

Comparing haloperidol with clozapine as treatments for schizophrenia

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Abstract. Schizophrenia affects about 1% of the total population. It is a complex psychological disorder that may be caused by the interaction between genetic and environmental factors. Studies have identified some candidate genes that may contribute to the cause of the disorder. However, most genetics finding in schizophrenia have not been implicated in clinical use. Antipsychotics are drugs commonly used to treat psychosis, such as schizophrenia. First-generation antipsychotics, or typical antipsychotics (e.g. haloperidol), were the first type of medicine for psychosis that was developed. They mainly target dopamine D₂ receptors in the basal ganglia and possibly the mesolimbic pathway as antagonists. Second-generation antipsychotics, or atypical antipsychotics, including clozapine, were developed after typical antipsychotics. They have multiple targets and cause less extrapyramidal side effects. Since atypical antipsychotics target multiple receptors, the complexity of these drugs is extremely high, and we now do not have a solid understanding of their mechanism of action.

Keywords: Clozapine, haloperidol, typical antipsychotics, atypical antipsychotics, schizophrenia.

1. Introduction

Psychological disorders are defined by the disrupted behaviours and mental patterns that deviates an individual from normal functioning; they are some of the hardest to treat diseases. Many psychological disorders are difficult to treat due to our lack of understanding of their causes and mechanisms of action. Furthermore, mental illnesses can be challenging to diagnose since the line between a “normal response” and “mentally ill” is often ambiguous. This paper discusses about the disorder, schizophrenia, and two existing treatments for it. The current understanding of schizophrenia is limited. However, studies are supporting that the disorder is caused by a combination of heredity and abnormal functioning of neurotransmitters [1,2]. The treatments for schizophrenia—antipsychotics—helped to elucidate the disorder’s mechanism of action better by examining the effects of antipsychotics on different receptors and binding partners. Antipsychotics are categorized as typical or atypical, both types are successful in reducing schizophrenia symptoms in patients, while the atypical drugs are evidently stronger [3]. However, all antipsychotics have a variety of side effects, indicating that better treatments may be needed moving forwards.

2. Overview of Schizophrenia

2.1. Symptoms of Schizophrenia

Schizophrenia is a chronic mental disorder characterized by the alteration in perceptions, beliefs and consciousness and the disconnection with reality [4]. Patients with schizophrenia may experience symptoms characterized by positive, negative, and cognitive symptoms. Positive symptoms describe the excesses in behaviour, which include hallucinations (false perception), delusions (false personal beliefs), thought disorder, and movement disorder; negative symptoms are associated with deficits in apathy, avolition, and blunted emotion; cognitive symptoms include impairments in executive function, attention, and memory [5]. Antipsychotics mainly target positive symptoms, while negative symptoms are more challenging to treat.

2.2. Impact of the Disease

Schizophrenia affects around 0.7-1% of the population [6]. A meta-review was conducted with a 90% confidence interval to show that individuals affected by schizophrenia are likely to have a high standardized mortality ratio of 2.5 [7]. The reduction in life expectancy associated with schizophrenia is about 10-20 years (compared with heavy smoking: 8-10 years), and the employment rate is as low as 10-20% [7,8].

2.3. Causes of Schizophrenia

The diathesis-stress model proposes that the symptoms of schizophrenia are triggered by psychosocial stress acting on preexisting vulnerable genetic disposition. In other words, the cause of schizophrenia is due to the combination of, or the interaction between genetic predisposition and the environment. The genetic factor contributes to the disease substantially. The risk of having schizophrenia for monozygotic twins is 45.6%, and up to 13.7% for first-degree relatives—a family member (sibling, one's offspring or parent) whose genetic information is about 50% identical to an individual [1]. Monozygotic twins have identical genes; if the genetic factor contributes solely to the disease, the twins will have a concordance of 100%. This emphasizes the effect of environmental factors, as well as the genetic component.

Furthermore, multiple studies indicate that multiple genes contribute to schizophrenia, making the disease polygenic. The phenotype heterogeneity (the wide variety of symptoms) of schizophrenia is believed to be associated with genetic heterogeneity, meaning a genetic disorder or a phenotype is caused by multiple alleles [9]. This hypothesis views each gene as a factor, along with environmental factors, contributing to the schizophrenia phenotypes. Each factor contributes towards a critical threshold at which symptoms will manifest. However, the degree of contribution of the genes remains unknown as the specific genes associated with schizophrenia still have not been identified.

