, are divided into two subfamilies. By activating G α s or G α olf proteins, the D1-like receptors (DRD1 and DRD5) promote the buildup of intracellular cAMP[19]. On the other hand, D2-like receptors (DRD2, DRD3, and DRD4) control different ion channels and block the

synthesis of cAMP by binding to G_{ai/o} proteins. Among these, DRD2 is a particularly important therapeutic target in psychiatry and neurology. All FDA-approved antipsychotic medicines work as DRD2 antagonists or partial agonists, while many antiparkinsonians treatments work by activating DRD2. Additionally, hyperprolactinemia, Tourette's syndrome, and restless legs syndrome are treated with medications that target DRD2[20]. There aren't any ligands that are actually DRD2-selective yet, despite its therapeutic significance. Highly selective DRD2-targeting molecules are required to better study and treat associated illnesses because the majority of drugs that bind to DRD2 also have affinity for DRD3 and/or DRD4 receptors. The transmembrane regions of D2-like receptors have a significant degree of sequence similarity—78% between DRD2 and DRD3, and 53% between DRD2 and DRD4—which has made it particularly difficult to develop DRD2-selective ligands. As a result, they have structural similarities in their orthosteric binding pockets (OBPs), which are the main locations for dopamine-related ligand binding. The development of DRD3- and DRD4-selective ligands has advanced significantly, however there hasn't been much work made on highly DRD2-selective molecules. Structure-based drug design (SBDD) has recently contributed to advancements in this field. Scientists have successfully created a number of selective ligands for DRD3 and DRD4 by determining unique stiff extended binding pockets (EBPs) for each receptor[21]. The DRD2 EBP was discovered in earlier research when the structure of DRD2 bound to the atypical antipsychotic risperidone was resolved. However, DRD2's EBP is less strict than DRD3's and DRD4's, which lessens the efficacy of SBDD initiatives[22]. Researchers have now determined the structure of DRD2 bound to haloperidol, a commonly used typical antipsychotic, in order to get around this restriction. Haloperidol shares structural similarities with the DRD2-preferring chemical L-741626 and is a strong DRD2 antagonist. The DRD2-haloperidol complex's structural investigation revealed a second extended binding pocket (SEBP) that had not been found before. In addition to its direct interaction with haloperidol, this SEBP is essential for agonist-induced DRD2 activation. O4SE6 and O8LE6, two DRD2 subtype-selective agonists that do not activate DRD3 or DRD4, were successfully created by researchers by utilizing this recently discovered binding and activation mechanism involving both the SEBP and OBP. This discovery opens up a viable avenue for developing DRD2-targeted treatments that are more effective and selective.[23]

Role of D2R protein in Schizophrenia

The dopamine hypothesis of schizophrenia posits that dysregulated dopaminergic transmission, particularly through D2 receptors (D2Rs), underlies psychotic symptoms. Elevated dopamine activity in mesolimbic pathways correlates with positive symptoms like hallucinations, as excessive D2R activation amplifies aberrant salience attribution to neutral stimuli²⁷. Antipsychotics alleviate symptoms by antagonizing D2Rs, with therapeutic efficacy tied to striatal receptor occupancy rates (60–80%)²⁷. For instance, aripiprazole achieves up to 90% occupancy while minimizing extrapyramidal side effects¹. Dopaminergic cell bodies that project to different parts of the brain are the source of each of these pathways, which control a range of behaviors and physiological processes^[27]. For example, the substantia nigra contains the cell bodies of the nigrostriatal pathway, which is essential for motor function. Conversely, cognitive processes like memory and learning are linked to the mesolimbic circuit. On the other hand, dopaminergic and noradrenergic fibres that project to the cortex provide input to the mesocortical pathway, which is linked to limbic system-regulated processes (Meltzer & Stahl, 1976). An indirect dopamine agonist called amphetamine is commonly used pharmacologically to investigate behaviors and brain substrates related to psychosis^[28]. Its effects are dose-dependent, but it mostly causes dopamine release in the striatal circuits. Amphetamine can affect different brain circuits and behaviors depending on the dosage (Seiden, Sabol et al., 1993)^[29]. Understanding schizophrenia advanced significantly with the discovery that DISC1 is a gene linked to the condition. However, research attention has switched to DISC1's broader significance and linkages to other mental illnesses as a result of the revelation that it is not always disturbed in schizophrenia cases. Studies incorporating samples of psychiatric disorders have increased as a result of this change. Notably, postmortem brain tissue from patients with major depressive disorder, schizophrenia, and bipolar disorder has been shown to have insoluble forms of the DISC1 protein. Furthermore, altered DISC1 function has been associated to schizophrenia in electrophysiological research examining the P300 wave, a measure frequently used to evaluate attention-related information processing abnormalities in psychiatric diseases, generating a lot of interest. Additional research showed that, in comparison to healthy controls, people with schizophrenia had higher levels of the DISC1 gene expression in peripheral blood mononuclear cells. Remarkably, even after 12 weeks of antipsychotic treatment, this increased expression remained. Additionally, genetic research has linked DISC1 polymorphisms to

schizophrenia. For example, DISC1 variations and the disease were found to be significantly correlated in a study done in an Iranian community. Additionally, rs11122324 and rs2793091, two particular single-nucleotide polymorphisms (SNPs) in DISC1, have been found in patients with attention-deficit subtypes of schizophrenia, while rs821597 has been connected to schizophrenia in people older than 40[30], [31]. An American family with co-occurring schizophrenia and schizoaffective disorder was the subject of a study that found a 4-base pair (bp) deletion at the extreme 3' end of exon 12 of the DISC1 gene. One sister with schizophrenia, another with schizoaffective disease, and their father who was unaffected all carried this gene. Interestingly, 424 control subjects did not have the mutation. The DISC1 protein's C-terminus now contains nine aberrant amino acids as a result of a frameshift mutation brought on by the deletion. Acute amphetamine injection worsens symptoms in people with schizophrenia (Angrist, Rotrosen et al., 1980; Laurell, Abi-Dargham et al., 1996)[32]. Likewise, amphetamine reduces performance on behavioral and cognitive tasks intended to simulate deficiencies associated with schizophrenia in animal models. These include sensorimotor gating evaluated by prepulse inhibition (Swerdlow, Mansbach et al., 1990), spatial learning tasks like the Morris water maze (Russig, Durrer et al., 2003), and latent inhibition tasks that reflect attentional control (Weiner, Lubow et al., 1988). In these rat models, amphetamine-induced deficiencies closely resemble human deficits (Gray, Pickering et al., 1992; Braff, David et al., 2001).

