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# Schizophrenia

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## Introduction to Schizophrenia

Schizophrenia is the most serious and disabling of all mental disorders, affecting just under 1 % of the population. While its etiological bases remain obscure and consequently its nosological boundaries are uncertain, the condition classically has its onset in childhood or early adolescence [1]. It is characterized by (1) “positive” psychotic symptoms like delusions (fixed false ideas that are held with unshakable conviction), hallucinations (perceptions without a stimulus), and thought disorder (difficulty in assembling a coherent stream of speech); (2) so-called negative symptoms like lack of motivation and pleasure, inability of expressing the full range of emotions, neglect of personal appearance, and disinterest in life events; and (3) cognitive impairment (memory and attention difficulties) [2]. All of these attributes, persistent over time, culminate in a decline in social and occupational performance. These features – coupled with the consequences of sustained impairment – result in comorbid depression (see chapter “[Major depressive disorder](#)”) among people with schizophrenia. Approximately 50 % of patients attempt and about 4 % of patients commit suicide. Schizophrenia is poorly understood by the public, and it is often highly stigmatizing [3].

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## Pathophysiology of Schizophrenia and Metabolic Alterations

The causes of schizophrenia are largely unknown [4, 5]. However, an ever-increasing portfolio of extensive, multinational genetic studies point to subtle yet reproducible genetic findings [6, 7]. Replicated genes like COMT (catechol-O-methyltransferase), implicated in dopamine and norepinephrine degradation, neuregulin-1 implicated in expression and activation of neurotransmitter receptors, including glutamate, dysbindin gene, DISC (disrupted in schizophrenia), DRD2 (dopamine receptor D2), and DAT (dopamine active transporter), likely represent only a minor part of genetic makeover of schizophrenia, while genome-wide studies reveal DNA variants (single nucleotide polymorphisms), which are common to schizophrenia and bipolar disorder, and structural genomic variants (copy number variants) shared by schizophrenia and neurodevelopmental disorders like autism [6].

Nongenetic influences include obstetric events like hypoxia and maternal malnutrition, birth during late winter and spring, advanced paternal age, urbanity, prenatal infections (such as rubella and maternal influenza), changes in inflammatory markers like cytokines, head injury, and use of cannabis [8].

The exact mixture and confluence of etiological factors that result in schizophrenia most likely differs from one patient to another [5]. On postmortem brain, patients with schizophrenia reveal a series of macroscopic and histological

abnormalities. The overall brain volume is reduced (by around 5 %, in both white and gray matter), and the temporal and frontal lobes are smaller. In addition, the hippocampus is smaller, with predominance of finding more left-sided reductions. In contrast, the ventricles (especially the lateral ones) are enlarged. On a cellular level, changes more of attuned arrangement rather than fundamental tissue loss or necrosis are observed, likely resulting from convergence of genetic and environmental factors, leading to abnormal neuronal connectivity and synaptic signaling and altering dopaminergic and glutamatergic pathways of neurotransmission in the brain.

Altered dopaminergic function is considered as the final common pathway in schizophrenia [1]. This hypothesis has most influenced antipsychotic drug development and the clinical treatment of schizophrenia, and it represents the best (yet still inadequate) explanatory model for schizophrenia and its treatment. According to this hypothesis, in schizophrenia, the mesolimbic dopamine pathway, believed to have a role in thought and perception, is disrupted, especially through dopamine receptor D2 (DRD2)-mediated effects. An overactivation of this receptor is a compelling pathobiological finding in schizophrenia. The hypothesis also explains other schizophrenia characteristics, as dopamine pathways in the brain affect cognition (through a mesocortical pathway, which is important in the flow of information in the frontal lobe), movement through the nigrostriatal pathway, which is instrumental as part of the basal ganglia motor loop, and endocrine function through the tuberoinfundibular pathway, which involves dopamine acting as an inhibitor of prolactin gene expression and secretion.

Other emergent hypotheses include an oxidative stress and phospholipid dysregulation hypothesis, a glutamate hypothesis [9], and a more “all-encompassing” neurodevelopmental hypothesis of schizophrenia [1, 8], which capitalize on the fact that the pathological brain abnormalities thought to be resulting from the gene-environmental factors implicated in schizophrenia (smaller prefrontal cortex and hippocampus, enlarged ventricles) appear to be static in nature,