Nevertheless, multiple studies attempted to identify the genes that cause the high heritability of schizophrenia. Linkage study is based on how recombination, or crossing over, occurs in homologous chromosomes during meiosis. Gene loci located closer together are more likely to be inherited together after recombination. In contrast, the probability that one gene is crossed over to the homologous chromosome increases when the two genes are farther away from each other [9]. If a schizophrenia gene is located next (linked) to a marker gene, then the probability of finding the disease causing gene increases (Figure 1). A recent study used a genome scan meta-analysis (GSMA) on genome-wide linkage scans of schizophrenia and found multiple schizophrenia candidate genes [11]. Chromosomes have two arms; the shorter arm is referred to as “p” (in petite), and the longer arm is denoted as “q”. The group discovered linkage on chromosomes 1q, 2q, 5q, and 8p. In addition, a more recent study discovered a linkage signal on the 22q11 chromosome, the gene which encodes for proline dehydrogenase, also known as proline oxidase [12]. Overexpression of gene 22p11 can cause interference with the metabolism of the amino acid L-proline, in turn affecting the synthesis of glutamate. This neurotransmitter may be one of the causes of schizophrenia [12,13].

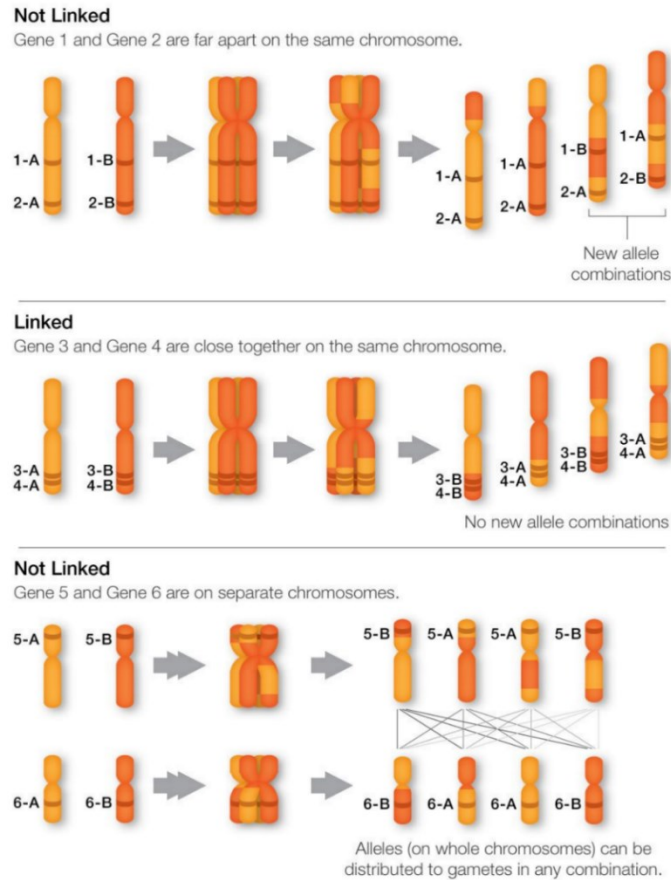


Figure 1. Linkage gene versus non-linkage genes during crossover in meiosis [10].

The catechol-O-methyltransferase (COMT) gene, also located on the 22q11 chromosome, was also studied. COMT is an enzyme that degrades catecholamines, including dopamine, by methylation [14]. Dopamine is a critical neurotransmitter that is hypothesized to be involved in a pathway that causes schizophrenia. The abnormal activity of the enzyme affects the prefrontal lobe, which is responsible for executive function; dysfunction of the prefrontal lobe is also associated with the disease [15]. Individuals with schizophrenia tend to have a lower prefrontal lobe volume. Additionally, the enzyme's low activity causes failure to break down the increased dopamine, thereby increasing the risk of developing schizophrenia.

In addition, cases where individuals develop schizophrenia without the influence of genetics (non-familial), are sporadic. These individuals may be phenocopies, in which the schizophrenia phenotypes are caused by psychosocial causes, drug misuse, or brain trauma, such as epilepsies [9].

