Psychosis (Schizophrenia Spectrum and Other Psychotic Disorders)

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19.1 Vignette

A consultation was requested for a 25-year-old Caucasian man on the medical service. He was brought to the hospital by the police after he barricaded himself in a motel room, not allowing the housekeeping personnel to come in for days. The patient was found to be agitated and mute. In the emergency department, he was found to have a fever of 40 °C, an elevated creatine phosphokinase (CPK), and increased serum osmolality. He was admitted to the general medical floor, and intravenous fluids were given.

To treat agitation, the psychiatric consultant might consider an antipsychotic or a benzodiazepine. In view of the patient's fever and elevated CPK and unknown history, neuroleptic malignant syndrome, a contraindication for an antipsychotic, could not be ruled out. Thus, intravenous lorazepam 2 mg q 2 h was recommended for agitation. The patient fell asleep after receiving 6 mg of lorazepam. The next morning, the patient started speaking, initially incoherently. He had a flat affect, and his responses to questions were often incoherent and tangential; he seemed to be responding to internal stimuli. He was placed on a regimen of lorazepam 1 mg t.i.d. po as his agitation subsided considerably.

Later that afternoon, he became somewhat more coherent, and stated that he was hearing accusatory voices. He denied visual hallucinations, and admitted to the feeling that there were people trying to do harm to him, perhaps drug

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dealers. He had barricaded himself in the motel room because he was afraid that the drug dealers would "come get me" if he stayed at home. He denied any drug use except for one occasion when he smoked marijuana. The patient's mother was located, who provided the history that the patient had been an excellent student until about age 16, when his grades started to plummet, and he would isolate himself in his room, staying awake most of the night. The patient became hyper-religious, constantly quoting the Bible, but did not attend church. The parents tried to bring him to a psychiatrist, but he resisted. The age and the insidiousness of onset, the persecutory delusions, the auditory hallucinations, the flatness of affect, and the absence of substance abuse history pointed to the diagnosis of schizophrenia. As the CPK was now normalized, and there was no history of antipsychotic drug use that might have caused neuroleptic malignant syndrome, lorazepam was discontinued and a regimen of aripiprazole 10 mg po in AM was instituted. Within 24 h, the patient's auditory hallucinations were significantly attenuated, and his loosening of associations abated. His affect remained flat. He was referred for outpatient therapy when discharged.

19.2 The Recognition of Psychosis

The symptoms and signs of psychosis are perceptual, cognitive, and behavioral abnormalities that suggest an involuntary break with reality. Cardinal symptoms include hallucinations, delusions, illusions, and bizarre behavior. Loose associations, tangentiality, flight of ideas, and illogical or incoherent speech may be present. Anxiety, agitation, insomnia, depression, euphoria, and suicidal or homicidal behavior may occur, often secondary to the delusions or hallucinations.

In the consultation-liaison (CL) setting, the nursing staff may report the patient's unusual behavior or speech, or blunted or inappropriate affect, resulting in a psychiatric consultation. When patients with an existing diagnosis of psychosis or schizophrenia are admitted to a general hospital, psychiatric consultation is usually generated even when they are psychiatrically stable. This is appropriate, as collaboration between medicine and psychiatry may be essential in considering adjustments of medications as well as meeting the patient's psychotherapeutic needs.

If the patient is severely psychotic, it may be impossible to obtain coherent history from the patient or perform a structured mental status examination. Under those conditions, it is imperative that collateral information from family or friends be obtained. Acute and severe psychotic symptoms in a patient with abnormal physical or laboratory findings should be considered to be delirium unless proven otherwise, and a workup for delirium should be initiated (see Chap. 12). Antipsychotic treatment may be necessary before a history can be obtained.

19.2.1 The Psychotic Mode of Experiencing and Its Function

Though patients with psychosis may seem bizarre, all normal people have at times experiences such as hallucinations and delusions, for example, during dreaming. Most normal people are capable of having psychotic experiences while awake, under the influence of psychotomimetic drugs such as D-lysergic acid (LSD) or under sensory deprivation conditions. In fact, delirium due to any cause is often associated with psychotic symptoms. Primary process, which involves a nonlinear-picture mode (rather than word-based mode) of cognition that may involve the nondominant hemisphere of the brain, is the language of the unconscious mind, of dreams, and of the creative process (Brakel and Shevrin 2005; Burns 2006; Mohler et al. 2008; Roiser et al. 2012).

