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Review

The Effects of Antipsychotic Drugs and Non-Pharmacological Therapies on Schizophrenia

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Abstract: Schizophrenia is a severe and complex psychological disorder characterised by psychosis, affecting approximately 20 million people worldwide, with its prevalence on the rise. It is hypothesised to arise from a multifactorial aetiology involving a complex interplay of genetic predisposition and environmental risk factors. The exact cause of schizophrenia remains unknown. There are significant interactions between genetic and environmental factors, making it a condition of great significance. Both pharmacological and non-pharmacological therapies are available to manage the various symptoms associated with this condition. Antipsychotic drugs are the primary pharmacological approach, addressing both the positive and negative symptoms of schizophrenia. However, their use has sparked controversies due to potential side effects and long-term consequences, necessitating individualised treatment plans. Non-pharmacological therapies, on the other hand, provide an alternative approach, focusing on reducing anxiety and fear and empowering patients to regain control over their lives. In this scientific review, an extensive analysis of existing research has been conducted to evaluate the efficacy and safety of antipsychotic drugs and non-pharmacological therapies for schizophrenia. Their impact on positive and negative symptoms as well as socio-economic implications have been assessed. Beyond treatment efficacy, this review also addresses broader societal aspects, emphasising the need for patient-centred mental healthcare services that consider individual differences and preferences. The review highlights the importance of a multidimensional translational approach to schizophrenia management and advocates for accessible mental healthcare services to cater to the unique challenges faced by individuals with schizophrenia. By considering advantages and disadvantages, we support the implementation of tailored treatment plans to optimise patient outcomes and overall societal well-being. A holistic translational approach to schizophrenia management, incorporating medical, psychological, and societal support systems is essential for improving the quality of life for individuals living with schizophrenia.

Keywords: schizophrenia; antipsychotic drugs; cognitive behavioural therapy; olanzapine; clozapine; chlorpromazine

Academic Editor: Huangxian Ju

Received: 4 December 2024
Revised: 24 February 2025
Accepted: 28 February 2025
Published: 10 March 2025

Citation: Nasim, R.; Nawaz, S.; Nasim, M.T. The Effects of Antipsychotic Drugs and Non-Pharmacological Therapies on Schizophrenia. *Targets* **2025**, *3*, 10. https://doi.org/10.3390/targets3010010

1. Introduction

Schizophrenia is a chronic and severe psychiatric disorder that has a profound impact on individuals and society [1–3]. It is characterised by a range of symptoms, including

hallucinations, delusions, disorganised thinking, and impaired social functioning [4–6]. The disorder affects approximately 1% of the global population and is associated with significant morbidity and mortality. Individuals with schizophrenia often experience a reduced quality of life, impaired occupational functioning, and increased risk of suicide. Additionally, the disorder places a substantial burden on healthcare systems and society as a whole [7].

The treatment of schizophrenia typically involves a combination of antipsychotic medications and non-pharmacological therapies [8–11]. Antipsychotic drugs are the cornerstone of pharmacological treatment and have shown to effectively reduce symptoms and prevent relapse [12–15]. However, there is growing recognition of the limitations and side effects of these medications, such as weight gain, metabolic disturbances, and extrapyramidal symptoms [16–19]. Non-pharmacological therapies, including cognitive-behavioural therapy, family therapy, and psychosocial interventions, have also proven to be beneficial in improving outcomes for individuals with schizophrenia [20–25].

Understanding the effects of both antipsychotic drugs and non-pharmacological therapies in the treatment of schizophrenia is of utmost importance. It is crucial to study the efficacy and potential side effects of these interventions to inform clinical practice and improve patient outcomes [26]. Furthermore, investigating the underlying mechanisms of schizophrenia and the factors that contribute to treatment response can help identify novel therapeutic targets and improve treatment strategies [27].

The purpose of this review is to provide a comprehensive evaluation of the effects of antipsychotic drugs and non-pharmacological therapies in the treatment of schizophrenia. By synthesising the available evidence from clinical trials, observational studies, and meta-analyses, this review aims to inform clinical decision-making and guide the development of evidence-based treatment guidelines [8,16]. Additionally, this review explores the potential mechanisms underlying the pathophysiology of schizophrenia and the factors that influence treatment response [1,4]. This review contributes to the advancement of knowledge in the field and has significant implications for clinical practice and the management of schizophrenia. Ultimately, this review strives to promote evidence-based and patient-centred care for individuals living with schizophrenia.

2. Pathophysiology

The pathophysiology of schizophrenia is a complex and multifactorial process involving abnormalities in neurotransmission, with key neurotransmitters, such as dopamine, serotonin, and glutamate, implicated in the disorder [1,28]. Abnormal activity at dopamine D2 receptors has been associated with several symptoms of schizophrenia, with an excess of dopamine believed to contribute to positive symptoms like hallucinations and delusions, while a deficit may relate to negative symptoms, such as blunted affect and social withdrawal [1,28]. Glutamate dysregulation, particularly in the N-methyl-D-aspartate (NMDA) receptor system, has been proposed as a potential mechanism underlying the cognitive deficits observed in schizophrenia [2]. Dysfunctions in the glutamatergic system can disrupt the balance between excitatory and inhibitory neurotransmission, leading to cognitive impairments and other symptoms associated with schizophrenia [2]. Additionally, increased serotonin levels in schizophrenic patients can lead to a range of symptoms, including shivering, high fever, and other autonomic dysfunctions, although the exact mechanisms remain not fully understood [28].

Within the genetic component of schizophrenia, several candidate genes have been identified that play crucial roles in various biological processes [29]. One key process implicated in schizophrenia is synaptic transmission, the communication between neurons. Genes such as Glutamate Ionotropic Receptor NMDA Type Subunit 2A (GRIN2A), which

encodes a subunit of the NMDA receptor critical for glutamatergic signalling, and Calcium Voltage-Gated Channel Subunit Alpha1 C (CACNA1C), encoding a calcium channel subunit essential for neurotransmitter release, are strongly linked to this pathway. Mutations in these genes can impair synaptic plasticity, leading to cognitive deficits characteristic of schizophrenia. Another central pathway is the dopaminergic system, which is crucial for understanding the psychotic symptoms of the disorder. The DRD2 gene, encoding the dopamine D2 receptor, is a major target of antipsychotic drugs, with overactivity in dopamine signalling being strongly associated with hallucinations and delusions. Similarly, Catechol-O-Methyltransferase (COMT), a gene involved in dopamine metabolism, affects prefrontal dopamine levels and has been linked to cognitive deficits observed in schizophrenia.

Genes associated with learning and memory processes also play a significant role. For example, Disrupted in Schizophrenia 1 (DISC1), which is essential for neurodevelopment and synaptic plasticity, is linked to deficits in working memory and neurogenesis, while NRG1, encoding neuregulin-1, regulates synaptic plasticity and neural network formation, with dysregulation impairing learning mechanisms. Additionally, disruptions in synaptic vesicle clustering, a process critical for neurotransmitter release, have been associated with schizophrenia. Genes such as Regulating Synaptic Membrane Exocytosis 1 (RIMS1), involved in synaptic vesicle priming, and SYNGAP1, which regulates synaptic strength and clustering, are implicated in these disruptions and may contribute to the cognitive and behavioural symptoms of the disorder.