3. Treatment for Schizophrenia

3.1. Typical vs. Atypical Antipsychotics

Antipsychotics (APDs) are psychiatric drugs that are prescribed to treat psychosis and psychosis-related symptoms, including schizophrenia, bipolar disorder, major depressive disorder, personality disorder, Etc [16].

Typical APDs, or first-generation APDs, are often known for their ability to treat the positive symptoms of schizophrenia [17]. They are also popular regarding their serious side effects, such as extrapyramidal side effects, tardive dyskinesia, metabolic syndromes, Parkinsonism, and potentially fatal conditions, such as neuroleptic malignant syndrome [18]. The cause of the motor impairment side

effects is believed to be the drug's high affinity to the dopamine D₂ receptors. All APDs block dopamine D₂ receptors, while typical APDs have a higher affinity to the receptors, meaning they bind more tightly to the receptors [17].

It was believed that typical and atypical APDs solely differ in their affinity to dopamine D₂ receptors [19]. Atypical APDs indeed have less affinity to the dopamine D₂ receptors, so they dissociate from the receptor quicker [17]. However, atypical APDs also target multiple other receptors—which is discussed below—on postsynaptic neurons (Figure 2).

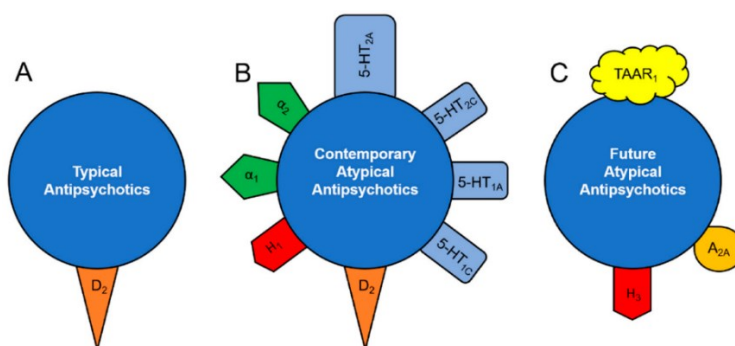


Figure 2. The receptors that different types of antipsychotics target [20].

Even though the adverse side effects of the first-generation APDs, they can still be found as first-line treatment for psychosis because they are relatively inexpensive [18]. Two APDs, haloperidol and clozapine, are chosen to be discussed herein.

3.1.1. The Discovery and Synthesis of Haloperidol

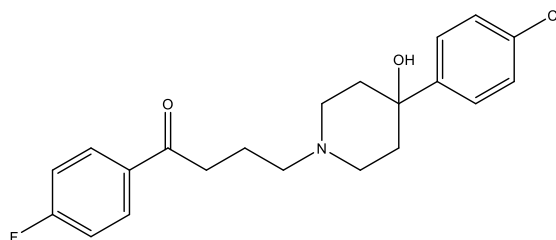


Figure 3. The chemical structure of haloperidol

Haloperidol, or 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one, is a butyrophenone derivative discovered in the 1950s by Dr. Paul A. J. Janssen [22]. Janssen was known for discovering dextromoramide, an analgesic with a brief duration of action [23]. After that discovery, he began to do research on pethidine (or meperidine), he obtained compound R951 (Figure 5) by the Mannich reaction of acetophenone with normeperidine [22,23]. Mannich reaction (Figure 4) is similar to dehydrative condensation, where a bond is formed between the reactants and water, is produced as the byproduct [26]. He then lengthened the carbon chain to produce R1187.

After numerous trials and errors, the compound R1625 (Figure 5, 6), haloperidol, was discovered as a potent tranquillizer in 1958 [22]. The compound mimics *chlorpromazine*, the first typical APD discovered, but was 50-100 times stronger than chlorpromazine.

