

Early Detection, Assessment, and Optimal Treatment of a First Episode of Psychosis

Case Study and Commentary, *Suzanne Archie, MD, FRCPC*

Abstract


- **Objective:** To present the principles and practices of early intervention for psychosis.
- **Methods:** Review of the literature.
- **Results:** Psychosis typically begins in young adulthood and may lead to disability that lasts a lifetime. Classic symptoms of psychosis include hallucinations, delusions, and disordered thinking. There is evidence that delay in treatment is correlated with poorer outcomes. Components of early intervention services include low-dose antipsychotic medication, case management or care coordination, family education, and psychosocial intervention. Pharmacotherapy is the cornerstone of early intervention and considered the first line of treatment for a first episode of psychosis.
- **Conclusion:** Clinicians must learn to recognize psychosis and prevent delay in treatment.

Serious mental illnesses such as schizophrenia and bipolar illness are chronic mental disorders that can affect young people. Primary care practitioners must be able to develop appropriate treatment strategies to decrease suffering and improve recovery from a first episode of psychosis, an episode that can lead to life-long disability among a particularly challenging group to engage in therapy. With adolescence beginning earlier, finishing later, and posing more complex struggles than ever, clinicians must learn to recognize psychosis and provide supports and treatment through this critical period of increased risk [1].

The principles and practices of early intervention for psychosis are now well documented in the psychiatric literature, a body of work concerning medication trials, family education, and psychosocial and rehabilitative interventions. This article will provide a summary of this literature focusing on a review of the symptoms commonly experienced, the components of a comprehensive assessment approach, and the treatment options and modalities that should be offered to a young person experiencing a first episode of psychosis (from here on, termed “patient”).

CASE STUDY

Initial Presentation

 Harry, a 17-year-old high school student living at home with his parents, is brought to the emergency department (ED) by police after Harry’s mother contacted them because Harry was yelling at his family over dinner and threw his plate of food on the floor.

Harry told the ED staff that his family was poisoning his food. He was clearly upset, but he was redirectable with no suicidal or homicidal ideations. His mother reported that his behavior had changed over the past 6 months: he was withdrawn, irritable and tired-looking, and his grades were dropping.

- **What are some strategies to use when interviewing a young person experiencing a first episode of psychosis?**

Putting together the pieces of a patient’s potentially confusing story may be extremely challenging because the youth may have poor motivation to report symptoms, may feel too threatened to answer questions, or may experience thought disorder and poor insight [2]. Because a comprehensive history is the cornerstone of a treatment plan, clinicians may need specialized skills to engage and interview young people experiencing psychosis for the first time.

To help establish rapport, simple reflective statements that are nonjudgmental may help patients feel more comfortable disclosing their experiences. Use of empathic statements, such as “... that sounds distressing...” may help engender feelings of trust. Clinicians should explore the history from the patient’s vantage point and in a manner that accepts their level of insight by starting with short open-ended questions, such as “tell me more” and “what did you do?” As a rule of thumb, in the beginning of an interview,

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Table 1. Common Delusional Beliefs Associated with a First Episode of Psychosis

Name	Description
Paranoia	The individual falsely believes someone is monitoring them, is trying to harm them, or is acting in a suspicious manner
Ideas of reference	The person believes neutral signs or symbols in their environment have special meaning that other people are unaware of or do not understand. For example, the color red may be a code that the police are sending the individual a message.
Thought control	The person experiences their own thoughts as being directly under the control of someone or something else
Thought insertion	The experience of having foreign thoughts inserted into one's own mind
Thought broadcasting	The person believes that their thoughts are being broadcast to others or that other people can read their mind

open-ended questions are more valid, albeit less reliable, but closed-ended questions too early in the interview can lead to invalid answers of yes or no [2]. Like a detective, the clinician must ask questions to unravel the mystery of what the ill person is actually perceiving because the patient's perceptions are likely very different from the rest of society's experience. If a patient provides vague or disorganized information, then the clinician should use interrelation, summarizing the illogical responses, and persuading the patient to explore the connections between the misleading details [2] until the clinician can make sense of the patient's understanding of their experience. Although the patient's beliefs may be irrational, delusions and odd behaviors may become more understandable to others once the ill person's context and perceptual disturbance is properly explored and appreciated.

Closed-ended questions play a much larger role once rapport has been attained, once the patient has had an opportunity to fully express their concerns and as soon as the clinician is ready to obtain a comprehensive functional inquiry of all of the relevant signs and symptoms. Before the assessment is complete, it is important to elicit the patient's short- and long-term goals to aid in developing a treatment plan that addresses their needs, a process that should ultimately improve their adherence.