The psychotic mode of being may also be adaptive at times of overwhelming stress, where a disconnection from reality may be advantageous for survival. We all possess the capacity for the psychotic mode of experiencing reality-the difference between this and psychosis as a syndrome is

the lack of control over the experience in the latter. The lack of control seen in psychosis may be due to endogenous or exogenous toxins, extreme stress, or neurodevelopmental abnormality (Devylder et al. 2013; Holtzman et al. 2013). Regardless of the cause, this lack of control is invariably frightening to the newly psychotic patient, and recognizing this frightened state is essential in approaching such a patient.

19.2.2 Psychotic Syndrome as a Final Common Pathway

Like mood syndromes and anxiety syndromes, psychosis is a final common pathway syndrome that can be contributed by many factors. Regardless of the contributing factors, a common neurobiologic pathway to the psychotic syndrome seems to be a functional hyperactivity of the dopaminergic (particularly D_2) neurons in the mesolimbic system. Dopamine agonists, such as LSD and amphetamines, can induce psychosis, and dopamine receptor blockers, such as haloperidol, are effective for psychotic symptoms regardless of the underlying etiologies.

One may conceptualize two broad categories of the psychotic syndrome—secondary and primary—based on the prominent contributing factors. Secondary psychoses comprise psychotic syndromes that are associated with diagnosable nonpsychiatric medical conditions, prescription and recreational drugs, or identifiable environmental factors such as sensory deprivation.

Primary psychoses consist of syndromes classified as psychiatric disorders, including schizophrenia, schizoaffective disorder, bipolar disorder, psychotic depression, delusional disorder, brief psychotic episode, and psychotic symptoms accompanying posttraumatic stress disorder (PTSD) and borderline personality disorder. Primary psychoses may be exacerbated or precipitated by the factors that contribute to secondary psychoses (e.g., LSD or delirium) and are the results of interaction among genes, early development, early, recent, and current stresses, and psychosocial support.

19.3 Diagnosis of Psychotic Syndromes

19.3.1 Secondary Psychosis

The most common underlying condition for secondary psychosis is delirium (see Chap. 12). In addition, many medical conditions and prescription and recreational drugs may cause psychotic symptoms (see Table 7.1 in Chap. 7).

19.3.2 Primary Psychosis

Psychotic syndrome manifested in a patient in whom the medical condition or prescription and recreational drugs are not sufficient explanations may be considered to be due to a primary psychosis. It is important to recognize, however, that primary and secondary psychoses are not mutually exclusive, but may be syncretic. For example, a patient with chronic schizophrenia with prominent auditory hallucinations may become delirious due to uremia, and develop visual hallucinations and agitation. Included in this category are schizophrenia, schizoaffective disorder, bipolar disorder, psychotic depression, delusional disorder, brief psychotic episode, and psychotic symptoms accompanying PTSD and borderline personality disorder. Stress may play a predominant role in inducing PTSD and a brief psychotic episode, while genetic factors may play greater roles in schizophrenia and mood disorders. There is some evidence that there may be a common genetic contribution to the psychotic symptoms of schizophrenia, schizoaffective disorder, and bipolar disorder (Green et al. 2010; Green et al. 2005; Hamshere et al. 2006).

19.3.2.1 Schizophrenia

Schizophrenia is the classic, representative psychosis, but it is important to note that it is a subset of psychotic syndromes. Schizophrenia is a final common pathway syndrome with multiple contributing factors, many of which are shared with other psychiatric syndromes.

History

The French psychiatrist Morel coined the term *demence precoce* in 1860 to describe an adolescent patient who became gradually withdrawn, gloomy, and silent. Emil Kraepelin, the German psychiatrist known as the father of descriptive psychiatry, systematically described the signs and symptoms of a psychiatric illness that was characterized by a progressive deterioration in mental functioning under the rubric of dementia praecox, which means premature dementia. Eugen Bleuler, a Swiss psychiatrist, radically changed the concept of schizophrenia by pointing out that not all patients who had the symptoms that Kraepelin described actually had an unremitting deteriorating course. He coined the term, schizophrenia, meaning "splitting of the mind" in his book, Dementia Praecox or the Group of Schizophrenias.

Clinical Manifestations

Bleuler proposed that there are four fundamental symptoms of schizophrenia, the "four A's"—disturbances in association and affect, and the presence of autism and ambivalence.

Disturbances in association include loosening of associations, tangentiality, derailment, clang associations, and neologisms. Affect may be flattened or inappropriate. Autism, or dereistic thinking, means that the patient lives in a world of his or her own, with a very tenuous relationship with external reality, which often leads to social withdrawal. Hallucinations, delusions, and illogical thinking may be part of autism.