Furthermore, D2 receptor antagonists and antipsychotic drugs can correct amphetamine-induced psychotic symptoms in both humans and animal models[33]. Accordingly, amphetamine is a useful pharmacological paradigm for studying cognitive deficits in schizophrenia (Weiner, Shadach et al., 1996; Weiner, Lubow et al., 1988; Kapur, 2003). It is commonly acknowledged that a major contributing element to the onset of schizophrenia is dysfunction in the dopamine neurotransmission pathway[34], [35], [36]. Treatments that mainly inhibit the dopamine D2 receptor (D2R) subtype are the most successful in treating the disease[37]. The "dopaminergic hypothesis of schizophrenia" first surfaced about thirty years ago, positing that the disorder results from a disruption in dopamine signalling in the mesolimbic and mesocortical pathways of the brain. Antipsychotic drugs, which block dopamine receptors in these areas, provide compelling evidence for this viewpoint. Studies using genetically engineered mice provide more proof that D2Rs play a part in schizophrenia[38]. Working memory problems, a fundamental cognitive impairment frequently observed in people with schizophrenia, are among the

abnormalities in prefrontal cortex functioning caused by D2R overexpression in the striatum of these animals. Current antipsychotic drugs, including atypical (olanzapine, aripiprazole, clozapine) and standard (chlorpromazine, haloperidol) ones, are very good in treating positive symptoms of schizophrenia, such hallucinations, delusions, and violent behaviour[39]. On the other hand, common antipsychotics frequently cause unwanted side effects, such as tremors, drowsiness, movement problems (such tardive dyskinesia), and in rare instances, neuroleptic malignant syndrome. Despite a slight improvement in tolerability, atypical antipsychotics still carry a number of serious risks, including the potential for agranulocytosis (clozapine), cataracts (quetiapine), metabolic problems like weight gain and an elevated risk of Type 2 diabetes (olanzapine, aripiprazole), and even extrapyramidal symptoms after prolonged use[40]. The dopamine system has been the subject of much research over the last 20 years in an effort to develop more effective antipsychotic medications. An increasing amount of data points to a key role for compromised dopamine signalling in the prefrontal brain in the development of schizophrenia. It's interesting to note that, in spite of the significance of D2R as a therapeutic target, there isn't much direct genetic or biochemical proof that dopamine receptor (DR) gene mutations cause schizophrenia[41]. Nowadays, it is generally accepted that intricate multi-protein assemblages called signalplexes control the intracellular signalling that is set off by D2R activation[42]. Dopamine receptor-interacting proteins (DRIPs) are a group of structural, regulatory, and signalling proteins that interact with the receptor and make up these structures[43]. The aberrant dopamine signaling observed in schizophrenia may be caused by anomalies in DRIP expression or function, or in the way DRIPs interact with D2Rs[44]. DRIPs are therefore a potential new class of molecular targets for the creation of safer and more efficient antipsychotic treatments[45].

Pathway

Signalling via Glutamate

Phencyclidine (PCP) and ketamine are examples of NMDA receptor antagonists that can exacerbate symptoms in people with schizophrenia. In healthy people and animal models, a single dose of these drugs can cause symptoms similar to those of schizophrenia[46]. Glycine, D-serine, and D-alanine are examples of allosteric modulators that have been studied with varying degrees of success, despite the fact that direct NMDA receptor agonists are not practical for clinical application[47]. By increasing glycine availability, blocking the glycine transporter may improve NMDA receptor function rather than directly stimulating the glycine site. Accordingly, sarcosine, a glycine transporter inhibitor, has demonstrated potential as an independent treatment for both positive and negative symptoms of schizophrenia; nevertheless, further studies are required to verify its effectiveness. Active research is now being done on additional glutamatergic system targets[48]. It has been demonstrated that the effects of PCP on rat locomotion, repetitive behaviours, and extracellular glutamate levels are reversed by activating metabotropic glutamate receptors (mGluRs). These and other results, such as the partial reversal of ketamine-induced effects in humans, led to the development of mGluR2/3 agonists for possible clinical application[49], [50]. These substances showed promise in reducing both positive and negative symptoms of schizophrenia in early trials. These early findings, however, have not been confirmed by later research. More recent studies are focusing on other metabotropic glutamate receptors, including mGluR5 and mGluR8[51]. Particularly in the forebrain, mGluR5 seems to play a role in controlling the activity of NMDA receptors. Similar to the effects of PCP exposure, rats lacking the mGluR5 gene show abnormalities in prepulse inhibition (PPI), a measure linked to sustained attention and thought to be a typical endophenotype of schizophrenia[52]. Similarly, rats given MPEP, a specific mGluR5 antagonist, prior to PCP treatment exhibit more severe cognitive deficits and increased hyperlocomotor activity. Currently, preclinical research is being conducted to create and investigate subtype-specific allosteric modulators that target different mGluRs[53].

Signalling via GABAergic

Schizophrenia patients' cortical areas have changes in several GABA neurotransmission indicators[54]. The decrease in the mRNA and protein levels of the 67 kDa isoform of glutamic acid decarboxylase (GAD67) is one of the most reliable and well-replicated results from imaging, animal, and postmortem investigations[55]. In the dorsolateral prefrontal cortex (DLPFC), a part of the brain essential for working memory and selective attention, this enzyme is principally in charge of generating cytosolic and vesicular GABA[55]. Interestingly, a subset of GABAergic neurons in the prefrontal cortex that express the calcium-binding protein parvalbumin (PV) seem to be the only ones affected by the decline in GAD67 mRNA[56]. According to studies, GAD67 mRNA is not detected in about 45% of PV-expressing neurons in people with schizophrenia. Rather than a decrease in the quantity of PV neurons, this alteration is ascribed to decreased expression of PV mRNA. In contrast, GAD67 mRNA is absent from only 10% of PV neurons in healthy people. Crucially, the decrease in PV mRNA is not present in the prefrontal cortex of primates receiving long-term antipsychotic medication, and it has also been noted in schizophrenia patients who have not received antipsychotic treatment[57]. These results imply that the reduction in PV mRNA is not a side effect of therapy, but rather a characteristic of the disease itself. Parvalbumin contributes to the regulation of GABA release and functions as a slow calcium buffer. When this protein is genetically deleted, GABA neurotransmission is disrupted in several ways[58]. The idea that PV neurons in the cortex of people with schizophrenia have a reduced capacity to produce and release GABA is supported by these data taken together.

However, a decrease in GAD67 mRNA may also reflect a slower rate of GABA metabolism, therefore it does not always signify a lower total GABA concentration[59]. It's interesting to note that a recent study employing high-performance liquid chromatography discovered that people going through their first episode of psychosis had substantially lower levels of GABA in their cerebrospinal fluid (CSF) than healthy controls[60]. Furthermore, decreased attention was linked to these patients' reduced GABA concentrations.

Impaired Neural Oscillations and GABA Circuit Deficits in Schizophrenia

The coordinated activity of sizable clusters of neurons both inside and between different parts of the brain is essential for many vital brain processes[61]. Because of their close connection to

intricate cognitive processes, gamma-frequency neural oscillations (30–80 Hz) in the prefrontal cortex (PFC) have been the subject of much research. It is believed that one of the main mechanisms causing cognitive abnormalities in schizophrenia is disruptions in gamma oscillations[62].

Higher working memory demands in healthy people cause an increase in gamma-band activity in the PFC[63]. Nonetheless, the frontal cortex's gamma oscillation amplitude and phase synchronization are markedly diminished in those with schizophrenia. Poor performance on tasks requiring working memory and executive function is linked to these disorders. Crucially, these gamma oscillation deficiencies seem to happen whether or not patients are on antipsychotic medication[64].