- **What are the features of a first episode of psychosis?**

Most studies operationalize this syndrome as the first episode of psychosis in a person aged 14 to 40 years [3] who

may have received early stages of treatment. Early stages is defined as a first admission to hospital or less than 6 months of use of an antipsychotic medication [4].

Many patients experience many of the general signs and symptoms of psychiatric illness: depression, anxiety, irritability, sleep disturbance, poor concentration, poor appetite, changes in energy level, and suicidality. However, specific signs include the classic symptoms of psychosis, such as delusions, hallucinations, and disorganization. **Table 1** outlines the most commonly experienced delusions: beliefs that are not shared by one's own cultural group, fixed ideas, and bizarre ideas which may lead to fear, suspicion, aggression, or odd behaviors.

Hallucinations are sensory experiences that are produced by the brain, generated without stimuli from the environment, and experienced by the individual as real phenomena. Hallucinations can be auditory, visual, gustatory, or tactile in nature. Furthermore, a person with psychosis often experiences perceptual distortions of real stimuli, known as illusions. For example, an illusion is when a person hears people talking on the other side of a doorway and the ill person misinterprets the sounds and believes that the other people are saying specific things about him or her. Disorganization is often evident when observing the ill person's behavior, speech, or habits and is perhaps a reflection of disturbances in perceptual and thought processes.

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- **What is the incidence of psychosis?**
 - **What are some of the risk factors for a first episode of psychosis?**
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Incidence

Most of the time, age of onset for psychotic illness is between the ages of 16 and 30 years, but gender differences exist: the incidence for males significantly exceeds the rate for females [5].

The annual incidence rates of broadly defined psychosis are approximately 20 to 42 new cases per 100,000 people between the ages of 15 and 50 years of age [6]. Broadly defined psychosis includes delusional disorder and affective psychosis. For narrowly defined schizophrenia, the annual incidence rate ranges from 8 to 15 cases per 100,000 people between the ages of 15 and 50 years [6].

Risk Factors

Psychosis usually occurs within a context of vulnerability that could be genetic, environmental, or both. Although the underlying mechanisms underlying the links between schizophrenia and these risk factors remain largely

unknown, it is prudent to look for these features when assessing individuals for psychosis [7]. Prenatal infections and obstetrical complications are associated with an increased risk for developing schizophrenia later on during adolescence and early adulthood [8]. Other early risk factors for psychosis include abnormal childhood experiences, such as atypical mothering, loss of a parent [9], or abuse [10]. Compared with the general population, individuals with developmental delay and low intellectual functioning are at a higher risk [11]; in fact, children who had neuropsychological deficits at age 13 were more likely to develop schizophreniform disorder as young adults [10].

Early cannabis use has been linked to increased risk of psychosis and need for care 3 to 5 years later if the use was regular and weekly during the vulnerable teenage years [12]. Furthermore, a large number of studies have found an increase in symptoms among patients with a substance use disorder; the evidence is more compelling for an association between positive symptoms and substance abuse rather than negative symptoms; cannabis abuse was more likely to be implicated in this association than alcohol abuse [4].

However, despite the numerous environmental risk factors that have been identified, the fact remains that the heritability of psychotic disorders, such as schizophrenia and bipolar illness, is higher than in many medical conditions [13]. For schizophrenia and bipolar illness a family history of these disorders predicted the development of psychosis among patients. In addition, for schizophreniform disorder, a gene-environment interaction has now been well documented; more specifically, the risk of developing schizophrenia-like symptoms during adulthood has been shown to increase significantly among youth who have the valine allele for the COMT gene, a gene that is important for dopamine production [14]. For the most part, the literature supports a polygenetic etiology of schizophrenia, with multiple genetic and environmental risk factors [15].

• **What are the core symptoms of schizophrenia?**

The illness schizophrenia consists of a complex group of symptoms and impairments which reflect emotional, cognitive, and behavioral changes. Positive symptoms, such as delusions, disorganized speech, and hallucinations, are additional experiences or symptoms that are “added” onto an individual’s mental state. On the other hand, negative symptoms are experiences which are “subtracted” or lost from an individual’s normal mental state. The list of negative symptoms includes affective flattening, avolition (a loss of motivation), anhedonia (loss of ability to experience pleasure), autism (a loss of social connectivity), and alogia

(a loss of logic) [16]. Negative symptoms can be difficult to distinguish from Parkinsonian side effects of medications, from depression, and even from normal teenage social withdrawal and lack of initiative [17]. Furthermore, cognitive disturbances are often quite prominent and cognitive disturbances may include problems with concentration, memory, and verbal functioning [16]. By definition, to make the diagnosis of schizophrenia, impairments in social and occupational functioning must also be present [18]; a decline in work functioning, poor educational attainment, social isolation, and poor self care are common examples.

