6
Schizophrenia

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Abstract In this chapter, we discuss history, current diagnostic criteria, epidemiology, genetics, etiology, clinical signs and symptoms, laboratory investigations, differential diagnosis, pharmacological and behavioral treatment modalities, prognosis and course of illness for schizophrenia. The emphasis in this chapter is the etiopathogenesis and relevant biological treatments for this disorder.

Keywords Schizophrenia • Etiology • Treatment

6.1. History

Schizophrenia is a debilitating disease of the brain which has been described by various physicians for centuries (1). Hippocrates referred to paranoia as a potential antecedent of present day psychosis (1). Aretaeus of Cappadocia referred to a form of mental illness he called insanity (1). Benedict Morel referred to one of the earliest descriptions of schizophrenia as démence précoce (precocious dementia) or deterioration of cognition in the adolescents (1, 2). Karl Ludwig Kahlbaum described catatonic symptoms as early as 1874 (3). Ewald Hecker was the first psychiatrist to refer to disorganized symptoms of schizophrenia as hebephrenia (4).

However, the greatest and most methodological and comprehensive description of schizophrenia was heralded by the German psychiatrist Emil Kraepelin who referred to this disease as dementia praecox and separated it from manic depressive psychosis (5). Indeed Kraepelin's predecessor Wilhelm Griesinger (6) of Berlin's Charité Hospital had already considered psychiatric disorders such as schizophrenia as brain disorders and influenced later psychiatrists on the importance of the organicity of schizophrenia (1) and other psychiatric diseases. Kraepelin's distinction between bipolar psychosis and dementia praecox with the latter disease, being an early onset psychosis which affected cognition permanently and had a poor outcome, opened the way for a true diagnosis of schizophrenia (1, 7).

Eugen Bleuler, another leading figure in the 20th century psychiatry, coined the term schizophrenia to describe the affective disturbance, the ambivalence and sense of isolation (autism), and associative (cognitive) disturbances observed in patients with dementia praecox (8). Bleuler also described schizophrenia as less of a dementing illness with more optimistic prognosis than Kraepelin had suggested (7, 8). Finally, Kurt Schneider, provided the concept of first and second rank symptoms (Table 6.1), to describe schizophrenia. It is now clear that while these symptoms are helpful in diagnosis of schizophrenia, that they are not specific to this disorder.

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TABLE 6.1 Schneider's Symptoms.

First rank	Second rank
Audible thoughts	Depressive or euphoric mood changes
Voices heard arguing	Emotional blunting
Voices heard commenting on one's actions	Perplexity
The experience of influences playing on the body	Sudden delusional ideas
Thought withdrawal and other interferences with thought	
Diffusion of thought	
Delusional perception	
Feelings, impulses and volitional acts experienced as the work or influence of others	

6.2. Current Diagnostic Criteria

The current diagnostic criteria for schizophrenia (9) require presence of two of five active-phase symptoms of delusions, hallucinations, disorganized speech, catatonic behavior, or negative symptoms for at least one month. The symptoms of schizophrenia must last for a minimum of six months and cause impairment of social and occupational functioning. Finally, one needs to rule out the presence of other diagnoses including schizoaffective disorder, bipolar disorder with psychotic features, medical or neurologic disorders or whether it is due to side effects of a medication or an illegal substance (9). A detailed account of these criteria can be reviewed in the recently published version of DSM-5 (9).

6.3. Epidemiology

Schizophrenia affects 1% of the adult population in the world (9). The point prevalence of schizophrenia is about 5/1000 population (10) and the incidence is about 0.2/1000 per year (10). This incidence rate was reported to be comparable in most societies (11); however, recent studies suggest greater variability (10). Schizophrenia has an earlier onset in males with mean ages of onset of 20 and 25 in males and females respectively (7, 10). Risk factors other than a familial history of schizophrenia include obstetric complications, parental age, prenatal infections, ethnicity, cannabis use, urbanicity and modernization (trends toward a faster-paced and more technological society) (10).

6.4. Genetics

Emerging evidence points to schizophrenia as a familial disorder with a complex mode of inheritance and variable expression (7, 12–14). While single-gene disorders like Huntington's disease have homogeneous etiologies, complex-trait disorders like schizophrenia have heterogeneous etiologies emanating from interactions between multiple genes and various environmental insults (12). Twin studies of schizophrenia suggest concordance rates of 45% for MZ twins and 14% for DZ twins (7, 15). Consistent with this, a metaanalytic study showed a heritability of 81% for schizophrenia (15). Despite this high genetic predisposition, an 11% point estimate was suggested for the effects of environmental factors on liability to schizophrenia (12, 15). Additionally, adoption studies show a lifetime prevalence of 9.4% in the adopted-away offspring of schizophrenic parents vs. 1.2% in control adoptees (16). The adoption studies also clearly show that postnatal environmental factors do not play a major role in etiology of schizophrenia (12).

The mode of transmission in schizophrenia is unknown and most likely complex and non-Mendelian (7, 12). Chromosomal abnormalities show evidence for involvement of a balanced reciprocal translocation between chromosomes 1q42 and 11q14.3, with disruption of DISC1 (disrupted in schizophrenia) and DISC2 genes on 1q42, being associated with schizophrenia (12, 17). Additionally, an association between a deletion on 22q11, schizophrenia and velocardiofacial syndrome has been reported (18). Mice with similar deletions exhibit sensorimotor gating abnormalities (19).

Linkage and association studies (12, 20, 21) show 12 chromosomal regions containing 2181 known genes (20) and 9 specific genes (12) as being involved in etiology of schizophrenia (12). Variations/polymorphisms in 9 genes including neuregulin 1 (NRG1), dystrobrevin-binding protein 1 (DTNBP1), G72 and G30, regulator of G-protein signaling (RGS4), catechol-O-methyltransferase (COMT), proline dehydrogenase (PRODH), disrupted in schizophrenia 1 and 2 (DISC 1 and DISC 2), serotonin 2A receptor (HTR2A) and dopamine 3 receptor (DRD3) have been associated with schizophrenia (Table 6.2).

More recently, genome-wide association study (GWAS) arrays have identified approximately 30 schizophrenia-associated loci including calcium channel, voltage dependent, L-type, alpha 1-C subunit (CACNA1C), serologically defined colon cancer

TABLE 6.2 Risk genes for schizophrenia.

Gene	Abbreviation	Locus
Neuregulin	NRG1	8p12-p21
Dysbindin	DTNBP1	6p22
G72	G72	13q34
D-amino acid oxidase	DAAO	12q24
RGS4	RGS4	1q21-22
Catechol-O-methyl transferase	COMT	22q11
Proline dehydrogenase	PRODH	22q11
Calcium channel, voltage dependent, L-type, alpha 1-C subunit	CACNA1C	12p13.33
Calcium channel, voltage-dependent beta 2 subunit	CACNB2	10p12.33-p12.31
N-deacetylase/N-sulfotransferse 3	NDST3	4q26-q27
Ankyrin 3	ANK3	10q21.2
Vaccinia-related kinase 2	VRK2	2p16.1
Transcription factor 4	TCF4	18q21.2
Dopamine receptor D2	DRD2	11q23.2
Metabotropic glutamate receptor 3	GRM3	7q21.11-q21.12
Ionotropic glutamate receptor AMPA 1	GRIA1	5q33.2
Ionotropic glutamate receptor NMDA subunit 2A	GRIN2A	16p13.2
Inter-alpha-trypsin inhibitor heavy chain 3	ITIH3	3p21.1
Inter-alpha-trypsin inhibitor heavy chain 4	ITIH4	3p21.1
Serologically defined colon cancer antigen 8	SDCCAG8	1q43

List compiled from (12, 22–26).

antigen 8 (SDCCAG8), inter-alpha-trypsin inhibitor heavy chain 3 and 4 (ITIH3, ITIH4), N-deacetylase/N-sulfotransferse 3 (NDST3), MIR137, ankyrin 3 (ANK3), vaccinia-related kinase 2 (VRK2), and transcription factor 4 (TCF4) (22–25). Furthermore, and very recently, a GWAS involving a large cohort of schizophrenic patients (n=36,989) compared to healthy controls (n=113,075) identified 108 loci that were associated with schizophrenia including DRD2, genes involved in glutamatergic transmission [e.g., metabotropic glutamate receptor 3 (GRM3), ionotropic glutamate receptor AMPA 1 (GRIA1), and ionotropic glutamate receptor NMDA subunit 2A (GRIN2A)]; and voltage gated calcium channels [CACNA1C, calcium channel, voltage-dependent beta 2 subunit (CACNB2)] (26).

Another means of studying the genetic basis of schizophrenia uses the technique of DNA microarray (14, 27). These studies are based on discovering genes either repressed or stimulated significantly in well-characterized postmortem brain tissues from subjects with schizophrenia and matched healthy controls; peripheral lymphocytes obtained from schizophrenic and matched healthy controls and antipsychotic-treated brains of rodents and relevant animal models of schizophrenia (Table 6.3). Genes involved in drug response, or in etiopathogenesis of schizophrenia can be compared and studied to better understand the mechanisms responsible for this illness. Lastly, a new study has reported identification of eight distinct groups of clinical entities based on genotypic networks that indicate schizophrenia is a heterogeneous group of disorders just as predicted by Bleuler nearly a century ago (258). However, this study clearly needs to be replicated further to confirm its veracity.

6.5. Etiology

The concept of schizophrenia as a neurodevelopmental disease dates back to the period of Kraepelin and Bleuler (7). Early manifestations of disease as exemplified by premorbid signs, and deficits in social interaction, were observed by Kraepelin and Bleuler (28) in children who later developed schizophrenia. Later Southard (Fig. 6.1) reported on the presence of neuropathological signs in brains of subjects with schizophrenia which further pointed to maldevelopmental origins of this disorder (29).

