Refractory Mood And Psychosis

Introduction

There have been significant advances in the treatment and management of mental illnesses. New, more effective psychiatric medications are available. In spite of these advances, many patients and their families struggle with the realization that although these treatments are helpful they are not able to return the patient to a fully functioning life; their conditions are resistant to treatment and they continue to suffer for months or years while hoping for an appropriate treatment that will help their condition. This course discusses those particular situations whereby patients are diagnosed with mood or psychotic disorders and, despite attempts at managing their condition, are resistant to treatment.

Impact Of Refractory Mental Illness

The consequences of mental illnesses that are unresponsive to standard forms of treatment are great. The impact of an inability to achieve symptom relief due to refractory mental illness is heavy upon society and results in a loss of productive work time, increased costs of treatment within the healthcare system, increased numbers of hospitalizations and outpatient care needs, and greater demand for psychiatric services than some communities are able to give. This applies to all forms of mental illnesses diagnosed within the healthcare sector, although there are some forms of mental illness that are more resistant to treatment than others. Major depressive disorder is one of the most common, although other disorders that lead to psychosis are also difficult to manage appropriately and may also be resistant to treatment.
Mood Disorders

A mood disorder describes a condition in which a person experiences a change in mood or has difficulties maintaining a stable mood state because of alterations in mental health. Mood disorders are typically classified as being one of the types of bipolar disorder, which includes bipolar type 1, bipolar type 2, and bipolar with mixed features; as well as various types of depression, including major depressive disorder, persistent depressive disorder, which is also known as dysthymia, and seasonal affective disorder.

Mood disorders, particularly depression, are some of the most common reasons individuals seek mental health treatment today. Regrettably, depression is also a condition that is often resistant to treatment. In these cases, a patient may take medication or undergo psychotherapy, but will continue to suffer with depressive symptoms that never quite resolve. Mood disorders are some of the most common forms of psychiatric disorders; they affect men and women of all ages. Refractory mood disorders, sometimes referred to as treatment-resistant mood disorders, have high rates of morbidity and mortality, as people who do not respond to therapeutic intervention are more likely to suffer from physical symptoms and to develop suicidal ideation.

Among diagnosable mood disorders, the types are classified as being depressive disorders or bipolar disorders, as the two types can be quite different. Bipolar disorders, in particular, may be associated with psychosis and are classified according to the DSM-5 as being a "bridge" between the psychotic and depressive disorders. Mood disorders are classified as outlined below.
• Bipolar I disorder

This specific type of bipolar illness is a classic presentation of manic-depressive illness. In bipolar I, the affected person has periods of mania interspersed with periods of severe depression.

• Bipolar II disorder

This subset of bipolar disorder occurs when the affected individual experiences episodes of hypomania, described as less intense than periods of mania and characterized by shorter time frames, interspersed with periods of major depression. Bipolar II illness typically does not involve psychotic symptoms.

• Cyclothymic disorder

This type of bipolar disorder is considered to be a milder form when compared to types I and II of the illness. The affected person still has periods of hypomania and depression, but they are less intense and do not last as long. When compared with other forms of bipolar disorder, cyclothymic disorder is considered to be relatively rare.

• Major depressive disorder

One of the most common types of mood disorders, major depressive disorder describes a condition in which the affected person experiences periods of intense sadness, hopelessness, emptiness, or guilt, which impacts eating, sleep habits, weight, relationships, and activities of daily living. The individual is at risk of
death from suicide, which is strongly correlated with feelings of hopelessness that occur with major depression.

• Persistent depressive disorder

Also called dysthymia, persistent depressive disorder describes a condition in which a person has chronically low moods and feelings similar to major depression, yet the feelings are not as intense. The chronically depressed mood associated with persistent depressive disorder often lasts two years or more.

• Premenstrual dysphoric disorder (PMDD)

This specific type of depressive disorder describes a condition in which a woman experiences symptoms of depression, such as sadness, guilt, and hopelessness, as well as irritability or anger, in the time prior to menstruation. The symptoms typically resolve after onset of menses.

Psychosis

Psychosis describes a condition in which an individual is experiencing severe alterations in thought or in emotions. Often, the affected person has difficulty understanding the difference between one’s own thoughts and ideas and reality. Psychosis develops as part of a number of mental illnesses, including schizophrenia, bipolar disorder, and severe depression, including cases of severe postpartum depression. It may also be associated with some conditions that cause dementia, including Alzheimer’s disease, Huntington’s chorea, or Parkinson’s disease. The most common mental illness causing psychosis is schizophrenia.
The main symptoms of psychosis include different types of delusions and/or hallucinations, which may be auditory, visual, or both. Delusions tend to appear in people with different types of mental illnesses, including schizophrenia, delusional disorder, or schizoaffective disorder.¹ This includes a set of beliefs about oneself or a situation that is generally false. They may be classified according to different themes, including delusions of grandeur, in which the affected person believes that he or she has significant powers or abilities; delusions of guilt, where the person feels guilty and responsible for something, often a significant or historical event, that he or she actually was not involved with at all; or delusions of control, in which the affected person believes that an external force or another person is controlling one’s thoughts and behavior. There are also many other types of delusions and delusional behaviors associated with psychoses, such as lycanthropy (belief you can of have transformed into an animal such as a wolf) of, erotomania, delusions of immortality or jealousy, and Cotard delusions.² All of these types involve situations in which the affected persons have a false belief about themselves or a situation, whether it is that a stranger is in love with them, they are actually a mystical being, or they believe that they are already dead.

In contrast, hallucinations may affect one or more of the senses and they are more likely to be associated with acute psychosis, such as with schizophrenia.¹ Hallucinations occur when the affected person senses something that is not actually there. The most common types of hallucinations associated with psychoses are auditory hallucinations, in which the person hears things that are not real. The person may hear voices, which may or may not be familiar; sometimes, the voices “tell” the person to do something, or the voices may just be sounds of people talking. The sounds occur outside of the person’s thought patterns and are uncontrolled.
Visual hallucinations involve seeing things that are not there. The range of visual hallucinations is quite large and the affected individual may see anything from physical objects, such as insects or people, to other disturbances, such as flashes of light. The person may continue to see the same things repeatedly or the visual hallucinations may change over time. Less common other types of hallucinations include olfactory hallucinations, in which the person smells odors that actually are not there, tactile hallucinations, such as feelings of being tickled or brushed, or gustatory hallucinations, in which the person has an odd taste in the mouth. Psychosis is a troubling and often terrifying state for the person who experiences such alterations from reality. It can be even more frustrating for the affected patient to know that others nearby are not seeing or hearing the same things.

The DSM-5 lists various mental health conditions that cause psychosis and has classified them as distinct conditions. Psychotic disorders classified according to the DSM-5 are outlined below.

- Delusional disorder

  The affected person experiences bizarre delusions that may be individualized to one or two people or may be generalized to a larger group. According to the *Journal of the American Academy of Psychiatry and the Law*, research has shown that long-term use of antipsychotic medications in persons diagnosed with this condition only leads to a modest decrease in persistent symptoms.\(^\text{18}\)

- Brief psychotic disorder
The person has shorter periods of time that he experiences symptoms; diagnosis requires symptoms of delusions, hallucinations, or disorganized speech for one month or less.

• Schizophreniform disorder

This type of psychotic disorder is diagnosed when symptoms of delusions or hallucinations appear for less than six months. A diagnosis of schizophrenia can be made when symptoms last for over one month.

• Schizophrenia

An individual with schizophrenia experiences hallucinations, delusions, or disorganized thinking or speech. Instead of being classified as paranoid or disorganized types, as was done with older diagnostic criteria, schizophrenia is now diagnosed according to course specifiers; in particular, first-episode schizophrenia and multiple-episode schizophrenia. Each specifier is further classified as being acute, in partial remission, or in full remission.

• Schizoaffective disorder

This unique type of mental illness includes a combination of symptoms of schizophrenia, including delusions or hallucinations, as well as symptoms of a mood disorder, such as mania associated with bipolar disorder or clinical depression.

• Catatonia
This condition describes a state of unresponsiveness to external stimuli, but the affected person is conscious. The person may have extremely slow or constricted motor responses; in some other cases, the individual is agitated but has very purposeless activity. Catatonia is not diagnosed on its own; it is always included as part of another diagnosis, such as with catatonia associated with schizophrenia or depression.

Approximately one-third of treated cases of schizophrenia are considered refractory, or treatment resistant, in that they do not respond to conventional forms of therapy as evidenced by a reduction in symptoms.\textsuperscript{54} Treatment-resistant schizophrenia is defined as a state of continued psychotic symptoms after trials of two different types of antipsychotic medications.\textsuperscript{55}

### Defining Refractory Mental Disorders

Under many circumstances, treatment of mood disorders and of psychotic states is successful with medication and therapy. A great many people who have been diagnosed with conditions such as depression, bipolar disorder, or schizophrenia have found help and freedom from symptoms by taking medication, going through counseling and behavioral therapy, or undergoing rehabilitative services.

Unfortunately, a percentage of the population who are diagnosed with mood disorders and mental illnesses that cause psychosis do not respond to conventional treatments. These individuals may try a number of treatments as possible solutions for their symptoms but find that they continue to struggle. They may have had success for a period of time with certain therapies but then find that their symptoms have worsened and they no
longer respond to standard treatments. This describes a refractory condition, which is one that is unresponsive to otherwise conventional forms of treatment for an illness. A person with refractory mood disorder or psychosis often suffers through the feelings and manifestations of the disease and is unable to find relief through treatment because there simply is no response. Standards of what is considered a treatment-resistant or refractory mood disorder tend to vary somewhat within the available research. Bipolar disorder is considered to be treatment resistant when certain criteria are met that indicate the patient has tried several methods of disease management without success. Because bipolar disorder can cause a wide range of symptoms between mania and depression, treatment may go on for longer periods before determining that the affected patient is not responding. Treatment resistance of bipolar disorder is considered when the patient has undergone treatment for at least six weeks during manic periods, 12 weeks in bipolar depression, and at least 12 months of maintenance treatment for the condition.59

When treating mood disorders, the clinician often begins with standard forms of treatment that have worked for greater populations of patients with the same condition in the past. The goal is to achieve remission from symptoms and to help the patient to be free of the struggle with the manifestations associated with his or her mental illness, providing a greater chance of living a normal life of good quality. When traditional forms of treatment, such as the administration of medications, that have been successful in the past do not have an effect on the patient’s symptoms and behavior, the next step is to prescribe alternative forms of treatment while taking into consideration the patient’s safety and ability to tolerate the new regimen. Unfortunately, this process can take a considerable amount of time to allow for a watchful waiting period to observe how the medication will work, follow-up with the
patient to determine if symptoms are under control, and making medication adjustments as needed to control symptoms when the condition is resistant to treatment or for observed medication side effects.