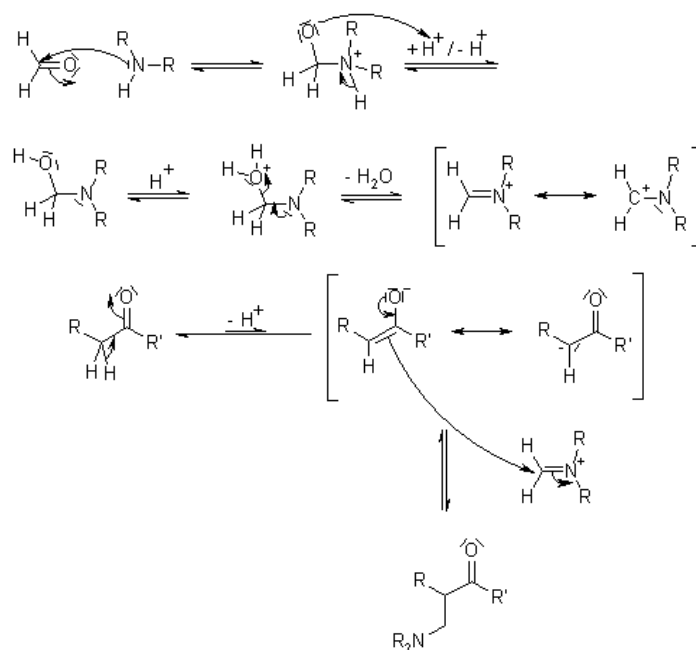


Figure 4. Mannich reaction mechanism shown by the reaction between an amine with formaldehyde, and carbonyl compound with an α acidic hydrogen [24].

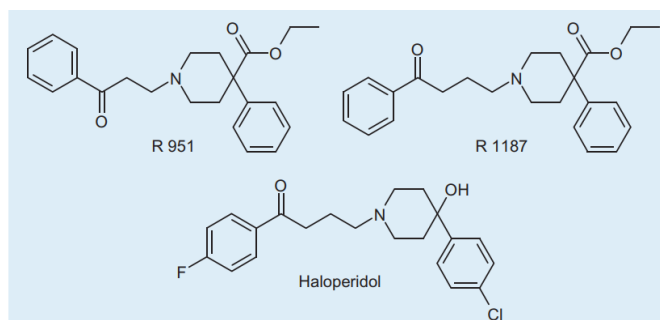


Figure 5. The important compounds Jenssen produced during his research about pethidine and piperidine [25]

3.1.2. Pharmacology of Haloperidol.

Haloperidol can be taken either orally, intravenously, or via intramuscular injection. Haloperidol is widely known for its antagonism of dopamine D₂ receptors. In addition, the drug also binds to 5-HT_{2A} (serotonin-2A) receptors, α_{1A} (adrenergic) receptors, and α_{1B} receptors [26]. Haloperidol is highly selective for dopamine D₂ receptors because it has a high affinity for them—about 100 times higher than clozapine [26]. All the receptors it affects are G-Protein Coupled Receptors (GCPR) involved in the functioning of neuronal pathways [27,28]. G-Protein coupled receptors are proteins with seven transmembrane domains that receives extracellular signals and translates them into intracellular signals [29]. G proteins are specialized proteins that can bind with GTP or GDP. When bound to GTP, G protein subunits are activated and can perform activities signalled by the extracellular receptor. Haloperidol may be affecting these receptors in the mesolimbic pathway, but no significant evidence was found [30].

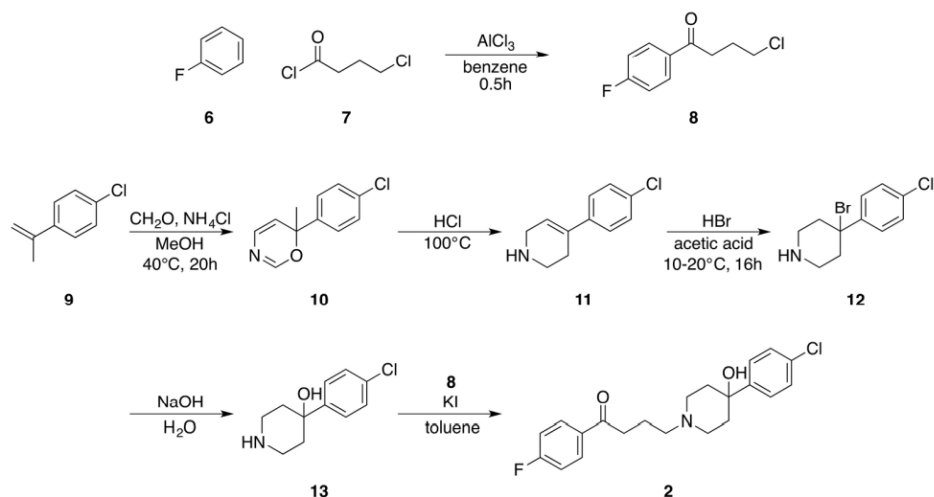


Figure 6. The original synthesis of haloperidol by Jensen Pharmaceutica [25].