Kurt Schneider described the most characteristic symptoms of schizophrenia that he called the "first-rank symptoms," the presence of even one of which merits serious consideration for the diagnosis of schizophrenia. They are complete auditory hallucinations (such as hearing two voices conversing with each other, voices commenting on one's own behavior, hearing one's thoughts spoken aloud), thought withdrawal (feeling that one's thoughts are taken away), thought insertion (others are putting thoughts in one's head), thought broadcasting, and delusions of control (e.g., one is controlled by radio waves from spaceships).

Positive and Negative Symptoms

It is useful to classify the symptoms of schizophrenia as positive or florid symptoms and negative or deficit symptoms as they may reflect underlying central nervous system (CNS) changes. The positive symptoms include hallucinations, delusions, and loose associations, which are present in all psychotic syndromes. The positive symptoms generally respond well to dopamine receptor blockers such as haloperidol and most antipsychotic medications.

The negative symptoms include flat affect, paucity of thought, anhedonia, and motor retardation, and they may be associated with cerebral cortical abnormalities and enlarged ventricles and sulci often associated with schizophrenia. The negative symptoms are resistant to treatment with antipsychotics in general, though the second-generation antipsychotics such as clozapine have some beneficial effect.

Types

In DSM-5, schizophrenia types have been eliminated from the formal diagnostic scheme. Nevertheless, based on predominant symptoms, schizophrenia has been typed as follows:

Paranoid type: delusions and paranoid ideations predominate

Disorganized (hebephrenic) type: bizarre behavior, hallucinations, and posturing

Catatonic type: catatonia, mutism, sometimes alternating with agitation

Undifferentiated type: mixtures of various psychotic symptoms

Residual type: usually occurs after a long course of illness; most positive symptoms have been under control or "burned out," with mostly negative symptoms persisting

19.3.2.2 Prevalence and Incidence

The lifetime prevalence is considered to be 0.3–0.7 %, with an incidence rate of approximately 15 per 100,000 per year (Brown 2011); (APA 2013).

In a general hospital population that is consulted by psychiatry, the prevalence rate of the diagnosis of schizophrenia in some 2,500 psychiatric consultations with a major psychiatric diagnosis was approximately 5 %. Among some 300

patients with psychotic symptoms, about 37 % were eventually diagnosed with schizophrenia (based on analysis of data at Community Regional Medical Center, Fresno, CA, USA).

19.3.2.3 Onset

The age of onset is in the teens to the mid-20s for men and late 20s for women. The onset is often insidious, with prodromal symptoms of social withdrawal, poor personal hygiene, deterioration in school or work performance, and day-night reversal. In general, the prognosis is poorer the earlier the onset.

19.3.2.4 Etiology and Pathogenesis

According to the neurodevelopmental hypothesis, the etiology of schizophrenia may involve pathologic processes, caused by both genetic, epigenetic, and environmental factors, that begin before the brain approaches its adult anatomical state in adolescence. These neurodevelopmental abnormalities, developing in utero as early as late first or early second trimester for some and thereafter for others, have been suggested to lead to the activation of pathologic neural circuits during adolescence or young adulthood (sometimes owing to severe stress), which leads to the emergence of positive or negative symptoms or both.

The neurodevelopmental abnormalities may result from embryologic maldevelopment, often caused by prenatal infections (Brown 2012; Khandaker et al. 2013). A "2-hit" model proposed by Keshavan posits that maldevelopment during two critical time points (early brain development and adolescence) combines to produce the symptoms associated with schizophrenia (Keshavan 1999; Keshavan and Hogarty 1999). According to this model, early developmental insults may lead to dysfunction of specific neural networks that would account for premorbid signs and symptoms observed in individuals who later develop schizophrenia. During adolescence, excessive elimination of synapses (pruning) and loss of plasticity may account for the emergence of symptoms (Fatemi and Folsom 2009).

Genetic Risks

Schizophrenia clearly runs in families. The risk of developing schizophrenia in the general population is somewhat less than 1 %, while the prevalence for parents of children who are known schizophrenics is 12 %. The morbidity risk for schizophrenia for full siblings of schizophrenic patients is 13–14 %. The risk for children with one schizophrenic parent is 8–18 %. If both parents are schizophrenic, the morbidity risk for their children may be as high as 50 %. In the case of twins, heterozygous twins have the same risk as other siblings, while homozygous (identical) twins have a concordance rate for schizophrenia of approximately 50 % (However, there is much variability in the concordance rate depending on the study, from practically 0–86 %.).