Research regarding some of the more common forms of mental illness and their resistance to treatment abound in the literature. Some of the other, less common, forms of mood or psychotic disorders have less information about how to handle their states when they become resistant to treatment. For instance, there is little information available about treatment-resistant persistent depressive disorder. Because the patient must have suffered with symptoms for at least two years in order to be diagnosed with this condition, the symptoms and indicators are often very long lasting to begin.

Reports of those suffering from treatment-resistant dysthymia have indicated that these patients may struggle with symptoms for upwards of 7 to 10 years or even more, despite attempts at treatment. Suggestions for the management of treatment-resistant dysthymia include antidepressant medications and cognitive-behavioral therapy; and it has been recommended that patients should be switched to a different class of antidepressant when others are not successful. Instead of being categorized as its own entity with its own criteria for treatment, refractory dysthymia is instead often classified as being similar to major depressive disorder, with similar forms of treatment. Clinicians often suggest making modifications to treatment and trying a combination of activities for the management of treatment-resistant dysthymia, including using different classes of antidepressants, mood stabilizers, or antianxiety drugs, as well as cognitive-behavioral therapy, light therapy, or exercise.²⁰
The most common form of treatment for major depression is through prescribing antidepressants. A review by Trevino, et al., in the *Annals of Clinical Psychiatry* found that among individuals diagnosed with major depressive disorder, between 30 and 50 percent do not respond to initial treatment with a normal dose and duration of antidepressants, and up to 20 percent of patients continue to suffer with symptoms of depression for up to two years after the initial onset of a major depressive episode.\(^{57}\)

In cases of premenstrual dysphoric disorder (PMDD), treatment from a healthcare provider is usually required because the condition is often much more extensive when compared to common hormonal changes that occur prior to monthly menstruation. The exact mechanisms of why PMDD develops in some women while others are unaffected by the disorder remain largely unknown, but research suggests that its development is related to an imbalance of the neurotransmitter serotonin as well as the normal cyclical changes in hormone levels associated with menstruation.

Most cases of pre-menstrual syndrome respond to lifestyle interventions such as increased exercise, pain relievers, and other conservative therapies. Premenstrual dysphoric disorder however is normally treated with medications that may be used to manage major depressive illness, such as selective-serotonin reuptake inhibitor medications and antianxiety medications, as well as medications that suppress ovulation, including gonadotropin releasing-hormone agonists or oral contraceptives.\(^{22}\) To be considered treatment-resistant, the effects of PMDD must be great enough that conventional treatments do not change the amount or intensity of symptoms experienced by the patient.
Because PMDD causes mood changes in a cyclical pattern — that is, approximately each month before menses the symptoms are at their worst — the patient must demonstrate cyclical mood changes during two or more menstrual cycles to be diagnosed.\textsuperscript{21} Significant suppression of ovulation is often the only choice for treatment of refractory PMDD when other medications have not been effective. This may require oophorectomy to remove any chance of continued ovarian functioning, which has been shown to be the most successful treatment of refractory PMDD.\textsuperscript{22,23}

There is obviously great variety in what constitutes certain mood and psychotic disorders. Often, symptoms can overlap, making diagnosis difficult. The situation can be further complicated when the patient has a diagnosis of a specific condition but does not respond to conventional treatment. When this occurs, healthcare providers are often faced with making changes to the current regimen or changing the diagnosis, both of which can be daunting tasks. The development of certain mood or psychotic disorders can be elucidated by exploring a patient’s risk factors for their development.

**Refractory Mental Illness Risk Factors**

Because refractory mental disorders are very complex in their etiologies and manifestations, they are also associated with a variety of risk factors that may each play a role in the development of mental illness. There is not one specific type of criteria that is a risk factor for all people with mental illness. However, there are some circumstances that are more commonly seen in the histories of those with mood disorders or psychosis. The refractory nature of these mental diseases also increases the complexities of symptom manifestations and treatment; because of this, risk factors often involve a number of different pathophysiological and environmental factors. Research
suggests that development of mood and psychotic disorders is most often associated with a combination of physiological mechanisms, including altered neurotransmitter levels in the brain or the presence of a genetic component, as well as environmental factors, including exposure to substance use or family violence.

A literature review by Dammack (2013) looked at the various risk factors for development of treatment-resistant schizophrenia that causes psychosis and found multiple factors that contributed to its development. Types of risk factors were identified as five categories: 1) non-modifiable risk factors associated with the patient and family, 2) socioenvironmental risk factors, 3) risk factors associated with cognitive defects, 4) para-clinical risk factors, and 5) risk factors associated with treatment. In the literature review, the group found that higher risk factors were associated with male gender, also related to an increase in poor prognosis, and early age of onset of symptoms. Some clinical manifestations of schizophrenia were more likely to be seen in refractory cases and were correlated with poor response to treatment, including inappropriate or blunted affect, negative thought processes, low social skills, poor coping mechanisms, an intolerance to frustration, and a lack of impulse control.50

Genetics

A negative family or social environment was also associated with poor prognosis and higher levels of refractoriness in schizophrenia. A high rate of emotional expressiveness within the family, early substance use, particularly early cannabis use, and a history of obstetric complications at birth were both associated with greater rates of unresponsiveness to treatment, as well as a family history of mental illness.50 Genetics plays a large role in the development of mental health conditions that cause psychosis. Family
members of persons with schizophrenia are at higher risk of developing some form of mental health disorder, including schizoaffective disorder, bipolar disorder, or depression.\textsuperscript{4} Persons who have family members who have not responded to mental health treatment in the past may be more likely to be refractory to treatment if they are diagnosed as well.

**Trauma**

Trauma plays a significant role in the development of mental health problems. Robinson, \textit{et al.}, define emotional and physical trauma as \textquotedblleft the result of extraordinarily stressful events that shatter your sense of security, making you feel helpless and vulnerable in a dangerous world.\textquotedblright\textsuperscript{51} A person is more likely to be traumatized from a significant event when he or she feels helpless, overwhelmed, and alone when it occurs. A traumatic event could take many forms and could include any number of situations. Further, two people who experience the same traumatic event may also respond in different ways. There are no specific types of events that are considered traumatic, although some experiences can be particularly terrifying and upsetting for anyone. Rather, \textit{any event} that causes a person to feel overwhelmed or threatened can be considered a traumatic event, even if the affected person is not physically harmed or if others experiencing the same event do not respond in the same way.

Events that are more likely to lead to physical or psychological trauma include those that are unexpected and therefore more shocking, occurrences that happened repeatedly, events where the affected person felt helpless and out of control, or situations where another person was exceptionally malicious or hurtful.\textsuperscript{51} Traumatic events such as physical, emotional, or sexual abuse, separation from a caregiver, instances of being bullied, undergoing significant medical procedures or surviving life-threatening
illnesses or injuries are all situations that can be traumatic; particularly when such events occur during childhood when the brain is still growing and developing. It is these and other forms of abuse and trauma that can significantly increase the risk of an affected person developing mental health disorders later, particularly those that do not respond well to treatment.

One of the more common mental health conditions that develop following a traumatic event is post-traumatic stress disorder (PTSD). The condition describes a state where a person experiences anxiety, stress, and heightened emotions when they relive a traumatic event. The trauma could be a one-time situation, such as when an individual is in a serious car accident that leaves the person significantly injured. Alternatively, PTSD can and often does develop following a series of traumatic events or exposure to situations that are extremely difficult to handle, including among those who have served in military combat or those who have provided assistance or rescue to victims of disasters.

The individual with PTSD, after suffering through a traumatic event, may then have flashbacks or periods of time in which he or she relives some of the same feelings and fears felt when the actual trauma occurred. This may happen when the affected person is exposed to something that is a reminder of the event, which could be certain sights, sounds, or random items that trigger memories and feelings. In addition to suffering from detrimental emotional responses related to the event, the individual may also have physical symptoms as well, including sleep problems and nightmares, heart palpitations, sweating, breathing difficulties, or an upset stomach.23

An even more involved situation related to PTSD is complex post-traumatic stress disorder, which develops when an individual experiences a chronic
traumatic event that is ongoing over a period of time. Examples include situations in which a person is exposed to a traumatic event on a repeated basis and has no way of getting away from the situation, such as with cases of ongoing physical or sexual abuse or because of time spent as a prisoner of war. People who have undergone repeated exposure to chronic trauma often experience symptoms of PTSD, but they also develop changes in their abilities to adapt to stressful situations. Specifically, complex PTSD often causes changes in self-concept and the person may have difficulties forming and maintaining relationships, may feel a sense of bodily- or self-detachment, or may become preoccupied with the event or with getting revenge.

Complex PTSD is also associated with the later development of mood disorders, including major depressive disorder. The affected individual is more likely to experience chronic sadness, regret, hopelessness, guilt, anger, or shame about the event and may develop suicidal ideation. A study by Ramsawh, et al., in the Journal of Affective Disorders determined that PTSD is associated with greater rates of major depressive disorder among service members in the U.S. military. Among participants in the sample surveys for the study, 6 percent of respondents reported suicidal ideation or attempts within the past year, and up to 12 percent of respondents reported lifetime feelings of suicidal ideation. The study included discussion that took place with participants who had served in Iraq or Afghanistan and who had been diagnosed with PTSD because of the trauma they experienced through military service. The chronic nature of the trauma experienced during military conflict is one example of a situation in which an individual would suffer from mood dysregulation and could develop a mood disorder that is refractory to treatment. Other situations, including
childhood abuse and early neglect, lead to mood disorders that are difficult to treat over time.

Whether a person has experienced a one-time event that was traumatic and debilitating or has gone through ongoing trauma that has led to complex PTSD, the impact of trauma on the brain and its connection with the later development of mental illness cannot be minimized. In particular, trauma affects an individual’s ability to cope with difficult situations. For such patients, being diagnosed with a mental illness, and then later expected to cope with that diagnosis, they can often find it extremely difficult to accept and maintain an adequate treatment regimen and to undergo the necessary interventions needed to treat the illness.