Although the definite mechanism of APDs has not yet been discovered, dozens of *in vivo* studies identified the blockage of striatal dopamine D₂ receptor when patients have been treated with typical APDs [31]. The *striatum* is a critical component of the basal ganglia (Figure 7) in our brain. Those parts of the brain are apart of the *nigrostriatal pathway*, which is responsible for motor control [2]. Therefore, the nigrostriatal pathway may as well be responsible for the extrapyramidal side effects [32].

3.1.3. Side Effects of Haloperidol

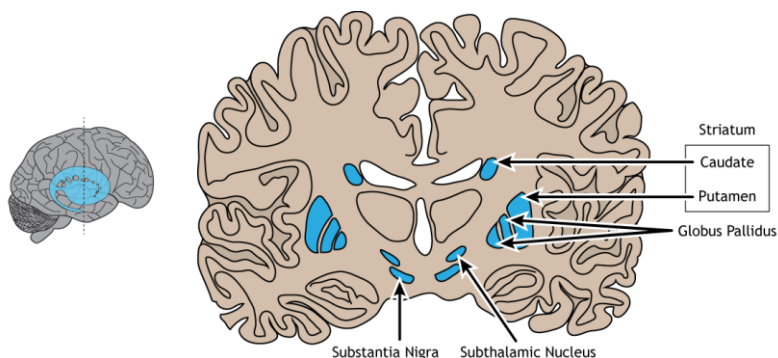


Figure 7. The location of the components of basal ganglia. The striatum is composed by the caudate and the putamen [35].

The basal ganglia use three different pathways to ensure the performance of the correct movement. The three pathways are the direct, indirect, and hyperdirect pathway [33]. This paper will only focus on the direct and indirect pathway (Figure 8). The direct pathway involves the striatum receiving excitatory information from the glutamatergic neurons from the cerebral cortex; then, the striatum sends signals through inhibitory neurons: GABAergic neurons to the internal globus pallidus (GPi) and the reticular substantia nigra (SNr). Information is relayed at the thalamus and sent back to the cortex by excitatory neurons [33]. In other words, the cortex sends excitatory signals (glutamate) to the striatum, stimulating it to send inhibitory signals (GABA) to the GPi. This suppresses the GPi to send inhibitory signals to the thalamus, leading the thalamus to release excitatory signals to the cortex, causing movement and triggering positive feedback.

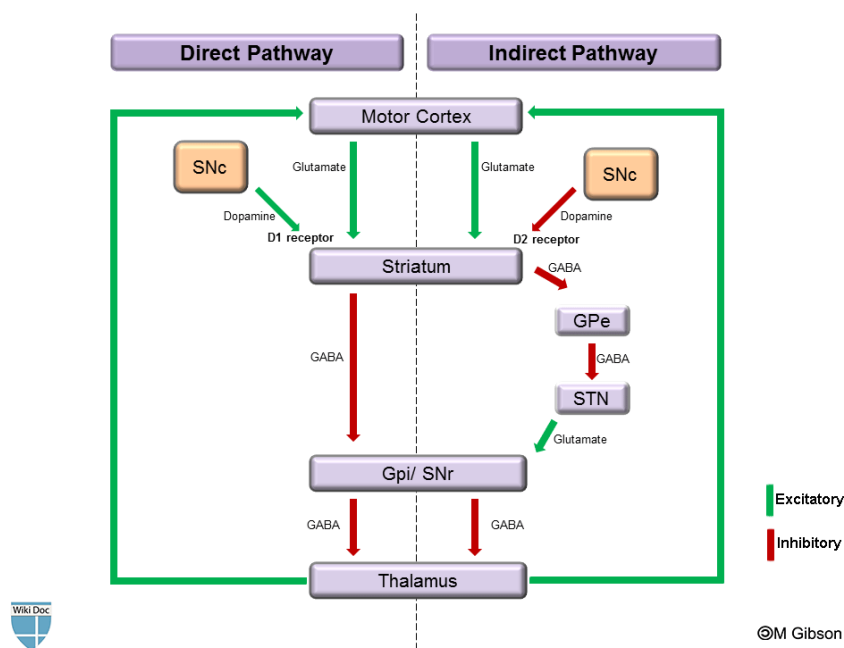


Figure 8. A diagram of the direct and indirect pathways [34]. SN stands for substantia nigra. SN is further divided into the reticular part (SNr), and the compact part (SNc). The globus pallidus is shortened as GP. GPe and GPi refers to the external and internal part. STN is the subthalamus nucleus.