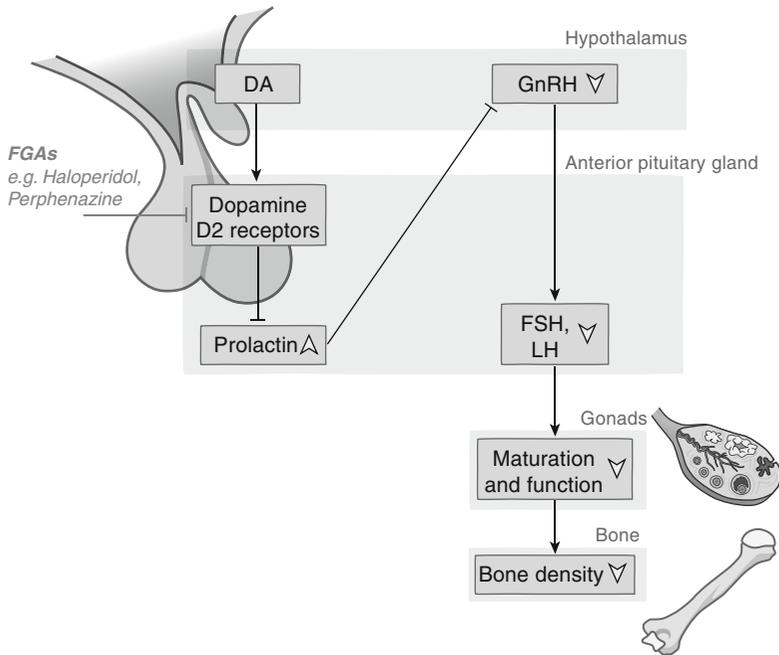
at least in a subgroup of patients, and occur without evidence of gliosis, commonly found in neurodegenerative disorders. More recent drug development is focusing on the glutamate system as novel and potentially (more) effective way to treat schizophrenia [9]. Schizophrenia has been associated with metabolic abnormalities independent of treatment with antipsychotic drugs; for example, treatment-naïve patients with schizophrenia have increased prevalence of abnormal glucose tolerance and insulin resistance compared to normal controls [10, 11].

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## Treatment of Schizophrenia

Antipsychotic medications form the bedrock of treatment for schizophrenia [12]. All these medications block dopamine (D2) receptors to some extent, although newer antipsychotic medications tend to have broader effects that extend to other (e.g., cholinergic, adrenergic, serotonergic) neurotransmitters. Antipsychotic medications should be used in all florid psychosis, except drug-induced psychosis and brief psychosis [12, 13].

Antipsychotic drugs are grouped into a first- and second-generation antipsychotics (FGAs and SGAs), based on their receptor and adverse effect profiles. When starting schizophrenia treatment (usually with a second-generation antipsychotic), the lowest effective drug dose should be used. Antipsychotic drugs often appear to work in about 48 h, although it may take up to 4 weeks at adequate dose to determine whether the drug is ultimately effective. Treatment response, tolerability, and side effects of any given drug are highly variable between patients [14], and side effects should thus be monitored closely. Switching antipsychotic medications may be indicated, for either lack of effect or presence of side effects on the present medications, although it is a complicated process and the switch to a new medication should be gradual and phased-in with a cross taper. Antipsychotic polypharmacy is common although probably not justified. At present, treatment remains a clinical approach of “trial and error” with the selection of each antipsychotic medication. The mechanism of action of the FGAs



**Fig. 1** Potential mechanism of side effects of antipsychotics on gonadal system and bone structure. First-generation antipsychotics (FGAs) act by inhibiting the binding of dopamine (DA), released from the hypothalamus, to D2 receptors in the pituitary gland. Without this activation, the DA block of prolactin secretion is released.

Increased prolactin can lead to gonadal dysfunction, via reduced amounts of gonadotropin-releasing hormone (*GnRH*), follicle-stimulating hormone (*FSH*), and luteinizing hormone (*LH*). Subsequently, gonadal failure can cause bone loss and osteoporosis

(e.g., haloperidol and perphenazine) is based primarily on the inhibition of dopamine D2 receptors. Clozapine, the initial SGA drug, only partially binds to dopamine D2 receptors. However, it also binds dopamine D4 receptors with high affinity. Other targets include dopamine D1, D3, and D5 receptors as well as serotonin, adrenergic, and histaminergic receptors. Other SGAs (like risperidone, quetiapine, and olanzapine) maintain the combined inhibition of dopamine D2 receptors and serotonin 5-HT<sub>2A</sub> receptors [14].