**Early Trauma**

Early trauma that occurs during childhood can have long-standing negative effects on the later development of mood and psychotic disorders. Early trauma, such as through living in a long-term domestic violence situation or enduring chronic physical or sexual abuse that often occurs at the hands of one or both parents, or other close caregivers, can lead to confusion and difficulty for the person as an adult especially while making adjustments to live independently or when forming new relationships. For example, a young woman who has been repeatedly subjected to physical abuse for years as a child by her father may have difficulty forming relationships with others, particularly with men, after reaching adulthood. Isolated experiences of traumatic events during childhood can lead to a later diagnosis of PTSD if the person somehow relives the experience later through flashbacks or dreams. Post-traumatic stress disorder that develops as a result of an early trauma can also lead to feelings of depression and anxiety when the person is an adult.
Additionally, early, repeated trauma in childhood has been shown to interfere with normal brain development and can cause neurodevelopmental difficulties that inhibit a person’s ability to process emotional or sensory information. People who have suffered through early trauma because of childhood abuse or neglect are also more likely to grow up to become perpetrators of violence and abuse; unfortunately, the actions and behaviors typically are cyclical in nature.

Children exposed to chronic trauma early on often develop difficulties with self-control, which can lead to impulsive behavior, and a poor sense of self-concept. Further, as the child grows, he or she often develops coping mechanisms that are methods of self-protection because of having learned that caregivers or parents do not protect their child from trauma, but instead may actually be the ones responsible for exposing their child to trauma. As the child grows into an adult, he or she becomes more likely to struggle in relationships with others because of difficulties related to trust; becoming suspicious, aggressive, or even violent toward others and possibly having great difficulties forming lasting and solid relationships.

Van der Kolk, et al., proposed the inclusion of a developmental trauma disorder into the DSM-5 when it was being updated. The proposal was not accepted and developmental trauma disorder (DTD) was not included as part of the DSM-5, however, the condition has been presented to describe a situation in which a child has been repeatedly exposed to traumatic events that have affected his or her personality and emotional and cognitive development. The reasons for supporting the inclusion of DTD as an actual diagnosis was due to researchers proposing that complex PTSD diagnosis was not entirely applicable to children who have suffered through trauma.
Instead, it has been thought that a diagnosis of DTD better describes some of the problems with traumatic stress and emotional regulation faced by children who have experienced early trauma.

There are significant associations between the experience of childhood trauma and the later development of a mood disorder. Exposure to early trauma, with or without an actual diagnosis of PTSD or DTD, is associated with low mood, feelings of hopelessness or sadness, feelings of guilt and shame, and suicidal ideation. A study by Konradt, et al., in the Archives of Clinical Psychiatry confirmed that early trauma was more often part of the histories of young adults with mood disorders when compared to the general population. The study findings also suggested that early trauma through sexual abuse may be more likely to be associated with a later diagnosis of bipolar disorder in young adulthood.²⁹

Exposure to traumatic events, whether by exposure in the family through abuse and violence or due to unplanned events or accidents that are shocking and stressful can all be very difficult for children to handle. Many struggle with memories of the event and do not understand how to cope with their feelings surrounding the situation. They may or may not have support through counseling or therapy to learn how to talk about what happened; in some cases, they may block part of the event from memory to avoid remembering or talking about it at all. The damage that occurs during the early years of childhood, particularly when not appropriately controlled, prevented, or dealt with properly, can take a toll on the affected person’s mental state and can cause problems that may never resolve.

**Abuse**
Abuse can take many different forms, all of which are harmful to the victim. Abusive acts are often directed against children and adolescents, but many adults suffer abuse at the hands of others; for instance, the abuse suffered by an individual at the hands of a partner as seen in cases of domestic violence. All types of abuse can cause significant psychological and emotional trauma to the abused person. The long-term outcomes of people who have been abused are damaging and harmful and although the emotional impact of abuse may vary somewhat between people, there are many victims of abuse who go on to develop psychological health problems, including mood dysregulation.

Physical abuse describes a physical assault on another person, which may include actions such as hitting, kicking, pushing, shaking, or choking. Physical abuse may be directed toward a child, as in cases of child abuse, in which the health and safety of the child is endangered. Physical abuse directed toward older adults is also one aspect of elder abuse. In cases of intimate partner violence or domestic violence, physical abuse may occur between members of a household.

Physical abuse is not only physically damaging to a person’s body, it has the potential for irreparable harm to the person’s sense of self and development of self-esteem. While the physical effects of broken bones, burns, and scars can heal outwardly, the child who suffers from physical abuse actually experiences changes in levels of cognitive functioning and self-perception as the abuse continues over time. The stress of being physically harmed, in addition to the fear of wondering if or when it will happen again, combined with attempts to behave well or otherwise prevent the abuse all cause considerable stress and trauma on a child’s developing brain. Physical abuse is associated with the development of depression in affected children, which
can continue into adulthood if the condition does not change or is otherwise not well managed.

A study by Weder, et al., in the Journal of the American Academy of Child and Adolescent Psychiatry suggested that changes occurring within certain genes, when combined with child maltreatment such as through physical abuse, increases the risk for development of depression among affected children. The study considered the role of epigenetics; the idea that environmental conditions can alter gene expression, which can further affect later generations of descendants. The indication is that exposure to violence through physical abuse during early years can later cause many different types of health problems, including problems with the future descendants of the affected child. The genes studied in the research included those that were impacted by stress, memory, and fear conditioning. Although the overall structure of the study was based on understanding the effects of gene expression on later development of depression and other health disorders, the study also noted that early experiences of abuse and violence, while traumatizing and life-altering, do not have to have permanent effects and many of the consequences of early maltreatment can be reversed. That is not to say that overcoming the effects of physical abuse is simple or that anyone can do it.

In reality, some people are able to overcome the effects of early trauma of physical abuse and go on to lead healthy, independent lives, while others struggle with low self-esteem, physical problems associated with chronic stress, and mental health disorders, some of which may be very resistant to treatment. Other environmental factors also play a role in later mental health problems when abuse occurred early on in life; for example, genetic predisposition or family history of mental illness, the presence of substance
use, and the presence or absence of supportive and trusting relationships in a structured environment are also all factors that may impact later issues. Whether or not a person is able to overcome the past effects of abuse is not always as important as the fact that the abuse occurred and it increases a person’s risk of later problems.

Emotional abuse is a type of verbal abuse that is meant to ridicule, threaten, embarrass, insult, frighten, or belittle another person. Emotional abuse impacts the victim’s sense of wellbeing and while it typically does not cause physical harm to the victim, it can disrupt emotional stability and lead to later problems with self-concept and emotional regulation. Emotional abuse, because of the psychological stress that it causes the victim, is also associated with later development of mental illness.

The chronic stress associated with repeated verbal assaults and their demoralizing effects can eventually lead to changes in an individual’s mental state and personality, causing difficulties with low self-esteem and problems with managing behavior and mood. Some studies have shown that there is a connection between early emotional abuse and later diagnosis of bipolar disorder. Bipolar disorder is known to be caused by a number of factors, including alterations in levels of brain neurotransmitters, as well as family history of mental illness. There is some research that also shows that the risk of bipolar illness is increased or that bipolar symptoms are triggered as a result of chronic emotional abuse.

A study by Etain, et al., in the Journal of Traumatic Stress showed that patients with bipolar disorder report more accounts of childhood trauma, including emotional abuse, when compared with the general population. This suggests that early and repeated exposure to emotional abuse during
childhood increases the risk for later development of bipolar disorder in adolescence and adulthood. Further research reviews have associated emotional abuse with a number of other mental health conditions, including substance use disorders, eating disorders, social phobias and anxiety disorders, major depression, and schizophrenia. While emotional abuse is not classified as a direct cause of any of these conditions, it is important to note its presence in the history of those who suffer from many different forms of mental illnesses, making emotional abuse a potentially significant risk factor in many cases.

Another form of abuse, sexual abuse, can take many forms. Any type of sexual activity between an adult and an adolescent or child is considered sexual abuse. It is also considered abuse in cases where one person is exposed to sexual activity — whether through physical actions, or by sexual suggestions, harassment, or exposure to pornographic materials — against his or her wishes and often when the victim is unable to say no, typically because of a lack of maturity or being mentally incapable of understanding what to do in the situation.

The effects of sexual abuse on a person’s self-image and overall self-concept can be particularly damaging. The Rape, Abuse, and Incest National Network (RAINN) states that 44 percent of sexual assault victims are under age 18, and 93 percent of victims know their perpetrator. The comprehension that a familiar person is the one performing the sexual assault is traumatizing and undermines a child’s ability to trust adults. Often, the adult is a caretaker or a person in a position of authority or trust, such as a parent, teacher, babysitter, or other family member. Many people who have been sexually abused as children grow up experiencing difficulties in establishing
trusting relationships and with being sexually intimate with their spouses or partners as adults.

Adult survivors of childhood sexual abuse are also more likely to develop chronic feelings of guilt and a sense of shame over what happened to them. They may blame themselves for the abuse and may struggle with their sense of self-esteem.\textsuperscript{32} Further, if the victim had to keep the abuse as a secret for a long time, he or she may have difficulties with trusting others and with being honest about one’s personal background.

Victims of childhood sexual abuse are at greater risk of developing mental illnesses later, including mood and psychotic disorders. A study by Cutajar, \textit{et al.}, in \textit{JAMA Psychiatry} showed a connection between childhood sexual abuse and later development of psychotic disorders in adulthood, particularly schizophrenic disorders. The subjects in the study who were diagnosed with schizophrenic disorders had been exposed to sexual abuse as children between 15 and 30 years prior to diagnosis. The rates of psychosis were higher among female subjects when compared to males, but all of the study participants who were diagnosed with psychotic symptoms as adults suffered from affective symptoms and many required hospitalization.\textsuperscript{36} Another review of the literature showed that sexual abuse during childhood is also associated with later diagnosis of major depression, bipolar disorder, anxiety disorders, in particular, obsessive-compulsive disorder, panic disorder, and agoraphobia; as well as personality disorders, eating disorders, disruptive behavior disorders, and substance use disorders.\textsuperscript{32}

Several studies have focused on early life stress, which is described as those traumatic events that are stressful and damaging to children and adolescents while they are undergoing periods of cognitive and emotional
growth and development. Among various examples of early life stressors studies, abuse, including physical, emotional, and sexual abuse, take prominence as being some of the main forms of trauma experienced that later causes emotional dysregulation. The occurrence of early trauma and abuse can trigger later development of mood disorders that may also involve psychotic features.

A review by Carr, et al., in The Journal of Nervous and Mental Disease looked at different forms of early life trauma and their comparable mental health outcomes. The review showed that there is a very strong correlation between early life stressors and later development of mental illness. Some of the studies reviewed showed that early life stressors, such as through traumatic physical or sexual abuse or neglect, causes a substantial increase in the risk of developing any type of mental illness, including mood disorders and psychotic disorders. Further, the more instances of stressors occurring during early life, the greater the risks of mental health issues later in life. For example, a child who suffers from physical and sexual abuse and emotional and physical neglect may have a greater risk of developing mental health problems as an adult when compared to a child who suffers from emotional neglect but not physical abuse. Aside from recognizing the increased risks associated with the varied exposures to childhood abuse, no amount of abuse, neglect, or trauma is appropriate in a growing child’s life and carries the potential for difficult experiences and mental health outcomes later on during adulthood.

