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A review on schizophrenia: Drugs, treatment and therapy approaches

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Abstract
Schizophrenia is one of the most serious neuropsychiatric illnesses, characterized by hallucinations, delusions, and cognitive issues. It is a complicated life disabling psychotic disease, affects 1% of the general population. The pathophysiology of schizophrenia has been related to structural brain changes and neurotransmitters disturbances. Symptoms of schizophrenia are manifested as three main groups; positive, negative, and cognitive symptoms. Effective treatment of schizophrenia is a challenging goal itself; it requires implementation of pharmacological, psychological, and environmental tools. This review has discussed all reported researches and inventions to deliver Second generation Antipsychotics' (SGAs) like Risperidone, Clozapine, Olanzapine, and Samidorphan, etc. According to recent studies there are various therapy and treatment used to treat schizophrenia without medication including Yoga therapy, Electroconvulsive therapy (ECT), Music therapy, Morita therapy.
Primary care is often the first point of contact for people living with mental disorders. Community pharmacists, pharmacy staff and students are increasingly being trained to deliver mental health care. However, there is still a gap in the literature exploring the characteristics of all available mental health training programs and their components and their influence on pharmacists, pharmacy staff and students' outcomes.

Keywords: Schizophrenia, neuropsychiatric, brain, psychological, neurotransmitter, second generation antipsychotics, therapy, electroconvulsive, treatment, symptoms, primary care, pharmacy staff, pharmacist, mental health care

1. Introduction
One of the most serious neuropsychiatric illnesses, schizophrenia affects 1% of the general population. Hallucinations (mainly auditory), delusions, pronounced thinking disorders, and affective problems are some of its defining characteristics. Schizophrenia can be diagnosed using a variety of diagnostic methods, but it is unfortunately exceedingly challenging [1]. It is a serious, chronic medical condition that causes hallucinations, delusions, disorganized thinking, and cognitive problems. It significantly contributes to the global burden of disease [2].

That is associated with significant morbidity; however, unlike other neurodevelopmental disorders, the symptoms of schizophrenia frequently do not manifest for decades. According to recent research studies, the lifetime suicide rate for people with schizophrenia ranges from 4% to 13%. In the majority of patients, onset symptoms such as positive symptoms, mood symptoms, cognitive symptoms, and social withdrawal occurred prior to the formal onset of schizophrenia [3]. In the year 1911, According to E. Bleuler, the "most serious of all schizophrenic symptoms" is "the suicidal drive [4]."
According to recent studies, the modal suicide rate is around 10% and the lifetime suicide rate for people with schizophrenia ranges from 4% to 13% [5]. The reported rates of attempted suicide in schizophrenia patients range from 18% to 55% [6]. Suicide is the major factor lowering life expectancy in schizophrenia patients. According to WHO statistics that were updated in April 2018, schizophrenia affects about 23 million people worldwide. It affects 12 million more men than women and begins earlier in men compared to women (9 million) [7].
Disabilities can have an impact on social functioning in a variety of broad domains, such as self-care, which includes personal care, dressing, and feeding. Work performance in paid jobs and household duties are also affected.
Schizophrenia patients consistently develop poor relationships with their family members and struggle to engage in social activities such as leisure time and other social gatherings.

Despite not being a fatal condition in and of itself, schizophrenia has at least a twofold higher death rate than the general population. In the past, poor conditions of long-term institutional care have been linked to the high mortality, which has resulted in a high incidence of tuberculosis and other communicable diseases [8]. Schizophrenia is more likely to occur in people between 15 and 30 years old [9]. Obstetric problems, the time of birth, behavioural variations, and exposure to drug abuse are all risk factors for schizophrenia [9]. Early-onset schizophrenia is frequently diagnosed in early adulthood (late adolescence to early twenties) and is more frequently seen in men. It is also linked to other psychiatric disorders, particularly affective disorders, and a positive family history of schizophrenia [10].

The American Psychiatric Association (APA) 2020 treatment recommendations strongly advise that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects [11]. Constipation, akathisia, sexual dysfunction, acute dystonia's, disfigurement, weight gain, Parkinsonism, myocarditis, and agranulocytosis are some of the more serious side effects of antipsychotic medications. These include relatively minor tolerability issues like mild sedation or dry mouth. Some side effects, like enhanced prolactin or serum lipid levels, don't have much of an immediate clinical impact [12]. Serotonin 5HTA receptors are easier for second-generation antipsychotics to block than dopamine D2 receptors. Extrapyramidal symptoms are less frequent because of this mechanism of action [13].

Atypical antipsychotics that are currently widely accepted for treating schizophrenia include clozapine, olanzapine, quetiapine, risperidone, paliperidone, ziprasidone, and molindone [14]. Due to their different mechanism of action, which involves being partial D2 agonists rather than antagonists, third-generation antipsychotics are distinct from other neuroleptics [15]. Similar to the previous point, no evidence-based comparison of FGAs and SGAs is given because neither antipsychotic class will necessarily consistently outperform the other in terms of efficacy [11]. In addition, it is impossible to accurately predict which agent will cause more side effects than another [11].

These conclusions are supported by a 2019 systematic review and meta-analysis that compared the effectiveness and tolerability of 32 oral antipsychotic medications for the acute treatment of adults with multi-episode schizophrenia [16].

2. Pathophysiology

Schizophrenia pathophysiology involves several factors, including genetic disposition, obstetric complications, increased neuronal pruning, immune system abnormalities, and neurodevelopmental disorders [17]. Over the last three decades, advanced neuroimaging, electrophysiological, and neuropath logical techniques have significantly contributed to our understanding of the pathophysiology of this disorder [18]. Global, cortical, and subcortical areas are among the landmark brain structures changes associated with schizophrenia [19]. Neurotransmission abnormalities have served as the foundation for theories about the pathophysiology of schizophrenia. The majority of these hypothesis development centre on either an excess or a deficiency of neurotransmitters such as dopamine, serotonin, and glutamate [20]. It has been reported that there is an increase in ventricular size and a decrease in grey matter [17].