• **What are the phases of illness in schizophrenia?**

There may be premorbid disturbances that occur during childhood and predate any acute disturbances. Minor physical anomalies or mild social, motor, or cognitive disturbances may be noted during this developmental stage of growth [10]. In retrospect, changes are often identified that occurred during a prodrome, a period where nonspecific signs and symptoms may appear as a precursor to illness, also known as a prepsychotic phase [19]. Although the presence of prodromal symptoms can be associated with the risk of developing psychosis, these symptoms are not considered to have a high specificity or sensitivity for schizophrenia [20]. Prodromal changes may occur during normal adolescence in as many as 5% to 40% of teenagers in the general population, depending upon type of problem: magical thinking (“often” 9.3%), unusual perceptual experiences (5.3%), social isolation or withdrawal (18%), markedly impaired role function (41%), blunted, flat, or inappropriate affect (22%), and lack of initiative or energy (40%) [21]. Prospective neuropsychological testing suggests that cognitive impairments, which tend to be more specific than other prodromal changes, can occur during the prodrome, before the onset of acute psychotic symptoms [22].

The first few years after the onset of psychosis is the most progressive stage of the illness, representing the period of greatest risk for the development of positive, negative, and mood symptoms, usually between adolescence and early adulthood [23]. This phase is considered to be critical for early intervention to prevent deterioration in social and educational functioning [1].

• **Which disorders are included in the differential diagnosis for psychosis?**

Psychosis is not synonymous with schizophrenia. Psychosis is a syndrome that can occur in a number of different

Table 2. Differential Diagnosis for a First Episode of Psychosis

Diagnosis	Description
Brief psychotic disorder	Psychotic symptoms that last < 1 month
Substance-induced psychosis	Psychotic symptoms up to 1 month after ingestion of substances that may cause psychosis
Schizophreniform disorder	Schizophreniform disorder characterizes patients who have psychotic symptoms that last > 1 month but < 6 months
Schizophrenia	Schizophrenia can be diagnosed after the individual has experienced positive or negative symptoms for at least 6 months and there is evidence of a decline in social or occupational functioning
Schizoaffective disorder	Schizoaffective disorder is similar to schizophrenia and major mood disorders, but it is unlike bipolar illness or depression because individuals will continue to experience psychosis in between episodes of mood disturbance. It is distinct from schizophrenia in that individuals with schizoaffective disorder experience prominent mood symptoms (mania or depression) during the course of their illness.
Bipolar disorder	Bipolar I disorder can include symptoms consistent with psychosis during an episode of either mania or depression. Patients can meet criteria for bipolar I disorder if their symptoms of psychosis occur only during an episode of mood disturbance.
Depression with psychotic features	An individual experiencing a major depressive disorder with psychotic features will meet full criteria for depression and either mood-congruent or incongruent psychotic features
Delusional disorder	Delusional disorder tends to produce less prominent perceptual disturbances or bizarre behavior and tends to cause less impairment in functioning than the impairment typically experienced by people diagnosed with schizophrenia
Obsessive compulsive disorder	Persons with OCD recognize that their repetitive and intrusive thoughts are from within their own mind, or ego-dystonic. Persons with schizophrenia often believe that their repetitive thoughts are in fact realistic concerns arising from real world problems, or ego-syntonic, meaning the person feels the problem resides outside of their self.
Organic psychoses	Psychosis can be caused by a variety of medical conditions, such as neurological, endocrine, or autoimmune disorders

disorders, but distinguishing between the disorders may be difficult because there is considerable overlap in the symptoms. Furthermore, diagnoses can coexist or change as the condition progresses over time. In psychiatry, there are no specific diagnostic tests for differentiating the disorders associated with psychosis, with the exception of substance induced psychosis or psychosis associated with a general medical condition.

In up to 40% of patients, the diagnosis may change within the first 3 months of presentation [24]. Because the early stages are fraught with fluctuations in presentation, a syndromal approach has been advocated that is focused on identifying and treating psychosis in disturbed or dysfunctional individuals. Use of the diagnostic term schizophrenia too early, before the person or their family understands the illness, may hinder engagement, may lead to confusion if the symptoms continue to change over time, and may suggest poor prognosis for recovery [20]. Despite the inherent uncertainty and problems, it is very important to eventually identify and use the correct diagnostic labels because treatment strategies and plans may vary depending upon the underlying disorder or comorbid disorders.

