Schizophrenia Aetiology and Drug Therapy: A Tale of Progressive Demystification and Strides in Management

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Abstract Schizophrenia is a chronic, debilitating and complex neuropsychiatric disorder which is known to be characterised by impairments in perception of reality, cognition, interpersonal relationships, mood and social/work function; and influenced by genes and the environment. Our understanding of the aetiology of schizophrenia and theories seeking to explain the accompanying changes in brain chemistry and structure has continued to undergo revisions, largely due to new insights from preclinical and clinical research. In this review, we discuss the evolution of our understanding of schizophrenia aetiopathogenesis as it relates to disease phenotype, symptom management and drug discovery. We also examine the important roles played by interactions between brain neurotransmitters and their receptors in disease expression and symptom management; and discuss how newer chapters in the management of the disease are being opened through the development and identification of newer disease-modifying and modulating agents.

Keywords Antipsychotic, Dementia Praecox, Mental Health, Neuroinflammation, Neurotransmitters, Neurodevelopment, Receptors

1. Introduction

Schizophrenia is a multifactorial mental health disorder that afflicts approximately 1% of the world’s population, with slight geographical and cultural variations in incidence and lifetime prevalence [1-4]. It is characterised by impairments in: perception of reality, interpersonal relationships, mood, social/work function and neuro-cognitive function [5]; and influenced by a heterogeneous genetic, environmental [6] and neurobiological backgrounds [2-4]. Schizophrenia usually undergoes a fluctuating and/or enduring course which is worsened by co-morbidities [7, 8] and has an age of onset which is generally between adolescence and early adulthood [9]. In comparison to the general populace, schizophrenics have a two to three-fold higher mortality rate [10]. However, despite years of research, the aetiopathogenesis [11] or extent of heterogeneity [1] of schizophrenia remains incompletely understood; and there are suggestions that schizophrenia is usually an outcome of complex interactions between genetic and environmental factors [3, 6, 12-15]. In recent times, an emerging consensus proposes that schizophrenia should be regarded as a disease spectrum with multiple causes and disease phenotypes [1], rather than a single disease entity. Theories explaining the possible aetiopathogenesis of schizophrenia have been proposed, disproved or confirmed through the years. Of these, some have become the basis of therapeutic interventions (such as the use of dopamine receptor blockers). Recently, the ‘two-hit’ hypothesis suggests that an initial prenatal genetic or environmental factor disrupts aspects of brain development (a “first hit”), predisposing to the development of schizophrenia that may follow a major life event (a “second hit”) occurring later in life [1, 13, 16].

This review examines schizophrenia from a perspective of where we have been to where we are now; and with a particular focus on aetiopathogenesis as it relates to disease phenotypes, symptom management and trends in pharmacotherapy. We also examine the important roles played by brain neurotransmitter/ receptor interactions in disease phenotypes; and examine how relating neurotransmitter/ receptor dysfunctions with other known aetiological factors like inflammation or oxidative stress, may lead to the development and identification of newer drugs.

2. Historical Perspective

The historical ‘beginnings’ of schizophrenia is difficult to pinpoint, since the earliest references to mental illnesses with symptoms that are similar to schizophrenia are masked by a belief system that attributes the presence of
strange behaviours to a demonic possession, or punishment for immoral behaviour. However, evidence for the presence of schizophrenia-related mental illnesses is probably as old as mankind, as revealed by the discovery of Stone-Age skulls with burr-holes drilled into them for the ‘release of evil spirits’; a procedure now known as trepanation [17].

The earliest documented history of schizophrenia or schizophrenia-like symptomatology dates back to ancient Egypt, around the second millennium BC [17, 18]; while Hindu descriptions which can be found in the Atharva Veda date back to approximately 1400 BC [17]. In Greek mythology and the Homerian epics, all forms of mental illness or ‘madness’ were thought of as ‘divine punishment’. However, by the time of Hippocrates (460-377 BC), mental illness became an object of scientific speculation. Hippocrates believed ‘madness’ was a consequence of an imbalance of the four bodily humours, and cure could only be achieved by rebalancing these humours with special diets, purgatives, and blood-lettings [18]; and for a while, the management of all mental illness followed the rules of ‘humoral pathology’, although a few scientists disagreed. Aretaios suggested that the origin of mental disorders might not be specifically localized, and that premorbidity personality might play an important role in the aetiology of mental disorders [17, 18]; an opinion that has become important in the diagnosis of schizophrenia in the 21st century. Aristotle (384-322 BC) and Galen (129-216) both expanded on the humoral theories of Hippocrates, although Galen also believed that mental diseases could stem from disorders in the brain or be the consequence of a derangement in other organs [17, 18].

In the middle ages, only the university scholars had a rational and scientific attitude towards madness, while the general populace still held the firm belief that it was a trial or a punishment from a higher being. In 15th century Europe, people with hallucinations and delusions were assumed to be possessed, and a number of women were thought to be witches and burnt at the stake. This however slowly gave way to asylums in the 16th century as medical notions again gained momentum [17-19].

### 2.1. Schizophrenia: Emil Kraepelin and Eugen Bleuler Era

The word ‘schizophrenia’, as first mentioned by Eugen Bleuler, is just over a hundred years old [17, 20]; however, several developments led to the evolution of the name. By the middle of the 19th century, scientists began to have a better understanding of the disease concept; with a number of European psychiatrists describing a chronic disorder of unknown aetiology, predominantly affecting the young [17, 21]. In France, the terminology ‘démence précoce’ was coined by Morel, while Clouston (from Scotland) referred to it as “adolescent insanity.” In 1851, Falvet described it as ‘Folie Circulaire’ meaning cyclical madness; while in 1871, Hecker (a German scientist) called it ‘hebephrenia’ referring to having a silly, undisciplined mind, a terminology he modelled after Hebe, the goddess of youth and frivolity [17, 19]. In 1874, Kahlbaum (another German scientist) described both catatonic and paranoid disorders of the mind, with the term catatonia referring to a movement disorder which is characterized by a mannequin-like muscle rigidity with unusual posturing and a pervading fear [17, 19].

In 1878, Emil Kraepelin integrated these various ‘disorders’ into a single nosological entity termed dementia praecox (DP) or ‘dementia of early onset’ referring to a common pattern of disease course culminating in a decline in behaviour and cognitive functioning/processing, occurring in a number of young patients [17, 19, 22]. The term praecox distinguishes it from other forms of dementia which occurred typically later in life. Kraepelin acknowledged the diverse nature of the various clinical scenarios classified under DP and identified four subtypes or nine clinical “forms,” each connected one to another by very fluid transitions. Simple DP is marked by slow concomitant social decline, social withdrawal and apathy, paranoid DP is characterised by ‘persecutory’ delusions and an attendant fear, hebephrenic DP shows disorganized thinking, attention, language and memory deficits, and catatonic DP is characterized by a poverty of expression and movement, culminating in hallucinations and delusions [17, 19, 22-24].

In 1908, Eugen Bleuler began to raise strong objections to the use of the terminology DP and the classifications of this nosological entity. He contested the presence of a global dementing process, and in 1911 coined the divisive term ‘schizophrenia’ from two words of Greek origin; schizo (split) and phrene (mind), to describe the fragmented thinking of the sufferers of the disorder. He defined schizophrenia using four “A’s”, which include 1) a diminished emotional response to stimuli or blunted Affect, 2) a disordered pattern of thought or loosening of Association, 3) Ambivalence which he described as an apparent inability to make decisions and, 4) Autism which is the loss of awareness of external events, and a morbid preoccupation with self. Bleuler went on to group the symptoms as either “positive” or “negative”. He also acknowledged that the clinical subgroups of schizophrenia as described by Kraepelin were not “natural” nosological entities [19]. Bleuler argued the inclusion of Wernicke's motility psychoses, atypical depressive/manic states, reactive psychoses, and other kinds of nonorganic, non-affective psychotic disorders into a group of schizophrenias; thereby, suggesting the possibility of heredity as an aetiological factor [19, 25-27].