Pathophysiology and Genetics of Schizophrenia

In spite of the demise of the term dementia praecox, cognitive disturbance has recently become a cornerstone of understanding schizophrenia. Schizophrenia is conceptualized as a neurodevelopmental disorder resulting in a reduction in cortical volume and dysfunctions in glutamatergic, GABA (γ-aminobutyric acid)ergic, and dopaminergic transmission. There seems to be a hyperfunction of the mesolimbic and a hypofunction of the mesocortical dopaminergic transmission. Mesocortical dopaminergic transmission is stimulated by glutamatergic transmission and reduced by GABAergic transmission, and it plays an important role in working memory often disturbed in schizophrenia (Barch and Ceaser 2012; Kegeles et al. 2012). There is evidence of dysfunction in schizophrenia of the GABAergic cortical chandelier cells that synchronize the firing of the glutamatergic pyramidal cells, which are necessary for proper functioning of the working memory. A fundamental disturbance in schizophrenia seems to be an inefficiency of the prefrontal cortex, particularly the dorsolateral area, in processing information, and increased "noise" in the local microcircuit function (Anticevic et al. 2012; Kyriakopoulos et al. 2012).

At least 15–18 single nucleotide polymorphisms (SNP) have been identified as candidate

genes for the susceptibility to schizophrenia including catechol O-methyltransferase (COMT) (chromosome 22q), dysbindin-1 (chromosome 6p), neuregulin-1 (chromosome 8p), metabotropic glutamate receptor 3 (GRM-3) (chromosome 7q), glutamate decarboxylase 1 (chromosome 2q), and disrupted-in-schizophrenia 1 (DISC1) (chromosome lq). It is important to note that these genes are not here to "cause schizophrenia," but are rather genes important in various neural, immunologic, and other normal functions the disruption of which may code for a risk of developing brain dysfunction, which may result in psychotic symptoms (and/or bipolar symptoms as in DISC1 gene).

The COMT gene affects prefrontal cortical function by changing dopamine signaling in the prefrontal cortex and brainstem. GRM-3 shows similar results on prefrontal function and has an effect on expression of various glutamate synaptic markers. DISC1 affects hippocampal anatomy and function. Dysbindin-1 seems to be a general cognitive capacity gene that is underexpressed in the cortex of schizophrenic patients (Nickl-Jockschat et al. 2012; Snyder and Gao 2013).

Schizophrenia is not a simple genetic disease; rather, it is a syndrome contributed to by susceptibility genes that have functions other than conveying susceptibility to schizophrenia, and by early experiences, developmental factors, and stress (King et al. 2005).

Evolutionary Considerations

Schizophrenia has conferred a reproductive disadvantage on the afflicted. Why, then, is schizophrenia extant at more or less a constant rate across human populations? An obvious explanation is that the alleles that, in certain combinations, may predispose one to schizophrenia may be involved in other functions that are adaptive. Some of these may be involved in creativity and eccentricity. In addition, the susceptibility genes may represent variations of ubiquitous genes subserving basic functions of the human brain. Crow proposed that schizophrenia may represent an extreme of normal genetic variation in the communication (Crow 1997a, b, 2012) between the two hemispheres that is critical in language, a uniquely human acquisition. He postulates that Schneiderian first-rank symptoms such as thought insertion and withdrawal may represent a dysfunction of the coordinated hemispheric communication—a right hemispheric intrusion into left hemispheric linear thinking. Schizophrenia may represent an extreme of variations in the interconnectivity of various structures of the brain, particularly those involved in social cognition and the working memory.

Regression and Projection

A prominent feature of many schizophrenic patients is the phenomenon of regression, a psychological defense mechanism characterized by a retreat to an earlier, child or infant-like way of experiencing the world accompanied by childlike or infantile behavior. In severe cases, patients may assume a fetal position with thumb sucking. Another defense mechanism often seen in schizophrenia, particularly in the paranoid type, is projection, by which the patient attributes to others the thoughts, feelings, or traits that are unacceptable to oneself; for example, when an aggressive impulse is projected, the patient may see others as having malicious thoughts against him or her and plotting harm.

As discussed earlier, schizophrenic patients often manifest cognitive deficits, especially in filtering out extraneous stimuli, in recognizing social cues, in the ability to change sets, and in concreteness. Primary process thinking, characterized by illogicality, nonlinearity, and pictorial thinking rather than linguistic, may be also prominent.