Psychotic episodes, if separated by periods of normal mental health, are more suggestive of a mood disorder [23].

If the psychosis only occurs when the individual is experiencing mood symptoms, then the symptoms meet criteria for an affective spectrum disorder, such as bipolar disorder or major depression with psychotic features [25]. Aloofness, suspiciousness, oddness, idiosyncratic communication, poor social performance, and poor vocational performance may indicate a schizophrenia spectrum disorder [23]. However, the classic psychotic symptoms (delusions, hallucinations, and disorganization) are not helpful in and of themselves in determining the correct diagnosis, especially when the assessment is based on one mental status examination alone [23]. It is the timing of the symptoms and evidence of a functional decline over time that helps to clarify a diagnosis of schizophrenia.

Although schizophrenia is the most common diagnosis given to patients presenting with a first episode of psychosis (50%–70%) [26], about 20% are diagnosed with schizoaffective disorder and as many as 6% are diagnosed with bipolar disorder. About 10% of first episode patients are diagnosed with a wide variety of other disorders, including delusional disorder, general medical disorder, and substance-induced psychosis. The disorders described in **Table 2** can overlap with schizophrenia and may feature symptoms that are consistent with psychosis.

Table 3. Routine and Special Baseline Investigations for Ruling Out Known Medical Causes of a First Episode Psychosis

Classification	Medical Disorders	Investigations
Metabolic and endocrine	Thyroid, adrenal	Kidney function, electrolytes, thyroid-stimulating hormone, fasting blood sugar, lipids
Autoimmune	Lupus	Erythrocyte sedimentation rate, antibodies, antinuclear antibody
Substance abuse	LSD, cannabis, etc	Urine drug screens
Hepatic disorders	Wilson's disease	Liver function, genetic testing, ceruloplasmin level
Nutritional deficiency	Thiamine deficiency, pellagra	Vitamin B ₁₂ , red blood cell folate, iron
Systemic infections	HIV, syphilis	Complete blood count, urinalysis, chest x-ray, testing for sexually transmitted diseases
Central nervous system abnormalities	Delirium, brain injury, epilepsy, Huntington's	MRI, CT, lumbar puncture, EEG
Chromosomal abnormalities	Fragile X, DiGeorge syndrome	22q11.2 deletion, CGG nucleotide repeats

By definition, an individual experiencing a major depressive disorder with psychotic features must meet full criteria for depression with either mood congruent or incongruent psychotic features. For example, a mood congruent delusion is one where the person believes that their body is rotting, also known as a nihilistic delusion. Because depression often manifests itself first among youth diagnosed with bipolar illness, the course of a young person undergoing a major depressive disorder with psychotic features should be monitored carefully for manic symptoms, which may emerge at a later stage. In addition, a young patient may present initially with manic symptoms, but later in the course of their illness develop chronic psychotic symptoms in the absence of mood symptoms, thereby changing the diagnosis from bipolar illness to schizoaffective disorder.

Some patients have a concurrent substance abuse disorder in addition to an underlying psychotic disorder. A number of clues may help the clinician to make a determination about whether the patient has a comorbid condition: the course of the illness, the presence of ongoing substance use, and the character of the hallucinations. For example, visual as opposed to auditory hallucinations may suggest a substance abuse use disorder. Obsessions and compulsions, symptoms found in obsessive compulsive disorder (OCD), may occur among patients diagnosed with schizophrenia at rates significantly higher than that expected by the prevalence of either condition alone [27].

Finally, psychosis can be caused by a variety of medical conditions, such as neurological, endocrine, or autoimmune disorders. Clinicians must rule out medical conditions by conducting a thorough history and physical examination, along with the appropriate laboratory and neuroimaging investigations (as listed in **Table 3**). Patients with organic psychosis can present in a manner that is indistinguishable from schizophrenia [23]. Extreme psychomotor slowing

from organic disorders may mimic severe depression, while delirium may present like acute mania

• **What are the major causes of delays in treatment?**

The duration of untreated psychosis (DUP) is the period between onset of psychotic symptoms and initiation of anti-psychotic or early intervention treatment [19]. DUP has ranged anywhere from a mean of 1 to 4 years [28–30]. Many different reasons are responsible for the delay. Clinicians may lack knowledge and skill in recognizing psychosis. Patients and families may not be able to acknowledge mental illness and may prefer to accept other alternative explanatory models. Stigma and shame may interfere with their ability to access appropriate professional help. If youth with psychosis access appropriate help, they may minimize the severity of symptoms, or patients and family members may lack confidence in the treatments offered [31–33]. Three systematic reviews have shown that shorter durations of untreated psychosis are correlated with better treatment outcomes [32,34,35].