### 2.2. Schizophrenia: Post-bleulerian Era

The definition of schizophrenia has continued to evolve, as scientists and clinicians attempt to accurately define and characterize different types of mental illnesses. However,
the absence of well-defined aetiologies would mean that classifications are still based largely on observed symptomatologies, which are not so different from the positions of Bleuler and Kraepelin.

Therefore, clinicians and researchers have continued to propose stricter sub-nosological distinctions within the broadening schizophrenia phenotype, to include subclasses like schizoaffective disorder [28], process-non process schizophrenia [29], schizophreniform psychoses [30] and paranoid-non paranoid schizophrenia [31]. Five types of schizophrenia were initially defined and used to reach a diagnosis (disorganized, paranoid, catatonic, residual, and undifferentiated); however, researchers began advocating the use of other classification systems that would be based on the prevalence of positive or negative symptoms, progression of disease, and the presence of co-morbidities [17].

In the 1950s, Kurt Schneider [32] described a set of core features designated as “first-rank” symptoms which include, hearing one’s thoughts spoken aloud, auditory thoughts or hallucinations, thought withdrawal, insertion and broadcasting, somatic hallucinations, delusional perceptions, or the experience of one’s thoughts as being controlled or influenced by outside; believing that these symptoms carried enough weight to decisively aid clinicians in the universal diagnosis of schizophrenia [17, 19]. The Schneiderian symptom ranking system, although criticised as either being non-specific or being deficient in its ability to predict severe deterioration and cognitive deficit [33], has been incorporated into a number of clinical diagnostic classification systems like the Research Diagnostic Criteria (RDC), Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD).

In 1999, Karl Leonhard [34] proposed and developed a classification of “endogenous” psychoses, a significant departure from the previously accepted (Kraepelinian and Bleulerian) nosology. Leonhard’s classification (Table 1) defined clearly-delineated entities based on the presence of a well-defined psychopathology that took into consideration objective signs like psychomotor behaviour, disease course, outcome, and family history. Leonhard's classification foreshadowed newer theories that proposed that schizophrenia be considered as more of a disease spectrum [35] than a single disease entity. This notion opened the door to broader classifications and subtypes of schizophrenia by researchers like Rado [36], Meehl [37], Chapman and Chapman [38]; and evolved to include the incorporation of schizotypal personality disorder (SPD) in the DSM-III diagnostic category.

To date, a diagnosis of schizophrenia relies on criteria outlined by either the ICD-10 [39] or the DSM 5 [40]. The ICD-10 uses both Kraepelinian and Schneiderian concepts in schizophrenia diagnosis, while the DSM-5 is based largely on reported abnormalities in behaviour, self-reported experiences of the patient, a clinical assessment by a certified mental health professional and evidence of symptom severity and/or impairment of activities of daily living. However, the classification/reclassification of schizophrenia [41-44], the defining/redefining of criteria needed to make a diagnosis of schizophrenia [45, 46] and inclusion criteria for newer forms of schizophrenia [47, 48] would continue to evolve as newer insights and better understanding challenge the validity of the classic subtypes [49] as we know them now.

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<tr>
<th>Table 1. Karl Leonhard's classification of the non-affective endogenous psychoses [19, 34]</th>
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<tr>
<td><strong>I. Group of systematic schizophrenias</strong> (Insidious onset, auditory and somatic hallucinations, delusions, early blunting of affect, continuous unremitting course, personality deterioration)</td>
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<tr>
<td>(a) Paraphrenias (Auditory hallucinosis, audible thoughts, thought broadcast, passivity experiences, delusional misidentifications, falsifications of memory)</td>
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<td>(b) Hebephrenias (Extreme autistic withdrawal, flat affect, impoverished or disorganized speech and behaviour)</td>
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<td>(c) Catatonias (Excessive parakinesias, mannerisms, verbigeration, posturing, stereotypies, mutism, auditory hallucinations)</td>
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<td><strong>II. Group of unsystematic (atypical) schizophrenias</strong> (Rapid onset, relatively preserved affect, remitting course, mild personality deterioration)</td>
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<td>(a) Affect-laden paraphrenia (Paranoid delusions with affective loading)</td>
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<td>(b) Catataphasia (schizophrenia) (Incoherent, pressured speech but well-organised behaviour)</td>
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<td>(c) Periodic catatonia (Episodic hyper- or hypokinesia, mixed excitatory and hallucinatory symptoms)</td>
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<td><strong>III. Group of cycloid psychoses</strong> (Sudden onset, pervasive delusional mood, multimodal hallucinations, labile affect, polarity of manifestations, typically complete recovery from episode)</td>
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<td>(a) Anxiety-happiness psychosis (Extreme shifts of affect, polarity intense fear - ecstatic elation)</td>
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<td>(b) Motility psychosis (Impulsive hypermotility - psychomotor inhibition)</td>
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<td>(c) Confusion psychosis (Incoherent pressure of speech - mutism)</td>
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3. The Aetiopathogenesis of Schizophrenia

The high individual and societal burden [50-52] of schizophrenia makes the discovery of better, more efficient and/or effective diagnosis, treatment and preventive interventions imperative. However, progress has been hampered by the lack of clearly-defined aetiologies. A number of aetiological theories have been proposed in an attempt to explain the possible mechanisms involved in the development of schizophrenia; also, the various abnormalities [4, 11], infection/inflammation [1, 54], immune and/or autoimmune dysfunctions [55, 56].

Over the years, researchers have considered the associations involving genetics [57, 58], environment [6, 59] and/or events surrounding brain development [4, 11]; although, recent scientific evidence considers schizophrenia as a heterogeneous syndrome. At the same time, an increasing number of clinical, epidemiological, and experimental studies have continued to show links between schizophrenia, brain development, neurotransmitter-receptor interactions, infection/inflammation [1] and oxidative stress [60].

Attempts at characterizing schizophrenia’s heterogeneity with respect to symptomatology, premorbid functioning and disease severity have only been modestly-successful in advancing treatment. Therefore, several researchers have proposed that a re-evaluation of our thought processes as it relates to schizophrenia has become absolutely necessary, if we are to devise solutions to this clinical/scientific puzzle that has baffled scientists for more than a century [61, 62].

3.1. Schizophrenia, Risk Factors

Numerous risk factors have been implicated in the development of schizophrenia [3]: with studies showing that environmental factors like prenatal/perinatal complications, urbanisation, immigration status, exposure to stressors (all forms of physical and sexual abuse) and drug abuse (amphetamine, methamphetamine, cannabis and cocaine) predispose to its development. Also, results from family, twin and adoption studies have provided newer insights into the nature of the roles of genetics [6, 12, 63, 64]; while the results of other studies have opened our eyes to the complexity of the associations between genetics and schizophrenia, and the challenges of translating this knowledge for therapeutic benefits [65-67]. Genes like the neuregulin (NRG1) [69-70], disrupted-in-schizophrenia-1 (DISC1) [71, 72], dystrobrevin binding protein 1 (DTNB1) [73-75], nuclear receptor related 1 protein (NURR1) [76], D-amino acid oxidase and regulator of G protein signalling (RGS4) [64, 77] are some of the candidate susceptibility genes for schizophrenia. DISC1 is arguably the most-characterized schizophrenia susceptibility gene and was originally discovered in a Scottish family with a high prevalence of schizophrenia and psycho-affective disorders [71, 72]. Genetic linkage studies have implicated mutations in DISC1 as a risk factor for schizophrenia [72, 78], while the NURR1 plays an important role in the maintenance of the brain dopaminergic system [76]; with its involvement in schizophrenia evolving.

Presently, schizophrenia is a relatively common disease entity with relatively constant lifetime prevalence (1%) worldwide. This implies that to maintain a stable global prevalence, the frequency of the causal factors must be constant, and the risk factors must also be common and ubiquitous [61]. Monozygotic twin studies have accorded only a 50% concordance rate for schizophrenia [79], also suggesting that for schizophrenia to develop, there must be at least two global risk-increasing categories, possibly genetic or environmental [61, 80]. Environmental factors like social isolation, maternal stress and immune activation have also been found to mimic or exacerbate symptoms of schizophrenia in genetically-modified rodents [80].