6.5.1. Neurochemistry of Schizophrenia

6.5.1.1. The Dopamine Hypothesis

Dopaminergic tracts are composed of four branches: 1) nigrostriatal tract, originating from the substantia nigra and ending in the dorsal striatum, deals with initiation of movement, motor control, sensorimotor coordination, cognitive integration and habituation (7, 30); 2) mesolimbic tract, originating from the ventral tegmental area and ending in hippocampus, amygdala and ventral striatum,

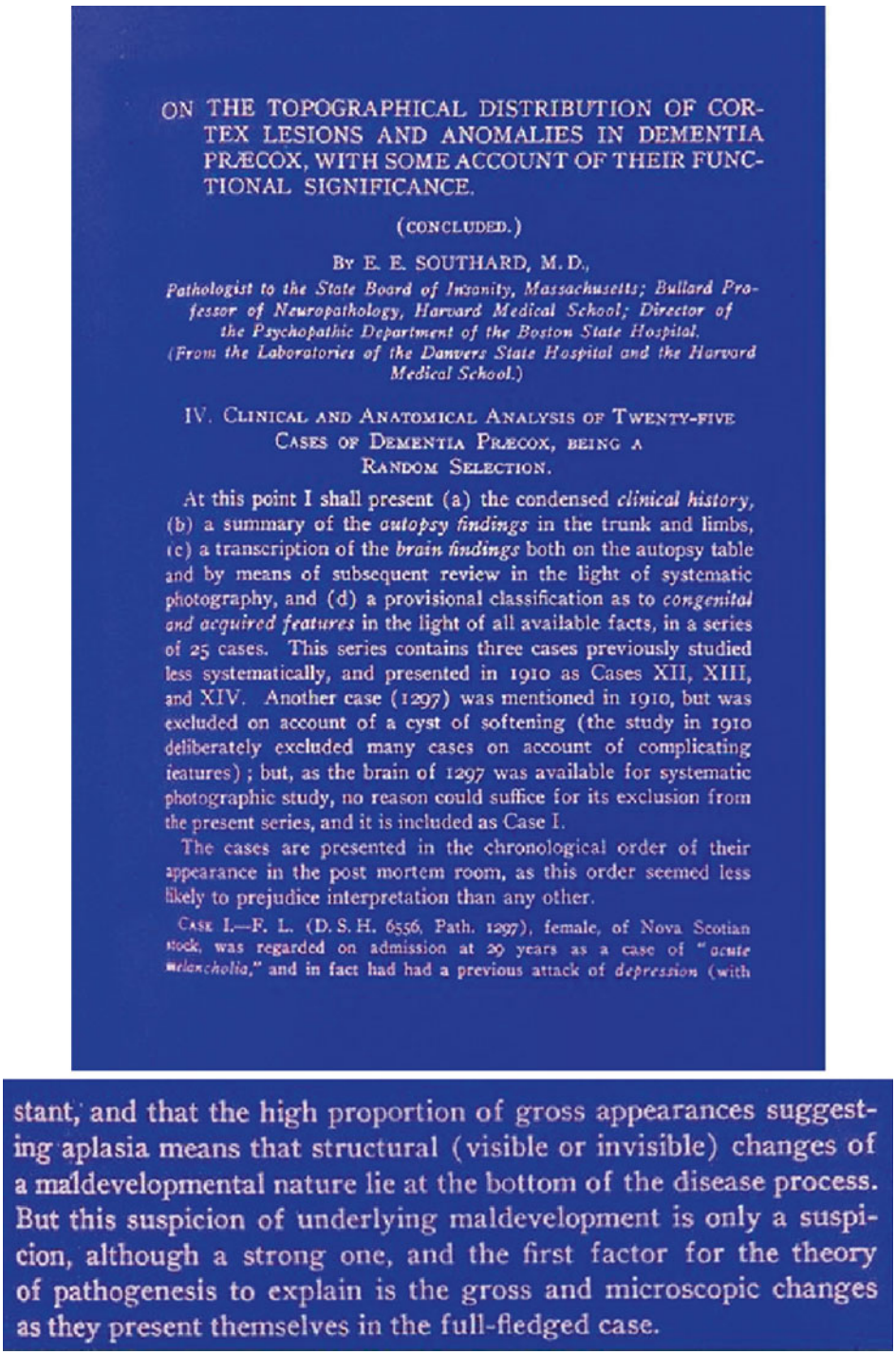
TABLE 6.3 Candidate genes: postmortem studies and animal models.

Gene	Abbreviation	Postmortem	Animal model
Adenosine A2A receptor	ADORA2A	+	+
Apolipoprotein D	APOD	+	+
CDC42 guanine nucleotide exchange factor 9	ARHGEF9	+	
Cholinergic receptor, muscarinic 1	CHRM1	+	+
Alpha7 nicotinic acetylcholine receptor	CHRNA7	+	+
Complexin 2	CPLX2	+	+
Catecholemine-O-methyltransferase	COMT	+	+
Dopamine and cAMP regulated phosphoprotein 32 kDa	DARPP-32	+	
Distal-less homeobox 1	DLX1	+	
Dopamine receptor D1	DRD1	+	
Dopamine receptor D2	DRD2	+	+
$GABA_A$ receptor, subunit alpha 1	GABRα1	+	
$GABA_A$ receptor, subunit alpha 2	GABRα2	+	
$GABA_A$ receptor, subunit alpha 5	GABRα5	+	+
$GABA_A$ receptor, subunit beta 1	GABRβ1	+	
$GABA_A$ receptor, subunit epsilon	GABRε	+	
$GABA_A$ receptor, subunit theta	GABRθ	+	
$GABA_B$ receptor 1	GABBR1	+	+
$GABA_B$ receptor 2	GABBR2	+	
Glutamic acid decarboxylase 2	GAD2	+	
Glial fibrillary acidic protein	GFAP	+	+
Glutamate receptor, ionotropic, AMPA1	GRIA1	+	
Glutamate receptor, ionotropic, AMPA2	GRIA2	+	
Myelin and lymphocyte protein	MAL	+	
Myelin basic protein	MBP	+	+
Neuronal PAS domain protein 1	NPAS1	+	+
N-deacetylase/N-sulfotransferse 3	NDST3	+	
Proteolipid protein 1	PLP1	+	
Reelin	RELN	+	+
Regulator of G protein signaling 4	RGS4	+	
Serotonin 5-HT-1A receptor	5HTR1A	+	
Serotonin 5-HT-2A receptor	5HTR2A	+	
Short stature homeobox 2	SHOX2	+	
Synapsin 2	SYN2	+	

List compiled from (14, 62–64, 115–121) and Papaleo F, Lipska BK, Weinberger DR. Mouse models of genetic effects on cognition: relevance to schizophrenia. Neuropharmacology 2012;62:1204–1220.

deals with cognitive/attentional, motivational and reward systems (7, 30); 3) mesocortical tract, originating from the ventral tegmental area and ending in the cortical structures, deals with attention, motivation and reward systems; and 4) the tuberoinfundibular tract, the cell bodies originating from the arcuate nucleus and periventricular hypothalamic areas and ending in the infundibulum and anterior pituitary, dealing with control of prolactin release (31–33). The dopamine (DA) receptors are classified into two distinct families of D1-like (D1 and D5) and D2-like (D2, D3, D4) receptors (30). The D1 receptors are localized to prefrontal cortex (PFC) and striatum. The D2 receptors are localized mostly to striatum but with lower concentrations in hippocampus, amygdala and entorhinal cortex. The D3 receptors are localized to ventral striatum. The D4 receptors are present in hippocampus and PFC. Finally the D5 receptors are found in hippocampus and entorhinal cortex (7, 30). Presynaptic DA receptors like D2 and D3 are localized to cell bodies or axon terminals of neurons (7). Dopamine helps in modulating glutamatergic inputs and pyramidal cell excitability (30).

The dopamine hypothesis of schizophrenia is based on the assumption that DA hyperactivity causes psychotic symptoms and that DA antagonists like chlorpromazine treat the psychotic symptoms (7). Additionally, administration of D-amphetamine to healthy volunteers leads to production of psychotic symptoms and worsens psychosis in schizophrenic subjects (7). One limitation of this hypothesis is that hallucinogens like LSD or psilocybin (acting on serotonin system) or dissociative anesthetics like ketamine or phencyclidine (acting on glutamate system) also cause psychotic symptoms (7, 30). A further limitation of this hypothesis is that consistent abnormalities have not been found in DA receptors or DA metabolites in subjects with schizophrenia (7, 30, 34). The two consistent postmortem findings include an increase in D2-like receptors in striatum of schizophrenics and lack of changes in striatal densities of D1 receptors or DA transporters (30). However, a recent finding of upregulated D1 receptor binding in dorsolateral PFC of schizophrenic subjects has been associated with impaired working memory performance (30).



ON THE TOPOGRAPHICAL DISTRIBUTION OF CORTEX LESIONS AND ANOMALIES IN DEMENTIA PRÆCOX, WITH SOME ACCOUNT OF THEIR FUNCTIONAL SIGNIFICANCE.

(CONCLUDED.)

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(From the Laboratories of the Danvers State Hospital and the Harvard Medical School.)

IV. Clinical and Anatomical Analysis of Twenty-five Cases of Dementia Præcox, being a Random Selection.

At this point I shall present (a) the condensed *clinical history*, (b) a summary of the *autopsy findings* in the trunk and limbs, (c) a transcription of the *brain findings* both on the autopsy table and by means of subsequent review in the light of systematic photography, and (d) a provisional classification as to *congenital and acquired features* in the light of all available facts, in a series of 25 cases. This series contains three cases previously studied less systematically, and presented in 1910 as Cases XII, XIII, and XIV. Another case (1297) was mentioned in 1910, but was excluded on account of a cyst of softening (the study in 1910 deliberately excluded many cases on account of complicating features); but, as the brain of 1297 was available for systematic photographic study, no reason could suffice for its exclusion from the present series, and it is included as Case I.

The cases are presented in the chronological order of their appearance in the post mortem room, as this order seemed less likely to prejudice interpretation than any other.

Case I.—F. L. (D. S. H. 6556, Path. 1297), female, of Nova Scotian stock, was regarded on admission at 29 years as a case of "*acute melancholia*," and in fact had had a previous attack of *depression* (with

stant, and that the high proportion of gross appearances suggesting aplasia means that structural (visible or invisible) changes of a maldevelopmental nature lie at the bottom of the disease process. But this suspicion of underlying maldevelopment is only a suspicion, although a strong one, and the first factor for the theory of pathogenesis to explain is the gross and microscopic changes as they present themselves in the full-fledged case.

Figure 6.1 Article by E. E. Southard demonstrating neuropathological signs in the brains of subjects with schizophrenia being of neurodevelopmental origin.

6.5.1.2. The Serotonin Hypothesis

The serotonin (5HT) neurons emanate from the midbrain dorsal and median raphe nuclei and project to several sites including hippocampus, striatum and cortex (7, 35–37). The number of various 5HT receptor types in the brain exceed 15 with the most important receptors being 5HT1, 5HT2, 5HT3, 5HT6 and 5HT7 (7). Inhibitory somatodendritic 5HT autoreceptors (5HT1A) are localized to raphe serotonergic neurons which upon activation lead to decreased firing of the neurons (7, 38). In contrast, terminal autorecceptors modulate synthesis and release of serotonin (7). 5HT3 receptors help to stimulate dopamine release (7). Additionally, pyramidal cells in the mesocortical areas bear post-synaptic 5HT2A receptors which subserve 5HT-DA interaction in various brain areas.

While LSD and other serotonergic agonists can lead to psychotic symptoms in healthy individuals, the latter symptoms consist mostly of visual hallucinations, which are less frequently seen in schizophrenic patients. Despite the shortcomings of the serotonin hypothesis of schizophrenia, the atypical antipsychotic agents used extensively today, are potent antagonists of the 5HT2 receptors which may help in treating negative symptoms of schizophrenia and reduce extrapyramidal side effects (EPS). A recent systematic review of the literature based mostly on postmortem studies indicates significant elevation in prefrontal 5HT1A and significant reduction in 5HT2A receptors in patients with schizophrenia (39). Evidence in support of other serotonin receptors has been limited (39).