Socioenvironmental Factors

Seasons and Infection

There is evidence that being born in the winter is associated with a higher risk of schizophrenia and mood disorders (Torrey et al. 1997). However, schizophrenia with deficit symptoms may be associated with being born in the summer (Messias et al. 2004), and may be associated with intrauterine cytomegalovirus infections (Khandaker et al. 2013; Torrey et al. 2006).

Role of Stress

Stressful early experiences particularly associated with low socioeconomic class and a ghetto urban environment may precipitate schizophrenia

in vulnerable individuals as there is a higher prevalence of schizophrenia in these groups (Brown 2011). The handicap of schizophrenic illness also often causes the affected persons to slide down the socioeconomic ladder (drift hypothesis). Abnormally stressful family interactions may contribute to the development of schizophrenia (e.g., a "double bind"—a "no win" situation for a child). Exacerbation of schizophrenia, especially to the point that it is severe enough to warrant hospitalization, seems to be associated with stress, and particularly associated with expressed negative emotions by family members (Cechnicki et al. 2013; Lenior et al. 2005).

Diagnosis of Schizophrenia in CL Setting

DSM-5 specifies that during a 1 month period, at least one delusion, hallucination, or disorganized speech was present, and has an additional symptom that may include grossly disorganized or catatonic behavior and/or a negative symptom. It further specifies that continuous signs of the disturbance persist at least for 6 months.

In the consultation-liaison setting, the diagnosis of schizophrenia in the presence of psychotic symptoms usually involves the following steps:

1. Rule out delirium, the most common cause of psychosis in the general hospital.
2. Determine by the history and collateral information whether the patient has a history or family history of psychiatric evaluation/treatment; if positive, the probability increases that the patient has a primary psychiatric condition such as schizophrenia or mood disorder.
3. Determine whether the patient's medical condition or a drug used to treat the condition is reported to be associated with psychosis. In this case, **Psychotic Disorder Due to Another Medical Condition** may be diagnosed.
4. Determine whether the patient used recreational drugs that might explain psychotic symptoms. In this case, **Substance/Medication-Induced Psychotic Disorder** may be diagnosed.

As it is rare for a medical patient to have the first schizophrenic break in the general hospital, every effort should be made to determine whether the patient has a prior history of psychotic episode. Even if a patient is known to be schizophrenic, delirium and substances can exacerbate underlying psychosis.

19.3.3 Other Primary Psychoses

If a mood disturbance (depression, euphoria, hypomania/mania) is prominent, then psychosis associated with a mood disorder may be suspected. If the history indicates that the psychotic symptoms are present only during periods of mood disturbance, then depression or mania with psychotic features may be diagnosed (see Chap. 15). When the history reveals that psychotic symptoms are present even when the mood disturbance is in remission, then a **schizoaffective disorder** may be diagnosed. If the psychotic symptoms are transient in a patient who has borderline personality disorder (see Chap. 25), then they may be part of the micropsychotic episodes associated with that syndrome. If such symptoms coexist with symptoms of posttraumatic stress disorder (PTSD), they may be part of the dissociative phenomena common in PTSD. If the psychotic symptom is confined to a delusion, then the diagnosis of delusional disorder may be appropriate.

As a final common pathway phenomenon, the psychotic symptoms, regardless of comorbid syndromes (e.g., depression, borderline personality, PTSD), may have common sets of susceptibility genes and pathophysiology. Most positive psychotic symptoms, regardless of the diagnosis, respond to antipsychotic medications. Except in schizophrenia and psychosis associated with mental retardation and dementia, negative symptoms are rare. Of note is that the prolonged use of first-generation antipsychotics (e.g., haloperidol) may cause negative symptoms such as flattening of affect.

19.3.3.1 Catatonia

Catatonia is a syndrome characterized by marked psychomotor disturbance in the form of decreased motor activity and decreased engagement during

interview. This may alternate with periods of extreme agitation. During decreased motor activity, there may be catalepsy (waxy flexibility), mutism, negativism, or stupor. There may be peculiar motor activity such as stereotypy.

DSM-5 does not treat catatonic syndrome as a separate class but classifies catatonia as being one of (1) catatonia associated with another mental disorder, e.g., psychotic, bipolar, depressive disorder, (2) catatonia due to another medical condition, and (3) unspecified catatonia.

19.3.3.2 Schizotypal (Personality) Disorder

This is usually classified as a personality disorder (See Chap. 25), characterized by odd, eccentric thinking and behavior. This is also listed as Schizophrenia Spectrum Disorder because some consider this personality trait to be genetically related to schizophrenia.