Other genes, such as Zinc Finger Protein 804A (ZNF804A), a transcription factor influencing neuronal connectivity, and GAD1, which encodes an enzyme critical for GABA synthesis, further highlight the intricate network of genetic contributors to schizophrenia. Variants in AKT1, a gene involved in dopamine signalling and synaptic plasticity, have been linked to altered prefrontal cortex function, further emphasising the interplay between genetic factors and brain function. Collectively, these genes underscore the complexity of schizophrenia's aetiology, influencing diverse processes, such as synaptic transmission, dopaminergic pathways, learning, and synaptic vesicle clustering. Understanding these genetic contributions not only enhances our knowledge of the disorder but also informs the development of targeted therapies aimed at addressing its psychotic and cognitive symptoms.

The axon guidance pathway plays a critical role in the development and functioning of the central nervous system, as it regulates neuronal migration and connectivity during development. Disruptions in this pathway have been implicated in psychiatric disorders, including schizophrenia, depression, and obsessive–compulsive disorder. Recent research highlights the importance of axon guidance, particularly through the interactions of netrin-1 (NTN1) and its receptors Deleted in Colorectal Cancer (DCC) and UNC-5 Netrin Receptor C (UNC5C), in psychiatric conditions.

The UNC5C gene, encoding a receptor for NTN1, is a key player in axon guidance and repulsion processes. Two novel compound heterozygous mutations within the UNC5C gene were identified in a patient with psychiatric disorders. These mutations, located in the cytoplasmic domains ZU5 and UPA-DD, disrupt critical processes required for the netrin-mediated repulsion of neuronal growth cones. The axon guidance process involves microtubule dynamics, which are essential for proper neuronal migration and connectivity. The ZU5 domain specifically regulates the supramodular protein structure and directly interacts with microtubules, ensuring the functionality of axon repulsion. Disruption in this mechanism likely contributes to the psychiatric phenotype observed in the patient.

The NTN1/DCC/UNC5C complex mediates chemotropic signalling along microtubules, directing axonal growth during adolescence, a critical period for brain develop-

ment. In particular, this complex is essential for establishing mesocorticolimbic pathways that regulate dopamine release. Disruptions in these pathways are associated with neuropsychiatric symptoms, including impaired cognitive function and emotional regulation. Previous research has linked DCC and NTN1 mutations to schizophrenia and other psychiatric disorders, further supporting the hypothesis that axon guidance disruptions are a common pathway in these conditions [30].

Beyond UNC5C, the study underscores the broader implications of axon guidance signalling in psychiatric disorders. Aberrations in genes like ROBO1 (Roundabout Guidance Receptor 1) and SLIT2 (Slit Guidance Ligand 2), which also influence axonal migration and synaptic connectivity, have been implicated in neurodevelopmental disorders. The axon guidance pathway interacts with dopaminergic and glutamatergic systems, highlighting its role in regulating neurotransmission, synaptic plasticity, and brain network organisation. The identified mutations in UNC5C are particularly significant as they directly impair the cytoskeletal dynamics required for axon guidance, potentially altering neural circuitry during critical periods of brain development [30].

The findings in this study suggest that the mutations in UNC5C may contribute to the psychiatric phenotype by disrupting microtubule-mediated axon repulsion and guidance, ultimately impairing neural circuit assembly in the prefrontal cortex. The prefrontal cortex, still developing during adolescence, is responsible for complex cognitive functions and is particularly vulnerable to disruptions in axon guidance signalling. This provides a plausible explanation for the behavioural and psychiatric symptoms observed in the patient.

Overall, the abnormalities in neurotransmission involving dopamine, serotonin, and glutamate have provided the basis for theories on the pathophysiology of schizophrenia. However, it is essential to acknowledge that the precise neurochemical and neuroanatomical alterations contributing to the development and progression of schizophrenia are still not fully understood, warranting further research in this area [28]. Understanding the underlying neurobiological mechanisms is crucial for the development of targeted and effective treatments for individuals affected by this complex psychiatric disorder.

3. History of Antipsychotic Drugs

Antipsychotic drugs are a class of medication that remained the cornerstone in the treatment of schizophrenia. The use of antipsychotics first began in 1933 in France. Development of antihistamines had led to the introduction of promethazine [31]. Promethazine was very effective in animals as it was able to put them in a state of tranquillity or allow them to sleep calmly. However, they were not as effective in humans. Nevertheless, they were still a good start and catalyst for future antipsychotic medication to arrive [32]. The 1950s were when antipsychotic medication rose in popularity. In the 1950s, antipsychotics had contributed to the shutting down of the old Victorian asylums, introducing a more sane and humane community-based care [33]. People with mental illness were often subjected to horrific, inhumane treatments during their time in the asylum. The fact that antipsychotics were a reason for them to shut down further emphasises the significance of them in the past. After the discovery of promethazine, several promethazine derivatives were developed. This included chlorpromazine, which was approved for usage as an antipsychotic in the USA and then, eventually, worldwide. Furthermore, from the 1950s to the 1970s, about 15 antipsychotics were released into the United States and 40 worldwide, as shown in [34]. These drugs were the first effective treatment for patients with severe mentally illnesses and were referred to as “miracle” or “wonder drugs”. There was a short pause in the development of antipsychotic drugs after the 1970s. Newer antipsychotics drugs had been discovered; however, they (e.g., clozapine) were initially thought to be ineffective. A lot of small studies appeared, which found that the patients who responded poorly to

older antipsychotics responded better to the newer ones, such as clozapine [35]. This then led to the introduction of clozapine treatment in the USA, which birthed the era of the atypical antipsychotic drugs (the newer second-generation drugs) [36]. These antipsychotic drugs were able to ease symptoms of schizophrenia, such as delusions and hallucinations, but could not cure schizophrenia. However, they were extremely effective in improving brain function and reducing and controlling symptoms. Additionally, they (e.g., clozapine) were effective at stopping dangerous and horrific events occurring, such as suicide [37]. The second-generation antipsychotics differ from the first generation ones, as they are 5HT2A/D2 antagonists, meaning that they block dopamine and affect serotonin levels instead of primarily blocking dopamine. They are also associated with a lower risk of EPS and higher risk of metabolic side effects [38]. Different first- and second-generation antipsychotics are displayed in Table 1. The history of Antipsychotics is significant but not solely specific to schizophrenia. For example, Risperidone has been widely used for autism spectrum disorder (ASD) [39]. Risperidone acts to block D2 receptors in the tuberoinfundibular pathway, leading to reduced dopamine inhibition on prolactin secretion [40].

Table 1. Classification of 1st generation and 2nd generation antipsychotic drugs.

1st Generation Antipsychotic Drugs	2nd Generation Antipsychotic Drugs
Chlorpromazine	Clozapine
Haloperidol	Olanzapine
Perphenazine	Risperidone
Fluphenazine	Quetiapine
Thioridazine	Aripiprazole
Loxapine	Ziprasidone

A comparison of the effectiveness of olanzapine, risperidone, and aripiprazole therapy in schizophrenia evaluated the clinical effectiveness of these atypical antipsychotics and examined their efficacy in reducing psychotic symptoms (see Figure 1).