6.5.1.3. The Glutamate Hypothesis

Glutamate is the main excitatory neurotransmitter in the CNS (7, 30). Approximately 60% of neurons and 40% of synapses of the brain are glutamatergic in nature respectively (30). The glutamate receptors consist of ionotropic and metabotropic families. The ionotropic glutamate receptors (those working through Ca^{++} channels) include N-methyl-D-aspartic acid (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA), and kainate receptors (5). The metabotropic family (receptors which indirectly regulate electrical signaling by activation of various second messengers) consists of groups I, II and III receptors (30). The glutamatergic hypothesis of schizophrenia is based on deceased levels of glutamate in the CSF of schizophrenic subjects (7, 31) and decreased expression of NMDA and AMPA receptors in hippocampus and thalamus of schizophrenic subjects (30, 40–43). A recent report indicates that altered glutamatergic function in the anterior cingulate is associated with more severe symptoms in subjects with schizophrenia (48). Changes in expression for various glutamate receptor types including NMDA receptors, AMPA receptors, kainate receptors, and metabotropic glutamate receptors in subjects with schizophrenia have been observed in multiple brain regions, however, a lack of consistent changes has also been noted (49). Mice with alterations in NMDA receptors, show hyperactivity and schizophrenic-like behaviors (44–47). Furthermore, altered N-glycosylation of NMDA, kainate, and AMPA receptors have been reported, suggesting that posttranslational modifications may lead to abnormal trafficking and expression of these receptors in subjects with schizophrenia (50, 51). Additionally, use of noncompetitive and competitive antagonists of NMDA receptors can lead to production of positive, negative and cognitive symptoms of schizophrenia (34). However, administration of clozapine, can block the NMDA antagonistic effects of PCP (34). Several compounds such as glycine, D-serine, and D-cycloserine have been reported to reduce positive and negative symptoms in subjects with schizophrenia (30, 34). Finally, genetic evidence also points to involvement of several genes (DAAO, G72, neuregulin, dysbindin, RGS4) which impact on glutamate system in schizophrenia (30).

6.5.1.4. The GABAergic Hypothesis

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain. Postmortem evidence suggests involvement of glutamic acid decarboxylase 65 and 67 kDa proteins (GAD65 and 67), the rate limiting enzymes that convert glutamate to GABA, in the cerebellum (52, 53) of schizophrenic subjects. Supportive data (54, 55) also point to decreases in GAD67 species in brains of subjects with schizophrenia.

Investigation of GABA receptors has shown altered expression in brains from subjects with schizophrenia (60–67). $GABA_A$ receptor alpha 2 (GABRα2) and $GABA_A$ receptor epsilon (GABRε) display upregulated protein expression in lateral cerebella of subjects with schizophrenia (63, 64). Protein levels of $GABA_A$ receptor beta 1 (GABRB1) and $GABA_A$ receptor theta (GABRθ) were found to be reduced in lateral cerebella of subjects with schizophrenia (63, 64). Additionally, protein levels of GABAB receptors 1 and 2 (GABBR1 and GABBR2) were found to be significantly reduced in lateral cerebella of subjects with schizophrenia (62). In BA9, protein level of GABRθ was found to be downregulated in subjects with schizophrenia (60, 61, 64–67). These reports provide further evidence of GABAergic dysfunction in brains of subjects with schizophrenia. Lastly, Reelin, an important factor involved in synaptic plasticity which colocalizes to GABergic interneurons is reduced in brains of subjects with schizophrenia (52, 56, 57, 59) (Fig. 6.2a).

6.5.2. Neurodevelopmental Theories of Schizophrenia

The accumulation of a large body of evidence over the last century points to involvement of pathologic processes that occur in utero and lead to development of schizophrenia in adolescence (5, 68, 69). These neurodevelopmental abnormalities, beginning in utero, as early as late first or early second trimester (68, 70) have been suggested to lead to activation of pathologic neural circuits during adolescence (7) which may underlie development of psychotic symptoms in the susceptible individual.

Theodor Meynert (70) referred to frontal lobe pathology as a cause for psychosis. Later, Alzheimer reported on disorientation of pyramidal cells and neuronal loss in frontal lobes of subjects with schizophrenia (71, 72). Elmer E. Southard, an American

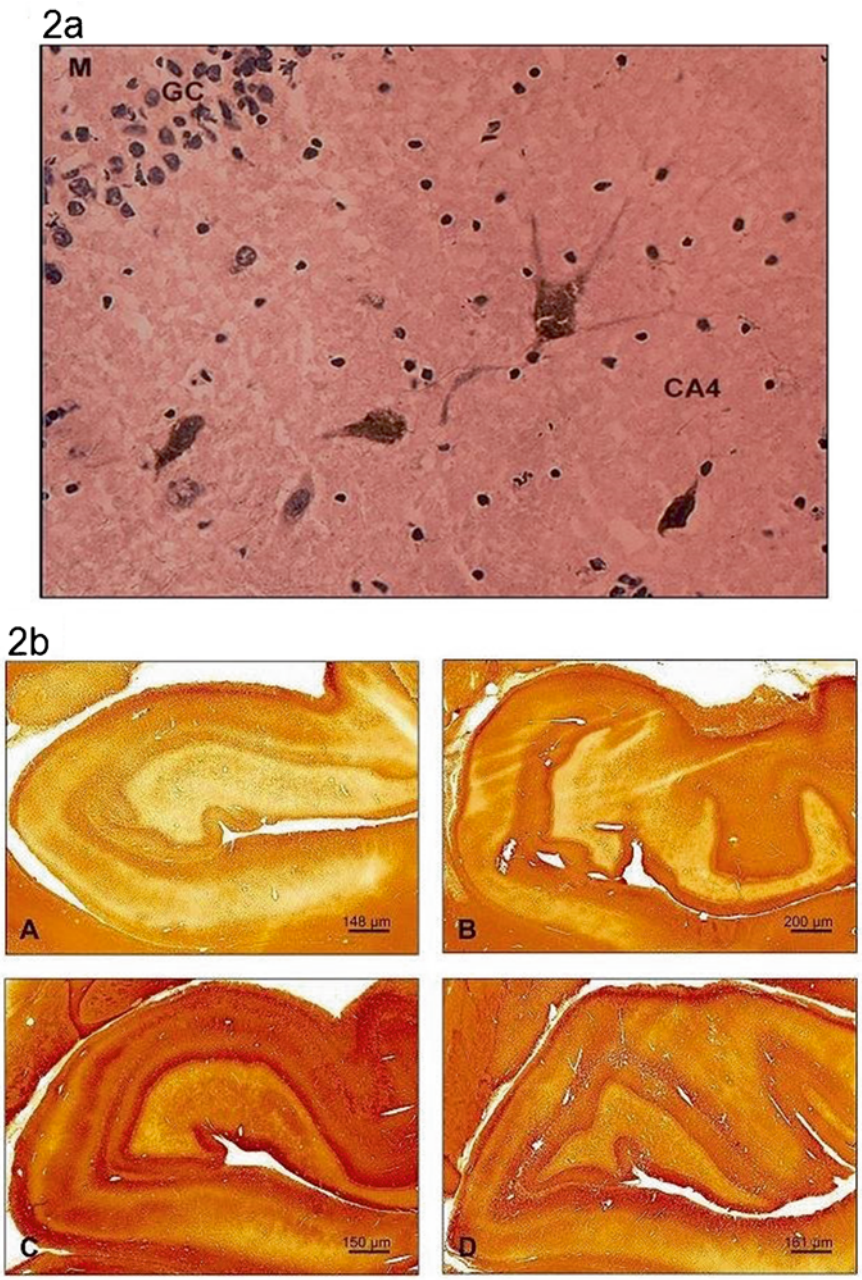

FIGURE 6.2 2a: Several Reelin-positive cells are localized to the hilus (CA4) of hippocampal complex. (M), dentate inner molecular layer, (GC), granular cell layer, 40 X magnification. 2b: SNAP-25 immunostaining is localized to various layers of ventral hippocampus in subjects with bipolar disorder (a), major depression (b) and schizophrenia (d) compared with a normal control (c). Note the diminution in SNAP-25 specific immunostaining in strata oriens and moleculare of patients with bipolar disorder (a) and schizophrenia (d) *vs* depressed (b) and control (c) subjects. 2a republished from (57), copyright (2000) with permission of Springer Science+Business Media. 2b republished from (58) (2001) with permission from Wolters Kluwer Health.

neuropathologist (73) who worked under Carl Weigert, visited Kraepelin's clinic and Franz Nissl's laboratory and produced the first convincing neuropathological study of schizophrenia (29, 73) that pointed to the maldevelopmental nature of schizophrenia. Southard also inferred that the cause for these maldevelopmental lesions may have been due to insults that interfered with brain cell growth and development (29). Resurgence of biological psychiatric research in the last four decades has strengthened Southard's pathological findings that schizophrenia is likely a neurodevelopmental brain disorder with significant genetic and environmental etiologies based on several lines of evidence which will be discussed in the following sections.

6.5.2.1. Obstetric and Perinatal Complications

There is a large body of epidemiologic research showing an increased frequency of obstetric and perinatal complications in schizophrenic patients (28). The complications observed include periventicular hemorrhages, hypoxia, and ischemic injuries (7, 74).

6.5.2.2. Brain Structural Studies

A consistent observation in schizophrenia is the enlargement of the cerebroventricular system. The abnormalities are present at onset of disease, progress very slowly, and are unrelated to the duration of illness or treatment regimen (7). Additionally, cerebroventicular enlargement distinguishes affected from unaffected discordant monozygotic twins. Furthermore, gross brain abnormalities have been identified in dorsolateral prefrontal cortex, hippocampus, cingulate cortex and superior temporal gyrus (7, 34). Some reports also indicate presence of brain structural abnormalities in individuals at high risk for development of schizophrenia and in unaffected first-degree relatives of subjects with schizophrenia (75). Additionally, studies of white matter tracts show evidence of disorganization and lack of alignment in white fiber bundles in frontal and temporoparietal brain regions in schizophrenia (76).

6.5.2.3. Histologic and Neuroimaging Studies

Numerous reports have documented the presence of various neuropathologic findings in postmortem brains of patients with schizophrenia (29, 77–80). These findings consist of cortical atrophy, ventricular enlargement, reduced volumes of hippocampus, amygdala and parahippocampal gyrus, disturbed cytoarchitecture in hippocampus, cell loss and volume reduction in thalamus, abnormal translocation of NADPH-diaphorase positive cells in frontal and hippocampal areas, reduced cell size in Purkinje cells of the cerebellum, and reduced synaptic spine density (77–79, 81). However, by far the greatest abnormalities have been found in prefrontal, ventral hippocampal and cerebellar cortices of schizophrenic brains (80). Collectively, these data reflect abnormal corticogenesis during the mid-gestation period in schizophrenic patients. Additionally, several various reports using MRI and diffusion tensor imaging (DTI) techniques have shown reduced white matter diffusion anisotropy (diffusion of water molecules in white matter) in subjects with schizophrenia (82–84). In brain white matter, water diffusion is highly anisotropic, with greater diffusion in the direction parallel to the axonal tracts. Thus, reduced anisotropy of water diffusion has been proposed to reflect compromised white matter integrity in schizophrenia (82). Furthermore, reductions in white matter anisotropy reflect disrupted white matter connections, which supports the disconnection model of schizophrenia (85). Reduced white matter diffusion anisotrophy has been observed in prefrontal, parieto-occipital, splenium of corpus callosum, arcuate and uncinate fasciculus, parahippocampal gyri and deep frontal perigenual regions of brain in schizophrenic patients (82, 86–90). There are also negative findings showing no white matter abnormalities in schizophrenia (91, 92). It is conceivable that downregulation of genes affecting production of myelin-related proteins as well as other components of axons may lay the foundation for white matter abnormalities which develop later in life in subjects who develop schizophrenia (93, 94).