19.3.3.3 Delusional Disorder

This disorder is characterized by one or more persistent delusions (duration 1 month or more), but not quite meeting the criteria for schizophrenia. Except for the consequences of delusions, the functioning of the patients is not usually seriously impaired.

Delusional disorders may be subtyped into: erotomanic type, grandiose type, jealous type, persecutory type, mixed type, or unspecified type.

19.3.3.4 Brief Psychotic Disorder

Psychotic episode of less than 1 month duration, with eventual full return to pre-morbid level of functioning. Usually considered to be stress-related. May be postpartum onset or with catatonia. About 9 % of first onset psychosis in the United States may be diagnosed as brief psychotic disorder (APA 2013).

19.3.3.5 Schizophreniform Disorder

This diagnosis is given to schizophrenia-like psychotic episode that eventually recovers within 6 months. "Provisional" diagnosis may be made if recovery has not yet occurred. Approximately two thirds of patients who receive the initial provisional diagnosis of schizophreniform disorder progress to the final diagnosis of schizophrenia (APA 2013).

19.4 Management and Treatment of Psychosis

19.4.1 Immediate Treatment in the General Hospital

Immediate treatment of psychosis in the general hospital involves (1) treatment of agitation (see Immediate Management of Agitation in Chap. 4), (2) treatment of psychotic symptoms, and (3) plans for follow-up.

For the treatment of psychotic symptoms, a first- or second-generation antipsychotic should be considered (Table 19.1). The main clinical differences between first-generation (or typical, so-called because they are all dopamine receptor blockers) antipsychotics and second-generation (or atypical and they have multiple actions on multiple receptors) antipsychotics are as follows: (1) first-generation antipsychotics have more extrapyramidal side effects, whereas second-generation antipsychotics are less likely to cause them; (2) first-generation antipsychotics are effective for positive symptoms only, whereas second-generation antipsychotics are effective for positive symptoms and also may be effective to varying degrees for negative symptoms, and (3) second-generation antipsychotics are associated with the metabolic syndrome (see below). Use of second-generation antipsychotics has been associated with an increase in mortality and the risk of stroke in elderly demented patients.

All antipsychotics may lower **seizure** threshold, may be associated with neuroleptic malignant syndrome (NMS; see below), may increase prolactin levels, and may cause tardive dyskinesia. Cardiotoxic effects such as **QTc prolongation** are common with antipsychotic agents, particularly thioridazine and ziprasidone. For patients with QTc over 450 ms, all psychotropic drugs should be used with caution, and for QTc over 500 ms, antipsychotic drugs should ordinarily not be used—benzodiazepines may be used to sedate the patient if necessary.

Table 19.1 Commonly used antipsychotics

Medication	Dose	Major side effects
First generation (*typical*)		
Haloperidol	0.5–15 mg/day po	EPS ++, TD, NMS QT prolongation, reduced seizure threshold
	1–100 mg/day IV	QT prolongation, torsades de points, reduced seizure threshold, NMS
	0.5–10 mg/day IM	EPS +++, QT prolongation, NMS, reduced seizure threshold
Haloperidol decanoate depot injection	50–100 mg IM q 4 weeks	As above
Perphenazine	2–32 mg/day po	Sedation +, EPS +, TD, reduced seizure threshold, NMS
	2–24 mg/day IM	Sedation +, EPS ++, NMS, reduced seizure threshold
Chlorpromazine	25–900 mg/day po	Orthostatic hypotension, sedation +++, anticholinergic, EPS +, TD, NMS, reduced seizure threshold
	25–500 mg/day IM	As above
Second generation (*atypical*)		
Olanzapine	2.5–30 mg/day po	Sedation, etc
	2.5–30 mg/day IM	As above
Risperidone	1–8 mg/day po	Sedation +, EPS +, QT prolongation, weight gain +, NMS
Quetiapine	25–900 mg/day po	Sedation +++, orthostatic hypotension, weight gain ++, NMS
Ziprasidone	40–160 mg/day po	Sedation +, orthostatic hypotension, QTc prolongation, EPS +, NMS
	10–40 mg/day IM	As above, usually for short term only
Aripiprazole	10–30 mg/day po	Orthostatic hypotension, reduced seizure threshold, constipation, akathisia

EPS extrapyramidal symptoms, *GI* gastrointestinal, *NMS* neuroleptic malignant syndrome, *TD* tardive dyskinesia

19.4.2 Maintenance Pharmacotherapy of Psychosis

Most psychosis associated with delirium, both due to medical disease or substance related, will clear up when the delirium clears. If the psychotic syndrome persists even when other signs of delirium abate, or when the diagnosis of a primary psychosis such as schizophrenia has been established, maintenance pharmacotherapy is usually necessary to manage the psychotic symptoms. Successful maintenance therapy may allow the patient to maintain a functional status in the society.