Other GABA-Related Gene Alterations in Schizophrenia

In addition to GAD67 and parvalbumin (PV), the brains of people with schizophrenia exhibit altered expression of a number of other proteins involved in GABAergic neurotransmission[65]. These include nicotinic acetylcholine receptor (nAChR) subunits $\alpha 4$ and $\alpha 7$, reelin (encoded by the RELN gene), NMDA receptor subunits (such NR2A and NR3A), brain-derived neurotrophic factor (BDNF), and GABA transporter type 1 (GAT-1)[66]. In postmortem investigations of patients with schizophrenia, all of these have been found to be decreased. With its effects on interneuron placement, neuronal growth, maturation, and synaptic plasticity, reelin plays a crucial role in the formation and operation of the brain. Its malfunction is believed to have a major role in the pathophysiology of schizophrenia. Reelin impairments are probably associated with a decrease in dendritic spine density, which is frequently seen in the brains of individuals with schizophrenia[67].

Reelin promotes the production of potassium chloride cotransporter 2 (KCC2), which facilitates inhibitory signalling, and inhibits the internalization of GAT-1, hence supporting GABAergic signalling at the molecular level[68]. Reduced reelin transcription results from the silencing of the RELN gene, which is frequently brought on by hypermethylation of its promoter and contributes to these deficiencies[69]. These molecular alterations are interesting candidates for

the creation of novel pharmaceutical therapies for schizophrenia since they are strongly linked to compromised prefrontal brain function.

Signalling by G protein-coupled receptors (GPCRs)

In general, two varieties of synaptic transmission exists: fast and slow. GPCRs, including glutamate and GABA (γ -aminobutyric acid) receptors, generate membrane depolarization signals in less than a millisecond during fast synaptic transmission[70]. On the other hand, biogenic amine, peptide, and specific amino acid receptors are involved in delayed synaptic transmission, which produces signals over a time span of hundreds of milliseconds to several minutes[71]. GPCRs are structurally identical membrane-bound proteins. that interact with heterotrimeric G proteins, which are made up of α , β , and γ subunits, to activate different intracellular signalling pathways[72]. Numerous neurotransmitters and neuromodulators, such as ions, vitamins, metabolites (such ATP and fatty acids), peptide and non-peptide hormones, natural substances, and pharmaceutical drugs, can alter GPCR activity[73]. Neuropsychiatric diseases have been linked to a variety of GPCR-mediated signalling pathways. Therefore, the development of successful therapeutic methods depends on a thorough understanding of the downstream signalling processes linked to disease-related GPCRs[74]. Two important conceptual ideas on dopamine's (DA) role in schizophrenia (SZ) have resulted from the long-standing central focus on DA in SZ research. Van Rossum postulated in 1966 that excessive dopaminergic activation is a factor in schizophrenia[75]. Later findings that dopamine agonists can cause psychotic symptoms and that antipsychotic drugs bind to D2 receptors supported this theory (2–4). This idea developed into a more complex paradigm throughout time, implying an imbalance marked by hypodopaminergic function in the cortex and hyperdopaminergic activity in subcortical areas[76]. Evidence of prefrontal cortical abnormalities in SZ and the importance of dopamine in prefrontal cognitive functions served as the basis for this modification[77]. Researchers can now more precisely examine dopaminergic transmission *in vivo* thanks to developments in neuroimaging technologies. Studies on the early stages of schizophrenia were made possible by the early identification of the prodromal phase and the responsiveness of the dopaminergic system to pertinent risk factors was investigated using stress-based paradigms[78], [79]. All together, these methods have produced consistent results in several investigations, showing

increased presynaptic dopamine transmission in the striatum, supporting the initial hyperdopaminergic theory. Further evidence of cortical dopamine deficiencies has also been found in recent data from our lab, which supports the updated model and also shows dopaminergic dysfunction in a number of extrastriatal locations that were not previously linked to hypodopaminergia in schizophrenia[80].

A catecholamine neurotransmitter, dopamine (DA) is essential for many physiological processes in the central nervous system (CNS)[81]. Schizophrenia is one of the CNS illnesses linked to dysregulation of dopamine signalling. G protein-coupled receptors (GPCRs), which fall into two primary classes—D1-like and D2-like receptors—are the site of dopamine's action[82].

Originally, these classes were separated according to whether they were coupled to inhibitory G_{ai} proteins or stimulatory G_{as} proteins. D1R and D5R belong to the D1-like receptor family, which is related to G_{as}, whereas D2R, D3R, and D4R belong to the D2-like receptor family, which is coupled to G_{ai}. GPCR kinases (GRKs) phosphorylate the receptor, which is followed by the recruitment of β-arrestins (βarrs), causing fast desensitization of GPCR signalling mediated by G proteins[83]. Receptor internalization, dephosphorylation, and recycling back to the plasma membrane are all triggered by this contact, which also prevents further G protein signalling. GRK isoforms (GRK2, 3, 5, and 6) and β-arrestins (βarr1 and βarr2) interact with dopamine receptors in the majority of cellular systems, causing desensitization and internalization[84].

β-arrestins serve as scaffolds for a variety of intracellular signaling proteins, such as kinases and phosphatases, in the more recent discovery of a G protein-independent form of GPCR signaling[85]. In particular, it has been demonstrated that βarr2—but not βarr1—mediates this alternative pathway for D1R and D2R by scaffolding important signaling molecules such protein kinase B (AKT), extracellular signal-regulated kinase (ERK), and protein phosphatase 2A (PP2A)[86][87]. Crucially, all antipsychotic medications (APDs) target D2 receptors, and selectively modifying D2R-βarr2 signaling offers a viable method for creating new therapeutic approaches to treat schizophrenia[88].

Cholinergic Pathway

Nicotinic and muscarinic receptors are the two primary receptor types via which cholinergic neurotransmission functions[89]. Despite the well-established significance of nicotinic receptors in schizophrenia, muscarinic receptors seem to play a unique role because of their unique interactions with other neurotransmitter systems, such as the inhibitory neurotransmitter GABA and the excitatory neurotransmitter glutamate. Via neural projections spanning many brain regions, muscarinic receptor activity—whether through stimulation or inhibition—also affects dopaminergic and serotonergic signalling[89]. Numerous subtypes of nicotinic and muscarinic receptors exist, each with distinct roles and patterns of regional expression[90]. Each of the five muscarinic receptor subtypes—designated M1 through M5—has a distinct distribution throughout the nervous system and brain. Nicotinic receptors, on the other hand, are divided into subtypes, such as N1 and N2, with N2 found in both the central and peripheral nervous systems and N1 on skeletal muscles[91]. Cholinergic neurotransmission has a crucial part in the development of schizophrenia, according to epidemiological research[92]. The substantial correlation between tobacco use and psychosis is one noteworthy finding[93]. According to a meta-analysis, regular tobacco users accounted for 58.9% of those who experienced their first episode of psychosis[94]. Additionally, according to the same data, tobacco usage was around six times more common among those who had psychosis than among those who did not. The high smoking rates in this population may be explained by the way nicotine seems to mitigate some of the negative symptoms and cognitive impairments linked to schizophrenia[95]. This argument is supported by the fact that smokers with schizophrenia typically take deeper and longer breaths than non-smokers, indicating a self-medication habit intended to alleviate symptoms.

Nicotine works pharmacologically by activating nicotinic acetylcholine receptors, which causes the release of neurotransmitters in particular parts of the brain, most notably the mesolimbic pathway[96]. Neurons in this circuit send dopaminergic signals from the ventral tegmental area (VTA) to regions such as the hippocampus, amygdala, and nucleus accumbens. A major component of the brain's reward system, the mesolimbic system is implicated in addiction and problems of emotional regulation[97]. In addition to its effects on dopamine and dopaminergic pathways, nicotine affects the release of a number of other neurotransmitters, such as gamma-aminobutyric acid (GABA), glutamate, noradrenaline, serotonin, opioids, and acetylcholine[98].