Several reports indicate that glial cells are either dysfunctional (96–99) or unaffected in schizophrenia (100). Thus, absence of gliosis in brains of schizophrenic subjects may no longer imply direct support for initiation of early insults in utero in these patients (7). Furthermore, microglial activation has also been identified from several studies (101–104), suggesting dysfunctional immune activity in the brains and peripheral blood lymphocytes of subjects with schizophrenia.

6.5.2.4. Biochemical Brain Marker Anomalies and Microarray Studies of Schizophrenia

Biological markers consistent with prenatal occurrence of neurodevelopmental insults in schizophrenia include changes in the normal expression of proteins that are involved in early migration of neurons and glia, cell proliferation, axonal outgrowth, synaptogenesis and apoptosis (Table 6.4). Some of these markers have been investigated in studies of various prenatal insults in potential animal models for schizophrenia thus helping in deciphering the molecular mechanisms for genesis of schizophrenia (Table 6.3).

Multiple reports implicate various gene families as being involved in pathology of schizophrenia using microarray technology (95), i.e., genes involved in presynaptic function (95), signal transduction (94, 105–113), cell growth and migration (106), myelination (93, 94), regulation of presynaptic membrane function (107, 108), and GABAergic function (94, 109). By far the most well studied and replicated data deal with genes involved in oligodendrocyte and myelin-related functions. Hakak et al. (94) using mostly elderly schizophrenic and matched control dorsolateral prefrontal cortex homogenates showed downregulation of 5 genes whose expression is enriched in myelin-forming oligodendrocytes, which have been implicated in the formation and maintenance of myelin sheaths. Later, Tkachev et al. (93) using area 9 homogenates from Stanley Brain collection showed significant downregulation in several myelin and oligodendrocyte related genes such as proteolipid protein 1 (111), myelin

TABLE 6.4 Neurodevelopmental markers and schizophrenia.

Neurodevelopmental event	Molecule	Findings in schizophrenia
Cell migration	PSA-NCAM	↓ in dentate hilar area
	Reelin	↓ in mRNA and protein of neocortex, hippocampus and cerebellum
Synaptogenesis and axonal growth	SNAP-25	↓ in hippocampus and frontal cortex
	GAP-43	↑ in prefrontal and inferior temporal cortex; ↓ dentate gyrus
	Synaptophysin	↓ in prefrontal cortex and hippocampus
	Synapsin	↓ in hippocampus
Survival of connections	BDNF	↓ in hippocampus
Neuronal cytoskeletal proteins	MAP-2	↓ in subiculum and entorhinal cortex
	MAP-5	↓ in subiculum
Synaptic plasticity	NRG1	Nrg1 type I ↑ significantly in dorsolateral prefrontal cortex
Regulation of neurotransmitter signaling	RGS4	↓ in prefrontal cortex, motor cortex and visual cortex
Glutamatergic transmission	G72	Association of polymorphisms with early onset and male schizophrenia
	DAAO	4 intronic SNPs associated with schizophrenia in a French Canadian sample
	DTNBP1	Family association studies in Germany and Israel; DTNBP1 haplotype associated with schizophrenia in Chinese and Swedish samples
	GAD67	↓ in lateral cerebellum, PFC, and temporal neocortex
Cognition	COMT	Location in region 22q11 deleted in VCFS; variations in COMT associated with schizophrenia
Production of glutamate and GABA	PRODH	Location in region 22q11.2 deleted in VCFS; complex pattern of association with schizophrenia
	GAD1	↓ in lateral cerebellum
	GAD2	↓ in lateral cerebellum
GABAergic transmission	GABRα2	↑ in lateral cerebellum
	GABRβ1	↓ in lateral cerebellum
	GABRε	↑ in lateral cerebellum
	GABRθ	↓ in lateral cerebellum and PFC
	GABBR1	↓ in lateral cerebellum
	GABBR2	↓ in lateral cerebellum

Adapted and expanded from (7, 14, 52, 53, 56, 57, 59, 62, 63, 64, 65).

associated glycoprotein (MAG), claudin 11 (CLDN11), myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP), neuroregulin receptor ERBB3, transferrin, olig 1, olig 2, and Sry Box10 (SOX-10) (93).

Mirnics et al. (107) showed downregulation of genes involved in presynaptic function in the prefrontal cortex such as methylmaleimide sensitive factor, synapsin II, synaptojanin 1 and synaptotagmin 5. Another important family of genes involved in schizophrenia are genes involved in glutamate and GABAergic function. Hakak et al. (94) showed upregulation of several genes involved in GABA transmission, such as, glutamic acid decarboxylase 65 and 67 kDa protein genes. However, several reports have shown decreases in these proteins in schizophrenia (54, 112, 113). Hashimoto et al. (109) showed downregulation of Parvalbumin gene, and Vawter et al. (108) showed downregulation of glutamate receptor AMPA 2. For additional details on expression of glutamate and GABA receptors, please see Sections 6.5.1.3 and 6.5.1.4.

Another gene family of import in schizophrenia deals with signal transduction. Hakak et al. (94) showed upregulation of several postsynaptic signal transduction pathways known to be regulated by dopamine, consistent with the dopamine hypothesis of schizophrenia (110, 114) such as cAMP dependent protein kinase II-regulatory subunit and NT-related protein 2. Moreover, qRT-PCR studies have identified increased expression of dopamine and cAMP regulated phosphoprotein 32 kDa (DARPP-32), in PFC and DLPFC of subjects with schizophrenia (115, 116). Mirnics et al. (105) also showed downregulation of RGS4 gene in PFC of schizophrenia. Moreover, COMT, which degrades dopamine, shows altered expression, and is inversely correlated with expression of RGS4 (117). The cholinergic muscarinic receptor 1 (CHRM1) has been shown to be reduced in cortical and subcortical areas in brains of subjects with schizophrenia (118, 119). Furthermore, CHRNA7 mRNA expression has been shown to be reduced in blood from subjects with schizophrenia (120, 121).

6.5.2.5. Effects of Adverse Environmental Events on Brain Development In Utero

There is ample evidence to indicate that the greatest risk factor for development of schizophrenia is being related to a person with schizophrenia, i.e., in some subgroups, heredity can explain more than 80% of the liability to schizophrenia (122–124).

However, there is also a robust collection of reports indicating that environmental factors, especially viral infections, can increase the risk for development of schizophrenia (125, 126, 253, 254). Emil Kraepelin (127) referred to potential for infections causing some forms of dementia praecox (schizophrenia) during early stages of brain development. Meninger (128) described 67 cases of schizophrenia in a large cohort of patients who contracted influenza during the pandemic of 1919. Later, Hare et al. (129) and Machon et al. (130) reported on excess of schizophrenic patients being born during late winter and spring as indicators of potential influenza infections being responsible for these cases. Indeed, the majority of nearly 50 studies performed in the intervening years indicate that 5–15% excess schizophrenic births in the Northern Hemisphere occur during the months of January and March (124, 131, 132). This excess winter birth has not been shown to be due to unusual patterns of conception in mothers or to a methodological artifact (124, 133). Machon et al. (130) and Mednick et al. (134) showed that the risk of schizophrenia was increased by 50% in Finnish individuals whose mothers had been exposed to the 1957 A2 influenza during the second trimester of pregnancy. Later, nine out of fifteen studies performed replicated Mednick's findings of a positive association between prenatal influenza exposure and schizophrenia (68). These association studies showed that exposure during the 4th–7th months of gestation affords a window of opportunity for influenza virus to cause its teratogenic effects on the embryonic brain (135). Additionally, three out of five cohort and case control studies support a positive association between schizophrenia and maternal exposure to influenza prenatally (136–138). Subsequent studies have now shown that other viruses such as rubella (139) may also increase the risk for development of schizophrenia in the affected progeny of exposed mothers (124, 139). An interesting report linking viral exposure to development of schizophrenia was published by Karlsson et al. (126), who provided data suggestive of a possible role for retroviruses in the pathogenesis of schizophrenia (125). Karlsson and colleagues (126) identified nucleotide sequences homologous to retroviral polymerase genes in the cerebrospinal fluid (CSF) of 28.6% of subjects with schizophrenia of recent origin and in 5% of subjects with chronic schizophrenia. In contrast, such retroviral sequences were not found in any individuals with noninflammatory neurological illnesses or in normal subjects (124, 125). The upshot of these studies and previous epidemiological reports is that schizophrenia may represent the shared phenotype of a group of disorders whose etiopathogenesis involves the interaction between genetic influences and environmental risks, such as viruses operating on brain maturational processes (125). Moreover, identification of potential environmental risk factors, such as influenza virus or retroviruses such as endogenous retroviral-9 family and the human endogenous retrovirus-W species observed by Karlsson et al. (126), will help in targeting early interventions at repressing the expression of these transcripts. An alternate approach would be to vaccinate against influenza, thus influencing the course and outcome of schizophrenia in the susceptible individuals (125).