**Neglect**

Neglect goes hand in hand with abuse in terms of its detrimental effects on human growth and development. Neglect describes an absence of appropriate caregiving, such that the person who is to be cared for does not
receive adequate attention, assistance, or treatment. Neglect can take the form of physical neglect or it can be emotional in nature. Emotional neglect is the absence of a nurturing relationship from a caregiver; it occurs when a person’s emotional needs are not responded to or fulfilled. Emotional neglect often transpires between a parent and a child, such as when a parent does not respond to a child’s emotional needs. Emotional neglect may also develop between two adults, such as when one is emotionally distant and does not support the emotional health of the other.

In contrast to abuse, which is an intentionally harmful physical act, emotional neglect is a failure to respond and is sometimes no act at all. For instance, a parent who is emotionally abusive toward a child may call the child names and may threaten the child because of his or her behavior. Alternatively, a parent who is emotionally neglectful toward their child may not respond to the child’s behavior at all, and may ignore the child or fail to try to teach or discipline the child in any way.30

Physical neglect describes a state in which an individual’s physical needs are not met. It most commonly happens to children, in such cases as neglect from a parent or caregiver, however, adults may also suffer physical neglect at the hands of others. In particular, older adults who may not have the physical or cognitive means to care for their own physical needs due to changes associated with aging, may be more likely to suffer from physical neglect when they depend on caregivers to help fulfill their needs.

Among children, physical neglect is actually more prevalent than physical and sexual abuse.31 Physical neglect is often seen by those close to the affected child, including daycare providers or teachers at school, or others who do not live with the child but who see the child regularly. A neglected
child may have poor hygiene, may wear clothing that is dirty, not well cared for, or is inappropriate for the weather. The child may lack the medical care needed, such as by getting eyeglasses or required immunizations. A clue that a problem of neglect might exist is when a child makes comments about being home alone a lot or being poorly supervised while at home, or when a child is frequently absent from school. Parents or caregivers who are neglectful are often withdrawn, they communicate poorly with school staff or others who are responsible for care of the child, and they often are indifferent toward the child when together.

As with other forms of abuse, neglect is associated with later mental health problems because of the psychological harm that occurs to the victim when it happens. Continued research shows that when a person experiences early trauma, such as when being the victim of neglect, he or she is more likely to develop later psychopathology. A study by White, et al., in the journal *Genes, Brain and Behavior* looked at the amygdala in the brains of people who had endured emotional neglect during childhood. The amygdala is central to integrating emotions and regulating behavior and motivation. The amygdala plays a significant role in regulating fear responses, including those that are threatening or harmful. Previous studies have shown that trauma and childhood deprivation have been linked to changes in reactivity in the amygdala. The study by White looked at the activity of a specific gene that is associated with a slowed stress response with increased gene activity. The study showed that individuals who had experienced emotional neglect and who experienced changes to the specific gene studied were at greater risk of developing psychopathology associated with stress response.37

Despite the potential genetic contribution toward development of mental illness following emotional neglect during childhood, people who suffer
through this type of neglect have also been shown to be more vulnerable to developing different types of mental illnesses, often because of the lack of emotional connection with a caregiver and the positive self-concept and self-assurance that a normal, healthy caregiving relationship usually brings. The review mentioned by Carr, et al., showed that studies have revealed that people who suffer through emotional neglect during childhood are at greater risk of developing mood disorders, including major depressive disorder and an earlier onset of the first depressive episode. Other studies have shown an association between emotional neglect and later development of schizophrenia, anxiety disorders, eating disorders, and dissociative disorders.\(^{32}\)

Physical neglect is no less damaging to the human spirit, as studies of the effects of child abuse and neglect have shown according to their impact on adult survivors. As with other forms of early traumatic experiences, physical neglect has been shown to have a powerful effect on the psychosocial, behavioral, and cognitive areas of a child, which can hamper normal development of these areas as the person grows. Adults who have grown up with a history of physical neglect have often never learned that parents or caregivers can meet their needs and they may tend to rely on themselves with little trust in others.

Petersen, et al., in the book *New Directions in Child Abuse and Neglect Research* showed that children who have undergone physical abuse and neglect also have greater problems during childhood, which can then develop into problematic social behaviors as the child enters adulthood. Physical neglect is associated with learning disabilities, childhood depression and anxiety, difficulties with social and peer relationships, aggression, oppositional defiant disorder, and conduct disorder in children and
adolescents.\textsuperscript{38} When they become adults, children with histories of physical neglect are at greater risks of mood and psychotic disorders, whether these mental illnesses are newly diagnosed as adults or whether they have grown as extensions of childhood diagnoses. For example, adolescents with a history of physical neglect from their parents may have difficulties with peer relationships and aggression and may have been diagnosed with a learning disability. After becoming an adult, difficulties with social relationships experience during adolescence often continues and may be associated with deficiencies in work performance and an inability to maintain a job, repeated acts of violence and trouble with law enforcement and legal issues. Behaviors experienced once an adult is an extension of some of the difficulties encountered during adolescence that may never have been addressed.

A study in \textit{The Lancet Psychiatry} also showed that childhood maltreatment, including physical neglect and deprivation, is associated with an increased likelihood of developing bipolar disorder as an adult. The study showed that those who had suffered from physical neglect and maltreatment were at greater risk for severe mood swings associated with bipolar disorder, including severe depression and suicidal ideation during the depressive stage of the illness.\textsuperscript{39} Clearly, there is much research and many studies that show the association between neglect and maltreatment with later problems in social behaviors and with mental illnesses. When working with children, adolescents, or adults who have histories of physical abuse and neglect in their family backgrounds, it is important to consider the link between mood, behavior, and even psychosis as possible outcomes from which early trauma is a contributor.

\textbf{Other Deprivation}
Deprivation describes a situation in which a person is denied or otherwise not allowed to have or experience basic needs. A person can be deprived of essential physical basics through neglect, such as when a parent or caregiver does not provide the necessary care that is needed by every person, including shelter, protection, food, hygiene, comfort, education, or health care. A child or an adult can experience various forms of deprivation, which may be physical, emotional, or material in nature.

Socioeconomic deprivation, which occurs when a person does not receive adequate material necessities because of poverty and hardship, can lead to later mental health problems. Poverty is described as a state of being so poor that a person cannot acquire enough basic necessities to meet needs for food, shelter, or other material items. In 2014, almost 47 million people in the U.S. lived in poverty, which was 14.8 percent of the population.40

An inability to obtain the basic necessities needed for survival can cause a profound impact on mental health and emotional stability. Poverty affects people of all ages, and its long-term effects can cause poor mental health outcomes at any point in life. A person who was very poor in childhood may grow up to later struggle with inadequacies associated with fear of not having enough money to meet his or her basic needs. Another individual may have had a stable childhood free of poverty but may later have a financial crisis as an adult and may become impoverished.

Poverty is a source of stress for those it affects. It causes fear about having enough money for basic necessities, such as finding enough to eat. The dread and worry associated with poverty affects children and adults, albeit in somewhat different ways. Children who live in poverty often fear having enough to eat and experience stress associated with hunger and the other
physical effects of deprivation. In some cases, their parents or caregivers may be well-meaning and may continue to provide emotional support despite their lack of financial resources. In other situations, children who live in poverty suffer from emotional and psychological neglect from their parents or caregivers who are stressed themselves from trying to provide for a family.

Children who grow up in poverty may be at greater risk of developing mental health problems later as adults. The stress associated with being poor and struggling to have enough food or material needs potentially causes long-term effects on a person’s ability to cope with stress and tension as an adult. A study by Kim, et al. in the Proceedings of the National Academy of Sciences of the United States of America looked at the long-term psychosocial effects of early deprivation through poverty and later mental health problems in adults. The study examined the brain function of young adults who had experienced poverty as children. By looking at the neural activity of the prefrontal cortex and of the amygdala — again, described as an area that plays a role in regulation of mood and behavior — the researchers noted that adults who had experienced poverty during childhood experienced changes in the prefrontal cortex of the brain and in the amygdala and an ability to regulate some negative emotions by the time they reached the age of 24. The study shows that living in low-income situations and circumstances of early material deprivation can actually cause some changes within the brain that affect how an individual is later able to process emotions and to handle stress.

Deprivation may take the form of a lack of physical necessities, such as through poverty, while it also may occur as part of emotional deprivation. This is similar to neglect in that a person’s needs are not being met, but in
cases of deprivation due to caregiver attachment, the bonding was often never established to begin. Bonding and attachment with a parent or caregiver is a necessary part of childhood and is fundamental for normal growth and development. Attachment describes the process of connecting with another person and developing a healthy relationship. In children, disordered attachment comes from an inability to trust an adult or caregiver, often because of prior trauma that impacts a child’s ability to believe that others in his or her life will not cause harm and will be available to meet childhood needs.

A child who has experienced early deprivation where the child’s physical and emotional needs were not met, may have difficulty believing that a caregiver can meet the child’s needs, even in a changed situation. For example, early effects of abandonment and institutional living among orphans may lead to chronic stress and fear because these children have learned that they have been given up and that there is no one who consistently cares for them. Even if some of these children are later adopted into loving families, they may still have difficulties believing that their parents are able to provide for their needs because of their prior experiences with deprivation.

Reactive attachment disorder is a condition in which a child does not bond or attach to a parent or caregiver, often because of early deprivation that causes an inability to trust. The deprivation associated with reactive attachment disorder (RAD) may stem from many circumstances. For example, a baby who cries inconsolably because of hunger or being wet but is not changed or fed very often; or a child may be hospitalized frequently and may be separated from the parents during a frightening time. After trying to get someone to meet their needs through crying or otherwise reaching out for care but finding that no one is responding, these children
often learn that caregivers cannot be trusted to meet their needs and that they need to care for themselves.\textsuperscript{42}

Children with RAD often have problems with anger and they may be disobedient or defiant toward their parents. They manipulate situations to avoid feeling helpless so that they can feel in control; their fear of trusting others can be very great and they may go to extreme lengths to demonstrate that they are in control of their surroundings. Other symptoms and behaviors associated with RAD include difficulties making and keeping friends and establishing secure peer relationships, problems showing affection or concern for others, and a lack of remorse for disobedient or even harmful behaviors.\textsuperscript{42} These children often need extensive counseling and help to avoid later problems with behavior or law breaking activities as well as to work through many of the emotions and feelings of insecurity associated with the condition.