Nicotine's pharmacological effects in schizophrenia involve complex interactions with antipsychotic medications and symptom profiles. By acting on nicotinic acetylcholine receptors (nAChRs), nicotine may ameliorate antipsychotic-induced extrapyramidal symptoms like akathisia through enhanced dopaminergic transmission in nigrostriatal pathways¹⁴. This occurs as nicotine stimulates $\alpha 4\beta 2$ and $\alpha 7$ nAChRs on midbrain dopamine neurons, partially counteracting D2 receptor blockade from first-generation antipsychotics. However, this dopamine-enhancing effect creates a therapeutic paradox. While mesostriatal dopamine modulation improves motor side effects, concurrent mesolimbic pathway activation risks exacerbating positive psychotic symptoms through excessive ventral striatal dopamine release²⁴. Clinical studies demonstrate smokers with schizophrenia exhibit 27% higher baseline D2 receptor occupancy in associative striatal regions compared to nonsmokers, potentially explaining the association between smoking and intensified delusions/hallucinations. A study that found that heavy smokers with schizophrenia had higher frequencies of positive symptoms than lesser smokers lends credence to this theory[99]. It's interesting to note that heavy smokers typically scored lower on negative symptoms in the same study. Patients with mild to moderate nicotine dependency scored higher on the Positive and Negative Syndrome Scale (PANSS) negative symptom subscale than patients with severe nicotine dependence, according to a more recent study on the relationship between nicotine dependence and schizophrenia. These findings imply that cholinergic pathways might be important in controlling negative symptoms in schizophrenia[100].

Diagnostics of Schizophrenia

Basic and practical (clinical or routine) components can be used to broadly classify the tasks involved in diagnosing schizophrenia.

Basic diagnostic duties concentrate on: figuring out the fundamental reasons and processes that lead to the emergence of schizophrenia and the syndromes or symptoms that go along with it. creating trustworthy techniques for early diagnosis and detection.

Typical clinical diagnostic duties include: assessing the likelihood of schizophrenia development. evaluating the prognosis, whether it is good or bad. establishing individualized objectives for rehabilitation, treatment, and prevention. These goals can currently be supported

by instrumental and laboratory studies in addition to clinical evaluations employing psychological tests and questionnaires. These consist of: structural MRI, which offers fine-grained pictures of the anatomy of the brain. EEG and functional MRI (fMRI), which provide information about functional changes in the brain. evaluations of other new biomarkers as well as innate and adaptive immune characteristics. Taking methodological factors into account when studying this complicated condition is another way to address the main difficulties in diagnosing schizophrenia. The incomplete knowledge of the molecular mechanisms underlying schizophrenia is one of the main barriers to its accurate diagnosis and treatment. Since schizophrenia is known to be a very diverse disorder , it is frequently misdiagnosed with other mental illnesses . For instance, bipolar illness is the most common first misdiagnosis for about 24% of people who are later diagnosed with schizophrenia. Nowadays, the majority of diagnoses are made through structured clinical interviews that are directed by classification systems like the International Classification of Diseases, 11th Revision (ICD-11) and the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). These methods, however, are subjective by nature and rely on the clinical interpretation of symptoms, which may cause differences amongst assessors. On a scale of 0 to 1, Cohen's kappa coefficients range from 0.56 to 0.59, indicating only modest diagnostic consistency across physicians using ICD-10 and DSM-IV. Another difficulty is that psychotic symptoms usually appear after a prodromal phase, which is when early symptoms of affective disorders and schizophrenia frequently overlap , making an early and precise diagnosis challenging. Research indicates that early intervention, especially in first-episode psychosis, produces better treatment outcomes and more noticeable biological benefits than treatment in later phases, despite the fact that there are no proven preventive interventions for schizophrenia.

Schizophrenia Diagnostic Criteria

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) and the international categorization of Diseases, 10th Revision (ICD-10) are the two main categorization systems used to diagnose schizophrenia[101]. Despite their widespread use, the diagnostic criteria of the two frameworks are rather different.

1. DSM-5-TR Standards:

The American Psychiatric Association's 2022 DSM-5-TR states that in order to diagnose schizophrenia, a patient must have at least two of the following symptoms for a substantial amount of time over the course of a month (or less if treatment is successful). Crucially, at least one of the symptoms needs to be either:

- a) Delusions
- b) Disordered discourse, such as poor track maintenance & overloading.
- c) Extremely erratic or catatonic conduct

Some negative hints can also be there, such as a loss of drive or a decrease in emotional expression

At least one month of active-phase symptoms must be present, along with ongoing indications of disruption for a minimum of six months. If successful treatment is given, this period of time might be shortened. Only negative symptoms or milder versions of active-phase symptoms may be present during the prodromal or residual phases. Schizoaffective illness, bipolar disorder or depression with psychotic symptoms, substance-induced psychosis, and symptoms from a general medical disease must also be ruled out in the diagnosis. Only when there is a noticeable presence of prominent delusions or hallucinations for at least one month can a person with a prior developmental disability (such autism spectrum disorder) be diagnosed with schizophrenia.

2. ICD-10 Standards:

For schizophrenia to be diagnosed, at least one of the following symptoms must exist for at least one month, according to the International Classification of Diseases, 10th Revision (ICD-10):

Think broadcasting, thought insertion or withdrawal, or thought echo

Delusional perception or delusions of power, influence, or passivity

Voices that continuously comment on the person's actions or talk about them among themselves are examples of auditory hallucinations. Chronic illusions that are obviously abnormal or culturally unrealistic.

Alternatively, if at least two of the following characteristics are noted for a month or more, a diagnosis can still be made even if the aforementioned symptoms are not entirely present: persistent hallucinations in any modality of perception, especially when they are coupled with

temporary or incompletely formed delusions[102]. The use of invented words (neologisms) or illogical or irrelevant speech are examples of disruptions in the flow of cognition. Posturing, rigidity, or stupor are examples of catatonic conduct. Adverse symptoms including diminished speech, apathy, or emotional blunting. A noticeable and persistent shift in behavior, usually manifested as a loss of interest and social disengagement

Methods:

Population Study

A clinical trial examining simvastatin supplementation in people with schizophrenia provided the data and samples used in this analysis (ClinicalTrials.gov identifier: NCT01999309) . According to the DSM-IV standards, all 119 participants in the study, who were between the ages of 18 and 50, had a diagnosis of schizophrenia spectrum disorder . Only those who had been unwell for no more than three years at the time of trial admission were included in order to guarantee the inclusion of people with recent-onset psychosis.

Participants were recruited for the clinical experiment between November 2013 and February 2019 at the University Medical Centers in Utrecht (UMCU) and Groningen (UMCG) in the Netherlands. The UMCU Research Ethics Committee gave the study ethical permission (protocol number 13-249). A similar study called "Investigating normal variability in brain volumes and cognition in a healthy population, which was also carried out at UMCU, involved the collection of healthy control samples. Protocols for sample preparation and recruitment were in line with those employed in the simvastatin experiment. Every participant gave their informed consent, and only those who agreed to the transfer of data and materials internationally were included in the current analysis. There were 26 healthy controls and 36 individuals with schizophrenia in this sample. Previous published research provide further details on study procedures, including specific inclusion and exclusion criteria.