There are at least two mechanisms that may be responsible for transmission of viral effects from the mother to the fetus: I) Via direct viral infection. There are clinical, as well as direct experimental reports (140–143) showing that human influenza A viral infection of a pregnant mother may cause transplacental passage of viral load to the fetus. In a series of reports, Aronsson and colleagues used human influenza virus (A/WSN/33, a neurotropic strain of influenza A virus) on day 14 of pregnancy, to infect pregnant C57BL/6 mice intranasally. Viral RNA and nucleoprotein were detected in fetal brains and viral RNA persisted in the brains of exposed offspring for at least 90 days of postnatal life thus showing evidence for transplacental passage of influenza virus in mice and the persistence of viral components in the brains of progeny into young adulthood (142). Additionally, Aronsson et al. (142), have demonstrated that ten to 17 months after injection of the human influenza A virus into olfactory bulbs of TAP1 mutant mice, viral RNA encoding the nonstructural NS1 protein was detected in midbrain of the exposed mice. The product of NS1 gene is known to play a regulatory role in the host-cell metabolism (144). Several in vitro studies have also shown the ability of human influenza A virus to infect Schwann cells (145), astrocytes, microglial cells and neurons (109), and hippocampal GABergic cells (146, 147), selectively causing persistent infection of target cells in the brain. II) Via induction of cytokine production. Multiple clinical and experimental reports show the ability of human influenza infection to induce production of systemic cytokines by the maternal immune system, the placenta, or even the fetus itself (148–152). Indeed, work by Brown et al. (69) show presence of serologic evidence of maternal exposure to influenza as causing increased risk of schizophrenia in offspring (69). Offspring of mothers with elevated IgG and IgM levels, as well as antibodies to herpes simplex virus type 2 during pregnancy have an increased risk for schizophrenia. Cytokines such as Interleukin-1β, (IL-1β), IL-6 and tumor necrosis factor α (TNFα) are elevated in the pregnant mothers after maternal infection (148, 149, 152) and after infection in animal models (150, 151). All of these cytokines are known to regulate normal brain development and have been implicated in abnormal corticogenesis (153–155). Additionally, expression of mRNA's for cytokines in the CNS is developmentally regulated both in man and in mouse (156–160), emphasizing the significant role that cytokines play during neurodevelopment. IL-1β, IL-6 and TNFα cross the placenta and are synthesized by mother (161), by the placenta (162), and by the fetus (152). Maternal levels of TNFα and IL-8 have been shown to be elevated in human pregnancies in which the offspring goes on to develop schizophrenia (69, 163). A more relevant series of studies in different animal models for schizophrenia show that maternal infection with human influenza mimic poly I:C, a synthetic double stranded RNA that stimulates a cytokine response in mice, can cause abnormalities in prepulse inhibition (164), or after maternal exposure to E. coli cell wall endotoxin lipopolysaccharide, cause disruption of sensorimotor gating in the offspring (165). Finally, maternal exposure to poly I:C also causes

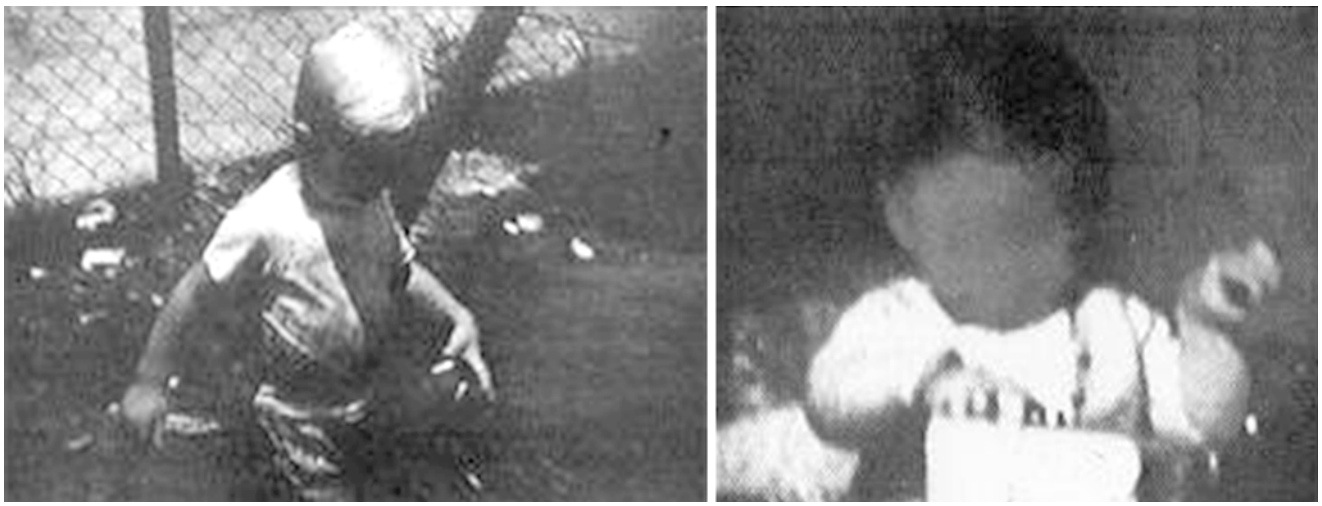

FIGURE 6.3 Abnormalities of left-hand posture in preschizophrenia children. Republished from (172), copyright (1994) with permission of Oxford University Press.

TABLE 6.5 Neurologic soft signs.

Choreoathetoid movements in preschizophrenic children
Abnormal gait
Abnormal body movements
Mannerisms
Grimacing
Stereotypies
Abnormal reflexes
Increased/decreased muscle tone
Abnormal rapid eye movements (saccades)
Frequent blinking
Dysdiadochokinesia
Astereognosis
Poor right-left discrimination
Anosognosia
Apraxia
Sympathetic arousal

disrupted latent inhibition in rat (166). All of these models suggest that direct stimulation of cytokine production by infections or immunogenic agents cause disruptions in various brain structural or behavioral indices of relevance to schizophrenia. Other factors associated with increased schizophrenic births include famine during pregnancy (124, 163) obstetric complications (167), Rh factor incompatibility (168) and autoimmunity due to infectious agents (169).

6.5.2.6. Congenital Anomalies and Developmental Dysfunction

Multiple markers of congenital anomalies indicative of neurodevelopmental insults have been found in schizophrenia (7). Such anomalies include agenesis of corpus callosum, stenosis of sylvian aqueduct, cerebral hamartomas, and cavum septum pellucidum. Presence of low-set ears, epicanthal eye folds, and wide spaces between the first and second toes, are suggestive of first trimester anomalies (7). There is, however, support for abnormal dermatoglyphics (Fig. 6.3) in patients with schizophrenia indicating a second trimester event (170). Multiple reports indicate the presence of premorbid neurologic soft signs (Table 6.5) in children who later develop schizophrenia (171, 172). Slight posturing of hands and transient choeoathetoid movements have been observed during the first two years of life in children who later developed schizophrenia (172, 173). Additionally, poor performance on tests of attention and neuromotor performance, mood and social impairment, and excessive anxiety have been reported to occur more frequently in high-risk children with a schizophrenic parent (174, 175). All of these findings are consistent with schizophrenia as a syndrome of abnormal brain development (255).

6.6. Clinical Findings

6.6.1. Clinical Signs and Symptoms of Schizophrenia

The current diagnostic criteria adopted by DSM-5 is based on extensive research dating back to initial findings of Kraepelin, Bleuler and Schneider (5, 8, 176). Unlike other medical conditions, no one sign is diagnostic of schizophrenia (7). Thus it is absolutely important to obtain as much clinical history about the patient to help establish a correct diagnosis.

As mentioned earlier, The DMS-5 criteria require presence of two or more of the following symptoms during a 1 month period: 1) delusions, 2) hallucinations, 3) disorganized speech, 4) grossly disorganized or catatonic behavior, 5) negative symptoms (flat affect, alogia or avolition). Alternatively, the diagnosis of schizophrenia may be based on presence of bizarre delusions alone, auditory hallucinations of a voice keeping a running commentary one one's daily activities, or two or more voices conversing with each other (7, 34). Delusions are fixed false beliefs not congruent with one's cultural or religious background. Schizophrenic patients may exhibit delusions that correspond to themes of persecution, grandiosity, outside control, guilt, thought broadcasting, thought withdrawal/insertion or ideas of reference (7). Bizarre delusions are highly implausible false beliefs (34). Hallucinations are abnormal perceptions of sensory experiences which occur in the absence of external stimuli. Hallucinations can be based on various types of sensory modalities such as auditory, visual, gustatory, olfactory, tactile or cenesthetic (change in the normal quality of feeling tone in a part of the body) (7, 177). Auditory hallucinations are more common in schizophrenic subjects, and occurrence of other types of hallucinations should be considered as potential signs of other medical/organic etiologies (7, 34). Command auditory hallucinations may lead the patient to act upon the command to harm self or others. Disorganized speech and behavior reflect underlying thought disorder or impairment (7, 34). Examples of abnormal speech include circumstantiality, tangentiality, derailment, illogicality, incoherence, concrete speech, clanging, neologims, echolalia, thought blocking, perseverations and poverty of content (7, 34). Disorganized behavior includes bizarre postures, stereotyped behavior, echopraxia, negativism, catatonic stupor/excitation, waxy flexibility, unprovoked outbursts of laughter or violent behavior, severe neglect of hygiene, poor self-care and grooming, grimacing, athetosis, and mutism. Grossly disorganized or catatonic behavior may also include verbigeration, primitive reflexes, autonomic hyperactivity, staring and rigidity. Finally, negative symptoms reflect deficits of normal functions and examples include affective flattening, avolition, alogia, anhedonia, social withdrawal, and diminished capacity to feel close to others (7, 34). These negative symptoms reflect endogenous markers of schizophrenia and are thus called primary negative symptoms (34). Negative symptoms such as depression or demoralization which may be due to side effects of medications, are called secondary negative symptoms.

Finally, as discussed earlier, social and occupational dysfunction, continuous presence of illness for six months and the ruling out of other illnesses or substance-related symptoms are required before a diagnosis of schizophrenia can be firmly established (9).

6.6.2. Mental Status Examination in a Subject with Schizophrenia

6.6.2.1. Appearance

Upon examination, a patient with possible diagnosis of schizophrenia may appear disheveled, exhibit evidence of poor self-care or grooming. Patient may appear suspicious, relate poorly to the examiner and exhibit bizarre postures, stereotypies, grimacing, athetosis, mutism or catatonic agitation or stupor (7). The clinician must look for presence of abnormal extra pyramidal signs (EPS) such as dystonia, tardive dyskinesia, rabbit syndrome or akathisia.

6.6.2.2. Affect

The subject may exhibit an affect which is incongruent with patient's state of mind and is described as inappropriate. Affect may also appear blunted, constricted or flat. However, absence of a sad affect does not rule out presence of a depressed mood. Flat affect may be secondary to drug induced parkinsonism or EPS.

6.6.2.3. Mood

Mood may be depressed or variable. As depression occurs frequently in schizophrenic subjects and causes a high rate of suicide, it is essential for clinicians to evaluate for presence of depression and to treat it promptly.

6.6.2.4. Speech

Evaluation of patient's speech may identify presence of loose, illogical or bizarre thought patterns. Additionally, patient may exhibit various abnormalities of speech such as tangentiality, circumstantiality, neologisms, clang association (speech directed by sound of a word rather than by its meaning) (177), perseveration and poverty of content (7). Patients may also express echolalia or thought blocking. Evidence of TD or dystonia affecting patient's speech should be investigated.

6.6.2.5. Thought Form and Content

Thought form can be ascertained while listening to patient's speech. Thus, presence of loose and illogical thought pattern is tantamount to evidence of formal thought disorder. Also, answering questions inappropriately (for example tangential responses: Q: What color is the sky? A: It rained yesterday) indicates formal thought disorder. Alternatively, thought content may be replete with evidence for delusions, ideas of reference, thought broadcasting, thought insertion or withdrawal, ideas of persecution or grandiosity or outside control. It is imperative to evaluate for presence of depression, mania, anxiety, panic, racing thoughts, irritability, suicidal and homicidal ideations or plans or past histories of suicide or violence towards others. Presence of obsessive-compulsive symptoms, past or recent histories of traumatic events and signs of PTSD should be evaluated.