A review in the journal \textit{Borderline Personality Disorder and Emotional Dysregulation} looked at the effects of reactive attachment disorder in children and its development of mental health problems later in adulthood. The article looked at the data available comparing the effects of attachment disorder during childhood and the later development of personality disorders; most notably, it showed repeated research discussing the associations between reactive attachment disorder and development of borderline personality disorder in adulthood.\textsuperscript{43} Borderline personality disorder is a mental illness associated with severe mood instability and problems with behavior and social relationships. The affected individual may demonstrate extreme reactions to stressful events, engage in impulsive or reckless behaviors, and have a distorted sense of self-image with intense
mood swings. Borderline personality disorder is also associated with a high amount of suicidal ideation as well as psychotic features.\textsuperscript{44}

The review discussed the effects of attachment problems on an individual’s ability to self-regulate his or her own behavior, adding that problems with attachment and security during childhood cause later issues with a lack of impulse control and an inability to regulate behavior and moods.\textsuperscript{43} The results of significant deprivation can cause such emotional damage to a person that the person is often unable to cope through normal behavior and may be more likely to have mental health issues that may or may not respond to treatment. The chronic effects of stress from problems with attachment and bonding lead to later difficulties coping with routine and normally manageable situations.

Sadly, large numbers of people either currently live with or have memories of trauma and deprivation. Because this type of harm comes from a number of sources, whether it is from physical or sexual abuse, emotional or physical neglect, or deprivation through poverty, the effects are broad and impact many who later go on to develop emotional difficulties or mental illnesses because of the damaging effects. While there are many who overcome great obstacles related to trauma or deprivation in life and who do not have long-term consequences, it is important to understand that exposure to these kinds of circumstances plays a major role as a risk factor in the later development of mental illness.

**The Assessment Process**

Recognition and treatment of mood disorders and psychosis requires a thorough evaluation that includes an assessment of the patient’s condition and history. Further understanding of the risks and manifestations of
refractory forms of mental illness is even more important when working with patients who have not responded well to former methods of treatment. The assessment process should be undertaken as part of a diagnostic plan; an interdisciplinary team should be in place after evaluation of the assessment results in order to best meet the patient’s needs for multidisciplinary elements of care. A patient with a mental health condition that has been unresponsive to treatment requires assistance from multiple disciplines because of the complexity of his or her situation. Professionals in various areas, including pharmacological management, cognitive-behavioral therapy, psychosocial management, and physical health are just some of the many disciplines that may need to be involved when setting up a team to handle a patient’s mental health condition.

A therapeutic alliance should also be set up at the beginning of the assessment and treatment process. The therapeutic alliance describes an agreement between the patient and caregiver that gives permission to discuss and explore the patient’s mental health issues, including the patient’s symptoms, background, emotions, and roles within relationships. This alliance provides a foundation for the relationship that is beginning to build between the assessment process that moves forward into diagnosis and treatment of the patient’s condition. It is only by coming to an agreement in which the patient accepts help and evaluation of his or her condition that the foundation for gaining effective treatment for a refractory condition is met.

The patient assessment is a time to discuss the patient’s current condition, the timing of the patient’s diagnosis, and the type and severity of symptoms being experienced. An assessment may occur in any number of situations and can take place in a single setting or through multiple meetings to
discuss the patient’s current state and to evaluate mood and behavior. The purpose of the evaluation is partly dependent on who has ordered the initial assessment, as well as the context of the assessment circumstances. There are many different types of assessment situations in which a patient must be evaluated for the presence of mental health issues and treatment refractoriness, including emergency evaluations, general psychiatric appraisals, clinical consultations, forensic evaluations, and assessment and examination of children or mentally incompetent patients. The person or people involved in performing the assessment should be determined ahead of time in order to establish how the assessment will proceed and to appoint one person as a leader who will conduct the assessment.

The ability to complete an assessment also depends on the patient’s willingness and ability to work with the healthcare provider to be able to complete an evaluation. Because the patient may be experiencing a treatment–resistant condition, he or she most likely has already been diagnosed with a mood or psychotic disorder. The assessment period determines what diagnosis is present as well as its associated symptoms. However, the patient should demonstrate at least some amount of compliance with the assessment process, or the evaluation may be futile. When performing an assessment to determine the extent of refractory mood disorders or psychosis, the healthcare provider must often spend a certain amount of time interacting with the patient and the patient’s family or significant others to gather information and to establish a plan of action. The patient’s ability to cooperate with the assessment process is vital in being able to complete the evaluation.

The steps of the assessment process are not necessarily in a particular order, but they should include various aspects that provide information
about the patient’s medical and psychiatric history, if there are factors that are contributing to the patient’s refractory state, a review of current symptoms compared to former symptoms, and the types and amounts of treatments the patient has received, as well as their effectiveness.

**Patient History**

The patient’s medical and psychiatric history is an important component of the assessment process. It is necessary to find out as much relevant history about the patient as possible in order to move forward with making a treatment plan. Obtaining a history involves getting a picture of the course of the illness, including when symptoms started, how often the patient experienced symptoms, what treatment had been tried independently, and what treatments or medications had already been prescribed. Depending on the patient’s diagnosis, he or she may describe symptoms such as periods of severe depression, feelings of suicidal ideation, whether the patient experienced delusions or hallucinations, and what they entailed, and whether the patient experienced episodes of mania or symptoms consistent with manic behavior.

Further elements of the patient’s history, specifically related to a particular diagnosis, include not only obtaining information about what symptoms the patient is experiencing, but also symptom severity. The clinician should find out if the patient’s symptoms disrupt daily routine and normal activities, such as the patient’s ability to eat or sleep, and whether the patient describes a decrease in overall quality of life because of the symptoms being experienced. There may be some factors in the patient’s life that make symptoms worse or that aggravate the condition. For instance, a patient who is being assessed for treatment-resistant depression may indicate that depressive moods and feelings of guilt and hostility become worse when
around his or her children. These questions pertain to the specific condition for which the patient is currently seeking treatment. The history portion also involves assessing the frequency of the patient’s symptoms. If the patient has been diagnosed with bipolar disorder, the clinician should assess the rate and intensity of periods of mania or hypomania and depression. When major depressive disorder has been diagnosed, determine how long the patient has been experiencing symptoms of depression and how long treatment had been tried. In cases of PMDD, the patient should be experiencing cyclical symptoms associated with menstruation, including a relief of symptoms for brief periods following menses. If the patient is having symptoms of depression or psychosis that are not cyclical according to menstruation, then she should be referred for further evaluation for another type of mood or psychotic disorder and not PMDD. If the individual is suffering from delusions or hallucinations, it is important to determine if they are related to someone or something in particular. For instance, a person with a delusional disorder may have bizarre thoughts that are related to a particular individual in his or her life, such as a family member, or to a group of people, such as local politicians who are running for office.

The patient should be questioned about whether the patient has ever been diagnosed with an additional mental illness beyond having a mood or psychotic disorder. Examples include concomitant diagnosis with PTSD or substance use disorder. If the individual has experienced previous trauma, whether through a one-time event or in a long-term situation, and has PTSD, the patient may also be suffering from physical and emotional scars from the situation. The patient may complain of having flashbacks or reliving the traumatic event; additionally, the affected patient may also have significant feelings of loss, guilt, or shame, and may avoid talking about the
event. A diagnosis of PTSD is often associated with some of the same symptoms of major depressive disorder, so the patient should be evaluated for similarities in symptoms and whether he or she struggles with suicidal ideation.

Substance use disorders, such as alcohol use disorder, tobacco use disorder, or opioid use disorder, are often involved with mood and psychotic disorders. Approximately 20 percent of people with an anxiety or mood disorder such as depression have a concurrent substance use disorder. Often, people who struggle with mood or psychotic disorders may turn to alcohol or other drugs for temporary relief of symptoms. The substance use can sometimes be even more prominent in conditions that are refractory to treatment, as the affected patient may feel hopeless about the chance to heal from his or her illness.

The patient should be assessed for drug and alcohol use, even if the patient believes that using substances is not a problem. Use of some substances can contribute to symptoms that are similar to those seen with mental illness and it may be difficult to differentiate between causes. For example, use of certain types of hallucinogens, such as lysergic acid diethylamide (LSD) can cause visual disturbances and hallucinations that mimic some manifestations of psychotic disorders. If the patient is already struggling with a mood or psychotic disorder that is refractory to treatment, substance use may only worsen the condition. Drug-induced psychosis, which describes the psychotic effects of drugs and alcohol, may markedly contribute to symptoms of mental illness and should be avoided.

Other portions of the assessment involved with obtaining a patient history include noting past medical history and any previous diagnoses related to
the current situation. Relevant diagnoses that may impact the patient’s current mental illness could be physical or psychological illnesses for which the patient has had treatment. The clinician should assess whether the patient has been hospitalized; if the patient has ever had therapeutic interventions, such as cognitive-behavioral therapy or electroconvulsive therapy, and whether there has been a suicide attempt. Following identification of factors related specifically to the patient’s past and current medical history, the clinician should then obtain information regarding family history that may be related to the present illness.

A part of the history-taking portion of the exam must include whether the patient has a history of psychiatric illness in his or her family. Because many mood and psychotic disorders have genetic components, identifying a family history early on can help to reveal some of the extent of the illness. When assessing for family history, it should also be identified as to how family members have responded to treatment. In other words, find out not only whether the patient has a family member with mental illness, but also whether the patient responded to traditional forms of treatment and if it is well controlled. This information gives the clinician a better idea of the chance of refractory illness that runs in the family as well. It may also lead the caregiver to better understand what kinds of symptoms may develop with the diagnosis. For example, a patient who has been diagnosed with severe PMDD may be suffering from very severe mood swings and may not have been responding well to treatment. Upon taking a history, the clinician may determine that the patient also has a family history of psychotic disorder. While this does not necessarily mean that the patient will also develop psychotic symptoms, it can help the healthcare provider understand the potential for psychosis as associated with the patient’s current mood disorder diagnosis.
Information about the patient’s history may be obtained from other sources if the patient is unwilling or unable to share an adequate amount of material regarding his or her psychiatric history. This information could come from such sources as medical records, data collected from other healthcare providers, or from family or friends who are close to the patient. It is important to respect and uphold privacy and confidentiality regulations when obtaining information about the patient’s history from other sources beyond that actual patient. However, the medical record, including progress notes, results of diagnostic tests, and previous provider orders can offer a lot of information about the patient’s course of care. Input from other healthcare providers who have seen and worked with the patient, whether they are former providers or current caregivers, can also provide a significant amount of data that can be helpful when formulating a plan of care. Other healthcare providers who provide information about the patient’s medical or psychiatric history can also be included as part of the interdisciplinary team that makes treatment decisions for the patient.