• **What is early intervention in psychosis?**

Often young people experience “late intervention”: long waiting lists for services [20], difficulty accessing health care for mental health problems, emergency room visits, and hospitalizations as their first point of contact into the system [36]. To address the need for rapid and specialized services, early intervention centers have been established to treat young people experiencing a first episode of psychosis and

Table 4. Psychosocial and Psychological Interventions Commonly Used by Early Intervention in Psychosis Programs

Intervention	Level of Evidence	Description
Psychoeducational psychotherapy	Systematic review [49] and 1 RCT [52]	Individual psycho-educational psychotherapy provides patients with individualized knowledge and information about their illness, symptoms, and diagnosis which aids in the recovery process [21]. Attention is paid to education about psychosis, treatments, stress management, recovery, relapse prevention, and lifestyle issues so that patients have a better understanding of their experiences.
Cognitive behavioral psychotherapy	Systematic review [49] and several RCTs [53–55]	Cognitive behavioral psychotherapy provides for a shared case formulation developed by the client and therapist, reality testing of automatic thoughts about psychosis and hallucinations, along with homework assignments to plot coping mechanisms, and help for the interpersonal and social context in which the symptoms occur [56]
Family psychoeducation	Systematic review and RCTs [47, 57]	Family psychoeducation is critical for obtaining corroborative history, managing crises, negotiating treatment plans and including the influence of the family in the treatment process [58]
Supported employment	RCT [59] and prospective cohort [60]	Supported employment helps to support the client's goal of finding competitive employment [61] with the use of vocational counsellors who find employment opportunities suitable for their clients and who provide supports to help maintain the client in their role

to support their families [19]. The first of these programs, the Early Psychosis Prevention and Intervention Centre (EPPIC), was developed in Melbourne, Australia [30]. Many major urban centers around the world have since developed their own early intervention centers [37] modeled after EPPIC. The main objectives of early intervention care are to reduce DUP and to optimize the delivery of care for patients and their family members [37,38].

Early detection programs have the potential to increase case finding [33] and to reduce the length of DUP, as demonstrated in a Norwegian study that achieved a reduction in DUP from about 100 weeks down to 17 weeks [39]. Reductions in DUP have been shown to significantly improve symptoms and functioning, not only at the point of initial contact and after 3 months of early intervention treatment [39], but also up to 2 years later, although the improvements that occurred at 2 years were restricted to negative symptoms, depressive symptoms, and functioning [40,41]. The early detection strategies consisted of the following approaches:

1. Rapid access to psychiatric services through multiple points of referrals, such as schools or youth-oriented services;
2. Community anti-stigma and education campaigns through the local media; and
3. Education of family physicians on how to identify psychosis in youth.

Experts in the field report that early intervention as a service differs from treatment as usual because it is phase-specific to the individual's developmental needs and stage of illness [42]. Early intervention programs focus on engage-

ment and retaining young treatment-naive patients. Family involvement and community and home visits are all common strategies used by these services to engage youth.

Although the quality of the evidence varies greatly, the components or "building blocks" of early intervention services include the following elements of care [20]: low-dose antipsychotic medications [43], case management [44,45] or care coordination [46], family education [47,48], and psychosocial interventions [49]. Early intervention in psychosis, as a service delivery model, has been associated with better outcomes compared with treatment as usual with respect to suicidality, symptom control, and functioning in randomized controlled trials (RCTs) [44,50], but one RCT failed to show improved efficacy [45].

Pharmacotherapy is the cornerstone of early intervention and is considered the first line of treatment for a first episode of psychosis, as described below. The other therapeutic components of early intervention are considered to be adjuncts to medication and include the psychosocial and psychological interventions outlined in **Table 4**. Table 4 lists some of the best available evidence for the efficacy of these nonpharmacological strategies [49,51] in first episode psychosis samples.