6.6.2.6. Perceptual Abnormalities

Presence of hallucinations, illusions, Déja vu, depersonalization, and derealization should be determined. Intensity, frequency and past or present occurrence of various types of hallucinations should be determined. For example, specifics of gender of voices heard, loudness, origin of voices emanating from inside or outside one's head should be investigated. Presence of command auditory hallucinations which may order patient to harm himself/herself or others should be ascertained. The form and color of visual hallucinations should be evaluated. Visual hallucinations occurring during sleep, prior to or immediately after sleep are not necessarily indicative of a pathological process.

6.6.2.7. Cognition/Sensorium

Subjects with schizophrenia generally present with an intact sensorium i.e. they are alert and oriented to place, person and time. Evaluation of immediate, short and long term memory and attention should be performed. Other cognitive domains may display major abnormalities either through bedside examination or by performance of a neuropsychological battery of tests. Insight and judgement are generally evaluated by questioning patient's awareness of their illness or their ability to interact normally with others respectively. These mental abilities are more likely to be impaired in a patient with schizophrenia. Use of proverb analysis and similarities may shed light on patient's degree of abstraction or concreteness of thought. Most schizophrenic patients exhibit IQ scores 10 points lower than general public and exhibit impairments in attention, working memory, visual spatial memory, semantic memory, recall memory, and executive functions (7). Presence of cognitive abnormalities in schizophrenia appears to be independent of positive, negative or disorganization symptoms (7).

6.6.2.8. Physical Examination

As in all other fields of medicine, every psychiatrist must be able to do a focused physical examination to identify presence of any general medical or neurologic abnormalities. However, because of potential boundary issues, presence of a nurse or a chaperone in the examination room is warranted. Patients with schizophrenia have a higher burden of medical comorbidities and thus should be evaluated fully. Review of systems should cover neurologic, cardiovascular, ear, nose and throat, gastrointestinal, genitourinary, dermatologic, and endocrine systems. Presence of neurological soft signs (Table 6.5) such as abnormal gait, abnormal reflexes, changed muscle tone, abnormal rapid eye movements (saccades), frequent blinking, dysdiadochokinesia, astereognosis, poor right-left discrimination, anosognosia, apraxia, sympathetic arousal, choreoathetosis, mannerisms, grimacing, stereotypies and abnormal body movements are indicators of the neurodevelopmental origins of schizophrenia (7). Because of increased risk for diabetes and metabolic syndrome due to atypical antipsychotics, it would be judicious to obtain baseline and follow-up weight, vital signs and waist circumference (Body Mass Index) for every patient examined (178).

6.6.2.9. Neuropsychological Testing

Formal objective tests such as the Halstead-Reitan Battery, the Luria-Nebraska Battery, the Wechsler Adult Intelligence Scale, the Wechsler Intelligence Scale for Children, the Wisconsin Card Sorting Test (WCST), and the Brief Assessment of Cognition in Schizophrenia (BACS) (179) and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (180) can identify various brain abnormalities and should be performed in all initial evaluations.

6.6.2.10. Laboratory Investigations

6.6.2.10.1. Blood, Urine and Cerebrospinal Fluid

While no specific blood, urine or CSF tests are available to demonstrate presence of schizophrenia unequivocally, performance of certain blood and urine tests to rule out presence of nonpsychiatric causes for psychotic symptoms is warranted in all initial examinations. Tests such as thyroid function (TSH, T3, T4), RPR, HIV, fasting lipid panel, CBC with differential, metabolic panel (electrolytes, liver enzymes, BUN, glucose, creatinine) ESR, ANA, RF, B12, folate, prolactin, urinalysis, urine tox screen, blood alcohol level and baseline ECG should be performed during the initial evaluation as warranted by clinical judgment of the examining psychiatrists. Evaluation of hemoglobin A1C to rule out presence of diabetes mellitus at baseline and after institution of atypical antipsychotics is warranted. In certain cases, when suspicion of infectious etiologies is present, referral of patient to a neurologist and consultation with an infectious disease specialist for performance of a lumbar puncture is warranted.

6.6.2.10.2. Brain Imaging

Ventricular enlargement and increased brain sulcal prominence can be identified in CT or MRI views. While the findings are supportive of brain abnormality they are not specific to schizophrenia. Additionally, despite identification of a number of other brain abnormalities such as smaller cerebral and cranial size, smaller medial temporal structures (hippocampus), enlargement of lenticular nucleus, cerebellar vermal dysplasia and smaller thalamus in subjects with schizohprenia, none are diagnostic of schizophrenia (7). Shepherd et al. (181) in a meta-review of 32 publications, identified increased volumes of the ventricles and cavus septum pellucidum and reduced volumes for frontal lobe, post-central gyrus, temporal lobe, anterior cingulate, hippocampus, amygdala, thalamus, and insula in subjects with schizophrenia. Changes in volumes for fusiform gyrus, amygdala, parahippocampus, and posterior cingulate cortex/precuneus were only identified in subjects with chronic schizophrenia, suggesting an impact of the duration of illness (181).

More recently diffusion tensor imaging (DTI), has shown presence of white matter tract abnormalities in schizophrenic patients (182). While DTI abnormalities may be due to disease process itself, antipsychotic medications can impact white matter volume, cell density, and oligodendrocyte and astrocyte counts (183, 184), and thus affect DTI studies. Recent DTI studies have focused on white matter changes in drug naïve patients. These studies found white matter abnormalities in the corpus callosum (185), reduced fractional anisotropy in the left inferior longitudinal fasciculus (186), and the right superior longitudinal fasciculus II, the right fornix, the right internal capsule, and the right external capsule (187).

6.6.2.10.3. Functional Brain Imaging

Use of functional MRI (fMRI), SPECT and PET imaging has provided a wealth of information about various brain function abnormalities in schizophrenia (188–191). These abnormalities include dysfunction of information storage and retrieval by dorsolateral prefrontal cortex (DLPFC), abnormal inhibitory response to sensory stimuli by anterior cingulate cortex, abnormal encoding and retrieval of memory by hippocampus, abnormal reception and integration of sensory information by thalamic nuclei, primary sensory cortices and the multimodal cortices and impaired performance of cognitive tasks by basal ganglia, thalamus and cerebellum (34, 192–195, 203). During auditory and visual hallucinations, PET and fMRI studies have demonstrated increased activity in the auditory cortex, visual cortex, as well as the right middle temporal gyrus and/or right superior temporal cortex (196–198). Imaging during cognitive function tasks has shown altered activity in the frontal cortex of subjects with schizophrenia (199–202).

6.6.3. Differential Diagnosis

Psychotic symptoms are present in a number of conditions and must be ruled out before entertaining the diagnosis of schizophrenia.

6.6.3.1. Mood Disorders

Psychotic symptoms such as mood congruent hallucinations or delusions may occur in severe depression or mania. Acquisition of detailed history and correlative clinical data should guide the clinician as to whether these symptoms occur due to mood abnormalities. Exclusive co-occurrence of psychotic symptoms with mood symptoms should denote presence of mood disorder with psychotic features (7). Alternatively, an uninterrupted period of illness during which, at some time, there is either a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia should point to possibility of schizoaffective disorder (9).

6.6.3.2. Psychotic Disorders Due to Medical, Neurologic or Substance-Induced Conditions

The chronology of psychotic symptoms occurring in relation to an inciting condition or in association with physical or laboratory signs indicative of a medical or neurologic disorder is helpful in distinguishing non schizophrenic psychosis. Many substances can cause psychosis such as amphetamines, substituted amphetamines such as ecstasy, hallucinogens, alcohol, barbiturates, cocaine, ketamine, PCP and belladonna alkaloids (7). Examples of medical or neurologic conditions that induce psychosis include infectious causes (herpes encephalitis, neurosyphilis, AIDS), metabolic events (acute intermittent porphyria, vitamin B12 deficiency, carbon monoxide poisoning, homocystinuria, heavy metal poisoning), neurologic events (temporal lobe epilepsy, frontal or limbic trauma, cerebrovascular accidents, Huntington's disease, metachromatic leukodystrophy, normal pressure hydrocephalus, Wernicke-Korsakoff syndrome, Wilson's disease, Jakob-Creutzfeldt's disease) and various conditions such as neoplasms, Fabry's disease, Fahr's disease, Hallervorden-Spatz disease and systemic lupus erythematosus. Clearly, obtaining historical details on clinical course, performing physical examination and doing pertinent laboratory examination will help the psychiatrist in identifying the cause of psychotic symptoms and ruling out schizophrenia (7).

6.6.3.3. Other Psychotic Disorders

Psychotic symptoms may occur during a period of mood abnormality such as depression, mania or mixed episode with mood symptoms present for a substantial portion of the total period of illness denoting schizoaffective disorder. In brief psychotic disorder, schizophrenic symptoms occur for at least 1 day but less than 4 weeks and these may occur in presence or absence of a marked stressor or with onset within 4 weeks postpartum (9). In schizophreniform disorder, prodromal, residual or active schizophrenic symptoms occur for at least 1 month but less than six months in duration. Delusional disorder refers to nonbizarre delusions in the absence of hallucinations, disorganized speech or behavior or negative symptoms or mood disorder. Finally, psychotic disorder not otherwise specified deals with disorders that do not meet the criteria for any of the above-mentioned diseases and for which adequate information is not available.

6.6.3.4. Other Axis I Disorders

Symptoms which may resemble hallucinations or paranoia may be observed in PTSD patients but these ensue following a traumatic event. Severe intrusive thoughts in OCD patients neither reach the level of delusionality seen in schizophrenia or if they occur in absence of insight do not accompany functional incapacity seen in psychotic patients. Finally, in subjects with hypochondriasis or body dysmorphic disorder no hallucinations or delusions are present (34).

6.6.3.5. Personality Disorders

Symptoms of schizotypal, schizoid, paranoid, and borderline personality disorders lack an exact onset of disease, are present throughout patient's life and are mild (7). However, these do not reach a level meeting criterion A for schizophrenia, and do develop as early as adolescence or early adulthood.

6.7. Pharmacological Treatments of Schizophrenia

6.7.1. Clozapine

Clozapine is a dibenzodiazepine and the prototype for most of atypical antipsychotics [agents which may treat positive, negative or cognitive symptoms of schizophrenia, have decreased liability for EPS and tardive dyskinesia, may be effective for a proportion of treatment nonresponsive patients and exhibit greater 5HT2 over D2 receptor antagonism and do not cause hyperprolactinema

(204, 205)]. It has a complex pharmacologic profile encompassing affinities for 5HT2A, 5HT2C, 5HT6, 5HT7, α1, α2 adrenergic, M1 muscarinic and histaminergic receptors (7). Clozapine exhibits inverse agonist activity at 5H2A and 5HT2C receptors blocking constitutive activity of these receptors (34). The ratio of 5HT2A to D2 receptor affinities may signal clozapine's low EPS profile (7).