Gathering and Preparing Samples

For this study, both serum and peripheral blood mononuclear cell (PBMC) samples were collected as biological materials. All procedures for sample handling adhered to the standardized protocols established by the University Medical Center Utrecht (UMCU) biobank. To obtain serum, blood was drawn into 9 ml serum separator tubes and left to clot at room temperature for 60 minutes. The samples were then centrifuged at 2000×g for 10 minutes, after which the serum (supernatant) was divided into 0.5 ml aliquots and stored at -80°C until further analysis.

For PBMC isolation, blood samples were collected in 9 ml sodium heparin tubes and processed within 24 hours. The heparinized blood was diluted 1:2 with phosphate-buffered saline (PBS) and carefully layered onto Ficoll-Paque. After centrifugation at 1000×g for 20 minutes at room temperature, the PBMC layer was separated, while the plasma was discarded to minimize platelet contamination. The isolated PBMCs were washed twice with 10 ml PBS and centrifuged at 250×g for 10 minutes each time. The washed cells were then resuspended in 1 ml of RPMI-1640 medium supplemented with 1% penicillin-streptomycin. For long-term storage, the PBMCs were cryopreserved in liquid nitrogen using a cryoprotective solution containing 10% dimethyl sulfoxide (DMSO).

Analyte measurements and laboratory procedures:

Immunoassays with multiplexes

The analytes evaluated in this investigation were selected on the basis of previous research that associated them with metabolic syndrome or schizophrenia. The Luminex MAGPIX multiplex immunoassay platform (Luminex Corporation) was used to quantify serum analytes. The target analytes that were measured were as follows:

(ProcartaPlex Human Apolipoprotein Panel 5-plex, Thermo Fisher, EPX050-15818-901)

Apolipoproteins: Apo A1, A2, B, C2, and E

IL-6 and TNF- α are examples of cytokines (Human Magnetic Luminex Performance Assay,

High Sensitivity Cytokine A, R&D Systems, LHSCM000).

Serpin E1, chemokine ligand 2 (CCL-2), leptin, adiponectin, C-reactive protein (CRP), resistin, and complement factor D are examples of metabolic and inflammatory markers (Human Obesity Luminex Performance Assay, R&D Systems, LOBM000).

Every assay was carried out in accordance with the guidelines provided by the manufacturers.

Analyte concentrations were calculated using five-point logistic standard curves, which were run in duplicate for accuracy, and optimized sample dilutions were used for every test.

Three quality control samples were included in each 96-well plate used for measurement, and duplicate measurements of each sample were made. Crucially, in order to reduce bias, experimenters were blinded to the samples' diagnostic status.

Flow cytometry

After being thawed at 37°C, peripheral blood mononuclear cells (PBMCs) were rinsed with full RPMI medium (RPMI-1640 supplemented with sodium bicarbonate [Sigma-Aldrich], 10% foetal bovine serum [Life Technologies], 50 U/ml penicillin, 50 µg/ml streptomycin [Life Technologies], and 2 mM l-alanyl-l-glutamine dipeptide [Life Technologies]), which contained 20 µg/ml deoxyribonuclease (Sigma-Aldrich). Following washing, cells were resuspended at a density of 1×10^6 cells/ml, plated on 96-well plates (Starlab) at a volume of 0.2 ml per well, and kept at 4°C until analysis the same day. After washing and resuspending in FACS buffer (PBS with 0.5% bovine serum albumin [Sigma-Aldrich] containing 20% human Fc receptor binding inhibitor (eBioscience), PBMCs were prepared for cell surface labelling. To prevent non-specific antibody binding, the cells were treated for 20 minutes at room temperature.

MRI

MRI has emerged as a valuable diagnostic adjunct in schizophrenia research due to its ability to detect neuroimaging biomarkers (Galderisi et al., 2019). Its role in personalized medicine is particularly notable, as MRI-derived neuroanatomical data can guide tailored interventions like transcranial magnetic stimulation (Zangen et al., 2023; Cole et al., 2022). Recent studies highlight MRI's utility in identifying structural and functional brain abnormalities in

schizophrenia, driving increased research investment (Zhao et al., 2022; Brenner et al., 2022). For instance, voxel-based morphometry analyses achieve 76–84% accuracy in distinguishing patients from healthy controls across multi-site datasets, despite scanner variability (Nemoto et al., 2020). Magnetic resonance imaging (MRI) has become an increasingly recognized adjunct diagnostic tool in schizophrenia research, primarily due to its capacity to identify neurobiological biomarkers (Galderisi et al., 2019). Beyond diagnosis, MRI advances personalized medicine by enabling neuroanatomy-guided interventions such as targeted brain stimulation, as evidenced by recent clinical trials (Zangen et al., 2023; Cole et al., 2022). The technology's ability to detect structural and functional brain differences between schizophrenia patients and healthy individuals has spurred significant research funding, with studies consistently reporting reduced gray matter volume and altered functional connectivity in key regions (Zhao et al., 2022; Brenner et al., 2022). For example, voxel-based morphometry achieves 78–85% diagnostic accuracy across multi-site datasets, even with scanner variability (Nemoto et al., 2020). Neuroimaging also reveals compounding effects of substance abuse, showing 14% greater hippocampal volume loss in patients with comorbid cannabis use (Walter et al., 2012). Structural MRI findings highlight clinical correlations, such as enlarged lateral ventricles predicting poorer treatment response (Lieberman et al., 2001) and progressive gray matter loss (1.2–1.8% annually) in treatment-resistant cases (Sone et al., 2023). First-episode, drug-naïve patients exhibit cortical thinning in the insula (mean thickness reduction: 0.3 mm) and superior temporal gyrus, patterns replicated across ethnic groups (Song et al., 2015). Diffusion tensor imaging (DTI) further identifies white matter pathology, with fractional anisotropy reductions of 0.12–0.15 in fronto-temporal tracts correlating with auditory hallucinations (de Weijer et al., 2011). Paradoxically, treatment-resistant patients show 7–9% larger frontal white matter volumes compared to responders, suggesting distinct neuropathological subgroups (Molina et al., 2008). Multimodal approaches combining structural and functional MRI data improve diagnostic specificity to 87–91%, particularly when analyzing default mode network disruptions (Antonucci et al., 2022). These advancements underscore MRI's dual role in both elucidating disease mechanisms and guiding therapeutic strategies, though challenges like scanner standardization remain critical for clinical translation.