2.1 Dopamine hypothesis

Dopamine hyperactivity in schizophrenia patients may be due to an increase in either dopaminergic receptor presentation or neurotransmitter release [21]. Studies showing that the clinical effectiveness of drugs depends on their capacity to block dopamine receptors, particularly the dopamine D2 receptor subtype, support the relationship between dopamine function and schizophrenia [22]. Additionally, amphetamines' capacity to promote psychosis by raising extracellular dopamine supported this theory [18].

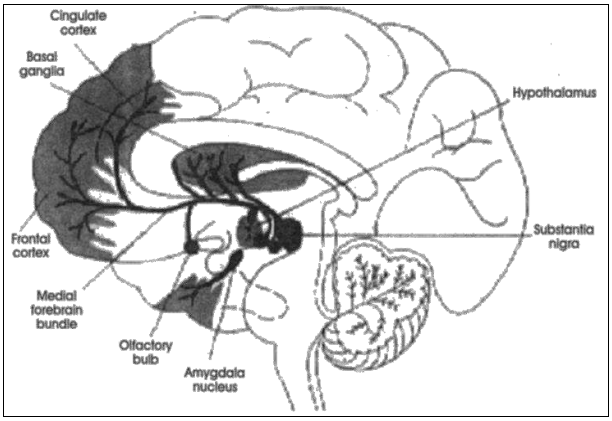

Figure1. Dopamine pathways in the brain. [100]

2.2 Serotonin hypothesis

The observation of behavioural and pathophysiological changes linked to the alteration of serotonin levels in the brain sparked interest in the role of serotonin in schizophrenia. While cortical atrophy or ventricular enlargement in schizophrenia patients have also been found to be correlated with decreased levels of 5-hydroxyindoleacetic acid (the primary metabolite of serotonin) in cerebrospinal fluid, lysergic acid diethylamide (LSD) has been found to enhance and potentiate the effects of serotonin in the brain [23].

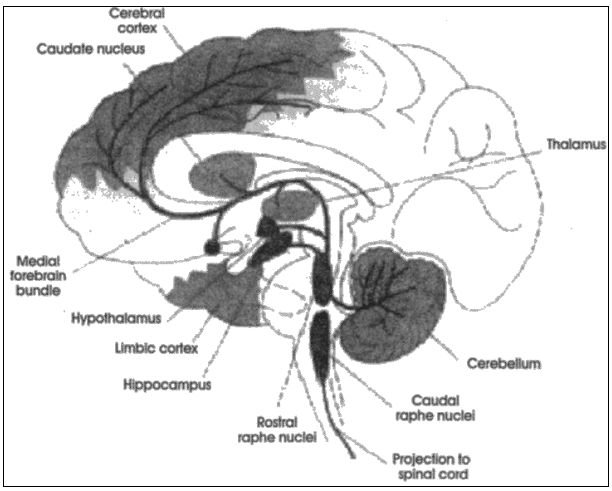

Fig 2: Serotonergic Pathways in the brain [100].

2.3 Glutamate hypothesis

According to the glutamate hypothesis, the development of both the disease's positive and negative symptoms is caused by N-methyl-D-aspartate (NMDA) receptors' reduced

functionality, particularly in the frontal cortex. This concept was created out of the discovery that the NMDA receptor blockers phencyclidine (PCP) and ketamine, which mimic both the disease's positive and negative symptoms, are both [22]. The Glutamate Hypothesis is appealing due to Glutamate's involvement in brain regions that are in charge of both positive and negative symptoms. Ketamine blocks the NMDA receptor, which results in a greater release of dopamine, which then occupying the receptors [24].

2.4 Neurodevelopment hypothesis

Schizophrenia is most definitely a disorder with a neurodevelopmental origin, according to a number of lines of evidence [25]. The "neurodevelopmental model" of schizophrenia, in its most basic form, proposes that the disorder may be associated with an aberration in the neurodevelopmental process that manifests much earlier than the onset of clinical symptoms and is brought on by a combination of genetic and environmental factors [26].

2.5 Key Facts in the Pathophysiology of Schizophrenia [20].

1. **Structural brain findings**
   - Ventricular enlargement
   - Subtle reductions in total gray matter volume
   - Reductions in gray matter volume of the hippocampus and other medial
2. **Temporal and limbic regions**
3. **Functional brain findings**
   - Decreased activation of prefrontal cortex (hypofrontality)
   - Increased activation of temporal regions during hallucinations
4. **Electrophysiological findings**
   - Diminished prepulse inhibition of startle response (PPI) and diminished
5. **P_{50} suppression**
   - Decreased amplitudes of the P300 response and mismatch negativity
   - Abnormalities in gamma oscillations
6. **Neuroendocrine, Oxidative, and Immunological**
   - Elevated markers of oxidative stress, varying by clinical status
   - Dysfunction of the hypothalamic–pituitary–adrenal axis (abnormal dexamethasone suppression)
   - Abnormal levels of inflammatory cytokines
7. **Neuropathology**
   - Reductions in dendritic spines and size of pyramidal neurons
   - Relative preservation of total number of neurons
   - The absence of gliosis and other neurodegenerative features
8. **Reduced expression of GAD-67 in the dorsolateral prefrontal cortex**
9. **Neurochemical**
   - Reduced *N* -acetyl aspartate in frontal and temporal regions
   - Reduced PME (marker of membrane phospholipid synthesis) in prefrontal
10. **Regions**
    - Elevated presynaptic dopamine function

3. Symptoms

Although schizophrenia has been characterised in the media as a condition characterised by "split personalities," it is actually a psychotic disorder with a strong biochemical basis that affects a patient's thoughts, perceptions, and behaviour [20, 27]. In most cases, a prodromal phase comes before the onset of schizophrenia symptoms. Attenuated positive symptoms, mood symptoms, cognitive symptoms, social withdrawal, or obsessive behaviours are all included in this phase. [28]. In addition to the fact that every patient may have a unique clinical profile, the signs and symptoms of schizophrenia are varied. However, symptoms are frequently divided into three main categories: positive, negative, and cognitive symptoms as described in Table 1:

Table 1

A List of the common symptoms of schizophrenia with a brief definition [29].