Clozapine has been shown to be effective in treatment resistant schizophrenia (206). This important study compared the efficacy of clozapine to chlorpromazine in 268 subjects with treatment resistant schizophrenia (defined as having failed to respond to at least three prior antipsychotics). By 6 weeks, 30% of the clozapine-treated group but only 4% of the chlorpromazine-treated group responded to the respective medications (206, 17). Thus, clozapine remains the only antipsychotic agent to date that is FDA-approved for treatment-resistant schizophrenia (206). Additionally, other studies have shown superiority of clozapine vs. typical agents in treatment of total psychopathology, EPS and TD and categorical response to treatment (206). Clozapine reduces positive, negative and cognitive symptoms of schizophrenia without causation of EPS, TD or hyperprolactinemia (34). Furthermore, clozapine has been shown to reduce depression and suicidality (7, 34).

The dose range of clozapine varies from 150–450 mg/day for most patients (259). The initial dose of 25 mg/day must be titrated upwards slowly (increments of 25 mg/3 days) due to hypotensive and tachycardic side effects (7). The average dose is about 400–500 mg/day as a twice daily regimen (7). Plasma levels of 350–400 ng/ml have been associated with good clinical response (7, 256).

Despite clozapine's important clinical efficacy, several side effects must be considered as potentially significant and life threatening. Agranulocytosis occurs within the initial 4–18 weeks of treatment, necessiting monitoring of while blood cell (WBC) and neutrophil count every week, for the first 6 months (34), every 2 weeks for the next 6 months and once monthly thereafter (7). If the WBC count falls below 3000 cells per mm^3 or the absolute neutrophil count below 1500 cells per mm^3, clozapine administration must be stopped. Upon diagnosis of agranulocytosis, administration of granulocyte colony stimulating factor (G-CSF) and hospitalization, is warranted. The death rate from agranulocytosis is ≈ 1 per 10,000 patients (34). Other side effects of clozapine include sedation, weight gain, seizures, OCD symptoms, hypersalivation, tachycardia, hypotension, hypertension, stuttering, neuroleptic malignant syndrome, urinary incontinence, myocarditis, constipation, hyperglycemia, eosinophilia and fever (7). Seizures can be treated with valproic acid or lamotrigine supplementation (207–209).

6.7.2. Risperidone

Risperidone is a member of the benzisoxazole family of atypical agents and the second FDA approved antipsychotic agent classified as atypical to be marketed in USA. Several studies suggest that risperidone may be more effective than typical antipsychotics in acute and maintenance treatment of schizophrenic subjects (207). While risperidone may be superior to typical agents in treatment-resistant patients, it is not considered as effective as clozapine in this vulnerable group of schizophrenic patients (210).

The recommended dosage of risperidone is 2–8 mg/day (9). Risperidone causes higher occupancy of D2 receptors than does clozapine and may cause mild EPS even at 2–4 mg/day dosage range (7). Additionally, risperidone causes hyperprolactinemia. Other side effects include akathisia, weight gain, sexual dysfunction, decreased libido and galactorrhea (7). Risperidone is available in depot form for injection.

6.7.3. Olanzapine

Olanzapine is a thienobenzodiazepine agent and the third FDA approved atypical agent marketed in the USA in late 1990's. This novel agent exhibits nanomolar affinity at several receptor sites including D1–D4, 5HT2, 3, 6, muscarinic M1–5, α1 adrenergic and H1 histaminergic sites (7). Additional novel findings show that olanzapine causes modulation of several important brain genes like Reelin, insulin, regulator of G-protein signaling (RGS2), pyruvate kinase, calbinden and homer 1 after chronic administration in rats (211). Furthermore, olanzapine was shown to increase glucogenesis in brain via multiple pathways potentially linking its ability to produce glucose for energy consumption in brain to its metabolic side effect profile in the treated subjects (212). Olanzapine also downregulates the soluble isoform of COMT in frontal cortex of rats helping in upregulating the levels of dopamine in this important brain area (213).

Olanzapine has several characteristics of an atypical agent such as low EPS propensity, chemical structural similarity to clozapine, lack of hyperprolactinemic side effect, broad efficacy and ability to treat negative symptoms of schizophrenia (7). Multiple studies have shown olanzapine to have some efficacy over typical agents in the acute and maintenance treatment of schizophrenia (210) and in treatment of refractory patients. The dose range for olanzapine is 5–20 mg/day (259). Despite olanzapine's beneficial effects, several side effects including weight gain, metabolic disturbances, sedation, dizziness and transient liver transaminase elevations should be watched for (7).

6.7.4. Quetiapine

Quetiapine is a member of dibenzothiazepine family of atypical agents with high affinity for 5HT2A, α1 adrenergic and H1 histaminergic receptors (7). Quetiapine also exhibits moderate affinity for D2 and low affinity for M1 muscarinic receptors (7). Quetiapine dose range is 300–600 mg/day with similar efficacy as typical agents and is associated with low EPS propensity and prolactin elevation (207). The most common side effects include sedation, dry mouth, agitation, constipation and orthostatic hypotension (7). Quetiapine can cause QT prolongation (257) and has the potential to cause torsade de pointes and has a warning label based on FDA recommendations.

6.7.5. Ziprasidone

Ziprasidone is a benzothiazolyl piperazine with high affinity for serotonergic (5HT1A, 5HT2A, 5HT2C, 5HT1D) and dopaminergic (more D3, less D2) receptors. It has weak affinities for muscarinic and histaminergic receptors (7). Recent data indicate that ziprasidone has similar antipsychotic efficacy to haloperidol, is associated with minimal weight gain, sedation or prolactin elevation (207). The dose range is 80–160 mg/day. Despite initial concerns for ziprasidone causing QT-interval changes, such as torsade de pointes, FDA does not require ECG acquisition prior to treatment and no published reports indicate any cardiotoxic effects (207).

6.7.6. Aripiprazole

Aripiprazole is the first FDA approved partial dopamine D2 agonist, marketed in 2002, with partial agonist activity at 5HT1A receptor and 5HT2A antagonism (34, 207). Aripiprazole has low EPS propensity, low liability for hyperprolactinemia and weight gain (207). The dose range is 10–20 mg/day (34). Aripiprazole is effective in short and long term treatment of schizophrenia (207). Side effects may include activation and nausea (34).

6.7.7. Paliperidone

Paliperidone was approved for the treatment of schizophrenia in 2006 and schizoaffective disorder in 2009 (214). Paliperidone, a metabolite of risperidone (9-hydroxyrisperidone), is a dopamine D2 receptor antagonist (215). The approved range of doses for paliperidone is 6–12 mg/day (216–219, 259). Clinical data from short-term treatment trials of paliperidone have demonstrated superior efficacy to placebo on several psychometric tests (216–218). Results from a long-term study also found that paliperidone was superior to placebo in preventing relapse [25% for paliperidone vs. 53% of placebo (220)]. Pooled data from three 52-week studies found that paliperidone treatment resulted in maintenance of clinical improvements and was well-tolerated (221). Meltzer et al. (219) using data from three six week studies (216–218) found that subjects treated with paliperidone showed no significant differences in weight gain or for a number of metabolic measurements including fasting glucose, triglycerides, lipoproteins, or cholesterol levels when compared with controls.

6.7.8. Iloperidone

Iloperidone was approved for the treatment of schizophrenia in 2009. Unlike other antipsychotic medications, iloperidone has relatively high affinity for noradrenergic alpha 1 receptors rather than serotonin 5HT2A and dopamine D2 receptors (222). Iloperidone needs to be titrated to its target dose of 12–24 mg/day, and is generally administered twice daily (222). There have been four short-term double-blind, placebo- and active controlled studies of iloperidone's efficacy (223–225). A meta-analysis of pooled patient data found that iloperidone was significantly more effective than placebo in reducing PANSS total score, PANSS positive subscale, PANSS negative subscale, and BPRS-derived total scores (226). Data from three, pooled long-term studies of iloperidone vs. haloperidol found that iloperidone had similar efficacy as haloperidol and a favorable long-term safety profile (227). More recently, Cutler et al. (228) similarly found that iloperidone was safe and tolerable long-term with regard to weight gain and metabolism, however, there was no improvement in total PANSS scores over baseline. Iloperidone is known to increase corrected QT interval (QTc), however, there have not been any reports of serious cardiac dysfunction associated with increased QTc (229).

6.7.9. Asenapine

Asenapine was approved for use in 2009 and is used for the treatment of schizophrenia and for acute treatment of manic or mixed episodes of bipolar I disorder (222). Asenapine is absorbed through the oral mucosa as its bioavailability is less than 2%

if swallowed (230–232). Asenapine has high affinity for multiple serotonin receptors (5-HT2A, 5-HT2B, 5-HT2C, 5-HT6, 5-HT7) and the dopamine D3 receptor (222). Asenapine does not need to be titrated and is dosed at 5 mg/day bid for acute schizophrenia and 10 mg/day bid for maintenance (222). A meta-analysis of four short-term studies of asenapine's efficacy (230, 233, 234) found that asenapine was more effective than placebo with regard to change in PANSS total score (235). Longer-term studies employing olanzapine as an active control found that olanzapine was more effective than asenapine in reducing PANSS scores at the end of 52 weeks (236) and the 16 item negative system assessment (NSA-16) at the end of 26 weeks (237). However, Buchanan et al. (237) found that during the extension study, that asenapine was superior to olanzapine in changing NSA-16 scores at 52 weeks. When compared with placebo, asenapine does not appear to have any effect on weight gain, fasting serum glucose, total cholesterol, or triglyceride levels (230, 238).

6.7.10. Lurasidone

Lurasidone was approved for use in 2010 and is used to treat schizophrenia and depressive episodes associated with bipolar I disorder (222). Lurasidone is a full D2 dopamine and 5-HT2A receptor antagonist (222). Unlike iloperidone or asenapine, lurasidone is taken once a day and has a target dose of 40–80 mg/day for the treatment of schizophrenia (222, 259). A number of short-term, six-week trials have shown that lurasidone, at a variety of doses, is superior to placebo for the treatment of acute schizophrenia as determined by reduction in PANSS scores (239–243). A long term extension by Loebel et al. (244) found that lurasidone produced higher rates of remission than quetiapine. A second long-term study found improvement in mean PANSS total scores, mean Clinical Global Impression Schizophrenia (CGI-S) score, and mean Calgary Depression Scale for Schizophrenia (CDSS) score (245). Lurasidone does not appear to cause increased weight or changes in metabolic values, nor does it impact QT interval (222).

6.7.11. Typical Antipsychotics

Results of CATIE trials (210) have indicated that there may not be significant differences between several atypical agents (clozapine, olanzapine, ziprasidone, aripiprazole and risperidone) and a typical agent (perphenazine) with regards to efficacy in treatment of schizophrenic positive symptoms. Indeed, introduction of chlorpromazine and later antipsychotic agents like haloperidol in the 1950's revolutionized the treatment of schizophrenia (7). These agents clearly treated positive symptoms in 60–70% of patients and enabled many patients to leave hospitals for the first time in decades. The early hypotheses suggested that action of typical antipsychotics in ameliorating the positive symptoms of schizophrenia were due to their dopaminergic antagonism (7). Recent genetic and microarray studies have revealed that most if not all antipsychotic agents probably treat schizophrenic symptoms by modulating a large number of brain genes whose upregulation or repression chronically, may lead to stabilization of positive, negative and cognitive deficits in schizophrenia (246–248). Thus, it appears that modulation of major neurotransmitters like dopamine, serotonin, glutamate, GABA and acetylcholine by various antipsychotic agents may only be part of a larger array of brain genes and proteins that may be involved in treatment of schizophrenia.