- **Are second-generation antipsychotic medications more effective than traditional antipsychotics for first episode psychosis?**

When the second-generation antipsychotic medications first became available, there was hope and optimism in the field

that these medications would deliver superior efficacy over conventional or traditional antipsychotic medications based on a few early RCTs [62–64]. These newer medications have become the mainstay of treatment for first episode schizophrenia. However, more recently, 2 larger scale RCTs have failed to demonstrate an advantage with respect to efficacy for the more expensive second-generation antipsychotic medications [65,66]. Therefore, clinicians must consider factors in addition to efficacy, such as side-effect profile and cost, when choosing the most appropriate medication for a patient.

- **What is the effective dose range for treating a first episode of psychosis?**

In addition to the traditional factors, such as gender, sex, and ethnicity, the dose of antipsychotic medications depends upon the person’s phase of illness. First episode patients are, in general, treated with lower doses, such as 1 to 3 mg per day of haloperidol or its equivalent [67]. The mean effective doses for olanzapine and risperidone have correlated with D₂ receptor occupancies of 72%, and these doses have been as low as 7.5 mg per day for olanzapine and 2 mg per day for risperidone [68,69]. Remission of positive symptoms has been shown to occur at approximately the same rate regardless of the dose, whether it is equivalent to 2 mg or 4 mg per day of risperidone [43]. Doses above 15 mg per day of haloperidol or its equivalent are no longer considered to be more efficacious than lower doses and are associated with an increased risk of side effects [70]. **Table 5** shows dose equivalents for second-generation antipsychotic medications [71].

Once an acute episode of psychosis has been stabilized for several months with antipsychotic medications, medication is still needed to provide prophylaxis against repeated relapse of symptoms. To alleviate side effects, the dose of antipsychotic medication is usually lowered, slowly and gradually, down to doses that are about 25% to 50% of the original doses needed for acute control [72,73].

- **What are the side effects of antipsychotic medications that are commonly experienced by first episode patients?**

Tardive Dyskinesia and Extrapyramidal Side Effects

Tardive dyskinesia (TD) and tardive dystonia are antipsychotic-induced side effects, mediated by D₂ receptor blockade, that are potentially irreversible. The patient experiences purposeless abnormal movements, which tend to be choreoathetoid, rhythmic, and writhing in nature for

Table 5. Dose Equivalents for Second-Generation Antipsychotics

Generic Name	Trade Name	Dose (mg/day)
Haloperidol	Haldol	2
Risperidone	Risperdal	2
Olanzapine	Zyprexa	5
Quetiapine	Seroquel	75
Ziprasidone	Zeldox	60
Chlorpromazine	Largactil	100

Adapted from reference 71.

TD but repetitive and spasmodic for tardive dystonia [74]. The most commonly affected areas include the tongue, oral facial areas, upper and lower extremities, and trunk.

Extrapyramidal side effects (EPS) are caused by D₂ receptor blockade of the nigrostriatal region of the brain and can cause rigidity, tremor, akathisia, bradykinesia, acute dystonia, as well as affective flattening and cognitive slowing [75]. Akathisia presents as a subjective and objective restlessness. Often patients experience it as an uncomfortable inner restlessness associated with pacing, restless legs, or rocking. Bradykinesia is a slowing of motor movements often affecting gait. Dystonic reactions are caused by sustained motor contractions, typically of muscle groups involving the eye (ocular gyric crisis), the tongue (protrusion), the larynx (laryngospasm), and the neck (torticollis).

Haloperidol and traditional antipsychotic medications are associated with the greatest risk of TD and EPS [75]. Clozapine and quetiapine are the least likely to cause TD or EPS because of their rapid release from the D₂ receptor [67]. Olanzapine [76] and risperidone [74,77] are both significantly less likely to cause TD and EPS than haloperidol. The traditional antipsychotic medications with the lowest D₂ receptor affinity tend to have the highest muscarinic receptor affinity and are less likely to cause EPS than medications with high D₂ potency because anticholinergic properties are protective [75].

Weight Gain and Metabolic Syndrome

Second-generation antipsychotic medications are associated with an increased risk of metabolic side effects, such as glucose intolerance, hyperlipidemia, weight gain, and hypertension [78,79]. After 1 year of treatment with olanzapine for the first time, up to 30% of patients had hyperglycemia, 56% had hypercholesteremia, and 86% gained up to 7% of their baseline weight [65]. Clozapine and olanzapine have the greatest risk of weight gain, followed by risperidone and quetiapine [80]. Ziprasidone and aripiprazole, relatively new second-generation antipsychotic medications, have the lowest propensity toward weight gain, followed by haloperidol and pimozide, which are highly D₂ potent traditional antipsychotic medications [80].