Table 1: Positive symptoms

Delusions	Clear false believe that indicates impairment in the thinking functionality of the affected person
Hallucinations	Disorders of perception Auditory (most common), visual, olfactory, gustatory, and tactile hallucinations
Disorganized thought	The speech is disorganized in a variety of ways resulting from thinking disorder
Disorganized behaviour	Difficulties in activities in daily living, unpredictable agitation or silliness, social isolation
Catatonia and motor symptoms	Stupor, rigidity, negativism and excitement

Table 2: Negative symptoms

Flattening	Reduced emotional expression (facial expression, voice tone, eye contact, and body language)
Alogia	Poverty of speech due to slowing or blocked thoughts
Avolition / apathy	Lack of motivation and difficulty to persist in goal-directed behaviour

Table 3: Cognitive symptoms

1.	Slow thinking
2.	Difficulty understanding
3.	Poor concentration
4.	Poor memory

Positive symptoms, which manifest as excessive actions and misinterpretation of typical functions, result from dopamine hyperactivity in some brain regions and glutaminergic hypofunction. On the other hand, dopamine hypo-activity in other brain regions is what causes negative and cognitive symptoms. The final two categories represent functional impairment [17]. Schizophrenia diagnosis is very difficult and takes time. To distinguish schizophrenia from other mental

illnesses like major depressive disorder with psychotic or catatonic features, mood disorders, and substance-induced psychoses, a thorough diagnosis is crucial. Since schizophrenia symptoms are numerous and non-specific, they must be conspicuous. Additionally, the affected person's symptoms are not all clearly combined [30].

4. Treatment

The treatment's objectives include reducing the targeted symptoms, avoiding adverse effects, enhancing psychosocial functioning and productivity, ensuring adherence to the recommended regimen, and involving the patient in the treatment planning process [17]. To develop a successful treatment plan for schizophrenia, it is essential to combine biological, psychological, and environmental perspectives [31]. The first step in providing effective care is a thorough evaluation of the patient, which should take into account all available information about their physical, social, and mental health. A more obvious picture of the case would be provided by the patient's family. The risk of harm to oneself or others, the level of functioning, diagnosable medical and psychiatric conditions, especially comorbid substance abuse, and the dimensions and severity of symptoms should all be covered in the initial assessment as primary checkpoints [32]. Antipsychotic medications are currently the mainstay of therapy for schizophrenia. The primary mechanism of action of first-generation antipsychotics is the blocking of dopaminergic D2 receptors [33]. According to research and the recommended treatment plan, antipsychotics monotherapy is frequently used to treat schizophrenia, related psychotic disorders, and acute symptoms of the disease. When treating certain conditions, such as refractory schizophrenia, inability of monotherapy to produce a satisfactory response, intolerable side effects, and patient trapping during cross-titration from one antipsychotic to another, a second antipsychotic is typically prescribed in addition to the first. [34]. A mental status examination, physical and neurological examination, a family and social history, a psychiatric diagnostic interview, and a laboratory workup should all be conducted prior to starting treatment (complete blood count [CBC], electrolytes, hepatic function, renal function, electrocardiogram [ECG], fasting serum glucose, serum lipids, thyroid function, and urine drug screen) [17].

Table 4 [35]: Classification of antipsychotics with their mechanism of action and specification

Classification	Drugs	Mechanism	Specification
Typical (first generation) FGA	Haloperidol; chlorpromazine; fluphenazine; thioridazine; sulpiride	Mainly acts by blocking dopamine type 2 (D2) receptors	Severe extrapyramidal effects e.g. hyperprolactinemia; dystonia; dyskinesia; akathisia and metabolic disorders led to their discontinuation
Atypical (second-generation) SGA	Risperidone; clozapine; olanzapine; quetiapine; lurasidone; paliperidone	In addition to D2 receptors blocking, also antagonize 5-hydroxytryptamine type 2 (5-HT2) receptors	Less severe adverse effects as compared to FGA
Partial Dopamine agonist	Aripiprazole	Act as functional antagonist in the mesolimbic dopamine pathway associated with positive symptoms, and act as a functional agonist in the mesocortical pathway associated with negative symptoms	Less severe adverse effects as compared to FGA, and improves positive, negative, and cognitive impairment.

5. Therapy

5.1 Art therapy

The National Institute for Health and Care Excellence (2014) and the World Health Organization (2019) both describe and suggest art therapy treatment programmes for people with schizophrenia. However, more in-depth examinations of the particular mechanisms at work when creating art in these kinds of environments are required [36]. this study responds by focusing specifically on the art-making process itself and the participants' interactions with the finished product. The experiences of making art are investigated using a phenomenological life world approach. It focuses on lived experiences and investigates the studio-based artistic process, which is primarily embodied and pre-reflective. The lived experience of mental distress, in particular the collection of subjective experiences that may result in a diagnosis of schizophrenia, and the lived experience of making art are the two main areas of the literature that have had a significant influence on the work. Attempting to grasp the distinct perspective and relationship of the mental health service user to their world [37]. This method has described specific and primary subjective symptoms of schizophrenia, including the perspective of a fundamentally altered or unnatural way of being in the world. [37,38]. The phenomenological research base has been informed by subjective accounts of psychotic and ambiguous experiences, which have highlighted a perplexing and even terrifying world that has lost its essential meaning and emotional resonance [39].