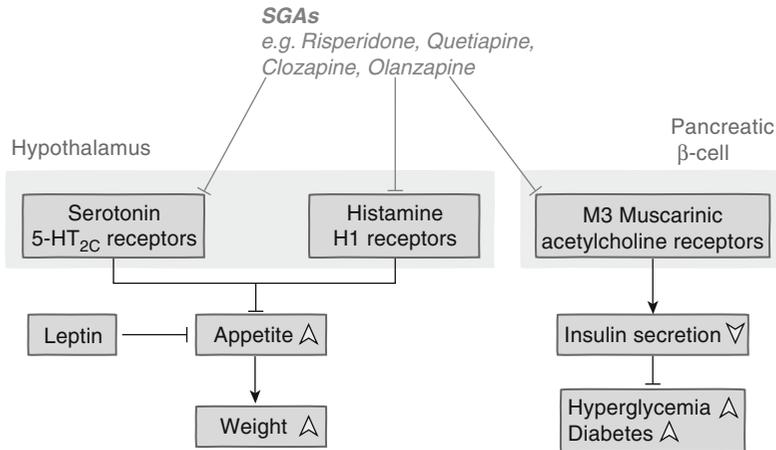
## Influence of Treatment on Metabolism

As dopamine affects many neurological systems in the brain (see above), antipsychotic and anti-dopaminergic treatments have broad therapeutic and adverse effects. Based on the all-encompassing hypothesis, there is some evidence

that medications may have neuroplastic effects [15]. On the other hand, there is lingering concern that antipsychotic medications might be neurotoxic and thereby contribute to progressive neurodegeneration in schizophrenia [16].

The FGAs have a side effect profile largely characterized by acute and long-term muscle impairments through their effect on the dopaminergic nigrostriatal pathway. In addition, FGAs, which antagonize the action of dopamine, which is also known as prolactin-inhibiting hormone (see chapter “[Overview](#)” under part “[Reproductive system](#)”), induce hyperprolactinemia by releasing the dopamine block of prolactin secretion in the pituitary gland. This can lead to gonadal failure and subsequently to bone loss and osteoporosis (see chapter “[Osteoporosis](#)”, Fig. 1) [17, 18].

SGAs show a more complex side effect profile that is increasingly characterized by metabolic disturbances [19]. While they yield less risk for movement disorders and hyperprolactinemia,



**Fig. 2** Side effect profile of second-generation antipsychotics. Second-generation antipsychotics (SGAs) show side effects different from the first generation due to their binding to 5-HT<sub>2C</sub> dopamine (5-HT) and H1 histamine receptors in the hypothalamus (*left side*) and M3 muscarinic acetylcholine receptors on pancreatic β-cells

(*right side*). Blockade of 5-HT<sub>2C</sub> and H1 receptors releases the inhibitory effect on appetite that these receptors share with leptin. Increased appetite results in weight gain and associated effects. Blockade of M3 receptors may reduce insulin secretion and subsequently cause hyperglycemia and diabetes

due to lower blockade of dopamine D2 receptors and concomitant serotonin antagonism, SGAs are known to induce dangerous metabolic effects [20], for example, weight gain, and alterations in glucose and lipid metabolism. SGAs increase appetite activating histamine H1 and serotonin 5-HT<sub>2C</sub> receptors [20]. Serotonin 5-HT<sub>2C</sub> receptors and leptin, a hormone implicated in the pathophysiology of food and energy regulation (see chapters “[Diabetes mellitus](#)” and “[Metabolic syndrome](#)”), have been associated with weight gain in replicated studies and may provide a basis for individualized adverse effect risk assessment in the future (Fig. 2) [21]. Therefore, guidelines on monitoring patients on antipsychotics for obesity, diabetes, lipid abnormalities, and cardiovascular risk have been issued [22, 23].

## Perspectives

In addition to the use of FGAs and SGAs in the treatment of schizophrenia, there are a variety of other novel approaches targeting specific aspects of the illness, e.g., treatment of negative symptoms, and treatment of cognitive impairments. The field is still awaiting a third generation of

drugs for schizophrenia, which can exercise therapeutic effect without considerable metabolic and endocrine risk [24]. Pharmacogenetic analyses have offered some insights into effectiveness, tolerability, and side effects in individual patients. However, the predictive potential to drive “personalized medicine” is still a long way off [25].

Although medications form the basis of treatment, medications alone are insufficient for treating schizophrenia. Other psychological and cognitive approaches (such as cognitive therapy adapted for schizophrenia and cognitive remediation training particularly when combined with functional adaptation skills training [26]) are important and impactful treatment modalities [27].

Research also focuses on earlier diagnosis and treatment of schizophrenia, thereby intuitively leading to better results and less secondary consequences of protracted psychosis. Indeed, research points to subtle signs of psychosis in advance of more florid psychotic manifestations [28]. Moreover, many of the neurobiological hallmarks of schizophrenia such as decreased gray matter in the temporal, frontal, and cingulate cortex as well as subtle clinical symptoms like attention difficulty, cognitive decline, social withdrawal, and affective flattening exist in early

states, albeit in much more attenuated forms [29]. Unfortunately, identification and clinical incorporation of disease biomarkers that could inform and reliably predict treatment outcomes prove difficult [30]. Moreover, the lack of fundamental understanding of the pathobiology of schizophrenia greatly hampers this quest.

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