Disrupting Pathways in Schizophrenia

(DISC1) protein pathway	function in regulating dopaminergic activity	[104]
Tropomyosin alpha-3 chain (TPM3) protein pathway	mutations in the TPM3 gene results in ineffective muscular contraction, muscle weakness	[105]
Cadherin-13 (CAD13)	Dysregulation leads to disturbed grey matter differentiation, morphology of the spine, synapse formation	[106]
The AKT signaling pathway	Mutation leads to impairment of regulatory functions like cell cycle, glucose metabolism	[107]
Neurogeulin / ERB4 pathway	Alterations leads to changes in glutamatergic transmission from the ventral hippocampus to the nucleus accumbens, resulting in PPI deficiencies	[108]
DTNBP1 signaling pathway	Leads to glutamatergic alteration	[109]

CHAPTER 3

Molecular Docking

Molecular docking is a potent computer technique that is essential for structural biology, drug development, and biomolecular interaction research, giving a comprehensive understanding of its significance in contemporary scientific research[110]. To predict about how very tiny molecule which is a potential drug, is going to interact with a target biomolecule, such as DNA or a protein, is known as molecular docking. In order to help discover or invent a novel drug molecule, enhance pre-existing molecules, and comprehend the typical relationships between medications and receptors, the technique judges the ligand's energetic and spatial compatibility with the receptor's active site. A computer method called "Molecular Docking" ranks and assesses various ligand-receptor conformations according to their binding energies. In order to separate high-affinity ligands from low-affinity ones and find viable drug candidates for experimental validation, a precise scoring function is essential. Molecular docking is used in several areas of drug progress, such as lead optimization, virtual screening, and structure-based drug development. When developing a structure-based medication, the three-dimensional structure of the target biomolecule is used to direct the choice of ligand that will interact with the active area. By quickly analyzing enormous chemical libraries, virtual examination speeds up the process of discovering possible therapeutic characteristics. On the other hand, iterative docking experiments that aim to improve pharmacological characteristics and binding affinity facilitate lead optimization. Numerous methods have emerged in the field of molecular docking to tackle the particular difficulties of biomolecular interaction research and structure-based drug design. The various docking approaches, their underlying theories, their uses, and their significance in expanding our knowledge of molecular interactions in various settings are all thoroughly examined in this paper. The necessity to account for various molecular kinds, target structures, and research goals gives rise to the variety of docking techniques.

METHODOLOGY

Data collection

The Protein Data Bank (PDB) provided the protein structure of D2R, the target receptor in molecular docking experiments. The resolution quality and wholeness of the active site were considered when choosing the compound's structure.

The Swiss Similarity tool (<https://www.swisssimilarity.ch/>), an online virtual screening platform, was used to identify the ligands. This software facilitates ligand-based drug development and therapeutic repurposing efforts by enabling the identification of structurally related compounds based on known ligands. Clonazepam, a clinically licensed D2R enhancer used to treat schizophrenia, had its SMILES notation obtained from PubChem and verified using the Drug Bank database to begin the screening process. Swiss Similarity was set up to search only inside the FDA-approved pharmaceutical library to guarantee that each hit that surfaced had established pharmacological and safety qualities.

The Swiss Similarity analysis produced a CSV file with 331 drugs that have a high level of structural resemblance to clonazepam. Since central nervous system (CNS) activity is essential for schizophrenia, these candidate drugs were then put through a blood-brain barrier (BBB) permeability filter utilizing SwissADME and associated ADME analytical methodologies. Substances thought to be non-permeable to the BBB were subsequently eliminated in order to concentrate on those that were more likely to have therapeutic effects inside the brain.

Preparation of the target protein

Induction of the D2R receptor has been selected as a potential treatment for schizophrenia. The RCSB Protein Data Bank (PDB) (<https://www.rcsb.org>), a comprehensive and meticulously curated resource for experimentally determined protein structures, is where the three-dimensional crystal structure of D2R was obtained. PDB ID pdb_00005ojm, which denotes the extracellular domain of D2R, was utilized to determine the precise structure utilized in this

investigation. This domain includes the alpha and gamma subunit, which is the primary target for ligand binding and contains the active site that drives enzymatic activity.

The protein structure was preprocessed using Auto Dock Tools (MGL Tools) to provide a pristine and physiologically suitable docking environment. At this stage, water molecules were eliminated to reduce noise and avoid fake interactions. Polar hydrogens were also removed because they are not gathered during docking and could make data more difficult to interpret. The structure was also transformed and saved in PDBQT format, which is necessary as an input file for docking simulations based on Auto Dock, and Gasteiger charges were added. Because it guarantees that the active site is precisely delineated, steric hindrance is reduced, and binding energy estimates are accurate, proper protein preparation is an essential precondition for precise molecular docking. Any errors made at this point could result in incorrect identification of possible lead compounds or erroneous docking results. As a result, meticulous target preparation enhances the docking data's precision, repeatability, and biological significance.

Ligand selection

Absorption, distribution, metabolism, and excretion, or ADME, are important pharmacokinetic factors that must be assessed in order to develop successful pharmacological treatments. These elements influence a compound's bioavailability, toxicity, and therapeutic appropriateness in addition to its drug-likeness, particularly for disorders involving the central nervous system (CNS), like Alzheimer's. This work made use of SwissADME, a publicly available online program created by the Swiss Institute of Bioinformatics (SIB) (<http://www.swissadme.ch/>), to guarantee the pharmacological importance of chosen ligands. Using SMILES (Simplified Molecular Enter Line Entry System) notation to enter chemical structures, this platform allows for thorough profiling of tiny molecules.

A multi-step screening procedure was used to select an initial library of 291 FDA-approved medications based on their structural resemblance to the well-known GABA A inducer. Lipinski's Rule of Five, which assesses critical characteristics such as MW, log P, HBD, and HBA—all of which are indicative of a compound's propensity to be orally accessible—was

applied in the initial screening step. Substances that failed to satisfy these requirements were discarded. The PAINS (Pan-Assay Interference Compounds) filter was used in the following step to eliminate substances that can cause false-positive results because of assay interference or non-specific biological activity.

Blood-brain barrier (BBB) permeability predictions were included in the selection process to make sure the compounds maintained the capacity to efficiently reach brain tissue because of the BBB's crucial role in CNS medication delivery. In the context of treating schizophrenia, only compounds that were anticipated to pass through the blood-brain barrier were deemed potential candidates for additional research. To support each candidate's pharmacokinetic profile, other attributes like water solubility, synthetic accessibility, bioavailability score, and gastrointestinal (GI) absorption were assessed.

Out of the initial 284 compounds, 42 drug-like molecules were found after a thorough ADME-based investigation; all of these compounds showed promising pharmacokinetic properties. To assess the binding affinity and interaction patterns of these chosen ligands, which were thought to be promising for CNS function, D2R molecular docking studies were conducted on a subunit. Only candidates with high potential, CNS permeability, and pharmacological significance made it to the final docking phase following ADME filtration.

Preparing the Ligand

To make sure that every molecule was in a format appropriate for molecular docking investigations, the ligand preparation procedure was an essential step. Finding molecules having structural similarities to the reference medication haloperidol was the first use of Swiss Similarity. The PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) helped in extracting the compounds corresponding three-dimensional structures. The National Centre for Biotechnology Information (NCBI) updates and maintains the publicly available chemical information repository PubChem, which offers a comprehensive compilation of compound data, including physicochemical properties, biological activities, and structural details. To display 3D chemical

structures and related metadata, the chosen compounds were downloaded in the Structure Data File (SDF) format.