These descriptions frequently include a disorganised sense of self as well as a number of atypical self-experiences [39, 40]. The presentation of the disorganised sense of self is explained by the phenomenological model known as the "ipseity (minimal / basic self)-disturbance hypothesis" [41]. in a conclusion, the phenomenological understanding of the self - outlines different levels of conscious awareness, starting at a fundamentally manifested and pre-reflective level and progressing to more reflective levels of conscious awareness [42]. It includes inherent and unconsciously held knowledge of the particular lifeworld. A person's meaningful and individually experienced world is referred to as their "lifeworld." More reflective levels of conscious awareness activate more complex self-understandings, arguments, and reflections by building on manifested consciousness. The ipseity (minimal / basic self) - disturbance hypothesis refers to disruptions of conscious processing at the primary and embodied level of selfhood (pre-reflective level) and conscious awareness. It is based on phenomenological research in the field of schizophrenia. The disruptions at the embodied level are not primarily explained by models like the Ipseity-Disturbance Model. However, we believe that art-making is particularly well-suited to provide support when a person with schizophrenia

experiences a disordered sense of self and an unsettling environment due to disturbances at the manifested level [43].

5.2 Music therapy

The term "music therapy" refers to "a systematic process of intervention wherein the therapist assists the client in promoting health by using music experiences and developing relationships through them as dynamic forces of change." [44]. Therapists have looked into auxiliary psychological intervention as an additional treatment in addition to drug therapy because antipsychotic medication has its limitations. According to some studies, patients with schizophrenia can benefit more from adjunct music therapy [45]. The three main types of music therapy formats are active, receptive, and a combination of active and receptive. These formats can be given individually or collectively [46]. Music therapy aims to elevate mood, behaviour, and quality of life by alleviating stress, pain, anxiety, and isolation [47]. It is important to note that music therapy is not the same as listening to music. Music therapy engages various musical elements, such as melody, timbre, rhythm, harmony, and pitch, to support and enhance physical, psychological, and social well-being through a therapeutic relationship between the participant and the therapist [48].The impact of music therapy on mental illness has attracted more attention as music therapy research and use have expanded [49]. The majority of patients have responded positively to music therapy as a non-drug, non-invasive treatment, and it doesn't require any musical ability on the part of the patients [50]. As it has some potential advantages over conventional talk-based psychological interventions for those who were diagnosed with schizophrenia, music therapy is also frequently thought of as a medium for people to communicate with others and express themselves without the use of language. For example, patients who are struggling to verbally express their thoughts and emotions to a traditional therapist due to the negative symptoms of schizophrenia (such as expressive deficits) [51]. However, music therapy may be able to get around this problem by promoting a complex bond between the patient and the therapist. Patients who receive music therapy can learn and hone musical skills that can improve their mood, coping mechanisms, cognitive functioning, social functioning, and self-esteem, as well as lessen the symptoms of mental disorder diagnoses. As a result, patients with schizophrenia might benefit from music therapy. There is some clinical research to support the use of music therapy as a therapeutic approach for schizophrenia [52].

5.3 Yoga therapy

Yoga has been found to be effective at enhancing cognitive abilities in healthy adults and the elderly [53]. Yoga is more effective than physical activity as an additional treatment for diminishing negative symptoms in people with schizophrenia (PWS) [54]. Additionally, it raises PWS patients' quality of life. More recent studies have looked at the neurocognitive benefits of yoga therapy and have shown cognitive improvements in PWS [55]. It's interesting to note that two randomised controlled trials (RCT) have shown improvements in Emotion Processing (EP), a crucial area of social cognition [56]. Increases in oxytocin are also connected to imitation and imitation of others [57]. During group supervision, the yoga training incorporates the idea of practising imitation and experiencing imitation. Insel recently argued that it is crucial to look into the biological mechanisms as well as the clinical effectiveness [58].

In this study, we aimed to

a) Compare the changes in comprehensive social cognition measurements (including theory of mind (ToM), emotion processing (EP), social perception (SP), and attribution style (AS)) in PWS assigned to waitlist (WL) or add-on yoga therapy (YT) groups.
b) Examine the differences between the WL and YT groups in prospective MNS activity as determined by Tran's cranial magnetic stimulation (TMS).

We indicated that 20 yoga sessions spread over six weeks would enhance PWS's composite score for social cognition. After 20 supervised yoga therapy sessions in PWS, our backup hypothesis was that MNS activity would also rise. [59].

5.4 Electro convulsive therapy (ECT)

The oldest neurological therapy in psychiatry that is still in use currently is electroconvulsive therapy (ECT) [60]. It is the most effective short-term treatment for severe depression and is also effective at easing psychotic symptoms in people with schizophrenia who are resistant to other treatments. [61] For some patients, ECT can save their lives and is very effective. Uncertainty exists regarding ECT's impact on suicidality in schizophrenia, though. We therefore set out to research the impact of ECT on expressed suicidality in schizophrenia in a sizable naturalistic cohort of patients with treatment-resistant schizophrenia receiving ECT. [62]. Schizophrenia reports for 47% of ECT prescriptions, with other common indications including schizoaffective disorder (20.3%), depression (20.4%), and mania (6.8%). ECT was successful in treating psychotic symptoms in 64.5% of schizophrenia patients, and it also enhanced their cognitive abilities [63]. By analysing an existing clinical database of patients with schizophrenia who were referred for ECT, we carried out a retrospective study of the effects of ECT treatment given to patients with schizophrenia in a real-world setting on expressed suicidality [63]. Two consultants and two medical officers who had received ECT training provided ECT, ensuring that it was administered consistently. Individualized dosing based on the clinically determined seizure threshold of each patient was used. In order to administer ECT, hand-held electrodes were used with the Thymatron system IV device (Somatics, USA) from January 2016 to December 2016 and the MECTA SpECTrum 5000Q device (MECTA, USA) starting in January 2017. ECT was given with either bitemporal, right unilaterally [64] or Positioning of bifrontal electrodes (Abrams and Taylor, 1973). According to IMH clinical ECT treatment protocols, bitemporal ECT was administered at 0.5 ms pulse width at 1.5x seizure threshold, bifrontal ECT was administered at 1.0 ms pulse width at 1.5x seizure threshold, and right unilateral ECT was administered at 0.5 ms pulse width at 5x seizure threshold. Suxamethonium was used as a muscle relaxant at 0.5 mg/kg, and propofol was used as an anaesthetic at 1 mg/kg. Participants, 2.2 [64].