In addition, the SNc sends dopamine to the striatal dopamine D₂ receptors via the indirect pathway (Figure 8). Dopamine excites the release of GABA to the GPe, inhibiting the release of GPe's GABA to the subthalamus nucleus (STN). The excitatory output from the STN to GPi increases inhibition of the thalamus, decreasing excitatory output to the cortex, thereby decreasing unwanted movement [35]. Thus, haloperidol blocks the binding of dopamine to D₂ receptors inhibits the release of GABA to GPe. Through cascade effect, the thalamus is not inhibited, leading it to send excitatory signals to the cortex, triggering unwanted movements [2,36]

3.1.4. The Discovery and Synthesis of Clozapine

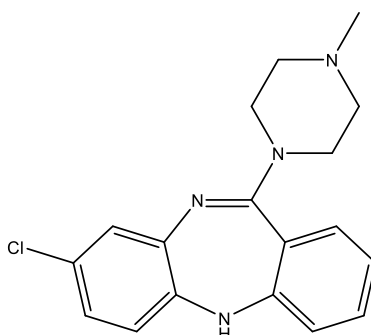


Figure 9. Chemical structure of clozapine

Clozapine (8-chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine) is a tricyclic benzodiazepine drug synthesized in the 1960s by a health care company called Sandoz (now known as Novartis) [38]. The first step of synthesis involves an Ullmann reaction between aryl halides **10** and **11** (Figure 10) catalyzed by copper [39]. A reduction of the nitro moiety of **12**, then refluxing the product in dimethylbenzene will result in the core structure **14**. POCl₃ provides the molecule with a better leaving group, chloride, to react with N-methylpiperazine to form clozapine **3** [38].

The drug is known for its efficacy in treating treatment-resistant schizophrenia patients and its low rates of causing extrapyramidal side effects [40]. A study in 1988 conducted a clinical trial with 286 patients who were unresponsive to haloperidol after 6 weeks of treatment [3]. Haloperidol nonresponders were randomly assigned to be treated with chlorpromazine or clozapine for 6 weeks. It was found 30% of clozapine-treated patients improved, while only 4% of chlorpromazine-treated patients were considered responders. Furthermore, typical APDs require ~75% striatal D₂ receptors occupancy effectiveness (haloperidol induces ~80% occupancy), while clozapine displays only <60% occupancy [36,38]. Thus, dopamine D₂ receptors must not be the only type of receptor which clozapine targets. In addition, the low D₂ occupancy may explain clozapine's lower propensity for extrapyramidal side effects.

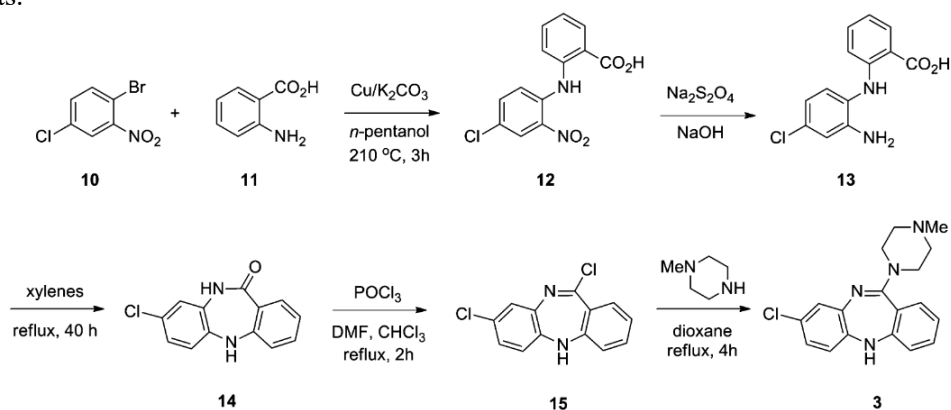


Figure 10. The original synthesis steps of clozapine [38]. Compound 14, 8-Chloro-5,10-dihydro-11H-dibenzo[b,e][1,4]-diazepin-11-one, is the core structure of clozapine, which can be synthesized in various ways.