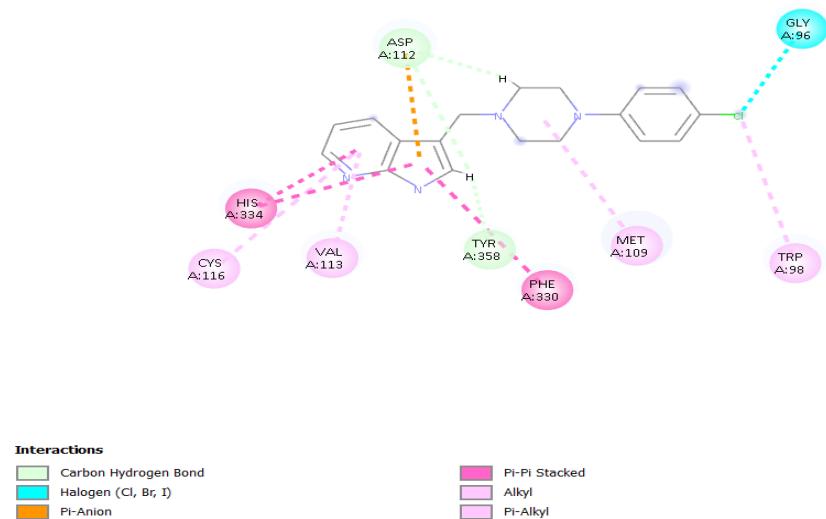
Discovery Studio was used to transform these files into a format that could be used with molecular docking tools. More than 110 distinct chemical file formats can be converted with the open-source chemical toolset Discovery Studio. Additionally, it facilitates molecular modeling tasks such as adding hydrogen atoms, improving geometry, and detecting molecular descriptors. To ensure correct alignment and processing during docking simulations, Discovery Studio Biovia was used to convert all of the ligand structures in this work from SDF to PDB (Protein Data Bank) format. The spatial arrangement and chemical integrity of the ligands were preserved because to this conversion.

Using Open Babel in PyRx or the ligand preparation tools in the docking suite, each ligand was further produced after format conversion by adding polar hydrogen atoms, allocating the appropriate atomic charges, and optimizing shape. To make sure that any interactions with the D2R target protein were accurately captured in the molecular docking data, this step was essential. Overall, high-quality structural data input was guaranteed by the ligand preparation procedure, which serves as the basis for consistent and repeatable docking outcomes.

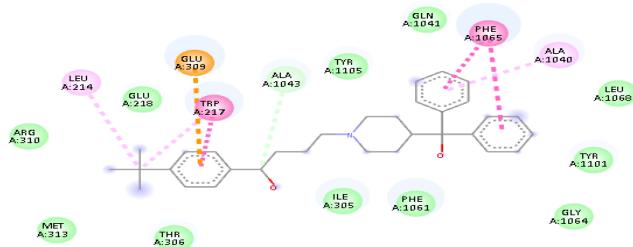
CHAPTER 4

RESULTS AND VISUALIZATION:

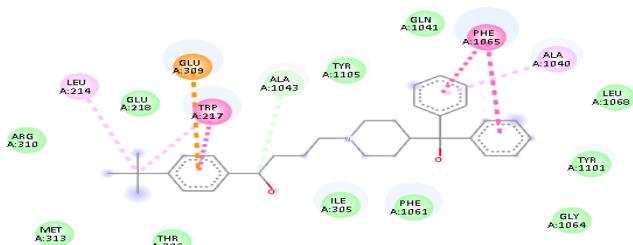
Following molecular docking of the selected ligands with the D2R receptor, the 2D and 3D binding conformations of the top-performing compounds were examined using BIOVIA Discovery Studio. The pictures made it evident what kind and how intense the exchanges were. Several stabilizing interactions were found in medications such as eliprodil, terfenidine, and haloperidol. These, which included pi-pi stacking, hydrogen bonding, hydrophobic interactions, and metal coordination with the catalytic zinc ion, enabled robust and accurate binding into the active region. The 2D interaction diagrams clearly showed significant contact residues, which are crucial components of the catalytic site. The 3D visualizations further confirmed that these ligands were well aligned with the substrate binding groove, fit well into the binding pocket, and were close to the catalytic core. These findings support the compound's potential as a promising modulator of D2R receptor sensitivity, which necessitates further testing.



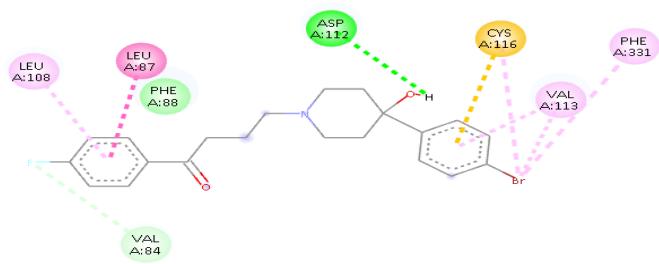
Demonstrating various interactions of Haloperidol with D2R receptor
Protein in a 2D graphical representation



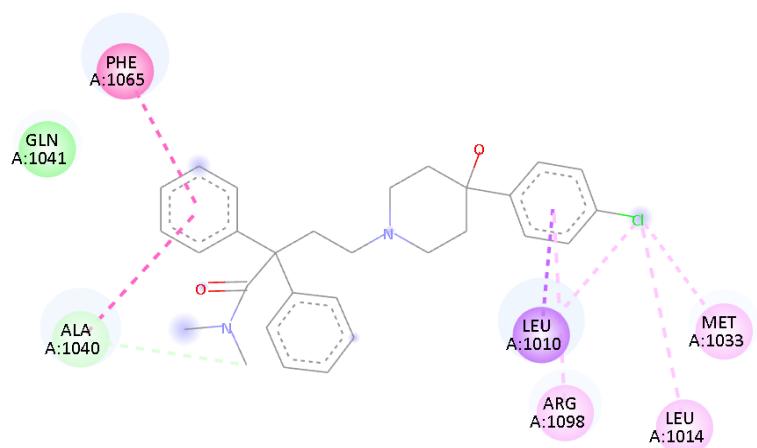
Demonstrating various interactions of Moperone with D2R receptor
Protein in a 2D graphical representation



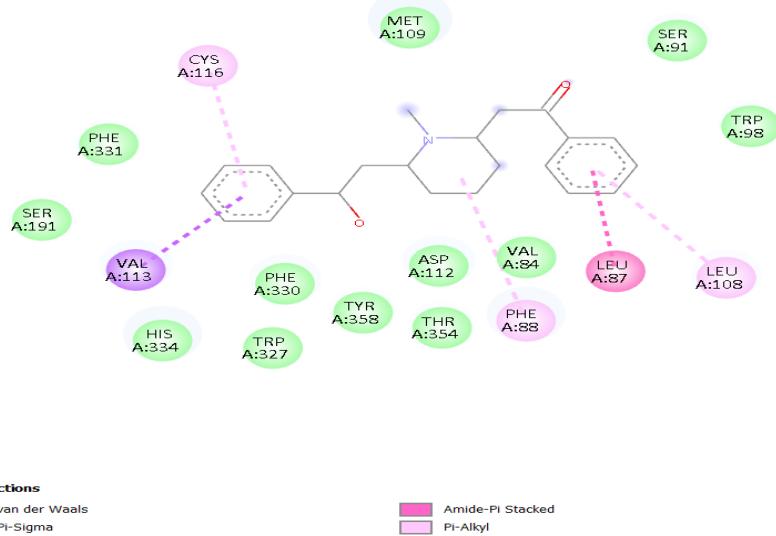
Demonstrating various interactions of Terfenadine with D2R receptor
Protein in a 2D graphical representation



Demonstrating various interactions of Bromoperidol with D2R receptor
Protein in a 2D graphical representation



Demonstrating various interactions of Ioperamide with D2R receptor
Protein in a 2D graphical representation