Evidences have continued to show the need to pay more attention to the immense impact of environmental exposures on the development of schizophrenia [59]; due to the availability of information from several birth cohort studies, extensive databases on prenatal and perinatal risk factors, and the improvement in the ability to measure environmental risk [59]. Epidemiological studies have demonstrated 1) an overall higher incidence in males, compared to age-matched females [46], 2) an increased risk among individuals living in urban, compared to rural areas [81, 82], with approximately 30% risk for developing schizophrenia ascribed to birth in an urban environment [83, 84], 3) an increased incidence amongst migrant populations [85]. These epidemiological studies also reveal that triggers such as social disadvantage [86], pre-conceptional and prenatal exposure to genital or reproductive tract infections [59 87, 88], maternal respiratory tract infections [89], bacterial infection [90] and pyelonephritis [91] have all been associated with an increased risk of schizophrenia in the offspring. Maternal micronutrient deficiencies like retinoids, folate, vitamin D [92-95], iron, essential fatty acids and other nutritional deficiencies have also been associated with increased risk [96]; and so is maternal stress and anxiety [97]. In early childhood and adolescence, exposure to cannabis [98], psychoactive drugs like phencyclidine and amphetamines, low socioeconomic status [99] and childhood trauma [100] have all been associated with an increased risk. The importance of the environment in the aetiopathogenesis of schizophrenia is highlighted by preclinical studies that have reported the presence of schizophrenia-like phenotypes following environmental exposures to anxiety/stress [101], infections, psychoactive drugs, nutritional/micronutrients deficiencies [102] and
malnutrition in the prenatal, early neonatal and adolescence periods; with putative biological mechanisms that implicate similar neuro-morphological and neurochemical substrates as observed in prior schizophrenia studies [103].

4. Neurobiology of Schizophrenia

Certain evolutionary theories have suggested that schizophrenia is a disorder that may have co-evolved with the evolution of the human brain [104]; stating that increases in energy demands that follow increase in the complexity and size of the human brain (relative to body mass) led to a greater demand of mitochondria. The use of post-mortem brain tissue to study the possible structural abnormalities associated with schizophrenia has long underpinned efforts to understand its neurobiology. However, the significant advances in the field of functional neuro-imaging (allowing real-time evaluation of changes in neurotransmitter metabolism, receptor density and neurotransmitter/receptor interactions) and improvement in immunohistochemical/immune-fluorescence staining techniques (that have enabled qualitative and quantitative examination of post-mortem brain tissue in both humans and rodents) have revolutionized our understanding of the neurobiology of schizophrenia. The roles of neurotransmitters, receptors and transporters in aetiology, as well as response to treatment, and other pharmacological manipulations have also been assessed; these sites are amenable to therapeutic manipulations, and in a number of cases, are the sites of drug action with proven antipsychotic activity [105].

Hypotheses that have implicated a number of neurotransmitter systems in the pathogenesis of schizophrenia have evolved from studies using drugs that target different neurotransmitters, receptors and transporters, to explain behavioural, biochemical and structural changes observed. Different markers have been used to demonstrate changes in some neurotransmitter (dopaminergic, serotonergic, cholinergic, glutamatergic and GABA) systems in the brain of schizophrenics [106]. A number of the changes observed are region-specific; and at times associated with alterations in levels or densities of non-neurotransmitter proteins like synaptosomal associated protein-25 (SNAP-25), syntxin, synaptobrevin, synapsin, synaptotagmin, and synaptophysin, which are involved in all neurotransmitter systems, and are critical to neurotransmitter release [107]. Interactions between these specific proteins ensure fusion of synaptic vesicles with the synaptic membrane and subsequent release of neurotransmitter [108]. Genome-wide linkage studies for schizophrenia-susceptibility genes have reported significant linkage to the chromosomal region 20p12.3-11, which contains SNAP-25, suggesting that 20p12.3-11 is a strong candidate region for the disease [109]. Alterations in postsynaptic density complex proteins have also been reported in schizophrenia, and have been linked to deficits in synaptic plasticity and molecular processes that underlie cognitive functions [110].

4.1. Neurotransmitter/Receptor Dysfunctions in Schizophrenia

There is extensive evidence implicating alterations in a number of neurotransmitter/receptor systems (dopamine (DA), glutamate, serotonin (5-HT) and γ-aminobutyric acid (GABA)) in the aetiopathogenesis of schizophrenia [111,112]. Theories and hypotheses have linked these neurotransmitter systems to a) risk of schizophrenia, b) symptomatology, c) disease progression d) response to therapy. The knowledge of these links has been employed in a number of preclinical studies, and have resulted in the development of validated pharmacologic and genetic disease models; which allow the replication of behavioural, neuro-developmental [11], neuro-morphological 113-116] and neurochemical phenotypes similar to those observed in humans [103]; and the investigation of novel therapies [117-122].

Early theories focused mainly on the involvement of the DAergic system, largely because the first successful therapies involved the use of DA antagonists. However, the development of more effective drugs such as clozapine shed more light on the possible involvement of other systems like the 5-HTergic, glutamatergic and GABA systems. More recently however, newer hypotheses address the interactions that exist between DA and 5-HT as well as the involvement of alpha-adrenergic, muscarinic, and histaminic receptors/ neurotransmitters in schizophrenia aetiopathogenesis.

In the early years of this century, growing concerns that alterations in brain functions modulated by the cholinergic system could result in schizophrenia-like behaviours led to the suggestion that changes in this system which modulates a number of central nervous system (CNS) functions (sensory perception, motor function, cognitive processing, memory, arousal, attention, sleep and psychosis) may be involved in the aetiology of the disease. This is coupled with the evidence of a high prevalence of nicotine (cigarette) usage in the population with schizophrenia [123], with nicotine-dependence linked to severity of symptom and poor outcome in schizophrenics; although the neurobiological mechanisms behind nicotine dependence in schizophrenia are still being studied [123]. The involvement of muscarinic cholinergic receptors in schizophrenia is supported by evidence from post-mortem, neuropyscho-pharmacological and neuro-imaging studies [124]. Post-mortem studies have demonstrated a decrease in the number of cholinergic interneuron in the ventral striatum in schizophrenia [125], some early studies also observed a decrease in the level of muscarinic receptor binding in the frontal cortex of schizophrenics compared to healthy subjects [126]. A number of these studies observed
that decreases in muscarinic receptor density in schizophrenia was disease-specific, with evidence demonstrating that these effects were not observed in other mental disorders. They also reported that these alterations were also region and subtype-specific, involving in particular the muscarinic M1-receptor subtypes [124]. Neuropharmacological studies have also demonstrated the efficacy of anti-cholinergics in the modest alleviation of negative symptoms, although worsening psychosis [127]; effects that have been attributed to an increase in dopamine release that follow anticholinergic use [128]. Anticholinergics have also been used to treat the motor side-effects of other antipsychotics.

4.2. Schizophrenia: Hypotheses and Theories

4.2.1. Dopamine Hypothesis

Dopamine (DA) is a major neurotransmitter with strong connections that serve to link different areas of the brain. These dopaminergic pathways are projection neurons that synthesise and release dopamine. The three main DAergic projections are the nigrostriatal (motor control), the mesolimbic/mesocortical (emotion and drug-induced reward mechanisms), and the tuberohypophyseal projections, which run from the hypothalamus to the pituitary gland. The DAergic receptors are G-protein-coupled receptors which are divided into the D1 family (D1 and D3) and the D2 family (D2, D3 and D4).