5.5 Morita therapy

Schizophrenia significantly impairs brain function and presents as a consequent combination of cognitive dysfunction and psychotic symptoms like hallucinations, delusions, and thinking disorders, greatly affecting patients'

quality of life. Pharmacotherapy, psychotherapy, electroconvulsive therapy, and targeted treatment are just a few of the many methods used to treat schizophrenia [65]. Dr. Shoma Morita created the Japanese psychotherapy known as Morita therapy in 1919. It is based on Zen Buddhist principles. It was designed to treat common psychological issues like depression, anxiety disorders, obsessive compulsive disorder, or a particular phobia [66]. It is appropriate for patients between the ages of 15 and 40. The therapeutic tenet of Morita therapy is "let it be as it should be." The goal of Morita therapy is to help clients achieve a mental state that will allow them to continue working and studying even though they are experiencing some mental health issues [67]. Consists of four stages: the bed phase, the light work phase, the heavy work phase, and the social psychotherapy phase [68]. First, it is advised that you spend a week in bed, with no reading, writing, talking, or other activities permitted during this time. This method's goal is to reduce thinking that is in conflict. The subsequent phase of light work lasts for 3-7 days. Conversation and communication are still prohibited, and daily bed rest is only permitted for seven to eight hours. During the day, patients are exposed to outdoor sunlight and fresh air, and at night, they write in a journal. This phase's goal is to motivate patients to take pleasure in their work. Doctors use diaries to converse with patients at the same time. The heavy work phase follows, and it lasts for at least a month or two. Patients are transferred to an open ward with no activity limitations. There is cleaning and manual labour. Last but not least, the social rehabilitation phase takes 1-4 weeks. To adjust to life, patients frequently need to leave the hospital and spend the night outside. They can attend work or school, but they must see a doctor once or twice a week [69]. Morita therapy instructs patients that unwanted symptoms like anxiety are natural features of human emotion rather than pathological symptoms that need to be controlled or eliminated, standing in stark contrast to Western psychotherapies like cognitive behavioural therapy. The use of Morita therapy as a treatment is growing, and several new trials are being conducted, such as a pilot randomised controlled trial (RCT) of Morita therapy for mental disorders being carried out in the UK [70]. In 2007, a meta-analysis of Morita therapy for adults with schizophrenia was released. An increasing number of studies have examined the impact of Morita therapy on adult-onset schizophrenia over the past 10 years. We conducted an updated meta-analysis to assess the clinical efficacy of Morita therapy for patients with schizophrenia in light of recently published data on its application in the treatment of schizophrenia [71].

6. Delivery of combinational antipsychotics

Conventional delivery of antipsychotics

Traditional dosage forms of antipsychotic medications, such as tablets and capsules, were created for the treatment of schizophrenia and related psychotic disorders.*Table3* Demonstrates how antipsychotic drugs are marketed in combination. The blood-brain barrier (BBB), which prevents antipsychotics from reaching the brain, prevents them from having the therapeutic effects that were predicted when using conventionally available treatments. Consequently, requiring higher drug doses, leading to an increase in dose-related side effects [72]. The quality of life may suffer as a result of medication discontinuation and patient non-adherence, which raises the risk of illness, relapse, and hospitalisation. To enhance the delivery of antipsychotics, more advanced dosage forms, including inject tables, emulsions, and complexation techniques, were created [73].

Table 5: Marketed formulation of antipsychotic drugs in combination.

Drugs	Brand Name	Strength
Risperidone+ Trihexyphenidyl hydrochloride	RISPY-PLU Tablet NUDON Plus RISPY-FORTE & SIZODON FORTE Tablet	Risperidone 3 mg + Trihexyphenidyl 2 mg Risperidone 4 mg + Trihexyphenidyl 2 mg
Olanzapine + Fluoxetine	Oso zap Forte Olorest-F-5	Olanzapine 10 mg + Fluoxetine 20 mg Olanzapine 5mg / 10 mg + Fluoxetine 20 mg
Trifluoperazine + chlordiazepoxide	Libocalm	Trifluoperazine 1 mg + chlordiazepoxide 10 mg

6.1 Treatment protocols

To develop an effective treatment plan for schizophrenia, the biological, psychological, and environmental perspectives must be combined [31]. Successful treatment is predicted to accomplish a number of objectives, including the reduction or elimination of symptoms, enhancement of quality of life, maintenance of recovery from the challenging effects of illness, and relapse prevention [74]. The first step in providing effective care is a thorough evaluation of the patient, which should take into account all available information about their physical, social, and mental health. A more clear-cut picture of the case would be provided by the patient's family. Primary checkpoints like symptom dimensions, symptom severity, comorbid psychiatric and medical conditions, especially comorbid substance abuse, the risk of harm to oneself or others, and level of functioning should be covered by the initial assessment [32]. Then, using the standard rating scales PANSS (Positive and Negative Symptoms Scale), SANS (Scale for the Assessment of Negative Symptoms), SAPS (Scale for the Assessment of Positive Symptoms), and BPRS (Brief Psychiatric Rating Scale), baseline assessments for symptoms of schizophrenia should be carried out to monitor treatment progress in comparison to the initial scores.