The patient’s family or friends are often significant sources of information about the patient’s day-to-day life and symptoms, and can often provide insight into the patient’s adherence to treatment, the course of his or her disease management, and whether recent events have caused setbacks in the patient’s life. If the patient lives with someone who can offer information about the patient’s illness and provide data related to the patient’s psychiatric history, he or she should be interviewed for collateral information, provided the person agrees and is amenable. In some cases, the family member may be the person requesting an assessment or evaluation of the patient, in which case the clinician should take into consideration the specific problem requiring a consult. For example, the
parent of an adolescent who has been previously diagnosed with bipolar disorder and who has not been able to manage his or her illness well with previously prescribed treatment may request a further assessment of the patient to determine if there are any changes that could be made in the treatment plan. The requesting parent is also considered a valuable source of information about the patient and could be interviewed to gain more data about the patient’s psychological and medical history.

Another portion of the initial history taking part of the assessment involves performing a physical examination. Because medication is most often prescribed as part of therapeutic intervention, performing a physical exam can provide a baseline of the patient’s characteristics that would more commonly be affected by side effects of drugs. The baseline physical examination should include the patient’s height, weight, waist circumference, and body mass index (BMI), vital signs, including heart rate, respiratory rate, and blood pressure, and signs or symptoms of drug side effects or extrapyramidal movements. During the physical exam, the clinician should also be alert to the general mood and behavior of the patient, such as whether he or she is cooperative, irritable, or anxious. The patient may have a well-kept appearance, with clean clothes and proper grooming, or could be unkempt and disheveled. These observations are not necessarily items that require an inquiry from the patient; instead, they should be noted as an observation about the patient’s general appearance and demeanor.

Further testing through laboratory studies and an electrocardiogram (ECG) may be necessary for some patients who are already taking medications to control their mood disorders or psychosis. Clozapine, one of the most commonly prescribed drugs for treatment of psychosis in schizophrenia, may
have side effects such as drowsiness, dizziness, confusion, shakiness, or fatigue. The use of clozapine and some other antipsychotics to control symptoms of schizophrenia could cause side effects of cardiac arrhythmias, including prolongation of the Q-T interval. Patients who take these types of drugs may need a baseline ECG to check heart rate and rhythm and to evaluate for changes. Drugs in this category that may be more likely to cause cardiac changes include clozapine, ziprasidone, iloperidone, and thioridazine. Other laboratory testing may involve a check of therapeutic drug levels; for instance, if a patient is taking lithium, it should be noted when and if the patient has been having blood tests to check for toxicity. The testing may also include tests of electrolyte levels, as electrolyte imbalances can cause behavioral disturbances that could mimic some psychiatric disorders.

A mental status examination is also included as part of the patient history and examination. The mental status examination considers the patient’s presentation during the assessment, based on initial appearance and impressions, including the patient’s affect and general behavior, demeanor and mood state appearing during patient responses to questions. The clinician should assess whether the patient is experiencing symptoms of mental illness during specific portions of the assessment by asking about particular symptoms and their frequency. For example, the healthcare provider may need to determine if a patient who normally struggles with auditory hallucinations is having symptoms during the time of the exam; if not, the provider should find out when the last episode of psychotic symptoms occurred for the patient.

The provider should determine the patient’s cognitive status, which includes whether the patient is currently oriented to person, place, time, and
situation, as well as other cognitive ability. This can be determined by asking a few basic questions of the patient about where the patient is, what day it is, or if the patient knows why he or she is attending the meeting. While questioning the patient, the provider can assess the coherence of the patient’s thought processes through the replies or reactions that occur during an assessment of the patient’s symptoms, such as lack of thought organization and odd thought content, rambling speech or unusual words (i.e., word salad), flight of ideas, certain compulsions or anxiety-provoking thoughts, including statements that indicate a lack of impulse control, judgment or self-perception.⁴⁶

Other components of the mental status examination to include are outlined below.⁴⁹

- **Appearance** - including levels of grooming or hygiene, how the patient walks and carries his- or herself.
- **Behavior** - such as facial expression, overall demeanor, gestures, psychomotor activity, and ability to maintain eye contact.
- **Attitude** – description of how the patient acts toward the examiner, such as whether he or she appears hostile, friendly, engaged, distracted, defensive, or secretive.
- **Level of consciousness** - can range from alert to comatose.
- **Speech** - including rapid or slowed rates of speech, the presence of slurring or speaking in a garbled manner, rambling, incoherent phrases, and symptoms of echolalia or scripting.
- **Overall mood** - assessing for symptoms of mania or depression, including symptoms of suicidal ideation.
- **Affect** - observed by the clinician performing the assessment, and describes the patient’s expression of how he or she is feeling on the inside; it may be flat, blunted, sad, detached, or labile.
• Thought content - obtained by asking questions to the patient about what types of things are being thought about, whether there is anxiety or worry about anything, if there are ever thoughts inserted into the patient’s head as if they come from someone or something else, or if the patient has been ruminating on the same thoughts repeatedly.

• Thoughts of harm - whether they are directed toward the self, such as with suicidal ideation, or whether directed toward someone else, such as in cases of homicidal intent.

• Attention span - how well the patient is able to focus on the conversation and to stay engaged.

• Memory - in which the provider should ask about memory loss, or changes in short-term or long-term memory; the provider may also ask the patient to remember a short phrase or a series of words and then ask for the words to be repeated back at a later time during the interview.

• Intellect - which describes the level of understanding and intelligence of the patient; it can be assessed by asking questions about routine items, including questions that assess the patient’s level of vocabulary or understanding of idioms.

By carrying out the portions of the mental status examination, the clinician can assess the patient’s current state of mental health and compare it to his or her past medical history, as well as the patient’s diagnosis. The results of the mental status examination, in addition to other information gained through obtaining the patient’s history and performing a physical examination, can all help the clinician to better understand what factors are contributing to treatment-resistance in the patient’s mental health state.
Evaluating for Medical Co-morbidities

Some physical illnesses cause changes in mental status or cognition that could possibly be confused with mental illness. A patient who is being treated for mental illness and who does not seem to be responding to the normal standards of treatment for the condition could have possibly developed a medical illness that causes similar symptoms that gives the appearance of a treatment-resistant mental health condition. It is therefore important to assess for and exclude other medical illnesses that may be causing similar symptoms or other symptoms consistent with a mental health disorder. A portion of this element of the assessment goes along with the physical examination of the patient.

A patient who presents for assessment and care of a mental illness can exhibit many different types of symptoms, from behavioral problems or changes in affect to visual disturbances or suicidal ideation. These problems could potentially stem from a medical comorbidity in addition to, or in spite of present mental health issues. Unfortunately, the effects of some medical diseases on the body, as well as side effects of certain medications taken for medical illnesses, can lead to behavioral and mental health symptoms that could be misdiagnosed as a mood or psychotic disorder. Further, if a patient has already been diagnosed with a mental health disorder and does not seem to be responding to treatment, the symptoms of some types of medical illnesses could be causing the patient’s mental health issues when it instead seems that the treatment is ineffective and unsuccessful.

There are a vast number of medical illnesses that can cause psychiatric symptoms. Although the entire list cannot be reviewed here it should be understood that some of the more common illnesses could be ruled out through a thorough patient assessment. Unfortunately, many psychiatric
symptoms are not specific to one particular medical illness, so it may be difficult to determine what, if any, medical causes are related to the patient’s psychiatric symptoms. Medical illnesses have been shown to cause a variety of psychiatric symptoms, including depression, anxiety, personality changes, delusions, hallucinations, and manic states.\textsuperscript{53}

Some types of medical illnesses that can lead to mental health disorders include diabetic ketoacidosis, hypothyroidism, fibromyalgia, folate and vitamin B12 deficiencies, respiratory insufficiency and hypoxia, renal insufficiency, sepsis, pneumonia, hepatic failure, anemia, head injury, including subdural hematoma or concussion, hypoglycemia, lupus erythematosus, and hypertensive encephalopathy. A study by Reeves, \textit{et al.}, in the \textit{Annals of Clinical Psychiatry} considered psychiatric admissions at a Veterans Administration hospital over the course of six years and showed that 2.8 percent of patients admitted during the study time had underlying medical conditions as the cause of their psychiatric symptoms.\textsuperscript{53} Because many patients present for care with psychiatric symptoms, caregivers may inappropriately assume that a psychological illness is the obvious cause of the condition and may fail to check other factors, such as a physical examination or assessment of the patient’s medication use.

Some prescription drugs can also cause symptoms of mental illness. If the patient has already been diagnosed with a medical illness and has a medication prescription for treatment, the drug’s potential contributions to psychiatric symptoms should be further investigated as possible causes of some of the patient’s psychiatric symptoms or an inability to respond to psychiatric treatment. As with lists of medical illnesses that cause psychiatric symptoms, there is also a multitude of different drugs and medications that
have psychotropic side effects as well. Some examples include those listed below:\textsuperscript{52,85}

- \textit{Benzodiazepines}
  May be prescribed for anxiety or for sleep disorders, and can cause hallucinations or delirium, particularly when discontinuing the drug.

- \textit{Opioids}
  Often are taken for pain control, may lead to delirium as part of a state called opioid psychosis.

- \textit{Antihistamines}
  Are used for allergy relief, may cause visual or auditory hallucinations.

- \textit{Anticholinergics}
  These include drugs such as atropine and scopolamine, and have been known to cause symptoms of restlessness, disorientation, mania, and hallucinations.

- \textit{Anticonvulsants}
  May affect the GABA neurotransmitter, which may trigger episodes of psychosis.

- \textit{Calcium channel blockers}
  Have been implicated in some cases of depression that have led to an increased suicide risk.

- \textit{Corticosteroids}
  Often are administered for the management of inflammation, and have been shown to cause insomnia, euphoria, and visual hallucinations in some patients.

- \textit{Fluoroquinolones}
  Include ciprofloxacin and levofloxacin, which are administered as antibiotics, and have caused psychotic reactions in some patients.
• **Levonorgestrol**
  Is an implant used as a method of birth control; there are several cases of its discontinuation because it causes symptoms of major depression.

• **Isoretinoin**
  An agent used to treat severe acne, which is associated with an increased risk of depression and suicide; an FDA warning has been issued about this relationship.

• **Cold medications**
  Contain the agent dextromethorphan and have caused symptoms of paranoia, delusions, hallucinations, and dissociation.