19.4.2.1 Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study

This large NIMH-sponsored multicenter study sought to examine the safety and effectiveness of second generation antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) and a first generation antipsychotic, perphenazine, in treating schizophrenic patients (Lieberman et al. 2005; Meyer et al. 2005). The primary outcome measure, time to discontinuation, served as an index of effectiveness and was remarkably short; only 26 % of subjects completed the 18-month trial on the medicine to which they were initially randomized. Subjects receiving olanzapine experienced a slightly longer time to discontinuation. Olanzapine showed greater effectiveness than the other agents despite its association with significant metabolic disturbance, especially weight gain. Perphenazine unexpectedly showed comparable levels of effectiveness and produced no more extrapyramidal side effects than the other agents. Despite modest prolactin elevation, risperidone was the best-tolerated medication. In Phase 2, clozapine demonstrated better effectiveness compared to other second generation antipsychotics (SGA) for subjects who discontinued their Phase 1 medication because of efficacy. Olanzapine and risperidone showed greater effectiveness in the

tolerability pathway. Improvements in cognition were modest among all the agents in Phase 1, and perphenazine was no less effective in improving cognitive performance than the SGAs. Cost-effectiveness analysis revealed a significant advantage for perphenazine, due to the impact of the high-priced, brand-name SGAs on overall health care costs (Manschreck and Boshes 2007). Aripiprazole and ziprasidone are less implicated in weight gain and metabolic syndrome and are less sedating than other SGAs.

There is evidence that genetically informed personalized medication regimen may become efficacious in the use of antipsychotic medications (Liu et al. 2012).

19.4.3 Notable Serious Side Effects of Antipsychotic Drugs

19.4.3.1 Extrapyramidal Symptoms, Tardive Dyskinesia

Parkinsonism-like symptoms, for example, muscle rigidity, tremor, bradykinesia, dystonias, and akathisia, are associated with the dopamine antagonism of antipsychotic drugs. With first-generation antipsychotics, particularly haloperidol and fluphenazine, the incidence of extrapyramidal symptoms (EPS) may approach 90 %, particularly in young males. Acute dystonias, such as torticollis, may be treated with diphenhydramine 50–100 mg IV or benztropine 1–2 mg IM. Extrapyramidal symptoms are usually controlled with anticholinergic drugs such as benztropine or antihistaminics such as diphenhydramine. Akathisia may respond to beta-blockers, such as propranolol 20–40 mg t.i.d. or q.i.d.

Tardive dyskinesia, a side effect of prolonged use, particularly of first-generation antipsychotics, is characterized by choreoathetoid movements of the tongue, lips, and extremities. There is no effective treatment for this condition.

19.4.3.2 Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially fatal syndrome associated with the use of dopamine-antagonist antipsychotics. Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, cardiac dysrhythmia). Sialorrhea and incontinence may occur. There is often elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), leukocytosis, and acute renal failure. Extrapyramidal signs such as tremor, rigidity, and cogwheeling are common. Differential diagnoses include infection, anticholinergic toxicity, the serotonin syndrome (see Chap. 7), heat stroke, and central nervous system (CNS) disease (e.g., encephalitis).

If NMS is suspected, all antipsychotic drugs should be discontinued, and the patient should be intensively monitored and supportive treatment given. Pharmacotherapy may include dantrolene (a muscle relaxant, an inhibitor of calcium release from sarcoplasmic reticulum), 1–3 mg/kg IV initially, and then 10 mg/kg/day IV or po in divided doses. Dopamine agonists, such as bromocriptine, 2.5–10 mg t.i.d. po, gradually titrated, or levodopa/carbidopa (Sinemet) 25/250 t.i.d. or q.i.d., may be used. During the acute phase, for behavioral control, benzodiazepines should be used rather than antipsychotics. If antipsychotic treatment becomes necessary after the resolution of NMS, for at least two weeks, it should begin in low doses very cautiously with careful monitoring.