6.2 Clozapine

Clozapine (CZP) is a second-generation antipsychotic that is well-tolerated and has fewer sympathomimetic side effects [75]. CZP is a class II biopharmaceutical classification system drug with low water solubility and high permeability, as well as relatively good absorption (ranges from 27 to 50% due to first-pass metabolism), when compared to other SGAs [76]. The only antipsychotic with evidence-based support for treating refractory schizophrenia is clozapine, which is widely used in the clinical community [77] and reduces general aggression and suicidal attempt, The most common side effects of clozapine are agranulocytosis, hepatotoxicity, and cardio toxicity [78]. It has been illustrated that clozapine reduces both positive and negative symptoms

in schizophrenic patients more effectively than conventional neuroleptics (chlorpromazine) [79]. Additionally, clozapine has demonstrated superior efficacy over conventional neuroleptics in reducing overall psychopathology in patients with treatment-resistant schizophrenia [80]. Additionally, clozapine expressed a markedly decreased propensity for tardive dyskinesia when compared to conventional neuroleptics and caused fewer sympathomimetic symptoms [81].

6.3 Risperidone

The FDA approved risperidone (RISP) in 2007. It has a special balance of serotonin and dopamine antagonists, and it definitely has a much stronger affinity for 5-HT2A receptors than for D2 receptors. It has been demonstrated that Risperidone is effective in managing both the positive and negative symptoms of schizophrenia. [82]. Risperidone-based conventional formulations have been incorporated into the transdermal patch. Polymers like polyvinyl pyrrolidine (PVPK30), hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and Polyethylene glycol RS 100 are included in the matrix. 10%, 20%, and 30% concentrations of glycerine and polyethylene glycol 400 (PEG-400) are used as plasticizers. After the necessary amount of methanol was used to dissolve the risperidone, plasticizers and polymers were added, the diffusion rate of RISP patches increases as glycerine and polyethylene glycol concentrations rise. In formulations containing glycerine as a plasticizer, the mixture of HPMC and Eudragit had a higher diffusion rate than HPMC and PVPK30 in terms of polymers. It was discovered that a higher proportion of hydrophilic polymer results in a faster diffusion rate. Since gelaneous pores are created when the soluble portion of the polymer matrix dissolves, this results in a reduction in the mean diffusion path length of drug molecules and an increase in the rate of drug release. Another study comparing the effects of sorbitan esters (Spans versus Tweens), cholesterol, and lecithin on the effectiveness of drug entrapment and drug release profile was conducted. There was a greater degree of entrapment efficiency with Spans-containing proniosomes. This outcome can be attributed to Spans' physicochemical characteristics. Spans are naturally lipophilic, which enables them to form an intact bilayer within which the highly lipophilic drug risperidone can be effectively trapped. Span 60 had greater entrapment than Span 40 and Span 20 due to its longer saturated alkyl chain. Due to the high phase transition temperatures of Span 40 and Span 60, a uniform bilayer is formed, preventing drug entrapment leakage. Comparing the release profiles of the two formulations, the span formulation showed a slower profile. Risperidone, a lipophilic drug, is rapidly released from hydrophilic tweens, which results in this expected finding. Risperidone desorption from the surface of the vesicles caused the initial phase of release, and swollen niosomal bilayers allowed for the late phase to be adjusted. To emphasise, skin moisture hydrates proniosomes and transforms them into niosomes. In situations where the lipid barrier is damaged by non-ionic surfactants, niosomes' adsorption and fusion to the skin's surface help drugs permeate. The formulation Span 60 demonstrated the greatest flow through the rat skin. Span 60 gel, an oral commercial solution, and pure risperidone were all used in *in vivo* pharmacokinetic studies. In comparison to oral administration, which had a Tmax of 4 hours, transdermal proniosomal formulation had a relative bioavailability of 92%. This guarantees that transdermal formulation is a trustworthy alternative to taking risperidone [29].

6.4 Olanzapine

Olanzapine is a thienobenzodiazepine synthetic derivative with antipsychotic, anti-nausea, and antiemetic properties. It is a highly affine selective monoaminergic antagonist that binds to serotonin, dopaminergic, muscarinic, histamine, and alpha-1 adrenergic receptors. Although the precise mode of action of olanzapine as a treatment for schizophrenia is still largely unknown, it is thought to act as a dopamine D2 receptor antagonist with instant ligand-receptor dissociation kinetics, which lessens sympathomimetic symptoms. In addition to being used as a treatment for schizophrenia, it is also used to treat bipolar disorders. Clozapine's counterpart, olanzapine, shares many of the same pharmacological characteristics, but it has fewer autonomic side effects and is not referred to agranulocytosis, which is common among other atypical second-generation antipsychotics [83]. Olanzapine is a commonly prescribed antipsychotic used to treat schizophrenia as well as to maintain bipolar disorder's agitation symptoms under control. For the treatment of schizophrenia, there is a long-acting injectable (LAI). As a medication for the treatment of schizophrenia, olanzapine received approval in 1996. According to a study titled Recovery after an Initial Schizophrenia Episode study's Early in Treatment, olanzapine is frequently used to treat schizophrenia in first-time episodes. According to Luan *et al* 2017's meta-analysis, there is evidence that olanzapine, when combined with fluoxetine, is an effective treatment for mood disorders. Clinical trials involving five studies and 3,020 participants revealed increased efficacy in reducing depressive and psychotic symptoms when compared to when used as a monotherapy. The combination of olanzapine and fluoxetine has FDA approval for bipolar depression. The combination of olanzapine and fluoxetine was found to have a higher treatment response rate than olanzapine monotherapy, but a similar response rate to that of fluoxetine. The side effects of this combination therapy included sedation, weight gain, increased appetite, sleepiness, fatigue, and peripheral oedema. In the treatment of psychosis, an acute neuropsychiatric disorder characterised by shifting levels of consciousness and compromised cognitive function, olanzapine has been found to be an effective substitute for haloperidol. Olanzapine was found by Riviere *et al*. to have a similar 82.4% reduction in delirium symptoms to haloperidol's 87.5% reduction in a systematic review. Olanzapine and haloperidol started working at low doses, with olanzapine working more quickly [83]. Kashimoto *et al* 2019.'S meta-analysis compared the effectiveness of various antipsychotics head-to-head using data from 59 studies and 45,787 participants. Risperidone, clozapine, and olanzapine were superior to a number of other second-generation antipsychotics in terms of all-cause discontinuation. Haloperidol and chlorpromazine were found to be inferior to olanzapine for preventing relapse [83].