Demonstrating various interactions of Benzoflavine with D2R receptor

Protein in a 2D graphical representation

RESULTS OF MOLECULAR DOCKING

Binding affinity score of ligand molecules

Drugs	Binding affinity (Kcal/mol)
Haloperidol	-8.3
Bromoperidol	-8.8
Moperone	-9.1
Clobutinol	-5.7
Chlofedanol	-6.4
Cycrimine	-7.6
Diphenidol	-9.3
Imidodicarbonimidic diamide	-7.6
Eliprotil	-8.8
Ifenprodil	-8.3
Benzoflavine	-9.1
Ioperamide	-9.3
Phenoperidine	-8.3
Pipamperone	-87
Terfenadine	-10.5.
Procyclidine	-7.7
Quifenadine	-7.6
Resiniferonol	-6.8
Trihexyphenidyl	-8.8

ADMET ANALYSIS

The pharmacokinetics of a medicine are evaluated by research on absorption, distribution, metabolism, excretion, and toxicity. A key component of drug discovery is predicting a drug's fate and the effects it will have on the body, particularly how well it will be absorbed when taken orally and in the gastrointestinal system. Potential drugs frequently fail due to a variety of issues, including insufficient efficacy and safety worries. This emphasizes how vitally important chemical compounds' absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics are at every stage of the drug discovery process. Consequently, a key element of computational drug design is ADMET research (Guan et al., 2019).

ADSORPTION

A chemical must first enter the bloodstream before interacting with any tissue. Before any medicine is absorbed by the targeted cells, it is usually given through mucous membranes such as the digestive tract, specifically through intestinal absorption. The degree of drug absorption after oral ingestion is reduced by a number of factors, including the compound's low solubility, the length of time it takes for it to pass through the intestines, the rate at which the stomach empties, the compound's incapacity to cross the intestinal barrier, and chemical instability in the stomach (Pires et al., 2015).

DISPLAY

The creation of extremely effective medications requires uniform drug distribution. A drug's distribution qualities dictate how it moves through the body from the site of administration to the desired area. It is widely believed that distribution is made easier by the easier movement of smaller, lower molecular weight molecules throughout the body. However, the FDA's clearance of some medications with molecular weights between 500 and 2000 Dalton has challenged this notion.

The toxicity

It is crucial to evaluate this crucial attribute in detail and with precision. Any effect a medicine has on the body that deviates from its intended therapeutic activity is referred to as toxicity.

Blood Brain Barrier (BBB)

A highly specialized, selectively permeable contact, the blood-brain barrier is essential for controlling the flow of chemicals between the brain and the bloodstream. By regulating the entrance and efflux of ions, nutrients, and other substances, it maintains the stability of the internal environment of the brain and the ideal circumstances for neuronal function.

The BBB is made up of a special network of endothelial cells that are structurally distinct from those seen in other organs. These cells have relatively few transcytotic vesicles and are closely linked by junctional complexes with high electrical resistance, which effectively restricts both paracellular and transcellular transport across the barrier. Pericytes, astrocytes, and microglia all contribute to the BBB's integrity and functionality by maintaining the barrier between the brain's neuronal tissue and the bloodstream. In the adult brain, the BBB is essential for maintaining the chemical milieu required for vital neural functions such as synaptic transmission, neuronal circuit maintenance, angiogenesis, and neurogenesis. A series of pathogenic processes, however, can be set off by any interference with its function, including impaired tight junctions, aberrant molecular transport, impaired angiogenesis, vascular regression, cerebral hypoperfusion, or neuroinflammation. The development and course of several neurodegenerative diseases, including as multiple sclerosis, Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS), are closely linked to these dysfunctions (Zlokovic, 2008). The BBB's restriction is one of the main obstacles in the creation of drugs for the central nervous system (CNS).

Peptides, monoclonal antibodies, recombinant proteins, RNA interference (RNAi)-based medicines, and gene treatments are examples of large-molecule therapeutics that usually cannot pass the blood-brain barrier in therapeutically meaningful quantities (Pardridge, 2019).

Therefore, the development of successful CNS-targeted treatments is still significantly hampered by the BBB (Morofuji & Nakagawa, 2020).

Future medication development approaches for neurological disorders must prioritize utilizing the BBB's natural transport processes. Drug distribution to the brain could be greatly improved and more effective treatment alternatives could be made possible by reformulating drugs to make use of endogenous transport systems.

ADME ANALYSIS OF ALL BINDING DRUGS

S.n o	Drugs	BBB permeability	Consens us Log P value	GI absorption rate	TPS A value	Lipinski violation
1.	Bromoperidol	Yes	4.30	“High”	40.54	0
2.	Ioperamide	Yes	4.67	“High”	43.78	0
3.	Moperone	Yes	4.0	“High”	40.54	0
4.	Diphenidol	Yes	3.91	“High”	23.47	0
5.	Eliprodil	Yes	4.39	“High”	23.47	0
6.	Benzoflavin e	Yes	4.03	“High”	64.93	0
7.	Terfenadine	Yes	5.73	“High”	43.7	0

Assessment of toxicity of drugs with high binding affinity with D2R by Protox 3.0

DRUGS	LD50 (mg/kg)	HEPAT OTOXI CITY	NEURO TOXICI TY	CARCI NOTOX ICITY	IMMUNO TOXICIT Y	MUTAG ENICITY	CLAS S
Bromoperidol	1190 mg/kg	-	+	-	+	-	4
Moperone	1190 mg/kg	-	+	-	+	-	4
Eliprodil	1190 mg/kg	-	+	-	+	-	4
Benzoflavine	100 mg/kg					+	3
Terfenadine	1190 mg/kg	-	+	-	+	-	4
Diphenidol	1190 mg/kg	-	+	-	+	+	4
Ioperamide	1190 mg/kg	+	+	-	+	-	4

CONCLUSIONS

With a complicated etiology and limited therapeutic options, Schizophrenia is one of the most difficult and complicated neurodegenerative diseases. Dopamine induction has become a prominent candidate among the several molecular targets since it is essential for it. It is critical and urgent to identify new, targeted pathways that may form the foundation of innovative drugs, particularly because all pharmaceutical treatments for Schizophrenia have so far failed.

Understanding how D2R is regulated is crucial for effectively regulating its activity in both healthy and pathological settings.

The pathophysiology of schizophrenia, a complex mental condition marked by abnormalities in thought, perception, and behavior, is mostly due to dopaminergic dysregulation, specifically involving the dopamine D2 receptor (D2R). Because of its crucial role in regulating psychotic symptoms, the D2R continues to be the principal target of the majority of antipsychotic medications, both conventional and atypical.

This study examined how several pharmacological drugs, such as well-known antipsychotics like bromoperidol and moperone, as well as experimental or repurposed substances like terfenadine, loperamide, and eliprodil, interacted with the D2 receptor. The binding affinities and interaction patterns of these ligands were thoroughly examined using molecular docking and interaction visualization methods (BIOVIA Discovery Studio).

The findings showed that a number of unconventional substances had significant binding interactions with D2R that were, in certain situations, on par with those of conventional antipsychotic medications. These results demonstrate the promise of structure-based screening and drug repurposing in finding novel treatments for schizophrenia that may have superior side-effect profiles.

To sum up, dopamine D2 receptor targeting is still a practical and successful strategy for treating schizophrenia. But there is hope for creating safer, more effective, and more sophisticated medicines by broadening the spectrum of D2R-targeting compounds through receptor-binding research, repurposing techniques, and computational drug design. To aid in the creation of next-generation antipsychotic treatments, future research should concentrate on the clinical translation and experimental validation of these discoveries.

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