Table 6. Routine Examinations and Investigations to Rule Out Side Effects of Antipsychotic Medications

Examination	Rationale
AIMS test*	Physical exam for tardive dyskinesia
ESRS†	Physical exam for antipsychotic-induced extrapyramidal symptoms
Waist circumference, BMI, blood pressure	Physical exams for metabolic syndrome
Fasting blood sugar, cholesterol, triglycerides, HDL, and LDL	Laboratory investigations for metabolic syndrome
AST, ALT, GGT, bilirubin	Lab tests to monitor liver function
Prolactin level	Monitor for hyperprolactinemia
Baseline EKG	Standard for clozapine, recommended for ziprasidone and patients < 18 yr or > 40 yr

*Abnormal Involuntary Movement Scale.

†Extrapyramidal Symptom Rating Scale.

Individuals who have first episode schizophrenia may be at a greater risk of developing diabetes and obesity than the general public. This is a risk that may be independent from that attributed to medications, possibly due to associated impairments in the hypothalamic-pituitary-adrenal axis [81–84].

Prolactin Elevation and Sexual Side Effects

Antipsychotic medications can elevate prolactin levels through D₂ blockade of the pituitary. Hyperprolactinemia, by inhibiting the hypothalamic-pituitary-gonadal axis, increases the risk of osteoporosis among patients, particularly those patients treated with antipsychotic medications for 10 years or longer [85]. In addition, compared to controls who do not take medications, first episode patients with high prolactin levels are significantly more likely to experience sexual dysfunction, including problems with libido, ejaculation, and reduced sexual satisfaction [86]. Other unwanted clinical reactions caused by hyperprolactinemia include galactorrhea, gynecomastia, and amenorrhea [87].

Although clozapine and quetiapine are the least likely antipsychotic medications to cause hyperprolactinemia, risperidone is one of the most likely second-generation antipsychotics to cause it [65,77]; the more D₂ potent the antipsychotic medication, the more frequent the occurrence [65]. This side effect may be experienced by as many as 40% to 80% of first episode patients [65].

Anticholinergic Side Effects

Most antipsychotics block muscarinic receptors, even at low doses, thereby increasing the risk of anticholinergic side

effects, such as dry mouth, blurry vision, constipation, and urinary retention (through peripheral system blockade). At high doses, blocking muscarinic receptors can also cause delirium and memory loss (from central nervous system blockade) [75].

Cardiac Effects

Orthostatic hypotension is a common side effect among antipsychotic medications, particularly traditional antipsychotics with low D₂ potency but also second-generation antipsychotics, such as quetiapine and clozapine. Some antipsychotics can increase the risk of ventricular arrhythmias by increasing the QT interval to above 500 milliseconds; in particular, ziprasidone and thioridazine are the worst offenders. In addition, clozapine can cause myocarditis, cardiomyopathies, and sinus tachycardia, even in young people. Risperidone and olanzapine both have a lower risk of cardiac effects than the aforementioned antipsychotic medications. Mackin has reviewed these common cardiac side effects and has outlined useful management strategies [88].

- **What investigations are routinely ordered to monitor side effects?**

There are a number of screening tests that are conducted to monitor for side effects of the medications. The AIMS (Abnormal Involuntary Movement Scale) test for TD needs to be conducted routinely every 6 months to check for abnormal movements [75]. It involves rating any involuntary movements on a scale from mild to severe, both before and after every 6 months of antipsychotic treatment [89] because the reported incidence of spontaneous abnormal movements among drug-naïve patients has varied from 7% to 10% [90]. Clinicians can also check for EPS by using the ESRS (Extrapyramidal Symptom Rating Scale) [91], observing the patient for tremor, festinating gait, flat affect, and restlessness as well as by moving the head and upper and lower limbs vertically and laterally at the joint, typically revealing cog wheeling rigidity or a ratchet-like movement upon palpation of the joint [75].

Because of the increased risk of metabolic disturbances, the tests and examinations outlined in **Table 6** should be conducted at baseline and every 6 months for first episode psychosis patients [92]. A baseline electrocardiogram is standard for clozapine to monitor for sinus tachycardia and myocarditis and is a consideration for ziprasidone due to the increased risk for prolongation of the QT interval, as well as for patients under age 18 or over age 40 due to the increased risk of arrhythmias or cardiac complications.