6.5 Samidorphan

Samidorphan (SAM), also known as 3-carboxamido-4-hydroxynaltrexone, is a recently developed opioid system

modulator that binds to the μ-opioid, κ-opioid, and δ-opioid receptors with a high affinity while acting as an antagonist at the μ-opioid receptors. The k-opioid and δ-opioid receptors are partially agonisted by it. Functionally, SAM mainly functions *in vivo* as an antagonist of the opioid receptor [84]. It is primarily excreted by the kidneys and the liver [85].

6.6 Quetiapine

Quetiapine is a dibenzothiazepine derivative. FDA approval was obtained in September 1997. It has a broadly distributed receptor occupancy profile. It has a strong affinity for the cerebral serotonergic (5HT2A), histaminergic (H1), and dopaminergic D1 and D2 receptors, while having weaker affinities for the α1- and α2-adrenergic receptors and negligible affinities for the muscarinergic M1 receptors. With sustained tolerability for a wide range of symptoms, quetiapine is confirmed to be an effective treatment for schizophrenia and manic episodes. [86] to deliver quetiapine transdermally, fair trials are carried out. It was discovered that the controlled release kinetics of quetiapine from a liposomal gel over a 12-hour period. The liposomal gel had a better transdermal flux than the standard drug gel. Upon observation after 6 months, the stability of the gel and optimised liposomal formulation was found to be satisfactory. When a patient is extremely ill physically, mentally, or both, for example, oral administration of quetiapine may not be an option. Consequently, it is critical to evaluate the potential of transdermal administration in comparison to other routes of administration. Quetiapine is administered orally, topically, and recally in a clinical trial to compare their efficacy; however, the findings are not made public on Clinicaltrials gov [29].

6.7 Asenapine

In 2009, the FDA approved Asenapine, a new sublingual second-generation antipsychotic, for the acute treatment of schizophrenia in adults and for the acute treatment of manic or mixed episodes related to bipolar me in adults. [87]. the liver is the main site of Asenapine metabolism. It is preferable to reduce the amount of the main metabolites, N-desmethyl-asenapine and asenapine N+ glucuronide, since it has been determined that they have no therapeutic effect. Due to extensive first-pass metabolism, the sublingual administration route is intended to increase the bioavailability of asenapine to 35% from 2% after oral administration. As a result, numerous research studies are being conducted to test alternative delivery methods for asenapine, such as intranasal and brain delivery [88], [89]. But in addition to tongue/oral mucosal numbness brought on by the local anaesthetic effect, nausea, and headaches, sublingual administration is also accompanied by a bitter or unpleasant taste. However, following sublingual administration, rapid absorption results in changes in the drug's plasma concentration. Additionally, it is obvious that consuming food and water after administration reduces bioavailability. Transdermal therapeutic system (TTS) was developed by Moher *et al*. to achieve constant sustained release using various polymers, avoiding the drawbacks of sublingual asenapine. With a polymer concentration of 40–60% by weight, the silicone acrylic hybrid polymer which includes acrylate or methacrylate is dissolved along with an asenapine-free base in ethyl acetate rather than n-hexane. It is then dried at a temperature of 50–80 ◦C [29].

6.8 Aripiprazole

Due to its partial agonist effect at D2 dopamine- and 5-HT1a serotonin receptors and antagonist effect at 5-HT2 serotonin receptors, it is said to be a promising candidate to serve as a prototype of a new third generation of antipsychotics (dopamine-serotonin system stabilisers). [90]. FDA has approved the therapeutic efficacy and tolerability of Aripiprazole in a random double-blind study in comparison to placebo and haloperidol. Despite aripiprazole's many benefits, it has a lot of drawbacks. After being taken orally, Aripiprazole undergoes an intense first-pass metabolism. In order to maintain an effective plasma concentration, Aripiprazole must be administered frequently. In order to avoid the aforementioned drawbacks, various researchers and inventors investigated the viability of applying Aripiprazole externally [91]. Developed a reservoir, detachable packing layer, and impermeable packing layer for a pressure-sensitive transdermal therapeutic system. The polymers in the reservoir's matrix were chosen from those based on acrylic acid and its esters, isobutylene, ethylene-vinyl acetate copolymers, natural rubbers, and synthetic rubbers. The pressure-sensitive adhesives used in this invention were primarily silicone-based. Whatever the matrix type, the reservoir needs to have a fibre material that the active substance is adsorbed to, the viscous, semi-solid, gel-like, or liquid form of the dissolved active substance is added to the reservoir at a concentration of 1 to 10% weight. Many different classes of permeation enhancers are also employed, including fatty alcohols (decanol and do decanol), fatty acids (oleic acid, myristic acid), Polyethylene fatty alcohol ethers (polyoxylauryl ether), Polyethylene fatty acid esters, esters of fatty alcohols with acetic acid or lactic acid, and oleic acid Diethanolamine. Although the invention's detailed composition is mentioned, there is absolutely no information provided about how it affects transdermal absorption [92].