Initial evidences linking dopamine dysfunction to schizophrenia were indirect, being derived from observations that amphetamine (which increases brain levels of dopamine) worsens psychotic symptoms and drugs like reserpine (that depletes vesicular stores of monoamines; hence reducing brain levels of DA) reduce psychotic symptoms [129]. As far back as the 1960s and 70s, the following facts were known: a) DA receptor blockade was involved in the alleviation of psychosis by phenothiazines and butyrophenones and, b) increased DA and/or norepinephrine activity exacerbates symptoms of schizophrenia [130, 131]. More recently however, biochemical studies in schizophrenics have revealed increased cerebrospinal and plasma levels of DA metabolite; and subsequent molecular imaging and functional imaging (positron emission tomography and single photon emission computerized tomography) in examining the relationship between schizophrenia, DA receptor and/or brain DA levels. From these, it was deduced that schizophrenia is associated with; a) demonstrable elevations of presynaptic striatal DA synthesis [139], b) increased striatal DA release following an amphetamine challenge [140], c) evidence of increased baseline DA receptor occupancy following application of a DA depletion technique [141], d) a region-specific increase in striatal D2/3 receptor density which is independent of the effects of antipsychotic therapy [142], and e) presence of cognitive impairment and/or negative symptoms that correlate with D1 receptor dysfunction [143, 144].

Genome-wide studies have also demonstrated the possible relationship that could exist between DA and heredity, with 4 of the top 10 gene variants most strongly associated with schizophrenia discovered to have direct involvement with DAergic pathways. The vesicular monoamine transporter protein gene variant has been reported to have one of the strongest associations to the DAergic system; the protein induces the accumulation of DA and other monoamines within vesicles. Other gene variants like the genes for methylene-tetrahydrofolate reductase have an indirect effect on the DAergic system [143].

The DA hypothesis states that antipsychotics reduce psychotic symptoms by decreasing DA activity. This hypothesis (with its revisions) eventually became one of the most enduring theories in psychiatry [111]. It had its origins first in the discovery of antipsychotic drugs, the seminal work of Carlsson and Lindqvit [133], Carlsson and co-workers [134] and later Seeman et al., [135]; who at different times demonstrated a relationship between available antipsychotic drugs, their ability to increase DA metabolism, and later their interactions at DA receptors. In its unrevised version, the DA theory attributes the pathophysiology of schizophrenia to an excess activity of the neurotransmitter DA. The excess DA activity could either be presynaptic (excess production) or postsynaptic (increased D2 receptor density or increased postreceptor action). However, this initial version of the theory could only account for the positive symptoms [136]; also, it could not articulate its relationship to genetics, neuro-developmental deficits, or other known risk factors of schizophrenia at the time, and it did not have any framework linking the dopaminergic abnormality to symptomatology [111].

The second version of the DA theory [137] challenged the hyperdopaminergic neurotransmission proposal of the initial version and brought to light the regional (cortical-subcortical) specificity of DA receptor distribution and interactions. This version suggests that an imbalance between excessive stimulation of D2 receptors in subcortical regions and an under-activation of D1 receptors in cortical regions may account for the presence of positive and negative symptoms [138]. So far, significant strides in investigational capacity have not only increased our knowledge base, it had also afforded the use of functional imaging (positron emission tomography and single photon emission computerized tomography) in examining the relationship between schizophrenia, DA receptor and/or brain DA levels. From these, it was deduced that schizophrenia is associated with; a) demonstrable elevations of presynaptic striatal DA synthesis [139], b) increased striatal DA release following an amphetamine challenge [140], c) evidence of increased baseline DA receptor occupancy following application of a DA depletion technique [141], d) a region-specific increase in striatal D2/3 receptor density which is independent of the effects of antipsychotic therapy [142], and e) presence of cognitive impairment and/or negative symptoms that correlate with D1 receptor dysfunction [143, 144].

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The role of environmental factors in the development of schizophrenia has also been buttressed by results from animal studies that have demonstrated the presence of long-term mesostriatal DAergic overactivity following exposure to pre- and perinatal factors [146], with prenatal stress or neonatal lesions of the hippocampus and frontal cortex increasing DA-mediated behavioural responses in rats.
Overall, DAergic disruption in schizophrenia is considered a final common pathway in the complex interactions between genes and the environment, resulting in presynaptic striatal hyperdopaminergia [146, 147], which may be secondary to pathophysiological changes in other neurotransmitter systems (e.g. pre-frontal glutamatergic or GABAergic systems). There have also been suggestions that prior NMDA receptor hypofunction and low-grade inflammation of the brain might predate increased dopamine synthesis [147].

4.2.2. Serotonin Hypothesis/ Serotonin-dopamine Hypothesis

Wooley and Shaw [148], and Gaddum and Hammed [149] were among the first set of researchers to consider the involvement of serotonin (5-HT) in schizophrenia; based on the psychotomimetic effects observed with lysergic acid diethylamide (LSD) and its antagonists, at brain 5-HT receptors. In 1962, Wooley published what can be considered a ‘prophesy’ on 5-HT’s relationship with schizophrenia [150]. These scientists believed that 5-HTergic activity might be decreased in schizophrenia; although this was faulted because of striking differences like, 1) the behavioural phenotypes observed with LSD intoxication did not include any of the major symptoms that were characteristic of schizophrenia [151], 2.) LSD was also associated with visual hallucinations which were believed to be rarely observed in schizophrenia [152]. However, more recent studies have demonstrated that the behavioural symptoms associated with the use of hallucinogens share common phenomenological similarities with the acute phase of schizophrenia [153].

Also, the prevalence of visual hallucinations in schizophrenia may be more frequent than commonly believed [154], with studies showing increased incidence during the acute phase of schizophrenia [155].

Another confounding factor was that classical hallucinogens like LSD were full or partial agonists at many 5-HT receptors [151, 156] and 5-HT antagonists like cyproheptadine and ritanserin did not have psychomimetic effects. The overall effects of these was a decline of interest in the 5-HT-deficiency hypothesis, followed by decades of limited consideration of the role of 5-HT in schizophrenia [157]; although a few biochemical studies assessing the regional density of specific types of 5-HT receptors in the brain reported findings which continued to suggest the presence of some form of serotonergic dysfunction in schizophrenia [157]. Renewed interests in the validity of the 5-HT hypothesis began with the identification of a number of 5-HT receptor subtypes and their extensive impact on multiple neurotransmitters, the realisation that the effectiveness of clozapine in improving schizophrenic symptoms (with fewer side-effects than typical antipsychotics) could be attributed largely to its ability to block 5-HT$_{2A}$ receptors [158], and suggestions of the existence of associations between 5-HT and DA. Evidence from a number of studies have implicated 5-HT in the development of deficits in early information-processing that is associated with alteration in cognitive processes such as memory, sensory gating, perception and attention, aggressive behaviours, appetite and pain sensitivity [159]; functions that are important in the development of cognitive impairments, and positive/negative symptoms which constitute the core abnormalities of schizophrenia [155, 157]. Studies also demonstrated that these deficits observed in schizophrenia [160] were also observed in rodents and humans who had received serotonin agonists [161].

Results of biochemical and anatomical studies demonstrating the extensive interactions of the 5-HTergic system with multiple neurotransmitters (DA, glutamate and GABA) provided evidence for the ability of 5-HT to influence behaviours [157]. The first clear statements relating to 5-HT emerged following suggestions that the positive symptoms experienced in schizophrenia could occur from enhanced DAergic and 5-HTergic neurotransmission in sub-cortical areas, while decreased DAergic and 5-HTergic activity in the prefrontal cortex may be associated with negative symptoms [162].

The 5-HT hypothesis was boosted by studies in humans [163] and rodents [164] that demonstrated that LSD or psilocybin produced psychomimetic effects mimicking schizophrenia-like behaviours through excessive activation of 5-HT$_{2A}$-receptor, and the demonstration of region-specific alteration in 5-HT$_{1A}$-receptor density in the brains of schizophrenic patients [165]. Pharmacologic manipulation of the 5-HTergic system have also been shown to exacerbate or mitigate schizophrenic symptoms (positive, negative or disorganization) and cognitive function, as well as modulate drug–related side effects of DA antagonists such as extrapyramidal symptoms, tardive dyskinesia and dystonia.