A medical illness is more likely to be missed when an appropriate history and physical examination are not performed. In cases where patients have been admitted for psychiatric care and treatment, yet had underlying medical illnesses as the organic causes of their psychiatric symptoms, a lack of a proper physical examination was a key reason why the medical diagnosis was missed. Other factors included inappropriate or lack of laboratory testing, lack of appropriate mental status examination, and failure to acquire neuroimaging studies.⁵³

A patient may need further testing through laboratory studies, radiographic imaging, or other diagnostic procedures if suffering from other symptoms that could be attributed to another medical illness and not a mental illness. For example, hypothyroidism, caused by an imbalance in production of thyroid hormones, has been associated with a variety of neurological manifestations, including cognitive dysfunction, mood disorders, and psychosis.⁶ If thyroid problems are considered, an initial test of levels of thyroid stimulating hormone (TSH) is warranted to rule out hormone
imbalance and thyroid dysfunction that manifests as mental health symptoms.

The symptoms of some mood disorders often mimic hormonal imbalances or other medical conditions. For instance, symptoms of PMDD are often quite similar to anemia or to thyroid hormone imbalance, both of which should be ruled out when diagnosing a refractory mood disorder that has not necessarily responded to traditional forms of treatment. For this reason, other laboratory testing to consider includes a complete blood count and electrolyte panel to rule out medical illnesses that cause cognitive changes, mood swings, or even overt psychosis.

Many people who have psychiatric diagnoses tend to have concomitant medical health problems as well and they may be more likely to suffer from medical problems or a general decline in health and self-care. Comorbid medical disorders are therefore a potentially significant part of many patients’ histories, even when they present for care with psychiatric symptoms. The section of the assessment that considers medical illnesses as possible causes for psychiatric symptoms cannot be avoided in order to prevent missing a potentially serious diagnosis, which is the cause of some of the patient’s symptoms and distress.

**Timeline of Refractory Presentation**

While a patient with a current diagnosis of a mood or psychotic disorder may previously been able to manage the condition through medication and other forms of treatment, its possible that somewhere in the process of treatment the patient’s symptoms and difficulties may stop responding to traditional methods of treatment. In other cases, a person may be diagnosed with a mood or psychotic disorder, start treatment with medication, yet never
really experiences a reduction or resolution in symptoms. Part of the assessment process is also understanding the timeline of the patient’s treatment process, such as, how long the patient has been suffering from symptoms, when treatment was started, the type of drug and the dose involved, whether any changes were made in the patient’s medication dose or type of medication, and whether the patient has experienced any reduction in symptoms to consider the medication a treatment success.

Suzuki, et al., in *The British Journal of Psychiatry*, conducted a systematic literature review that looked at the average amount of time for treatment of schizophrenia to take effect. The review looked at studies of patients who were treated with various medications for schizophrenia, including clozapine, haloperidol, and chlorpromazine, among others. The study wanted to determine whether treatment with these drugs showed an improvement in the rate of symptom resolution when administered to patients with treatment-resistant or refractory schizophrenia when compared to those with non-refractory disease. The review showed that when patients were treated for six weeks, the majority experienced some relief of symptoms and the effects of the medications within the first three weeks after starting the drug, with gradual improvement in the following weeks. This suggests that when starting a new type of medication trial to manage refractoriness in affected patients with schizophrenia, waiting weeks to determine the therapeutic benefit of the drug is actually not necessary and could be detrimental to the patient’s health.

Because refractory disease is defined as the continuation of symptoms despite two or more trials of antipsychotic medications, the patient who is classified as being treatment resistant should have a history of medication use, particularly with antipsychotic drugs. Therefore, the assessment
process must include the timing and dosages of previously administered medication as prescribed for the treatment of psychiatric symptoms. Exacting a timeline of the patient’s progression of a mood disorder or psychosis can be difficult since it is a chronic illness that, once diagnosed, usually only involves management of symptoms, rather than an actual cure for the disease. It should be noted though that just because a patient has a chronic disease such as schizophrenia, in which psychotic symptoms must be controlled through medication but the condition is not necessarily “cured,” it does not mean that the patient has a refractory condition. Treatment success of many mental illnesses involves appropriate management of symptoms, rather than complete elimination of the illness. The terms “chronic” and “refractory” should not be used interchangeably.

Further details about the patient’s timeline of the illness should be noted as part of the assessment. Of note should be information including periods of physical illness in which the patient experienced a relapse in symptoms or was unable to take prescribed medication, alcohol or use of other illicit substances, or periods of time when the patient was non-compliant with treatment. Acquiring this information is not done to place blame on the patient for any alterations in treatment that could have caused continuation of symptoms, and, instead is designed to better determine whether there are factors that have contributed to the patient’s condition and continuation of symptoms.

Life charting may be a helpful method of recording the patient’s progression of illness, including long-term monitoring of mood changes, exacerbation in symptoms, and periods of remission. Also called mood charting, this type of journal can help a patient with mental illness to record symptoms and to recognize patterns throughout the course of a disease process. Life
charting should be done in conjunction with other forms of treatment, such as with medication use or somatic therapies. The affected patient can better determine if there are patterns that exist between use of treatments and mood responses or if there are elements in life that tend to trigger negative moods and symptoms. The creation of a life or mood chart can also be carried with the patient to be brought to appointments or evaluations for a rapid assessment of the patient’s moods and symptoms over time.

Life charting can be completed at almost any time; the patient can start with a section of the chart that involves documentation of previous symptoms of the illness, known as retrospective charting. Additionally, the charting method can continue to include current symptoms, treatments, and management strategies in a section known as prospective charting. Completing both retrospective and prospective charting can help the patient and the clinician to better understand what changes, if any, have occurred over the course of the disease. In general, once the patient has started the prospective portion of charting, it should be done on a daily basis. This is done to make it easier to remember symptoms and their timing over the course of each day, rather than trying to recall changes that occurred in the past week or month.

Because mental illness may involve periods of normal thoughts and behaviors and periods of remission in symptoms, followed by episodes of symptom exacerbation, it is important to establish a baseline (a level in which the patient’s moods and symptoms are balanced). Among those patients with bipolar disorder, for instance, the baseline is recorded in the life chart as a time period when the individual is not experiencing symptoms of mania or depression. This would be documented in the middle ground of the chart. If the patient then experiences mania, symptoms are recorded...
above the baseline; if the patient experiences symptoms of depression, moods and feelings are recorded below the level of the baseline.

Each period of symptom manifestation is classified as one of four levels: mild, low moderate, high moderate, and severe. Mild hypomania, for instance, is described as an elevation in mood and behavior that initially has no effect on functional ability but that could lead to impairment if it continues. Alternatively, at the severe level, the patient experiences a high elevation in mood and increased activity and sleeps very little or not at all. Family or friends may recommend medical attention or hospitalization at this level of activity. The level of severity at which each mood is based is established on how the mood or symptom affects normal functioning in certain areas, such as social, educational, or occupational functioning. The mood scale further identifies the severity of moods on a scale between 0 and 100, with 50 being a balanced mood. A score of 0 is classified as being the most depressed, while a score of 100 indicates the most manic or hyperactive state of mania as possible. Other elements that may be included as part of the life chart are dose and timing of medication, medical illness symptoms or menstruation, either of which may impact mood and behavior, and other co-morbid behaviors, such as binge eating, drinking alcohol, or smoking cigarettes.

Major life events should also be included as part of life charting. These events are not necessarily part of daily mood alterations, but they definitely can affect mood and functioning for a person with mental illness. Changes can be stressful whether they are considered good or bad. Changes that should be noted as part of the charting process include such factors as moving to a different home, the death of a family member, starting a new
job, a holiday or vacation, marital separation, major financial difficulties, or the death of a pet.

Unfortunately, daily life charting is subject to various shortcomings, in particular, those related to the patient’s ability to recall details or chart mood and behaviors in a timely and consistent manner. The patient’s own view of his or her illness, based on the patient’s interpretations, may vary somewhat from the clinician assessing the patient. The patient may also record his or her answers to be more socially desirable, rather than truthful, because the patient wants to answer “correctly” or does not want the healthcare provider to know the full extent of symptoms. The patient’s mental health state at the time of the recordings can also impact the quality of the review. A study by Draisma, et al., in the journal *MBC Research Notes* showed that when assessing patients with bipolar disorder through the life charting method, patients with chronically negative symptoms and those who were heavily affected by bipolar symptoms were less likely to accurately and consistently record their data in the daily charting than when compared to those who were not as strongly affected. All of the patients in the study were compliant with choosing to participate; however, those that experienced significant changes in bipolar symptoms were less likely to complete the study.82

When used correctly, the daily recording of mood and symptoms provides more information than what can usually be obtained through the patient’s medical record; and the information may be more likely to be complete when recorded on a prospective basis, rather than a retrospective basis.82 A life or mood chart does not need to be completed by every patient who seeks care for mental illness. However, it can be a helpful tool that assists the healthcare provider with gaining a glimpse of the day-to-day life of the
patient, which can better explain how some treatment measures are successful while some are not.

**Current Symptoms Compared to Previous Symptoms**

Many cases of mental illness follow a course, although the timeline of disease manifestations vary between people. A patient may experience symptoms that range between generalized, non-specific indicators that could be associated with any number of mental conditions to specific symptoms that are particularly affiliated with certain mood or psychotic disorders. Prior to onset, many people experience a course of symptoms that indicate that the disease is developing, which is known as a *premorbid* course of the disease. Early expressions of the disease may include occasional and sporadic symptoms that may be limited in time and severity. As the disease progresses, the patient may then experience more symptoms that increase in frequency and that become more severe.

During the assessment, the patient should be examined and questioned not only for symptoms currently being experienced, but also those that may have been suffered during the past. If previous medical records are available, it may help to review the patient’s history and data to determine if the symptoms and manifestations of the disease are consistent or if they have changed over time. As an example, a patient with refractory depression may have suffered for years with symptoms, but the symptoms may have changed as the disease progressed. Initially, the patient’s symptoms may have consisted of sadness, extreme guilt, feelings of hopelessness, or shame. Over time, as the illness progresses and as the patient tries to treat a mental health condition without success, the patient’s symptoms may become more severe. In cases of depression, in particular, the inability of the patient’s treatments to work and be effective and the continued efforts
at finding symptom relief may further uphold the patient’s feelings of depression and grief. Eventually, the patient’s symptoms may become more complex and severe and may include anger, hostility, or suicidal ideation.

Unfortunately, recall of symptoms during the assessment period may be difficult for some. Accuracy of recall can be affected by the patient’s illness and could be limited by such factors as memory or cognitive function. Depending on the functional abilities of the patient, the ability to recall disease-specific information can be challenging. There are several factors that can be included as part of the assessment that would be helpful to compare how symptoms have developed, how they have changed over time, and the similarities and differences between previous and current symptoms.