Table 4 [35]: Advantages and disadvantages of combination antipsychotic therapy

Advantages	Disadvantages
Avoidance of withdrawal symptoms after discontinuation of first antipsychotic	Unnecessarily high doses and Increment in side effects
Achievement of clinical response in unresponsive patients to initial antipsychotic	Unnecessarily high doses and Increment in side effects
No need to cope with the substituted agent to get better therapeutic outcomes	Higher cost, Increased mortality risk
he addition of a second drug may add favorable effects restoring benefits of the first drug	Cause and effect of multiple drugs is difficult to determine
Switching from one antipsychotic to another is minimized and also the additional care and supervision.	Documented and evidence-based risk and benefits of combination therapy are very poor

7. The role of the pharmacist, pharmacy staff and students to prevent and treat mental health of schizophrenia

The worldwide disease burden is significantly increased by issues with mental health [93]. According to estimates, this global issue impacted 792 million people in 2017, with depression and anxiety being the most common mental health disorders [94]. Additionally, suicide ranked as the 17th leading cause of death in 2019 with 1.3% of all deaths occurring globally [95]. There are still a significant proportion of people with mental disorders who do not seek help, despite the fact that awareness of the treatments for mental health issues has increased [96], [97]. Primary care is crucial for the delivery of mental health care, as evidenced by problems with access to mental health specialists in regional and rural areas and some patients' resistance to receiving a mental health referral [98]. In particular, primary care professionals (such as general practitioners and pharmacists) offer mental health support, which includes early identification of mental disorders, treatment of common mental disorders, management of stable psychiatric patients, and referral to specialists. In spite of the fact that primary care is frequently the first point of contact within the healthcare system, screening rates for mental health disorders in some primary care settings still seem to be underwhelming. It has been demonstrated that interdisciplinary cooperation among primary care providers enhances the treatment of mental health disorders and enhances patient clinical outcomes. In rural and remote areas, where communities are cut off from resources, the significance of collaboration in primary care is especially relevant. It has been determined that providing collaborative mental health care in primary care settings is a practical solution for a variety of mental health disorders in a wide range of populations [99]. Due to their demonstrated abilities in dealing with and preventing drug-related issues, ensuring the safe and effective use of medications, providing detailed drug information, encouraging medication adherence, and promoting health promotion and lifestyle changes for their communities, international institutions and government organisations have supported the integration of community pharmacists in multidisciplinary primary care teams. Due to their high accessibility, community pharmacists serve as front-line providers and are frequently the first point of contact for those who are at risk or who are suffering from mental health disorders. The early detection of depression across community pharmacy-based screening programmes has been demonstrated to increase, allowing for early intervention for those who might not have otherwise sought treatment for their mental health disorders. Additionally, it has been demonstrated that the community pharmacist's involvement in mental health care improves patients' understanding, attitudes, and perceptions of their progress in receiving psychotropic medication (e.g., antidepressants). There is evidence that psychotropic medications are frequently misused, and the proper use of these medications is essential to the efficient treatment of mental illnesses. Community pharmacists have demonstrated their ability to collaborate closely with individuals who have first-hand experience with mental disorders to improve medication-related outcomes, including those relating to poly pharmacy, DE prescribing, and easing medication withdrawal. These results show how community pharmacists continue to have a positive influence on the provision of mental health services. Participation in specific mental health training programmes, such as the Mental Health First Aid (MHFA) course, helps community pharmacists, pharmacy students, and staff members increase their knowledge and skills in this area. The MHFA course was initially created in 2000 with the goal of instructing community members on how to recognise the signs of various mental disorders and mental health crises, how to offer and provide initial help, including directing a person toward appropriate treatments and supportive help. Following this, a blended MHFA (BMHFA) course for pharmacy was created. It consists of 6–8 hours of self-paced online learning followed by a practical classroom session (delivered face-to-face or by live webinar) [99].

8. Conclusion

This systemic review concluded that, Schizophrenia is a serious mental disorder in which people have abnormal perceptions of reality. Schizophrenia can cause hallucinations, delusions, and extremely disordered thinking and behaviour that interfere with daily functioning and can be disabling. Antipsychotic medications are the most commonly prescribed drugs in schizophrenia treatment. They are thought to control symptoms by influencing the neurotransmitter dopamine in the brain. Various therapies are used. The therapy's goal is to help people improve their emotional and relational skills and knowledge, reduce psychotic symptoms and depression, increase quality of life, and produce neurobiological changes.

List of Abbrevation

1. **AS:** Attribution style
2. **BBB:** Blood brain barrier
3. **BPRS:** Brief Psychiatric Rating Scale
4. **CB:** Complete blood count
5. **CZP:** Clozapine
6. **ECG:** Electro cardiogram
7. **ECT:** Electro convulsive therapy
8. **EP:** Emotion processing
9. **HPMC:** Hydroxypropyl methylcellulose
10. **LAI:** Long acting injectable
11. **LSD:** Lysergic acid diethylamide
12. **MHFA:** Mental Health First Aid
13. **NMDA:** N-methyl-D-aspartate
14. **PANSS:** Positive and Negative Symptoms Scale
15. **PWS:** Person with schizophrenia
16. **RCT:** Randomised controlled trials
17. **SAM:** Samidorphan
18. **SANS:** Scale for the Assessment of Negative Symptoms
19. **SAPS:** Scale for the Assessment of Positive Symptoms
20. **SP:** Social perception
21. **TMS:** Transcranial magnetic stimulation
22. **TOM:** Theory of mind
23. **TTS:** Transdermal therapeutic system
24. **WL:** Waitlist
25. **YT:** Yoga therapy

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