• **How are side effects of antipsychotic medications managed?**

Cortese has outlined a comprehensive approach to the management of antipsychotic-induced side effects [75]. If the patient has shown a positive clinical response to the medication, the clinicians gradually reduce the dose of medication down to 25% to 50% because most side effects are dose related. Switching patients to another antipsychotic medication is another strategy, especially when relapse or poor symptom control is an issue and a medication with a lower risk profile for the particular side effect is available. In many cases, use of adjunctive medications may help alleviate side effects such as EPS. Benzodiazepines, benzotropine, and propranolol have all been shown to be effective for EPS, and vitamin E has been shown effective for TD. Finally, clozapine has been effective for treating tardive dyskinesia, hyperprolactinemia, and intractable EPS. Intensive diet and exercise counselling have shown limited success in reducing weight gain and metabolic disturbances caused by these medications [93].

• **What are the main predictors of outcome?**

At the onset of illness, a number of factors predict outcome and prognosis many years later. Generally speaking, females have more favorable outcomes than males [5]. Patients who had good premorbid adjustment, affective symptoms, and an acute onset of illness tend to have a better course of illness than individuals who experienced schizoid traits, slow insidious onset, and a long DUP. Shorter DUP is associated with reduced severity of negative symptoms [32,34], and strategies that reduce DUP have been shown to be effective in reducing the level of negative symptoms up to 2 years later [41].

After 1 year of early intervention involvement, at least 66% of first episode psychosis patients are in remission [33,94], but it is not unusual for about 25% to experience residual symptoms and a chronic course [94], especially between middle ages up to senescence [95]. In general, for about 15% of all patients diagnosed with a first episode of psychosis, symptoms resolve without any further relapses or hospitalizations up to 5 years after entry to an early intervention program, but about 15% are institutionalized (living in supported housing or being admitted frequently to hospital) and about 30% to 40% are in the community but continue to experience ongoing psychotic symptoms [26,73].

Only 30% to 50% of first episode psychosis patients

achieve good adherence to their medications; good adherence is defined as rarely or never missing a dose [96]. Medication compliance is influenced by a complex interplay of psychosocial, pharmacological, and cognitive factors. The degree of family support is an important psychosocial predictor of adherence, highlighting the need for family education about the disorder and its treatment [97]. Other psychosocial issues that may influence adherence to medications include the role of stigma, quality of life, and premorbid functioning [96]. Side effects are commonly cited by patients as reasons for discontinuing their medications, such as weight gain and sexual side effects. Compared with those with good adherence, nonadherent patients are more likely to be heavy alcohol and cannabis users [4], as well as to have an early onset of illness and be younger in age [96]. The risk of relapse is still 70% at 1 year and over 90% at 2 years after discontinuation of medication, even for patients who have been stable for 2 years prior to discontinuation of their medication [98].

Case Follow-up



Harry agreed that life was getting overwhelming and that he may be misinterpreting things and feeling unnecessarily suspicious of his family. He agreed that the best way to cope with this stress was to seek help for himself and his family at an outpatient early intervention in psychosis program.

When Harry was interviewed, it was evident that he was experiencing auditory hallucinations and paranoid ideation. He reported daily marijuana smoking since age 14. A full psychiatric assessment was performed, which included screening blood work, MRI, corroborative history from his mother, neuropsychological testing, and occupational therapy assessment.

Harry and his family were given information about psychosis, mood disturbance, and cannabis abuse and feedback about how some of Harry's problems could be caused by these syndromes. The differential diagnosis included bipolar disorder, schizoaffective disorder, and cannabis-induced psychosis. He was given the option of being treated with olanzapine, risperidone, or perphenazine. He chose risperidone because it was less likely to cause weight gain than olanzapine and less likely to cause motor side effects than perphenazine.

Once a therapeutic alliance was developed with the treatment team, a treatment agreement was negotiated for the next 6 months, based on his goals of finishing high school, getting back on the football team, and eventually going to college to become a computer engineer. The components of his treatment agreement included taking antipsychotic medication as negotiated with his psychiatrist, discussing his thoughts and feelings with the team, decreasing marijuana

use, and going for walks 5 times per week to help him feel more comfortable out in the community and to improve his physical conditioning. In addition, his mother agreed to meet with the family educator to help support his recovery.

He continued to use marijuana but decreased his use from daily to once a week once he realized his hallucinations were often worse a day or two after using, even though it helped him feel calm at the time of use. His nurse worked with him on some simple cognitive behavioral strategies to help him cope with anxiety and depressive symptoms. His psychiatrist helped him to understand that stopping treatment led to resurgence of symptoms after a 2-week period of noncompliance. His occupational therapist liaised with his guidance counsellor to help negotiate a gradual return to high school once Harry's paranoia, auditory hallucinations, and concentration were improved for about 6 months.

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