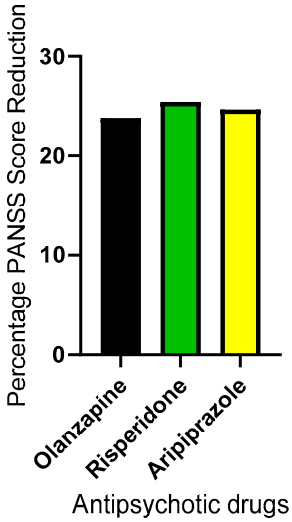

Figure 1. A bar graph showing the efficacy of Olanzapine, Risperidone, and Aripiprazole by examining the percentage reduction in the Positive and Negative Syndrome Scale caused by each antipsychotic drug [38].

The graph above shows the effectiveness of olanzapine, risperidone, and aripiprazole in reducing the positive and negative symptoms associated with schizophrenia. These

antipsychotics are commonly used in the treatment of schizophrenia. No significant differences between the three antipsychotics were found; the data obtained concluded that olanzapine, risperidone, and aripiprazole were equally effective in reducing the psychotic symptoms of schizophrenia. This research compared olanzapine, risperidone, and aripiprazole therapies based on a 12-week assessment of the mean reduction in PANSS scores. The results indicated similar efficacy among the three medications, with reductions of 23.79%, 25.41%, and 24.65% in the olanzapine, risperidone, and aripiprazole groups, respectively. However, the study had limitations regarding sample size and long-term outcomes.

More recent research comparing the efficacy, mechanism, and side effects of clozapine and risperidone in patients with schizophrenia found clozapine to be the gold standard for treatment-resistant schizophrenia, as it was demonstrated to be more efficacious than other antipsychotics [41]. This research was focused on clozapine and risperidone in patients with schizophrenia who did not respond to other atypical antipsychotics. It found clozapine to be more effective for this subgroup and emphasised its potential for metabolic side effects. However, this review lacks primary data alongside a direct comparison with newer atypical antipsychotics. In conclusion, both studies provided valuable insights, but their limitations indicate the need for further research and consideration of a comprehensive body of evidence when making treatment decisions for schizophrenia. This is supported by research reviewing the use of clozapine in China, where it remains one of the most prevalent antipsychotic medications, as 25–60% of patients with schizophrenia in China receive clozapine [42].

4. Mode of Action

Antipsychotics improve psychosis by blocking a specific subtype of the dopamine receptor (D2 receptor), which, in turn, blocks abnormal dopamine transmission. They do not block the normal dopamine transmission, which is essential for marking and responding to motivationally salient stimuli [43]. Dopamine, as well as serotonin, noradrenaline, and acetylcholine, are chemicals in the brain that have the effect of changing behaviour and emotions [44]. Antipsychotic drugs can alter the effects of these chemicals preventing the experience of hallucinations, delusions, thought disorders, and extreme mood swings.

These antipsychotic drugs exist in two forms; there are the first-generation (e.g., perphenazine, loxapine) and second-generation drugs (e.g., olanzapine and quetiapine). Recently, the usage of these first-generation drugs have dropped in popularity due to the development of newer antipsychotics [45]. However, they remain as a valuable, cheaper alternative [46]. The first-generation drugs, such as perphenazine and loxapine, block the D2 receptor in the mesolimbic pathway and reduce dopamine hyperactivity, improving positive symptoms. They inhibit dopaminergic transmission and work best when they block about 72% of the D2 dopamine receptors in the brain [47]. They also block D2 receptors in areas outside of the mesolimbic pathway, such as the Tuberoinfundibular pathway. This results in the worsening of the negative symptoms. The second-generation drugs, such as olanzapine and clozapine (Table 1), block D2 receptors and further block serotonin receptors (5HT2A) [48]. The blocking of D2 receptors and serotonin receptors is displayed in Figure 2. A combined action at both these receptors is said to treat both positive and negative symptoms. Both generations of antipsychotics modulate four dopamine pathways in the brain, including the Mesolimbic Pathway, Tuberoinfundibular Pathway, Nigrostriatal Pathway, and Mesocortical Pathway [49]. Unintended dopamine blockage causes motor side effects associated with the nigrostriatal pathway and disrupts dopamine's regulation of prolactin secretion in Tuberoinfundibular Pathway. Antipsychotics are very effective at reducing the positive and negative symptoms. However, they are still controversial due to the number of side effects that are still associated with them. The distinction

between the efficacy of first- and second-generation antipsychotics are that first-generation drugs primarily treat positive symptoms, whereas second-generation drugs primarily treat negative symptoms. Furthermore, the distinction between the side effects relate to risk of EPS, sedation, and weight gain.

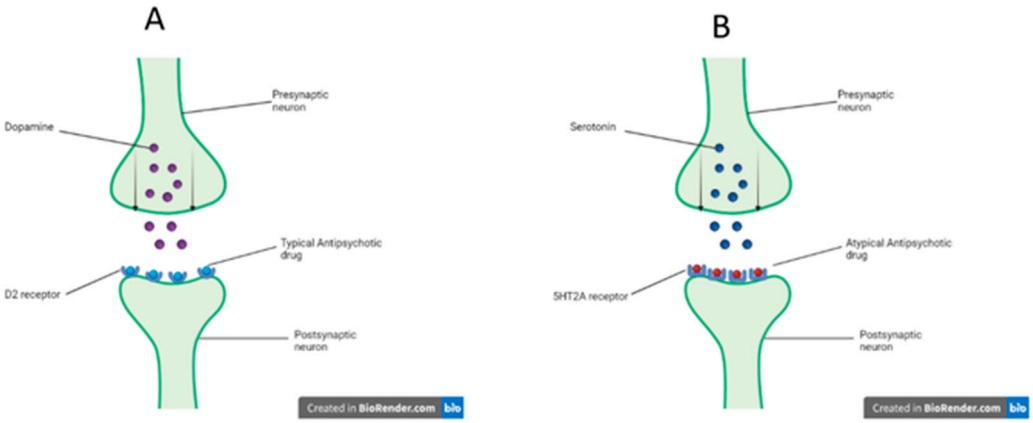

Figure 2. Mode of action for typical and atypical antipsychotic drugs. (**A**). The typical antipsychotics block the D2 receptors preventing dopamine binding. (**B**). The atypical antipsychotics block the 5HT2A receptor as well as D2 receptors, preventing serotonin binding.

5. Side Effects of Antipsychotic Drugs

Some of the side effects associated with antipsychotic drugs are quite minor but are still irritating, whilst other side effects are life-threatening (Table 2). Minor side effects include sleep disturbances (somnolence), weight gain, diabetes, dry mouth, and blurred vision [50]. Examples of two life threatening side effects are agranulocytosis and myocarditis, which will be discussed.

Table 2. Antipsychotic drugs with their side effects [46,48,51–53].