6.7.12. Multiple Phases of Pharmacologic Treatment

In acute phase treatment, patients with florid psychotic symptoms are generally admitted to a hospital setting and given short acting antipsychotic agents (ziproasidone, olanzapine or haloperidol) alone or in combination with benzodiazepines and/or anticholingerics. The clinical decision to begin antipsychotic treatment is dependent on several factors including side effect profile, past history of response to medications and patient preference (Table 6.6). The order of antipsychotic agents of choice based on decreased propensity for metabolic side effects/EPS/TD may be aripiprazole, quetiapine, risperidone/paliperidone, ziprasidone, olanzapine, haloperidol. In cases of noncompliance, depot medications such as long acting risperidone, haloperidol or fluphenazine may be administered (34).

In continuation phase treatment, patient's response to antipsychotic agent, side effect profile, tolerability and compliance will be monitored carefully (34). It is generally expected to achieve optimal response to most agents by 4–6 weeks, however, longer periods of therapy may be necessary in certain individuals. In some patients, residual constellation of positive, negative or cognitive symptoms may remain. In some cases, one antipsychotic agent may be switched with another medication. Alternatively and specifically in treatment nonresponsive patients, clozapine alone or in combination with other agents such as valproate, benzodiazepines, antidepressants or lithium may be necessary to treat various symptoms.

TABLE 6.6 Commonly used antipsychotic drugs.

Class and drug name	Dosage range (mg)	Clorpromazine equivalents (mg/day)	Parenteral dosage (mg)	Galenic forms
Typical drugs				
Chlorpromazine	200–600	100	25–75	O, L, I, S
Fluphenazine	2–20	2.5	5–10	O, L, I
Fluphenazine decanoate	–	–	25–50 every 1–4 weeks	–
Fluphenazine enanthate	–	–	25–50 every 1–4 weeks	–
Haloperidol	4–20	2.5	5–10	O, L, I
Haloperidol decanoate	–	–	50–150 every 1–4 weeks	–
Loxapine*	60–100	10	25–50	O, L, I, OH
Mesoridazine	75–300	83	25–50	O, L, I
Molindone	30–100	10	NA	O, L
Perphenazine	8–32	8	6–12	O, L, I
Pimozide	2–6	1	NA	O
Thioridazine	150–600	100	NA	O, L
Thiothixene	5–30	5	2–4	O, L, I
Trifluoperazine	5–20	5	4–9	O, L, I
Atypical drugs				
Aripiprazole	10–20	7	NA	O, L, I
Asenapine	10–20	5	NA	OD
Clozapine	150–450	67	NA	O
Iloperidone	12–24	6	NA	O
Lurasidone	40–80	20	NA	O
Olanzapine	5–20	5	10–15	O, I, OD
Paliperidone	6–12	2	234 mg on day 1; 156 mg one week later; and 117 mg monthly for maintenance	O, I
Quetiapine	300–600	167	NA	O
Risperidone	6–8	1.3	NA	O, L, I, OD
Risperidone microspheres	–	–	25–50 every 2 weeks	I
Ziprasidone	80–160	40	20–40	O, L, I

O, oral; L, liquid; I, Injection; OH, oral inhalation; S, suppository. OD, oral disintegrating form.
*Loxapine is now FDA approved as the first inhalational-based antipsychotic.
Baldessarini RJ. Chemotherapy in Psychiatry. Pharmacologic Basis of Treatments for Mental Illness, 3rd edition. New York, Springer;2013.
Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. Am J Psychiatry 2010;167:686–693.

In maintenance phase treatment, patients who have responded well to various agents should be treated indefinitely to prevent relapse and worsening of disease process. In treatment refractory cases, clozapine appears to be the only drug with proven efficacy (34).

6.8. Antipsychotic Related Side Effects

One of the major reasons for choice of new second generation antipsychotics relates to high frequency of several side effects which are more prevalent with typical agents. For example, extrapyramidal side effects (EPS) such as dystonias (repetitive involuntary skeletal muscle contractions, (Fig. 6.4), dyskinesias [slow or tardive dyskinesias (TD) or severe involuntary choreiform, athetoid, or rhythmic muscular contractions which may involve face, neck, tongue, hands, trunk, legs], pseudoparkinsonism, rabbit syndrome, akathesias occur secondary to use of high potency typical antipsychotics. All of these side effects except for TD can be treated by judicious use of anticholinergics, benzodiazepines or propranolol or reduction in dose of antipsychotic agents or by changing to an atypical agent. There are no proven treatments for TD. Non-neurologic side effects may include hyperprolactinemia, gynecomastia, impotence, amenorrhea, weight gain, hematologic effects, jaundice and cardiac effects (7).

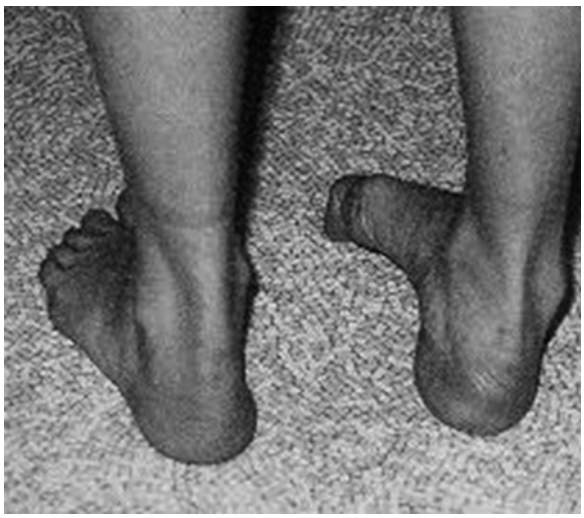

FIGURE 6.4 Foot dystonia, which is most obvious when the patient attempts to walk. Republished with permission of Taylor and Francis Group LLC Books from Uiti RJ, Francois G, Vingerhoets G, Tsui JKC, Limb Dystonia, in: Handbook of Dystonia, King J, Tsui JKC eds. copyright (1995); permission conveyed through Copyright Clearance Center, Inc.

6.9. Electroconvulsive Treatment of Schizophrenia

ECT treatment (6–12 treatments) may be an adjunct in treatment-refractory patients and when required in rapid control of excited catatonia and severe agitation. Long term use of ECT in treatment of schizophrenia is not supported by current literature (7).

6.10. Psychosocial Treatment

There are several psychosocial treatment modalities like cognitive-behavioral therapy, personal therapy, compliance therapy, acceptance and commitment therapy as well as supportive psychotherapy which have been found to help patients and their families to deal with the disease process, noncompliance issues and improvement of patients' living and work functioning (34). Application of case management, token economy, reduction of expressed emotion by patients' family and assertive community treatment, social skills training and cognitive rehabilitation strategies can all help patients with schizophrenia to have a better outlook on life and to improve their compliance with medication regimen (34).

6.11. Time Course of Schizophrenia

Disease onset is quite variable. The prodromal phase consists of a period during which patient may experience social withdrawal, decreased motivation, poor cognition, increasing odd behavior and restricted affective range (34). During the active phase (first psychotic break), patient exhibits florid psychotic symptoms either in response to life stressors or following substance abuse (34). In residual phase, there remains some schizophrenic symptoms which persist despite treatment.

6.12. Prognosis and Course of Illness

The modern concept of the prognosis of schizophrenia is based on multiple outcome measures. Four types of outcome measures have been identified: psychopathology, work function, social function, and rehospitalization. These measures could vary independently in schizophrenia, and although they are central to evaluating outcome in schizophrenia, other measures such as cognitive function, general health, and suicide are also important.

Outcome in schizophrenia can be predicted partially by age at onset and by the nature of the prodrome and first episode (Table 6.7). Early age at onset (e.g., 14–18 years) is often associated with a worse outcome than is later age at onset. An insidious rather than an abrupt onset is also associated with a poor outcome. If the initial clinical presentation is characterized mainly by negative symptoms, outcome is likely to be poor, both in the short and long term. Conversely, florid psychosis and an abrupt onset are both likely to be associated with a good prognosis because antipsychotic drugs are much more effective against positive symptoms and disorganization than they are against negative symptoms and cognitive disturbance.

TABLE 6.7 Predictors of course and outcome in schizophrenia.

Factor	Good outcome	Poor outcome
Age at onset[1]	About 20–25	Below 20
CT/MRI studies[1]	Normal morphology	Dilated ventricles, brain atrophy
Initial clinical symptoms[1,2]	Catatonia, paranoia, depression, schizoaffective diagnosis, atypical symptoms, confusion	Negative symptoms (e.g., flat affect, poverty of thought, apathy, asociality); obsessive-compulsive symptoms
Occupational record[1]	Stable	Irregular
Onset[1]	Acute, late	Insidious
Rate of progression[1]	Rapid	Slow
Sex[1]	Possibly females	Possibly males
Length of episode prior to assessment[2]	Months or less	Years
Being in a developing country[3]	Present	Absent
Cannabis use[3]	Absent	Present
Optimal prenatal care[3]	Present	Absent
Precipitating factors[3]	Present	Absent
Socioeconomic status[3]	Middle, high	Low
Substance abuse[3]	Absent	Present
Stressful life[3]	Absent	Present
Early treatment with medications[4]	Present	Absent
Long term drug maintenance[4]	Present	Absent
Response to medications initially[4]	Present	Absent
Family history of mental illness[5]	Affective	Schizophrenia
Other adverse social factors[5]	Absent	Present
Prenatal adverse events[5]	None	Present
Presence of certain gene polymorphism e.g., COMT. NMDA2A[5]	Absent	Present

1 = Clinical; 2 = Diagnosis; 3 = Environment; 4 = Treatment; 5 = Genetic; adapted from Meltzer et al. 2008 (218); Perkins et al. 2006 (249).

Results from several long term reports studying outcome in schizophrenia show that over a 15 year period several disease courses may emerge: 1) 9–38% of patients will have a sustained recovery (249); 2) 10% of the patients will have a persistent unremitting course (249–252); 3) 67% of patients will have a good outcome (249, 250); 4) 32% of patients will have a poor outcome (249, 250); and 5) 10% will die by suicide (249). Generally, the overall prognosis of schizophrenia is more favorable now than before neuroleptics were introduced, mostly because of improvements in pharmacologic therapies and, to some degree, changes in psychosocial treatment strategies. The increased mortality in patients with schizophrenia today is the result of suicide, accidents, and diseases (e.g., infections, type II diabetes, heart disease, and in females, breast cancer) (249).

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