3.1.5. The Polypharmacology of Clozapine

Clozapine is administered orally; 12.5 mg initially and increase by 25-50 mg to 300-450 mg over a two-week period if no side effects are observed [40].

Meltzer (1989) was the first to propose the serotonin-dopamine hypothesis for schizophrenia [41]. Clozapine acts on both the serotonin (5-HT) and the dopamine systems because it is a potent blocker of the 5-HT_{2A} receptors and a weaker antagonist of dopamine D₂ receptors [41]. Clozapine also blocks 5-HT agonists, such as quipazine and MK-212 [41]. MK-212 binds to the 5-HT_{2A} receptor and stimulates the secretion of cortisol and prolactin in human [42]. Another study reported that clozapine is an *inverse agonist* for 5-HT_{2A} [43]. The 5-HT_{2A} receptor is also a GPCR located on postsynaptic neurons, requiring a ligand for activation. An antagonist only blocks the action of the ligand but does not alter the basal activity (the ability for the receptor to be activated) of the receptor [44]. An inverse agonist will lower the basal activity. This may increase presynaptic dopamine levels in nigrostriatal neurons, further decreasing the risk of developing Parkinsonism and other extrapyramidal side effects. Additionally, Meyer and Stahl reported that the inverse agonism decreases dopamine in the mesolimbic system, which is responsible for its antipsychotic effect mentioned earlier [43].

Positron emission tomography (PET) studies show that basal ganglia D₂ receptor occupancy of clozapine is <50%. Cortical 5-HT_{2A} occupancy is as high as 90% for clozapine and other atypical APDs, including risperidone and olanzapine [45].

However, as shown in Figure 2, the drug also shows considerable affinities to multiple other receptors, such as 5-HT receptors subtypes, D₁, D₄, α_1 -adrenergic, α_2 -adrenergic, H₁ histaminergic, and M₁ cholinergic receptors [45]. This leads to the question of which pharmacological property is responsible for the drug's therapeutic efficacy.

3.1.6. Side Effects Clozapine.

Clozapine may induce neutropenia and severe neutropenia (also known as agranulocytosis in old literature) [46]. Severe neutropenia occurs when the absolute neutrophil count is $<500/\mu\text{l}$. In 1975, 0.7% of clozapine patients in Finland developed severe neutropenia, and 50% of these patients died from secondary infections [47]. Thus, patients treated with clozapine must undergo hematological monitoring of their neutrophil count. A study discussed the pharmacogenetic factor of clozapine-induced neutropenia [48]. The study suggested that patients with lower genetic risk may be less likely to develop neutropenia, thus can relax the monitoring.

Furthermore, metabolic syndrome, such as weight gain and type II diabetes, induced by clozapine is also a source of distress for patients. The antagonism of 5-HT_{2C} receptors can cause obesity in mice, which could also contribute to weight gain in humans [49]. 5-HT_{2C} indirectly acts on the hypothalamus, a structure that is involved in the central control of hunger and feeding [50]. Appetite is suppressed by 5-HT signalling on pro-opiomelanocortin (POMC) neurons within the hypothalamus. Treatment for obesity often includes medications that are 5-HT agonists to induce an anorexigenic effect. Additionally, clozapine can cause orthostatic hypotension, seizures, and myocarditis, observed in 3% of schizophrenia patients [51]. Severe cases of myocarditis may show respiratory and cardiovascular symptoms.

4. Conclusion

The definite mechanism of both haloperidol and clozapine (in fact, all APDs) is yet to be understood, just as the cause of schizophrenia. However, evidence shows that haloperidol works on dopamine D₂ receptors, leading researchers to hypothesize the mesolimbic pathway and dopamine hypothesis. Likewise, the polypharmacology of clozapine leads researchers to propose the serotonin-dopamine hypothesis [41]. From this, we can deduce that the belief that typical APDs and atypical APDs solely differ in their affinity to D₂ receptors is incorrect. Clozapine is concluded to be superior to haloperidol in treating both positive and negative symptoms and more severe and lethal in the side effects it causes [52]. In addition, most psychological disorders are caused by genetic disposition and the environment. It is likely that schizophrenia is a polygenic disorder, such that multiple genes contribute to the manifestation of the symptoms. In future experiments, studies could potentially be done on the polygenicity aspect of schizophrenia. Whole-genome sequencing applications could help identify all disease-causing alleles so we could attempt to understand their biological mechanisms [53].

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