Antipsychotic Drug	Side Effect	Major or Minor
Olanzapine	Somnolence	Minor
Olanzapine, clozapine	Weight Gain	Minor
Olanzapine, clozapine	Diabetes	Minor
Chlorpromazine, haloperidolRisperidone, olanzapine	Sexual problems	Minor
Clozapine, chlorpromazine, risperidone and haloperidol	Myocarditis	Major
Clozapine, Chlorpromazine	Agranulocytosis	Major

5.1. Somnolence

Sleep disturbances are common in patients who take antipsychotic drugs. It was reported that 20–40% of patients taking from low to high doses of olanzapine had reported somnolence [54]. These studies indicate that the more olanzapine a person consumes, the chance of somnolence increases, thus contributing to sleep disturbances. Subsequent studies carried out on 53 patients found that 6–11% of patients taking low (300 ng/day) to high (600 mg/day) does of quetiapine reported somnolence, suggesting that the sleep disturbances may also be linked to the consumption of this drug [55].

The increased risk of somnolence associated with higher doses of olanzapine suggests a dose-dependent relationship between the drug and sleep disturbances [55]. The exact mechanisms by which antipsychotic drugs induce somnolence are not fully understood.

However, it is believed that the sedative properties of these medications, particularly their effects on certain neurotransmitters in the brain, contribute to the sleep disturbances experienced by patients. Antipsychotics can affect the levels of neurotransmitters such as dopamine, serotonin, and histamine, which are involved in regulating sleep–wake cycles and arousal.

Sleep disturbances caused by antipsychotic drugs can have significant implications for patients. They can lead to daytime drowsiness, impaired cognitive function, and reduced quality of life. Sleep disturbances can also affect patients' ability to conduct daily activities and may contribute to the development of other health issues.

Managing somnolence caused by antipsychotic drugs is an important aspect of patient care. Healthcare providers should carefully monitor patients for sleep disturbances and assess the impact on their daily functioning. Adjustments to the dosage or timing of medication administration may be considered to minimise the effects of somnolence. In some cases, adjunctive medications or behavioural interventions may be recommended to improve sleep quality and mitigate the impact of sleep disturbances on patients' lives. It is crucial for healthcare providers to educate patients about the potential side effects of antipsychotic medications, including somnolence, and the importance of reporting any sleep disturbances experienced. Thus, open communication between patients and healthcare providers is important in identifying and addressing these issues promptly.

5.2. Weight Gain

One of the minor side effects that comes from taking antipsychotic drugs is weight gain. Studies have shown that patients taking antipsychotic drugs increased their waist to hip ratio, indicating fat deposition around the abdomen. Both conventional and newer antipsychotic drugs are associated with weight gain [56]. The risk is very high with the newer drugs, including olanzapine and clozapine; however, even with older, more conventional drugs (e.g., chlorpromazine), the risk of weight gain is still medium to high [57]. Weight gain increases more during the initial period after starting antipsychotics, but people still gain weight in the long term. Antipsychotics cause weight gain by stimulating appetite, causing food cravings, binge eating, and making people hungrier and wanting to eat food in general. The part of the brain that is responsible for food intake is the hypothalamus, and antipsychotic drugs are said to have effects on the hypothalamic regions of the brain [58]. The hypothalamus intaking food is a complex system, and it is not fully understood how antipsychotics disrupt it. However, the antipsychotic drugs that are most associated with weight gain, olanzapine and clozapine, bind strongly to histamine and serotonin receptors. These neurotransmitter systems, as well as noradrenaline and dopamine, are responsible for food intake and body weight regulation [59]. Experiments on mice to test the effect of the antipsychotic olanzapine on weight gain were carried out, and it was found that the female mice that were fed olanzapine moved less and ate more, thus leading to weight gain. However, in males, overeating was less prominent and, therefore, male mice gained less weight [60]. This experiment was only conducted on mice and no equivalent study on humans has been reported; therefore, the effect may not be the same for humans. A large experiment involving 5923 human participants was carried out in order to fix this problem [61]. In total, 23% of the people were randomised to a placebo, 59% were randomised to paliperidone (a second-generation antipsychotic), 9% were randomised to risperidone (a second-generation antipsychotic), and, finally, a further 9% were randomised to olanzapine. The results indicated that the probability of experiencing excessive weight gain increased by 12.6% when the person was on olanzapine, 6% on risperidone, and 4.6% on paliperidone. Therefore, olanzapine had the highest chance of having the largest effect on excessive weight gain (with an 88% chance). Risperidone had the second-highest chance with 11%,

and paliperidone had the lowest chance with less than 1%. To conclude, the experiment had shown that antipsychotics drugs were leading to excessive weight gain, not just in mice, but in humans too. On the bright side, however, weight gain is manageable and there are ways to deal with it. Exercising and eating healthy are good ways to lose weight and the doctor might prescribe a medication, such as metformin, to help deal with weight gain.

5.3. Diabetes

The weight gain caused by antipsychotics can lead to obesity, leading to further complications [62]. These may include high cholesterol or high blood pressure. However, it most commonly causes diabetes. In general, it is recognised that type 2 diabetes and hyperglycaemia are more common in patients with schizophrenia compared with the general population. The prevalence of diabetes in a sample population of patients with schizophrenia was 15.8%, whereas for the general population, it was 3.2% [63]. Antipsychotic drugs escalate this further; they are known to make pre-existing diabetes even worse. Since clozapine and olanzapine have a high-risk factor of weight gain, it is not surprising that these drugs are also a high-risk factors for diabetes [64]. This has also been proven in a meta-analysis from over 270,000 subjects. A study also carried out by the US food and Drug Administration reported 242 cases of new-onset diabetes in patients treated with clozapine. Also in the same study, there were 54 cases of exacerbated diabetes, proving that antipsychotic drugs worsen diabetes. The combination of having diabetes and being schizophrenic is a very serious and deadly combination that must be dealt with immediately. Usually to deal with this, monitoring blood glucose levels frequently in patients with diabetes who also use antipsychotic drugs is essential. Also, diet and exercise are essential and need to be emphasised to patients with schizophrenia [65]. A final way to deal with the highly dangerous combination is, if psychotic patients have a history of diabetes and are from an ethnic group with high prevalence of diabetes, it is advised that they use an antipsychotic that has a lower potential of causing diabetes. Therefore, they should ideally be using conventional, first-generation antipsychotic drugs.

5.4. Sexual Problems

Another side effect that is associated with antipsychotics is causing sexual problems. Sexual dysfunction is a common condition in patients who take antipsychotic medication. It is around 45–80% in males and 30–80% in females [66]. It is said to be a problematic symptom of schizophrenia due to it being distressing, possibly leading to further problems like depression. This problem, however, is not as common in unmedicated schizophrenic patients compared to antipsychotic patients. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study indicates that sexual dysfunction is common in both conventional and newer antipsychotics (first- and second-generation drugs) [67]. Older, typical, antipsychotic drugs are associated with a higher rate of sexual dysfunction compared to newer, atypical antipsychotics, such as olanzapine and clozapine. This is based on the blockade of dopamine D2 receptors. Older drugs, such as risperidone, are classed as prolactin-elevating antipsychotics, whereas newer drugs, such as clozapine and olanzapine, are classed as prolactin-sparing drugs [68]. Prolactin is a hormone produced by the pituitary gland at the bottom of the brain. High prolactin levels in men can cause a reduced desire for sex and an inability have an erection during sex (impotence) [68]. A high prolactin level in women can cause trouble with pregnancy and galactorrhoea. An example of an atypical drug lowering prolactin levels is clozapine. A cross-sectional study with 60 schizophrenic male patients showed that atypical clozapine was associated with lower prolactin levels compared to older, more conventional antipsychotics. Even though clozapine is an atypical drug that does not cause high prolactin levels, there are still

atypical drugs that do cause higher prolactin levels. One example is risperidone, which has had a high probability of prolactin elevation. A five-year study involving 128 men and 90 women reported that risperidone was involved in causing higher prolactin levels compared to any other atypical antipsychotic [69]. Therefore, both typical and atypical (first- and second-generation) antipsychotic drugs can be involved in raising prolactin levels, causing sexual dysfunction. However, this problem can be avoided. A significant improvement in sexual functioning when the participants switched from risperidone to olanzapine was reported (i.e., switching from a conventional to a newer antipsychotic) [70].