19.4.3.3 Metabolic Syndrome Associated with Second-Generation Antipsychotics

Metabolic syndrome or syndrome X, consisting of insulin resistance, impaired glucose regulation and type II diabetes mellitus, obesity, hypertension, hypertriglyceridemia, increased low-density lipoprotein (LDL), and low high-density lipoprotein (HDL) cholesterol levels, may be associated with second-generation antipsychotics. Appetite stimulation through the blockade of histamine H_1 and noradrenergic A_1 receptors seems to be the underlying mechanism (Zarate et al. 2004). Clozapine and olanzapine seem to be most associated with this syndrome (Hartling et al. 2012), risperidone and quetiapine may be intermediate in risk, and ziprasidone and aripiprazole seem to have minimal risk for this syndrome.

Patients receiving second-generation antipsychotics should be monitored for weight, body mass index, fasting glucose, and the lipid profile for possible development of the metabolic syndrome. If such development is suspected, switching to drugs less likely to cause the syndrome should be considered, and dietary and exercise programs should be initiated as well as possible medical intervention, including the use of weight loss medications such as sibutramine, orlistat, and rimonabant (Filippatos et al. 2008; Fujioka 2006).

19.4.3.4 Drug Interactions

Common Considerations

The sedative effect may be accentuated with concurrent use of other sedating agents including alcohol. Orthostatic hypotension may be potentiated with the use of other hypotensive agents. Most antipsychotics, due to the dopamine antagonist action, may antagonize the effects of levodopa and other dopamine agonists. Most antipsychotics are metabolized by the cytochrome P-450 enzyme systems in the liver; enzyme inducers such as carbamazepine decrease the antipsychotic blood levels, and enzyme inhibitors such as ketoconazole increase the blood levels. In general, antipsychotics do not necessitate changes in dosing of other medications.

Olanzapine

Drugs that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance; thus a dosage increase of olanzapine may be necessary. Inhibitors of CYP1A2 may inhibit olanzapine clearance. Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine and may result in a mean increase in olanzapine.

Olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Risperidone

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. Carbamazepine and other enzyme inducers may decrease the effective level of risperidone by 50 %. Coadministration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and threefold to ninefold, respectively.

Quetiapine

Enzyme inducers such as phenytoin, carbamazepine, barbiturates, rifampin, and glucocorticoids may increase the oral clearance of quetiapine up to fivefold, necessitating an increased dose. Caution should be exercised if phenytoin is withdrawn and replaced with a noninducer (e.g., valproate). Coadministration of quetiapine and divalproex increases the mean maximum plasma concentration of quetiapine by 17 % without affecting the extent of absorption or mean oral clearance. Thioridazine increases the oral clearance of quetiapine by 65 %. Cytochrome P-450 3A inhibitors (e.g., ketoconazole, itraconazole, fluconazole, and erythromycin) may reduce oral clearance of quetiapine and may result in a 335 % increase in maximum plasma concentration of quetiapine. Quetiapine reduces the oral clearance of lorazepam.

Aripiprazole

Drugs that induce CYP3A4 (e.g., carbamazepine) may increase aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels. If aripiprazole is to be coadministered with quinidine, a potent CYP2D6 inhibitor, the aripiprazole dose should be reduced to half of its normal dose. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, should be accompanied by similar dose reductions. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not

undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Ziprasidone

Ziprasidone should not be used with any drug that prolongs the QTc interval. Carbamazepine, an inducer of CYP3A4, may increase the clearance of ziprasidone and lower blood levels. Ketoconazole, a potent inhibitor of CYP3A4, may increase blood levels of ziprasidone by about 35–40 %.

Haloperidol

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, and elevated serum enzymes, BUN, and fasting blood sugar level) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established. Patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear (Boora et al. 2008; Normann et al. 1998). Rifampin reduces plasma haloperidol levels by about 70 %.

19.4.4 Psychosocial Management

Experiencing psychotic symptoms in a general hospital is frightening for the patient, especially if these symptoms had not been experienced before. The consultant should inform the health care professionals that most acute psychotic experiences in the medical setting are caused by delirium or side effects of medications and that they should reassure the patients that the symptoms, frightening as they are, are transient, and that both the underlying cause and the symptoms can be treated. For patients who are paranoid, explaining each procedure and medication before they are administered can be helpful.

As psychotic patients are often hypervigilant, the environment should be as quiet as possible, and any discussion about the patient should take place well out of earshot of the patient to reduce ideas of reference and misinterpretation.

For patients with existing primary psychosis, recognition by the health care personnel that such patients may have special needs for privacy and that their behavior may be unusual, may be helpful.

An important aspect of the psychosocial management of chronic psychotic patients is ensuring that the patient continues ongoing outpatient psychiatric treatment after discharge.

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