In examining the extent of involvement of 5-HT in the aetiopathogenesis of schizophrenia, a number of studies have been conducted to assess the ability of 5-HTergic agonists or antagonists to either exacerbate or ameliorate the symptoms that are associated with schizophrenia; with a large number of 5-HT$_{2A}$ receptor antagonists ameliorating these symptoms with minimal motor side-effects [166]. Also, both direct and indirect 5-HT agonists such as fenfluramine, m-chlorophenylpiperazine, tryptophan and 5-hydroxytryptophan were observed to worsen these symptoms [167]. A number of human studies have also demonstrated alterations in blood and cerebrospinal fluid levels of 5-HT and its metabolites, as well as hormonal and behavioural changes in response to 5HT-based therapies [157]. Alterations in 5-HTergic neurotransmission and receptor density in post-mortem brain specimens have also been reported; with a number of studies reporting a decrease in the density of prefrontal cortex 5HT$_{2A}$ receptors in schizophrenia [168], changes that have been associated more with the pathology of the disease than an effect of drug therapy during life. There are also studies that have demonstrated that in the planum...
temporal (the cortical area just posterior to the auditory cortex), changes in density of 5HT2A receptors observed have been associated with both pathological and antipsychotic drug effects [105]. Critics of the 5-HT hypothesis have suggested that a link between 5HT2A receptor and specific gene mutations is necessary if it was to be accepted that 5-HT receptors were central to schizophrenia aetiology and pathogenesis; and there have been studies that have reported mutations in the gene for the 5HT2A receptor using peripheral tissue DNA from schizophrenic patients [169]. There was however no observed gene mutations or alterations in receptor density in post-mortem brain tissue [170, 171].

4.2.4. The two-hit Hypothesis and the Neurodevelopmental Theory

As first put forward by Olney and Farber [172], the N-methyl-D-aspartate (NMDA) receptor dysfunction hypothesis of schizophrenia is a theory that stemmed from the observation that non-competitive NMDA receptor antagonists, like phencyclidine (PCP), dizocilpine (MK-801) and ketamine have central effects which closely resemble positive and negative symptoms of schizophrenia [173, 174]. Chronic ketamine users also exhibit psychotic-like symptoms [175]. The above findings led to the use of NMDA receptor antagonists in the modelling of schizophrenia. Olney and Farber [172] also showed that administration of NMDA receptor antagonists in animals led to development of neurotoxic changes and volume changes in cortical brain regions, which were similar to those seen in patients with schizophrenia [172]. They also discovered that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonists could block the downstream effects of NMDA receptor antagonism on neurotoxicity, and went on to hypothesise that glutamate release probably underlies the neurotoxic effects; a position that was subsequently confirmed by microdialysis studies [176] and proton magnetic resonance spectroscopy (1H-MRS) studies using animals that were administered ketamine [177]. NMDA antagonists like ketamine and PCP have been used to model both acute and chronic forms of schizophrenia in rodents, depending on the administration regimen; however, the regimen that employs repeated administration is known to mimic both behavioural and brain structural changes that are seen in schizophrenics [178-180]. Subchronic administration of PCP to rats was shown to cause long-lasting deficits in set-shifting ability [180] and reductions in functional connectivity [179]; while longer term administration of ketamine to rats caused cognitive deficits [181]. Hence, repeated administration of NMDA antagonists in rodents has been associated with brain behavioural and structural changes that closely resemble clinical schizophrenia.

4.2.5. Inflammation and the Immunologic Theory of Schizophrenia

Cytokines and the immune system have been discovered to influence and modulate behaviour and the development of the CNS [188]. Reports from studies investigating the involvement of genetics, environment, developmental biology, and the late adolescent/early adulthood onset of schizophrenia; the "two-hit" hypothesis was considered. It is based on assumptions that genetic or environmental factors disrupt early CNS development; with these disruptions resulting in long-term vulnerability to a "second hit" which then leads to the onset of schizophrenia symptoms [182]. The numerous cell-cell signalling pathways that exist at the different stages of morphogenesis and differentiation (in the brain) could be targets for a "first hit" which may then predispose the CNS to a pathologic response of a "second hit", either through the same or other related signalling pathways [13]. Proponents of this hypothesis are of the opinion that neither the first or second insult by itself is enough to induce schizophrenia [182].

Predating the two hit hypothesis is the neurodevelopmental hypothesis which suggests that schizophrenia is a neurodevelopmental disorder affecting young adolescents, the aetiology of which may involve pathologic processes that involve genetic and environmental disruptions occurring during brain development [183, 184], for a more detailed review on the neurodevelopmental theory of schizophrenia, see review by Fatemi and Folsom, [184] and Rapoport et al. [183]. There is ample evidence linking neurodevelopmental abnormalities occurring as early as the late first or early second trimester or thereafter, to a predisposition to the development of schizophrenia in adolescence [184]. The “two-hit” model proposed by Keshavan [185], and Keshavan and Hogarty [186] was able to link the neurodevelopmental hypothesis framework in which maldevelopment at two critical periods of brain development (early brain development and adolescence) interact to produce the symptoms associated with schizophrenia. This model accounted for presence of premorbid symptoms (which may be due to the early developmental insults leading to disruption of specific neural networks) that have been observed to predate the development of the full-blown schizophrenia symptoms; while excessive dysfunction of synapses and loss of brain plasticity at adolescence may then account for the emergence of schizophrenia [185, 186].

More recently however, the opinion that the development of schizophrenia is likely more complex than can be explained by the two-hit hypothesis continues to gain popularity. This is buttressed by emerging evidence of very complex processes involving genetic risk interfacing with multiple potentially-interacting hits and vulnerability factors occurring at key periods of neurodevelopment, culminating in the expression of the disease state [187].
possible influence of prenatal immune activation [189, 190] on the development of schizophrenia, and the discovery of susceptibility genes which have regions that are related to immune function [191] have reawakened interests in the immunologic theory and the autoimmune theory of schizophrenia [54, 192]. Early studies reported alteration in immune function, coupled with the presence of antibodies targeted against CNS tissue in schizophrenics [56]; while imaging studies have demonstrated increased inflammation [54, 193] in schizophrenics. Initial studies evaluating the mechanisms of cytokine involvement in schizophrenia were of the opinion that a shift away from a T-helper-1 response towards a T-helper-2 response [194] was responsible for this disorder. However, more recent biomarker studies have revealed mixed response (type 1 and type 2) alteration in cytokine activity involving Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour Necrosis Factor alpha (TNF-α) which are type 1 responses; and type 2 responses like IL-4 and IL-13 [195], for a more detailed review on the role of inflammation in schizophrenia see Feigenson et al. [1].

5. Pharmacotherapy Past, Present and Future

Today, schizophrenia is viewed as a heterogeneous entity associated with separate genotypic networks that manifest as several distinct clinical syndromes [196, 197]; along this line, a poor response to certain drugs might be as a result of an encounter with a distinct subtype of schizophrenia, and not necessarily a manifestation of the ‘severity’ of illness [198]. In 2014, Howes and Kapur [199] proposed the neurobiological classification of schizophrenia (to be used in determining treatment options) into type A (hyperdopaminergic: characterised by elevated striatal dopamine synthesis and release capacity) and type B (normodopaminergic: characterised by an absence of dopaminergic alterations); based on observations linking the development of psychotic symptoms to alterations in dopamine levels in the majority of patients with schizophrenia, and also emerging evidence demonstrating that this is not common to all patients [199]. Treatment options for schizophrenia have however continued to evolve.