5.5. Life-Threatening Side Effects

Antipsychotic medications are the mainstay of treatment for schizophrenia and have been effective in managing the symptoms of the disorder [71–74]. However, it is important to recognise that these medications are not without their risks, and some of them can have life-threatening effects.

One of the most concerning life-threatening side effects of antipsychotics is the increased risk of cardiovascular events. Research has shown that certain antipsychotic medications, particularly the older typical antipsychotics and some of the newer atypical antipsychotics, can lead to adverse cardiovascular outcomes, such as myocardial infarction, stroke, and sudden cardiac death [75–80]. These medications can cause changes in heart rhythm, increased blood pressure, and can lead to metabolic abnormalities, such as weight gain, dyslipidaemia, and insulin resistance, all of which contribute to the increased risk of cardiovascular events [75–77,81].

Another life-threatening effect of antipsychotics is the potential for neuroleptic malignant syndrome (NMS). NMS is a rare but potentially fatal condition characterised by hyperthermia, altered mental status, muscle rigidity, and autonomic dysfunction. It is largely associated with the use of high-potency typical antipsychotics. However, some cases of NMS have also been reported with atypical antipsychotics [78–80]. NMS requires immediate medical attention and the discontinuation of the offending medication.

Additionally, antipsychotics can increase the risk of respiratory complications, particularly in elderly patients. These medications can cause sedation and impair respiratory function, leading to respiratory depression and an increased risk of pneumonia and other respiratory infections [77,80,81]. This is especially concerning in patients with pre-existing respiratory conditions or compromised lung function.

Furthermore, the significant metabolic effects caused by antipsychotics (outlined above) increase the risk of developing metabolic syndrome and type 2 diabetes [77,82]. Metabolic syndrome is a cluster of conditions that includes high blood pressure, high blood sugar, abnormal cholesterol levels, and excess abdominal fat. It significantly increases the risk of cardiovascular disease and other serious health complications.

It is important for healthcare providers to carefully monitor patients on antipsychotic medications for these life-threatening effects. Regular assessments of cardiovascular risk factors, including blood pressure, lipid levels, and blood glucose, should be conducted. Patients should also be monitored for signs and symptoms of NMS, such as fever, muscle rigidity, and altered mental status. In cases where the benefits of antipsychotic treatment outweigh the risks, close monitoring and appropriate management of these potential adverse effects are crucial.

The minor side effects are either disfiguring to a person (weight gain) or have been unpleasant (sexual dysfunction). It is, however, possible that the side effects become even more severe and have a life-threatening effect. Two examples of this are agranulocytosis and myocarditis, which can either be infective or non-infective, depending on its cause [78,83,84] (see Figure 3).

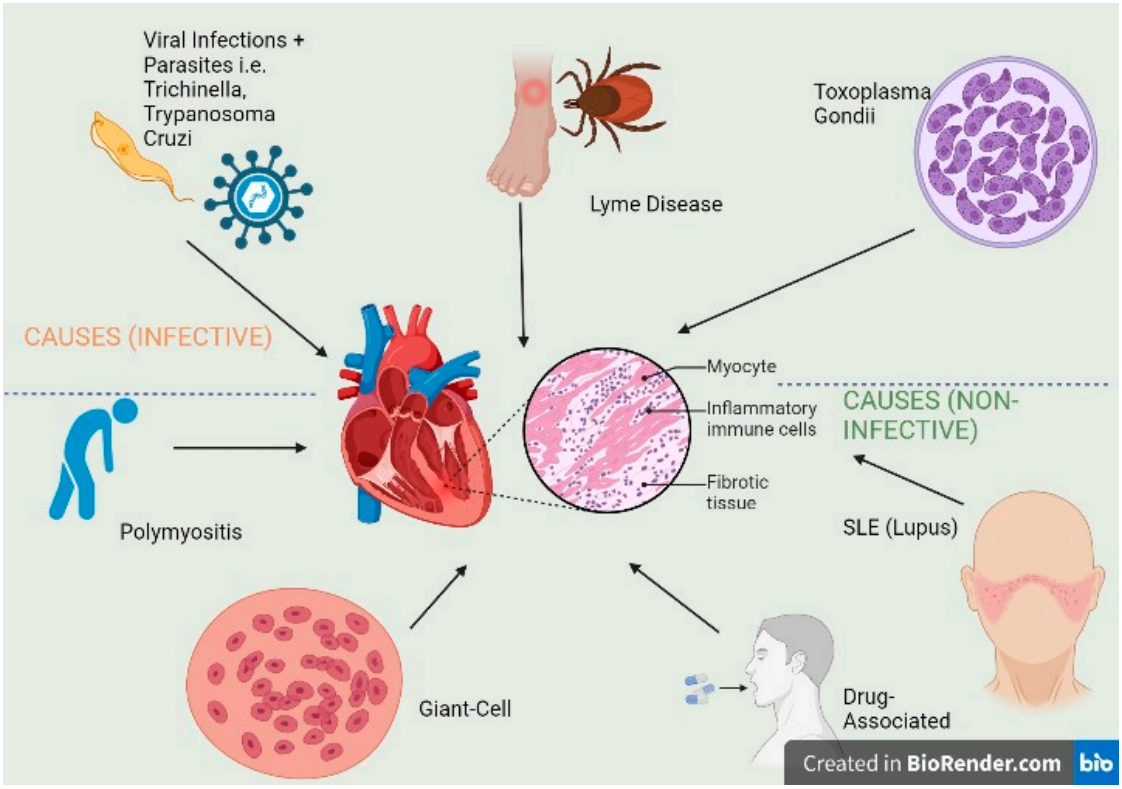

Figure 3. Infective and non-infective causes of myocarditis. Infective causes include infectious triggers such as viral infections, i.e., adenovirus, parasites, lyme disease, and toxoplasma gondii. On the other hand, non-infective causes include non-infectious triggers, such as polymyositis, lupus, and inflammation, caused by giant-cells or induced by drugs, i.e., antibiotics. Both infective and non-infective causes contribute to the inflammation of myocardium, causing myocarditis. Both types of myocarditis may present similarly, i.e., with chest pain, dyspnea, and palpitations; however, the underlying triggers and mechanisms of each type may differ.

Myocarditis is an inflammation of the heart muscle and can reduce the heart's ability to pump, causing abnormal heart rhythms (arrhythmias), leading to heart failure. The antipsychotic drug that is associated with this is reported to be clozapine. The World Health Organisation database showed that clozapine is significantly reported more in relation to cardiomyopathy and myocarditis compared to other drugs. Myocarditis is also associated with chloropyramine, risperidone, and haloperidol [85]. Since it has been proven that antipsychotics do cause myocarditis, early diagnosis is essential in order to prevent long-term heart damage.

As mentioned before, myocarditis is not the only life-threating problem that can result from the use of antipsychotic drugs. Another life-threating problem that can arise is agranulocytosis. Agranulocytosis is an acute condition that results in a lowered white blood cell count. White blood cells are responsible for protecting the body against infection and, therefore, with a lower count, a person has a higher chance of developing frequent or chronic infections. If not treated, it can lead to death, most commonly through septicaemia (which is bacterial infection of the blood) [86,87]. Not only does clozapine cause myocarditis, but it is also associated with causing the rare but potentially fatal side effect agranulocytosis. Out of 11,555 patients who received the clozapine drug, 73 patients had developed agranulocytosis, and out of these 73 patients, 2 of them died from infectious complications [88]. The episodes of Agranulocytosis had occurred in 61 patients only 3 months after the treatment had begun. The data collected also showed that the risk of agranulocytosis had increased with age and was higher among women. Although the chances of developing agranulo-

cytosis are low, its consequences are severe and life-threatening due to the lowered white blood cell count.

As antipsychotics drugs can cause a variety of different side effects, ranging from mild to life-threatening, it is important that these side effects are managed thoroughly. Some antipsychotics can have life-threatening effects, including an increased risk of cardiovascular events, neuroleptic malignant syndrome, respiratory complications, and metabolic abnormalities. Healthcare practitioners should be vigilant in monitoring patients for these potential adverse effects and take appropriate measures to mitigate the risks. The benefits and risks of antipsychotic treatment should be carefully weighed, and individualised treatment plans should be developed to ensure the best possible outcomes for patients with schizophrenia.

6. Non-Pharmacological Therapies

Non-pharmacological therapies have gained attention as potential treatment options for schizophrenia, particularly in cases where patients are non-adherent to oral antipsychotic medication or do not respond to traditional pharmacological interventions [89–95]. Non-pharmacological therapies are usually used in addition to antipsychotic drugs (not instead of) because they complement each other. Therapies and interventions provide awareness about the importance of the drugs and ensure that the person does not stop taking antipsychotic drugs due to false beliefs or delusions. Although psychological intervention can help a person cope with their symptoms and learn to accept them, antipsychotic drugs are also required to treat a person with schizophrenia. However, such therapies in the treatment of schizophrenia have shown mixed findings and inconsistent implementation, suggesting that adherence to such therapies might not always be sustainable for patients [96–99]. Figure 4 shows some of the most frequently recommended non-pharmacological therapies globally.

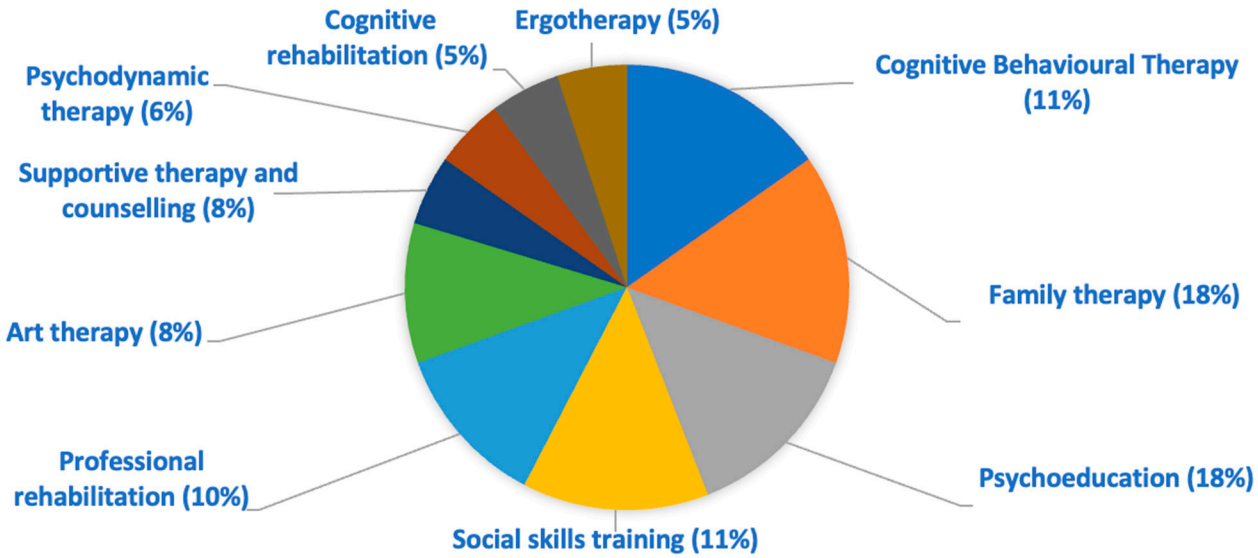

Figure 4. A pie chart illustrating the distribution of non-pharmacological treatments in schizophrenia. The chart highlights the diverse range of non-pharmacological interventions [95–99].

Non-pharmacological therapies, such as psychotherapy, are important in the treatment of schizophrenia, as these therapies are used to help optimise long-term outcomes. These include cognitive behavioural therapy (CBT), individual therapy, and family therapy, which are the most popular and widely recommended approaches worldwide.

6.1. Family Therapy

Family therapy provides support and education to a lot of families that must deal with schizophrenia. It consists of psychotherapeutic strategies for working with the relatives of people who suffer from schizophrenia. A good relationship builds up between the family and the treatment team in order to help the patients make progress towards recovery. More than 50 controlled trials have been conducted in order to test the reliability of family intervention; the results derived from these studies have shown that family therapy makes a positive impact on patients' recovery. However, family therapy does require a series of demands from the family. These demands can include transportation, money, motivation, and energy. Some of these interventions can be expensive, and it takes a lot of dedication and commitment from everyone for the therapy to function effectively.

6.2. Cognitive Behavioural Therapy (CBT)

Cognitive behavioural therapy is another available treatment, which teaches a person to modify their beliefs or thinking patterns that lead to experiencing negative emotions [100]. CBT is gaining more interest now as an adjunctive method to treat schizophrenia in both the USA and the UK. Even though CBT has been gaining more interest and popularity recently, it is not a new concept. In 1952, Aaron Beck successfully applied CBT by treating a delusional belief held by a patient with schizophrenia [101]. The patient was a 28-year-old WW2 veteran and, after returning home, had incorrect beliefs that former members of his military unit were monitoring him. Using cognitive treatment methods, the patient was able to reason himself out of all his incorrect beliefs. The therapies involve use of role playing, simulation, and learning behavioural coping skills, among other methods [102]. Initially, it was developed to treat the acute symptoms of schizophrenia; however, more recent studies have shown that it can be used to treat persistent positive and negative symptoms. With popularity increasing in CBT, the question arises whether it is more effective than other supportive therapies. An experiment was carried out by Sensky and colleagues on 90 medication-resistant patients with schizophrenia [84]. The patients were randomised to receive either 20 weeks of CBT care or 20 weeks of befriending therapy plus standard care. Both groups showed significant improvement on their schizophrenic condition; however, patients who received cognitive care showed a bigger improvement compared to those who received befriending therapy and standard care. CBT has substantial evidence demonstrating that patients with schizophrenia benefit from cognitive techniques. The benefits occur in both the short term and long term, as improvements in the patient's mentality and condition persist even after treatment completion. The accumulation of all the evidence has shown that it is an essential adjunctive therapeutic method for treating schizophrenia.