Till the first half of the 20th century, a lot of trial and error treatments (many of which were painful, bizarre and unsuccessful) for schizophrenia were being applied [17]. These treatments, sometimes called ‘biological therapies’ include fever therapy (induction of fevers by injecting sulphur and oil, or causing abscesses), gas therapy, electroconvulsive therapy, frontal lobotomy, simple sedation, deep insulin coma, lobectomy/leucotomy, and so on [17, 200]. Many of these ‘treatments’ are fanciful but ineffective, and dangerous by today’s standard; but they were applied in an era when there was a lack of understanding of the neurochemical basis of the disorder. In the 1950s, relatively-specific pharmacotherapy came by way of the discovery that chlorpromazine was effective in curbing agitation in psychotic patients [201]. The advent of chlorpromazine marked the beginning of the “psychopharmacological era” [202] as it became the first effective antipsychotic drug; and was later followed by the synthesis of haloperidol in 1958 [202]. Clozapine was synthesised in 1958, and by 1966, human trials confirmed that clozapine was an effective antipsychotic with no disabling neurological side-effects. Currently, antipsychotic agents in use can be put under three generations. First generation: dopamine antagonists (low potency drugs e.g. chlorpromazine; high potency drugs e.g. pimozide, haloperidol, fluphenazine); second generation: dopamine-serotonin antagonists (risperidone, paliperidone) and multitargeted antipsychotics (clozapine, olanzapine, ziprasidone, quetiapine, asenapine, iloperidone); third generation: dopamine-functionally selective (aripiprazole, brexpiprazole, cariprazine) [200]. These classifications also give some clues regarding the neurotransmitter receptors that the drugs interact with. The first generation drugs interact primarily at dopamine D2 receptor; the second generation drugs act at multiple receptor sites, including D1, D2, D3, and D4, adrenergic (alpha1 and alpha2), serotonin (5HT2A and 5HT2C), histamine and muscarinic receptors. Third generation drugs are considered as functionally-selective/partial D2 agonists (“DA-stabilisers”) with possible actions on 5-HT1A and 5-HT2A sites.

5.1. Linking Aetiological Theories to Pharmacotherapy of Schizophrenia

5.1.1. Dopamine-based Therapy and First Generation Antipsychotics

DA-based therapies have continued to play a central role in the management of schizophrenia [203]. Chlorpromazine replaced surgical and electroconvulsive therapies, and this was heralded as a significant turning point in the field of psychiatry [203]. First generation antipsychotics act at the dopamine D2 receptor and produce effects by its blockade. The first generation antipsychotics (also called typical or classic antipsychotics) include drugs in the following sub-classes: phenothiazines, butyrophenones, thioxanthenes, dibenzoxazepines, dihydronidoles, and diphenylbutylpiperidines. They are believed to act via postsynaptic blockade of brain dopamine D2 receptors; and evidences supporting this include strong antagonism at D2 receptors in both cortical and striatal areas, a high correlation between D2 receptor-binding and clinical potency, and also, a consistent requirement of 65% D2 receptor occupancy for antipsychotic efficacy in functional imaging studies [175, 204, 205]. In the brain, their binding is not region-specific; hence, their ability to block DA receptors in the mesolimbic DA system is responsible for the amelioration of positive symptoms [206], while their effects at
mesocortical, nigrostriatal and tuberoinfundibular DA receptors are believed to account for the Parkinson’s-like symptoms (muscle rigidity, tremors, tardive dyskinesia) and hyperprolactinemia that tend to be associated with their use [207]. Their binding is also not receptor-specific (with individual drugs showing distinct activities at 5-HT2A, alpha-1, histaminic, and muscarinic receptors; accounting for further side-effects). First generation drugs are also ranked as either high- or low-potency drugs. The high-potency drugs (fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thiothixene, and trifluoperazine) are associated with little sedation, weight gain, or anticholinergic activity, but a high risk for extrapyramidal side-effects; while the low-potency drugs (chlorpromazine and thioridazine) require higher doses, have high histaminic and muscarinic activity (and anticholinergic effects), but reduced occurrence of extrapyramidal side-effects. Generally, these drugs are only partially-effective or ineffective in certain subsets of patients. However, despite the limitations associated with their use, they have continued to play an important role in the management of schizophrenia [208].

Second-generation antipsychotics (atypical antipsychotics) were approved in the late 1980s, with the belief that they were more effective at treating symptoms of schizophrenia with minimal extrapyramidal side-effects [207]; however, like typical antipsychotics, the atypical drugs also bind to dopamine D2 receptors, although with lesser affinity. Atypical antipsychotics also show an affinity for the serotonin-2A (5-HT2A) receptor [138]; and the ratio of 5-HT2A to dopamine D2 receptor affinity separates typical from atypical antipsychotic drugs.

5.1.2.1. Limitations of the Dopamine-Based Treatment

About one-third of schizophrenics do not respond to non-clozapine antipsychotics [209], or manipulations that are based on D2 receptor occupancy or depletion of presynaptic dopamine [210]. Hence, for a significant number of schizophrenics, the pathophysiological basis of their symptoms involves more than DAergic excess, or may be unrelated to dopaminergic dysfunction. Also, it appears that patients who are likely to respond to dopamine-based drugs tend to show a raised dopamine synthesis capacity [141, 211]; so, from the aforo-going, the suggestion of the existence of a ‘non-dopaminergic’ sub-type of schizophrenia seems logical [199]. Dopaminergic dysfunction is linked to both negative and cognitive symptoms of schizophrenia [129]; however, in clinical practice, DA antagonists and partial agonists only have modest to no effects on cognitive impairments and negative symptoms [212], or they may worsen cognitive function [213].

5.1.2. Serotonin Based Therapies

5.1.2.1. Serotonin Antagonists: Second Generation Antipsychotics

Clozapine was the first antipsychotic agent that showed efficacy in the management of treatment-refractory schizophrenia [207]. Atypical antipsychotics are classically defined as drugs in which there is a marked dissociation between doses that inhibit amphetamine-induced stereotypy and those that result in catalepsy; implying a dissociation between the antipsychotic effect and the presence of extrapyramidal symptoms (EPS). Clozapine has a very high affinity for 5-HT2A, 5-HT3, 5-HT4, and 5-HT7 receptors, and the use of clozapine is also devoid of EPS; which are abnormalities of muscle tone and movement that may be serious enough to warrant extra therapy, or lead to discontinuation of a drug. The advent of clozapine corrected the erroneous impression that for a drug to have antipsychotic potential, it must be able to induce EPS experimentally. Second generation antipsychotics are devoid of EPS because the location of 5-HT2A receptors presynaptically on DA terminals in the nigrostriatal and mesocortical pathways allows the augmentation of dopamine release which counteracts the effects of D2 antagonism (resulting in fewer extrapyramidal side-effects). These antipsychotics also ameliorate positive symptoms by their ability to transiently occupy and dissociate from D2 receptors, allowing DA neurotransmission [204, 214 215]. The efficacy of 5HT antagonists also lies in the expression of 5-HT2A receptors throughout the cortex, where they contribute to the effects of atypical antipsychotics in improving cognition and affective symptoms, reducing negative thoughts and suicidal ideation [216], benefits not commonly observed with first generation antipsychotics [217, 218]. Although, atypical antipsychotics result in fewer EPS, they are however associated with a number of metabolic side-effects like glucose intolerance and weight gain [219].

Today, second and third-generation antipsychotics e.g. olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole have become the mainstay of the treatment of psychotic disorders [208]. Also, data showing their superior efficacy (relative to first generation drugs) have been inconsistent [220], except clozapine in treatment-resistant patients. A major point in favour of second generation drugs is a lesser tendency to be associated with EPS. For the first generation drugs, both therapeutic (antipsychotic) effect and side-effects (EPS) are related to D2 receptor occupancy [221]; therefore, side-effects are a direct extension of desired effects. Second-generation drugs exert their therapeutic effects through D2 antagonism (to some extent), but mainly through blockade of 5HT (mainly 5HT2A) receptors. D2 receptor affinity is a strong measure of the antipsychotic efficacy of first generation, but not second generation drugs; in fact, clozapine (which is the most effective) also has the lowest D2 affinity. Risperidone and olanzapine, both of which have high 5-HT2A receptor blocking activity relative to their D2 affinity [222] also show greater efficiency for treating negative symptoms of
schizophrenia. Second generation drugs also differ in their binding to D2 receptors [223]. However, a number of studies have shown that second generation drugs do not have significantly superior tolerability compared to typical antipsychotics; and even though they generally cause less EPS, there are still considerable variations within the class [224]. Presently, however, they are still recommended by current guidelines as the first-line therapy in the treatment of schizophrenia [225].