6.3. Individual Therapy

Individual therapy consists of sessions in which a therapist teaches a person how to deal with their emotions, thoughts, and behaviours. Just like family therapy, this requires a lot of time and commitment, as the sessions are frequent and regular. The sessions usually involve scheduled talks between the patient and a mental health professional, such as a psychiatrist, psychologist, or nurse, as shown in [87]. The different therapies available can help improve communication, social interactions, and participation in daily activities. Individual therapy ensures that a person stays on their medication, as it educates the patient about the importance of adhering to their treatment plan. Taken together, individual therapy helps most people manage their illness with schizophrenia.

6.4. Acupuncture

Acupuncture is a traditional Chinese medicine practice that involves the insertion of thin needles into specific points on the body. It has been suggested that acupuncture may have potential benefits in improving glutamatergic neurotransmission, which is implicated in the pathophysiology of schizophrenia [94]. Whilst there are some evidence supporting its efficacy, the studies conducted so far have been limited by small sample sizes, methodological issues, and heterogeneity in treatment protocols. Therefore, further preclinical and clinical studies are needed to establish treatment guidelines, clarify the mechanisms of acupuncture in these disorders, and determine its long-term efficacy and safety.

6.5. Functional Near-Infrared Spectroscopy

Another non-pharmacological intervention studied is functional near-infrared spectroscopy (fNIRS), a non-invasive neuroimaging technique that measures changes in haemoglobin concentration in brain tissues, providing an indirect measure of brain activity. fNIRS has shown promise in identifying brain activity patterns in patients with schizophrenia and may serve as a biomarker for predicting clinical outcomes and treatment response [87]. However, the use of fNIRS in schizophrenia research is still in its initial stages, and more research is needed to explore its potential applications, including investigating fNIRS differences in various clinical stages, examining the effects of antipsychotic medications on fNIRS measures, and developing more accurate biomarkers for schizophrenia.

6.6. Physical Activity

In addition to these non-pharmacological therapies, physical activity interventions have also been explored as potential treatment options for schizophrenia. One study investigated the effects of soccer practice as an add-on treatment for psychotic subjects and found that it improved self-reported health quality of life and sports performance in these individuals [88]. This suggests that physical activity may have positive effects on the overall well-being and functioning of individuals with schizophrenia. However, it is important to note that the study had a small sample size and did not include a control group, highlighting the need for larger, controlled studies to further explore the potential benefits of physical activity interventions in this population.

6.7. Non-Antipsychotic Medication

Furthermore, there is evidence to suggest that medications other than antipsychotics, such as sublingual dexmedetomidine, may be effective in managing acute agitation in patients with schizophrenia and bipolar disorder [92]. Sublingual medications are considered less coercive and more collaborative than intramuscular options, which may improve patient experience and higher levels of adherence.

While non-pharmacological therapies and interventions show promise, it is essential to acknowledge that the efficacy of these treatments is still being explored and the evidence is limited. For example, the effectiveness of non-pharmacological interventions in cancer prevention, screening, and treatment in people with mental illness has been found to be quite limited [99]. Similarly, the use of non-pharmacological augmentation methods, such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), in combination with clozapine for treatment-resistant schizophrenia, has shown some positive results, but further research is needed [80].

It is also important to consider the comparative efficacy of non-pharmacological therapies versus traditional antipsychotic drugs. Antipsychotic medications, such as clozapine, have been shown to be the most efficacious among the available treatment options for

schizophrenia [93]. However, a significant proportion of patients do not respond to these medications, leading to the exploration of alternative interventions, as discussed previously. Non-pharmacological therapies may offer additional benefits, such as improved adherence and reduced side effects, but more research is needed to determine their comparative efficacy and effectiveness in treating schizophrenia.

In conclusion, non-pharmacological therapies, including acupuncture and functional near-infrared spectroscopy (fNIRS), hold promise as potential treatment options for schizophrenia. However, the current evidence is limited, and further research is needed to establish treatment guidelines, clarify the mechanisms of action, and determine their long-term efficacy and safety. Physical activity interventions have also shown potential benefits, but larger, controlled studies are required to validate their effectiveness. Non-pharmacological therapies should be considered complementary approaches to traditional antipsychotic medications, and individualised treatment plans should be developed based on the specific needs and preferences of each patient.

7. Combined Approaches

Combination therapy, which involves the use of multiple treatment approaches, has been explored as a potential strategy for the management of schizophrenia. The dopamine hypothesis of schizophrenia has been a prominent theory in the field, suggesting that dysregulation of dopamine neurotransmission plays a central role in the pathophysiology of the disorder [103,104]. This hypothesis has guided the development of antipsychotic medications that primarily target dopamine receptors. However, the dopamine hypothesis has evolved over time, incorporating new evidence from neurochemical imaging studies, genetic research, and investigations into environmental risk factors [90]. The current version of the dopamine hypothesis, version III, proposes a final common pathway model that links various risk factors to increased presynaptic striatal dopaminergic function [104]. This highlights the complexity of the neurobiological mechanisms involved in schizophrenia and the potential need for combination therapies that target multiple pathways.

In the treatment of schizophrenia, combination therapy has been explored in various contexts. One study examined the use of combination therapy in managing attention deficit/hyperactivity disorder (ADHD) in adults [105–107]. The findings revealed that combination therapy, involving the use of multiple ADHD medications, was not uncommon. However, the predictors of combination therapy in ADHD management were not well understood [107]. This highlights the need for further research to identify the factors that influence the decision to use combination therapy in the treatment of psychiatric disorders.

Treatment guidelines for schizophrenia often recommend a combined approach that includes both pharmacological interventions, such as antipsychotic medications, and non-pharmacological interventions, such as psychotherapy and psychosocial support [96]. Non-pharmacological interventions, including occupational therapy, social skills training, and group therapy, have shown promise in improving various aspects of functioning and quality of life in individuals with schizophrenia [97,103]. For example, a randomised controlled trial investigated the effectiveness of a combination of occupational therapy and social skills training in people with schizophrenia [93]. The results demonstrated that the combined intervention led to improvements in social participation and performance in daily activities [97].

Psychological evaluation plays a crucial role in the diagnosis, treatment planning, and long-term management of schizophrenia. Cognitive biases, such as jumping to conclusions (JTC) and bias against disconfirmatory evidence (BADE), are common among individuals with schizophrenia and are closely linked to delusions [105]. These biases, rather than being cognitive deficits, represent systematic distortions in the way information is processed and

interpreted, contributing to the persistence of psychotic symptoms. Psychological evaluation, through structured clinical interviews, neuropsychological assessments, and insight evaluations, is vital in identifying these biases and tailoring appropriate interventions. The study underscores the effectiveness of psychological therapies in addressing these cognitive distortions, reporting small to moderate beneficial effects on cognitive biases (Hedges' g = 0.27), positive symptoms (Hedges' g = 0.30), and insight (Hedges' g = 0.35). These findings reinforce the necessity of comprehensive psychological assessments to develop targeted interventions that address both symptomatology and cognitive distortions.