5.1.2.2. Selective Serotonin Re-uptake Inhibitors

The continued administration of selective serotonin reuptake inhibitor (SSRI) has been observed to increase serotonergic activity through the inhibition of 5-HT uptake and desensitization of the 5-HT auto receptor, leading to increased 5-HT release. Goff et al. [226] reported that the addition of fluoxetine to typical antipsychotics in nine treatment-resistant patients improved positive and negative symptoms. Fluoxetine also alters postsynaptic receptor dynamics, resulting in increased responsiveness to 5-HT1A agonists, and enhanced cortical release of DA with clinical evidence of improvements in negative symptoms, when added to depot neuroleptic [226]. In an era where individualised treatment for schizophrenia is enjoying a strong advocacy, the indications for application of SSRIs may be at the brink of a renaissance. Some studies using animal models are beginning to suggest that for schizophrenia management in certain subsets of patients, drugs such as SSRIs may be considered as the mainstay, instead of being an adjuvant. In a recent study, Onaolapo et al. [120] showed that in a mouse model of ketamine-induced schizophrenia, sertraline administration alone led to significant attenuation of ketamine-associated behavioural changes. The improvement in symptoms due to administration of these drugs may be due to either enhancement of serotonergic or mesocortical/mesolimbic activity, or both.

5.1.2.3. Serotonin Receptor Agonist

The 5-HT1A receptor is a subtype of serotonin receptor which is can be presynaptic and/or postsynaptic. The activation of this receptor has been associated with the anxiolytic, antidepressant and antipsychotic activities of some medications. There are suggestions that 5-HT1A receptor agonists may have antipsychotic-like properties [227], and also be effective in reducing antipsychotic-induced EPS [228]. Ziprasidone, one of the new atypical antipsychotic drugs, is a potent 5-HT1A agonist, while clozapine is a partial agonist at the 5-HT1A receptor. Buspirone is another partial 5-HT1A agonist with mixed reports (improve, or have no effect) on positive and negative symptoms in schizophrenic patients receiving typical antipsychotics. It has also been shown to be beneficial on EPS and akathisia [229]. Therefore, apart from their benefits in reducing EPS, the role of 5-HT1A receptor agonists in the management schizophrenia needs to be further studied.

5.1.3. Glutamate-based Therapies

Effects of NMDA receptor antagonists on brain structure and function lend supportive evidences to the glutamatergic transmission dysfunction hypothesis of schizophrenia. Also, the role of NMDA receptor hypofunction in the aetiology of schizophrenia has been supported by drug trials that demonstrated the benefits of glutamatergic agents in schizophrenia management [230]. According to earlier postulations (which were later validated through microdialysis studies), NMDA receptor antagonism can lead to increased cortical glutamate release and excitotoxicity, via reduction in the inhibitory tone of GABAergic interneurons that express NMDA receptors [172, 231]. Studies have investigated drugs that modulate NMDA receptor through direct agonism at the glycine modulatory site (e.g. glycine or D-serine), or through increasing synaptic glycine levels by inhibiting glycine transporters (e.g. sarcosine). While it is believed that modulation of the glycine site may hold promise in the drug therapy of schizophrenia; the degree of derivable benefits from such manipulation is still being investigated. A meta-analysis of published studies suggested that when administered in addition to existing antipsychotic treatment, NMDA receptor modulators led to a significant improvement in residual positive and negative symptoms in patients with schizophrenia [232]. However, the outcome of a large clinical trial using D-serine, found the drug of no benefit in the management of schizophrenia [233]. Other glutamate-based medications include the glycine transporter inhibitor Bitopertin, which had in an initial trial had shown promise in the management of negative symptoms [234], however, two recent phase III studies, concluded it has no benefit in the management of negative symptoms [235], while its effects on positive symptoms have so far being modest at best.

Other drugs whose mechanisms of action are linked to the glutamate pathway include minocycline, an antibiotic with neuroprotective properties; which in animal models has been shown to counter the effects of multiple NMDA antagonists [236]. An initial open label study [237] demonstrated significant improvements in both positive and negative symptoms; and in controlled studies, it was associated with clinically-significant benefits regarding negative symptoms [238]. However, its mechanism of action might also involve an inhibition of the formation of reactive oxygen species [239]. Preclinical studies had shown that sodium nitroprusside can abolish the behavioural effects of phencyclidine [240]; and its administration has been associated with improvements in schizophrenia symptoms [241], probably via a glutamatergic mechanism involving modulation of NMDA receptor activity [242]. LY-2140023 (developed by Eli Lilly & Co) is a methionine amide prodrug of the orthosteric metabotropic glutamate receptor agonist
patients who continue to respond poorly to standard regimens; or better still, in the application of the pharmacology in general, or schizophrenia management and hormonals (for a detailed review on repurposed drugs, tetra-cyclic antidepressants, antinarcoleptics, antioxidants have a place as alternative or adjuvant treatment options for management of schizophrenia. Presently, repurposed drugs were mentioned earlier, are repurposed for the anaesthesia. Lamotrigine, topiramate and minocycline that shows high selectivity for the metabotropic glutamate receptor group II subtypes mGluR2 and mGluR3 [244]. LY-404039 is believed to act through modulation of glutamatergic activity, and reduction of presynaptic release of glutamate at synapses in limbic and forebrain areas. An initial study documented significant improvements in positive and negative symptoms in patients with chronic schizophrenia [245]; but phase II trial did not show any significant benefit over placebo [246]. Lamotrigine reduces glutamate release and has been reported to inhibit ketamine-induced psychosis-like behaviours in healthy volunteers [247]. It also inhibits ketamine-induced changes in brain function, as measured by fMRI [248]. Early clinical data had suggested a significant benefit in the subset of patients who respond only partially to clozapine treatment [249]; however, subsequent meta-analyses suggest that effects were relatively modest [250]. Topiramate is an AMPA receptor antagonist anti-seizure agent that regulates effect of excess downstream glutamate; however, its AMPA antagonism only occurs at higher doses, and its inhibitory effects are probably more through enhancement of GABA transmission than glutamate regulation [251] It was shown to reduce the behavioural effects of MK-801 in rats [252]; and an initially- promising open trial [253] using topiramate augmentation in treatment-resistant schizophrenia was also replicated in a randomised controlled trial [250]. Current clinical evidence demonstrates small to moderate benefits in relation to symptom control with topiramate augmentation; also, evidence suggests that topiramate may be useful in the prevention of antipsychotic-induced weight gain [254].

5.2. Repurposing of Old Drugs and Adjunctive Therapies in Schizophrenia Management

The concept of drug-repurposing is not new to pharmacology in general, or schizophrenia management specifically. Modern day pharmacotherapy of schizophrenia started with a repurposed drug, as chlorpromazine was originally developed as an adjunct to anaesthesia. Lamotrigine, topiramate and minocycline that were mentioned earlier, are repurposed for the management of schizophrenia. Presently, repurposed drugs have a place as alternative or adjuvant treatment options for patients who continue to respond poorly to standard regimens [255]; or better still, in the application of the concept of individualised management, where drugs used are specifically-targeted at the symptom clusters exhibited by a patient. Different classes of drugs have been repurposed for schizophrenia treatment and they include; non steroidal anti-inflammatory agents, antiepileptics, tetra-cyclic antidepressants, antinarcotics, antioxidants and hormonals (for a detailed review on repurposed drugs, see Bumb et al. [25] or Lee and Kim [256].

(a) Non steroidal anti-inflammatory agents

Presently, it is known that inflammation probably plays an important role in schizophrenia [257]; and research had shown up-regulation of certain genes that regulate expression of pro-inflammatory proteins, leading to increase in enzymes such as TNF-alpha, IFN-alpha and IFN-gamma, as well as changes in myelination [258]. Neuroinflammation is known to trigger microglial activation, leading to the production of inflammatory cytokines, increased activity of phagocytic cells/proteins, and disruptive changes in the blood-brain barrier [259]. In a randomised, placebo-controlled, double-blind trial using aspirin as adjuvant treatment [260]; there was a significantly larger reduction of PANSS (positive and negative syndrome scale) positive scores, but not PANSS negative scores and cognitive function (in comparison to placebo). However, celecoxib, a selective inhibitor of cyclooxygenase-2(COX-2) showed no demonstrable benefit (in relation to measured clinical outcomes (including psychopathology, functional disability, and extrapyramidal side effects) when used as add-on treatment [183] in chronic schizophrenia; although Müller et al [261] reported significant improvement in symptoms when used as an adjunct in early schizophrenia. Evidence of COX-2 involvement in synaptic activity, memory consolidation, neurovascular coupling, long-term potentiation and depression [262] has however renewed interests in the possible role of COX-inhibitors in schizophrenia management; and according to the findings of a recent meta-analysis, adjunctive celecoxib outperformed placebo in relation to positive symptoms, negative symptoms, total and general psychopathology scores in first-episode patients; but not in chronic schizophrenics [263].