Among the psychological interventions examined, cognitive behavioural therapy for psychosis (CBTp), metacognitive training (MCT), and cognitive remediation therapy (CRT) have emerged as particularly effective. The MCT, which specifically targets cognitive biases, significantly enhances metacognition, cognitive insight, and symptom management. By training patients to recognise their biases and apply corrective thinking strategies, MCT reduces the impact of delusional beliefs and improves decision-making processes. Similarly, CBTp has been shown to be effective in challenging maladaptive thoughts, enhancing coping strategies, and alleviating distress caused by hallucinations and delusions. c Cognitive bias modification (CBM) and the Maudsley Review Training Programme (MRTP) address specific biases through structured cognitive exercises. These interventions not only mitigate cognitive biases but also indirectly contribute to symptom reduction and improved insight, underscoring their clinical significance.

The integration of psychological interventions with pharmacological treatments is essential for the comprehensive management of schizophrenia. While antipsychotic medication remains the primary treatment for reducing positive symptoms, it does not effectively target cognitive biases or negative symptoms. The meta-analysis findings indicate that psychological therapies provide additional benefits by enhancing cognitive flexibility, improving insight, and addressing biases that contribute to delusions. Furthermore, the study demonstrated that cognitive interventions increase treatment adherence by improving patients' awareness of their condition and encouraging a more critical perspective on their beliefs. This is particularly significant, given that poor insight is a major contributor to non-adherence and relapse in schizophrenia. By incorporating psychological evaluations into standard psychiatric care, clinicians can better identify patients who would benefit from these interventions, ultimately improving treatment outcomes.

The study also highlights the importance of addressing cognitive biases early in the course of the illness, particularly in individuals at clinical high risk (CHR) or those experiencing their first episode of psychosis (FEP). Data derived from the meta-analysis suggest that interventions aimed at correcting cognitive biases can mitigate symptom severity, improve insight, and potentially prevent the progression to full-blown psychosis. This has profound implications for early intervention strategies, reinforcing the need for proactive psychological assessments to identify at-risk individuals and provide timely support. Given that cognitive biases are present in both clinical and subclinical populations, addressing them early may yield long-term benefits in preventing the chronic progression of schizophrenia.

Despite the promising findings on psychological interventions, challenges remain in scaling up these treatments and integrating them into routine clinical care. The study highlights the heterogeneity of treatment effects and the need for high-quality, randomised controlled trials to further substantiate their efficacy. Additionally, access to trained therapists remains a barrier, particularly for interventions such as CBTp and MCT, which require specialist training. Future developments should focus on digital interventions, such as mobile-based cognitive training programmes and virtual reality-enhanced social cognition training, to enhance accessibility and engagement. The study also stresses the need for

active control conditions in future research to better isolate the specific effects of cognitive interventions and reduce potential biases in study outcomes.

In conclusion, the studies on psychological interventions for cognitive biases in schizophrenia provide robust evidence that cognitive biases are modifiable and that targeted interventions significantly contribute to symptom reduction and improved insight. Psychological evaluation, through structured interviews and cognitive assessments, is essential in identifying these biases and tailoring interventions accordingly.

Combination therapy has also been explored in the context of substance use comorbidity in schizophrenia. Integrated treatment approaches that combine interventions for substance use disorders and psychiatric disorders have shown promise in reducing substance use and improving outcomes in patients with schizophrenia [103–107]. For example, a combined motivational interviewing, cognitive-behavioural therapy, and family therapy approach has been effective in reducing substance use among patients with schizophrenia [107]. These findings highlight the potential benefits of addressing both substance use and psychiatric symptoms in a comprehensive treatment approach.

While combination therapy holds promise, it is important to critically evaluate the evidence. Some studies have reported conflicting findings regarding the effectiveness of combination therapy compared to monotherapy in schizophrenia treatment. For instance, a study comparing monotherapy and combination therapy in patients with schizophrenia found that combination therapy was associated with shorter hospital stays and decreased overall mortality rates [100]. However, other studies have reported different conclusions, emphasising the importance of individualised treatment approaches and considering factors such as treatment compliance and severity of illness [106].

Non-pharmacological interventions, such as occupational therapy, social skills training, and group therapy, have shown promise in combination with pharmacological interventions. Integrated treatment approaches for substance use comorbidity have also demonstrated positive outcomes. However, further research is needed to better understand the predictors and effectiveness of combination therapy in schizophrenia treatment. Personalised treatment plans that consider the unique needs and characteristics of each patient are crucial for optimising outcomes in schizophrenia management.

8. Conclusions

With all the information considered, we believe that antipsychotic drugs should be used to treat schizophrenia. Although there are many side effects associated with the drugs, their overall effectiveness makes them worth taking. They are the only medication available that can treat the different symptoms of schizophrenia. These symptoms include hallucinations, anxiety, incoherent speech, and confusion, among others. Despite the use of non-pharmacological therapies outlined above (i.e., fNIRS, acupuncture), these therapies cannot be used as a primary source to treat schizophrenia. Although they indicate potential as effective treatments for schizophrenia, the existing evidence is limited and further research is needed to establish treatment guidelines, understand their mechanisms of action, and assess their long-term efficacy and safety. Physical activity interventions also hold potential benefits, but larger controlled studies are required to validate their effectiveness. It is essential to view non-pharmacological therapies as complementary to traditional antipsychotic medications, and treatment plans should be personalised according to individual patient needs and preferences. Further research is required to better understand the efficacy of combination therapy so that treatment plans will consider the individual needs and characteristics of each patient, hence optimising outcomes in schizophrenia management.

Overall, these therapies represent exciting avenues for exploring and translating new treatment options for schizophrenia and improving patient outcomes, but they have to be used in addition to antipsychotic drugs. The experience of antipsychotics cannot be denied: the drugs have been around for 70 years and, since their inception, they have been the primary treatment available for schizophrenic patients. The side effects associated with the drugs are still a problem, but they can be treated. For example, sexual dysfunction can be dealt with using sildenafil, whilst myocarditis can be treated by using drugs to reduce the risk of blood clots in the heart. There are risks associated with these pharmacological drugs, but, as explained above, the reward at the end makes it worth using, which is why antipsychotic drugs together with non-pharmacological interventions should be used to treat schizophrenia.

Taken together, while pharmacological treatments remain a cornerstone of schizophrenia management, integrating psychological therapies enhances treatment efficacy, reduces relapse rates, and improves long-term functional outcomes. Moving forward, a multimodal approach that combines psychological and pharmacological interventions will be fundamental in optimising patient outcomes and enhancing the quality of life for individuals with schizophrenia.

Author Contributions: Conceptualization, writing, reviewing and editing: R.N., S.N. and M.T.N. All authors have read and agreed to the published version of the manuscript.

Funding: Research carried out at MTN laboratories was funded by the GrowMedtech, the Royal Society grant (R00609 to MTN), the Commonwealth Scholarship Commission (CSC), the Great Britain Sasakawa Foundation (grant B70 to MTN), and the University of Bradford (UoB).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: We thank Rajendran Gopalan, School of Pharmacy and Medical Sciences, University of Bradford, for critically reviewing the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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