(b) Antiepileptics, antidepressant and other CNS medications

Sodium valproate, an anticonvulsant approved for use in the control of manic episodes in bipolar disorder [264] has in recent times become a frequently-prescribed mood-stabilizer in schizophrenics [265]; its use follow suggestions that its actions at voltage-gated ion channels and on the GABA system could modulate mesolimbic dopaminergic activity in schizophrenics. In an open-label study, the positive effects of valproate as an add-on to second-generation antipsychotics like olanzapine and risperidone in patients with severe schizophrenia [266] were demonstrated. However, there is yet to be an approved role for sodium valproate in the management of schizophrenia.

Memantine is used in the management of Alzheimer's disease; it acts on the glutamatergic system by blocking NMDA receptors. Studies conducted to ascertain the possible use of memantine monotherapy or add-on in the management of schizophrenia have generated mixed
results [267-270]; Uribe et al. [267] reported that neonatal administration of memantine to adult rats exposed to early maternal deprivation reduced social interaction deficits, while Omranifard et al. [270] in a double blind, randomised control study concluded that add-on therapy of memantine in schizophrenics treated with atypical antipsychotics reduced positive/negative symptoms of schizophrenia, and general psychopathology. Kishi et al. [268] also concluded on the possible beneficial effects of memantine add-on treatment in the management of negative symptoms in schizophrenics.

The use of antidepressants as add-on therapy in the management of schizophrenia has been researched extensively, but inconclusively [271]; however, in general, add-on antidepressants were not observed to worsen psychosis. Administration of mirtazapine, a tetra-cyclic antidepressant was reported to show consistent improvement of negative and extra-pyramidal symptoms [272] with enhancement of neurocognition; although it did not show consistency in the alleviation of the core symptoms of schizophrenia [266]. In a meta-analysis of the efficacy of mirtazapine as add-on therapy, it was concluded that adding mirtazapine to treatment can improve negative symptoms in schizophrenia [273]. Addition of mianserin to typical antipsychotics may be of benefit to patients with chronic treatment-resistant schizophrenia who have an acute psychotic exacerbation [274]; co-administration of mianserin was also found to attenuate or reverse haloperidol-induced motor deficits [275].

Modafinil is a eugeroic drug that has diverse effects on numerous neurotransmitter systems such as DAergic, GABAergic, glutamatergic, noradrenergic, 5HTergic and histaminergic pathways; and also exerts additional influence on orexinergic pathways. In a 2004 trial, a four-week modafinil add-on therapy led to improvement of cognitive and positive symptoms of schizophrenia, without inducing severe side effects [276]. Other trials have also reported improvement of PANSS positive and negative scales [277], and improvement of clinical outcome measures [278]. Pramipexole, a synthetic non-ergot aminobenzothiazole dopamine (D_{1}/D_{3}) receptor agonist used in the management of Parkinsonism has also been associated with improvement of PANSS positive and negative scales [279].

(c) Antioxidants, hormonals, trace elements and immunomodulators

The two-hit, neuroprogressive, neurodevelopmental, inflammation and immunologic hypotheses present accumulating evidences that implicate oxidative stress in the development of schizophrenia. Antioxidants are biomolecules that can mitigate oxidative stress and/or its consequences [60]. A number of studies [280-282] have evaluated the possible effects of substances or compounds with antioxidant potential on schizophrenia; with reports that adjunctive therapy with β-carotene, quinones, and vitamins E and C at the acute stages of schizophrenia may prevent further oxidative injury and the development of full-blown symptoms of schizophrenia. N-acetylcysteine is another anti-oxidant drug that has effects on neurotransmission via its influence on cysteine and glutamate levels; and D_Aergic transmission. In trials, it had been associated with improvements in PANSS total and negative scales [283]; and improvement of PANSS positive and negative scales [284]. Also, as said earlier, minocycline’s mechanism of action might involve the inhibition of formation of reactive oxygen species [239].

Abnormalities in polyunsaturated fatty acid (PUFA) metabolism have been implicated in the possible aetiopathogenesis of schizophrenia [285]. A number of studies [286-289] have examined the possible effects of N-3 PUFA eicosapentaenoic acid (EPA) when added as supplements to antipsychotics; with reports of positive improvement of primary efficacy and secondary outcomes [288, 289], there is also evidence suggesting that N-3 PUFA may reduce adverse effects secondary to antipsychotic use [286].

Hormones have been implicated in the possible aetiopathogenic mechanisms of schizophrenia; with reports of gender-related-differences in schizophrenia [290] incidence, which have been largely attributed to the effects of gonadal steroids. The oestrogen hypothesis postulates that oestrogen exerts a neuroprotective effect in females, modulating the development and/or severity of schizophrenia [291]. In a number of studies, the beneficial effects of adjunctive treatment with oestrogen in males and/or females have been reported [292, 293]. The neuroprotective effect of oestrogen in schizophrenia has also been associated with its effect on the DA system [294].

In studies in which oestrogens were administered to post-menopausal women or women with chronic schizophrenia, there were reports of improvement in PANSS total, positive and negative scales [295] but in a few, no obvious benefit was demonstrated [296]. Also in studies examining the effect of the antioestrogen, raloxifene; improvement of PANSS total score [296], or PANSS positive and negative scales [297] were observed.

Melatonin has been linked to the aetiopathogenesis of schizophrenia [298]; and an emerging area in schizophrenia research focuses on the impact of immunomodulatory drugs like melatonin [119], with studies assessing the therapeutic potential of exogenous administration of melatonin. In a recent study using a ketamine model of schizophrenia in mice, significant improvements in behavioural and brain oxidative stress parameters were recorded following melatonin administration as a sole agent [119, 121] or adjunct [299]. The findings of the studies are in line with earlier observations that administration of melatonin may augment the efficacy of antipsychotics through suppression of neuroinflammation; and its potent antioxidative effects [300].
Other hormones such as oxytocin has been associated with improved performance in emotion recognition task [301], improvement of verbal memory [302]; and improvement of PANSS total, positive and negative scores [303]. Studies also showed improvement of cognitive function [304] and attention/memory functions [305] respectively, with erythropoietin. Pregnenolone [306] and dehydroepiandrosterone [307] have also been studied with favourable results.

Trace elements are important in antioxidant defence and regulation of metabolic reactions [308]. A number of studies have suggested that trace element deficiencies may be associated with the aetiology and pathophysiology of schizophrenia [309]. Zn is one of the trace elements whose abnormal homeostasis had been implicated in the expression of symptoms of schizophrenia [309]. Trial of Zn add-on therapy (to risperidone) has proven the efficacy of Zn as an adjuvant in the management of schizophrenia [310]. Also in an animal study, Zn proved beneficial (either as monotherapy or as adjunct to haloperidol or olanzapine) in the attenuation of behavioural deviations or brain antioxidant changes in mice that were given repeated ketamine injection [122]; although more research is needed to ascertain its role in schizophrenia management.

6. Conclusions

An evolving understanding of the aetiopathogenesis of schizophrenia has continued to improve our approach to the management of symptoms. However, while its aetiology is still not completely understood, and many factors had been implicated (and are still being implicated) in its evolution; our position regarding the understanding of the disorder is much stronger than it was centuries ago. Also, from decades of experience, it is obvious that appropriate application of drugs for the management of schizophrenia has its foundation in an adequate understanding of its aetiology; therefore, research must continue to be directed towards getting a complete picture of the causes of the disorder, as this is intimately-linked to the development, discovery and application of better therapeutic agents.

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Conflict of Interest

All authors of this paper declare that there is no conflict of interest related to the content of this manuscript.

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