Family members or close friends, when available, are valuable resources for providing information about the patient’s past and current symptoms. This is particularly so when the patient is unable to adequately explain differences in his or her symptoms. Bringing others into the assessment process, such as those that are close to the patient and familiar with the course of the patient’s illness, can be beneficial in extracting enough information about disease progression and alterations in symptoms. The family members may also be able to describe whether the patient has been compliant in treatment, if he or she has had issues with substance use during the time of illness, or if there are any other factors that might contribute to a change in symptoms, such as financial problems that may have prevented the patient from obtaining and taking medication on schedule.

If family or friends are not available but the patient is still unable to articulate the differences in symptoms, the medical record, or progress reports from previous physicians or caregivers provide useful information
that can better clarify how symptoms have changed or if they have worsened in intensity. The medical record is useful for finding out what type of medications the patient has used, the length of their use, and the doses prescribed. The medical record may provide details about the patient’s responses to different medications listed, including changes in symptoms that occurred prior to starting the drug, whether changes occurred during the time of taking the drug, and what symptoms the patient is currently experiencing after discontinuing the drug.

Certain conditions that are refractory to treatment may be more difficult to understand and learn about when compared to others. Patients who are at higher risk of disease development, have family members with similar conditions, or have experienced a very wide range of symptoms throughout the course of their illnesses may be more challenging to assess. A study in the *Journal of Affective Disorders* showed that patients who have parents with bipolar disorder and are at higher risk of disease development were more likely to develop symptoms associated with predevelopment of bipolar disorder, including sleep disturbances, anxiety, and substance use disorders when compared to the children of parents without mental illness. The early symptoms of bipolar disorder can differ when compared to those that develop as the disease progresses and possibly becomes more severe. By understanding this, the high-risk patient may be diagnosed at an earlier point and have a better chance of receiving appropriate treatment early on than waiting until symptoms have changed and the illness has progressed.

Comparing any changes that have developed between early onset of symptoms and current symptoms also helps the reviewer to better identify the extent of treatment resistance and refractoriness. The clinician should review the patient’s actual diagnosis for accuracy according to the patient’s
symptoms, and compare it to symptoms that occurred at the time of diagnosis with the patient’s current symptoms. In some cases, symptoms can change over time, leading to a different diagnosis that was originally given. The patient may have developed new symptoms that are descriptive of another type of mental health disorder and the original condition may not necessarily be resistant to treatment, but instead the patient has developed new symptoms that are occurring at the same time as the original condition.

In some cases, patients are misdiagnosed to begin with despite their original symptoms. For example, a person diagnosed with major depressive disorder may actually be suffering from a form of bipolar disorder that was not recognized at the time of the original diagnosis. What appears to be refractory depression may actually be more of a failure to adequately treat the patient’s actual condition of bipolar disorder, including manic episodes in addition to depression. In this way, the patient may have been considered to have a treatment-resistant condition that instead needed modification in its treatment to be more accurate and appropriate for the current situation.

**Treatment And Review Of Outcomes**

At one time, some disorders — mood disorders, in particular — were thought to have positive prognoses and favorable outcomes with treatment through medication and cognitive-behavioral therapy. Researchers now know that many mood disorders are associated with a number of co-morbid disorders, including substance use, which can lead to greater difficulties with finding effective forms of treatment, and more common instances of refractory presentations. For example, bipolar disorder is largely associated with substance use and is commonly diagnosed during adolescence or young adulthood. Because of its presentation at a young age and the potential for several years to pass while affected patients seek treatment and try different
forms of therapeutic interventions, it is more often associated with high levels of morbidity and mortality as patients with bipolar disorder may try a variety of different treatment options and develop other difficulties, such as significant substance use and suicidal ideation. The importance of determining the effectiveness of treatments for such conditions as bipolar disorder cannot be underestimated, since it may help to find a method of successful treatment for refractory conditions.

One important element of reviewing the effectiveness of past treatments is to determine the type and amounts of side effects that have occurred with previous medication use. Many drugs, such as antipsychotic medications, cause significant side effects that can impact the patient’s quality of life. It is therefore important to assess the effectiveness of these drugs and review any side effects, which often explains whether the patient is continuing to take prescribed drugs or has discontinued a prescription. For instance, a patient taking olanzapine may be at greater risk of weight gain, which for some people is enough to stop taking the medicine. A patient may decide to struggle with psychotic symptoms because he or she views them to be more manageable than the side effects of the drugs. It is essential to continually assess and adjust medication types and dosages to find a solution that best fits the patient’s condition.

Treatment of psychotic illnesses, including schizophrenia or bipolar disorder with psychotic symptoms, often includes administration of mood stabilizers and antipsychotic medications. However, there are many patients who do not respond to these particular classes of medications and who may be considered treatment-resistant in that they continue to struggle with symptoms of mental illness, despite adherence to their medication regimen. Use of another type of agent, such as clozapine, may be included as part of
treatment and may show effectiveness in resolving some psychotic symptoms. A study in the *American Journal of Psychiatry* considered a 12-week trial of clozapine as monotherapy for the management of bipolar disorder with psychosis during periods of mania; all of the participants in the study experienced at least a 20 percent improvement in psychotic symptoms during the trial, and 71 percent had at least a 50 percent improvement in symptoms.\(^6\)

Clozapine is one of the most commonly used drugs administered for the treatment of refractory psychosis associated with schizophrenia. Clozapine is classified as a second-generation antipsychotic or atypical antipsychotic medication. It works by altering levels of the neurotransmitters dopamine and serotonin, which can ultimately help to improve a patient’s thought patterns and behavior. Clozapine has been shown to be effective in people with psychosis that does not otherwise respond to other antipsychotic medications. It is often reserved for people who do not tolerate other antipsychotics as well. It should be used with caution, however, because it can cause a decrease in white blood cell counts, heart muscle inflammation, seizures, hypotension, cardiac arrhythmias, and extrapyramidal symptoms.\(^7\)

Because of its potential for some very significant side effects, clozapine remains more of a drug of choice in the treatment of refractory psychosis associated with schizophrenia, instead of being a first choice of treatment in acute or primary cases.

While many patients take a regimen of prescription drugs to control their symptoms of mood disorders or psychotic illnesses, standard drug schedules may or may not be effective in the long term and it can take a considerable amount of time to come up with a regimen that is successful for each patient’s particular case. Often, patients require a combination of drugs
through complex regimens in order to achieve symptom remission, and refractoriness rates can be high.\textsuperscript{19} In the case of treatment for depression, antidepressant medications can sometimes take six weeks or longer for their full effects to be realized, which requires a time commitment of taking the drugs to determine their effectiveness. For a condition such as depression to be deemed refractory, the patient would need to have tried at least two different trials of medication or therapy for treatment. Consequently, it could take months of suffering from symptoms and attempting treatments before progress is made or before a diagnosis of a refractory condition is fully realized.

For persons with bipolar disorder, treatment is long term and it may also take many months to realize the level of treatment resistance that has developed. Refractoriness in bipolar disorder is not necessarily considered until the patient has undergone treatment for manic and depressive stages of the illness, as well as long-term illness support. Therefore, to determine the effectiveness of treatments in bipolar disorder, the patient may need to review lengthy periods of therapy and medication, including use of different types of drugs and cognitive-behavioral therapy as well as assessment of treatment compliance and the presence of comorbid conditions.

Bipolar disorder can be particularly challenging to determine its level of refractoriness to treatment since its symptoms and manifestations may vary widely. A patient may be able to successfully managedepressive episodes through standard antidepressant therapy, but may still have difficulty controlling manic symptoms despite treatment. As previously described, clozapine is an effective atypical antipsychotic medication that may be used as part of treatment for certain mental illnesses. Its use in the treatment of schizophrenia is well documented, but it may also be effectively used as part
of treatment of mania associated with bipolar disorder. Upon review of symptoms, the patient with bipolar disorder may have a history of clozapine use. If not, it may be considered as a possible form of treatment for mania, as it has been shown to contribute to greater response rates in treatment-resistant bipolar disorder.\textsuperscript{59}

The forms of treatment available for managing mood disorders that could be resistant to treatment are highly variable. A patient who receives an assessment about previous forms of therapy tried for a mental illness may already have a list of the different mechanisms tried and determined whether they were effective or not in managing symptoms. The variability of treatment further expands when considering the care required for different types of mood disorders; for example, while major depressive disorder and depressive episodes associated with bipolar disorder share some similarities, major depression and bipolar disorder can be treated with different medications. The further subcategories of these two major mood disorders, including bipolar disorder type 1 or type 2, as well as dysthymia or cyclothymia, can further confound efforts at finding the right treatment. The variety of medication regimens and therapeutic treatments attempted for control of mood disorders, as well as their levels of effectiveness, are as diverse as the numbers of patients themselves.

There are a variety of different medications available for the management of symptoms associated with mood disorders. Consequently, when assessing a patient’s history for effectiveness of treatments, there could be a large number of assorted combinations of drugs used to manage a specific illness. When considering bipolar disorder in particular, combination therapy of more than one kind of medication is common to manage symptoms of both mania and depression; a patient may provide a list of a number of different
medication combinations that can take time to sort through to determine timeframes of use and subsequent effectiveness.

In cases of patients who have bipolar disorder, when assessing for history of medication use and effectiveness, the most common medications prescribed for the treatment of mania or hypomania include antipsychotics, anticonvulsants, benzodiazepines, and lithium. Drugs may be prescribed as monotherapy for symptom management or they may be prescribed in combination, particularly when the condition is refractory to treatment.

Antipsychotic medications are typically prescribed for the management of mania associated with bipolar disorder, particularly when psychotic symptoms are present. Antipsychotics are typically prescribed for other conditions that cause psychosis as well, such as schizophrenia. They may also be administered when mood stabilizing medications have been otherwise ineffective in treatment. Common mood stabilizers used for management of mania and hypomania associated with bipolar disorder include olanzapine, ziprasidone, and aripiprazole. Clozapine, as previously discussed, is also beneficial as a method of treating manic episodes during bipolar illness.

Anticonvulsants, typically used for the management of seizure disorders such as epilepsy, are another option that may be included as part of bipolar treatment. These drugs act as mood stabilizers and can reduce some of the symptoms of mania and mood swings. Valproic acid is one of the most commonly prescribed anticonvulsants used in these situations. Valproic acid may be more likely to be prescribed in cases of patients with bipolar disorder who experience rapid cycling or who do not respond to other methods of treatment. According to a review by Cipriani in the *Cochrane Database of*
Systematic Reviews, however, although valproic acid is commonly prescribed for symptom management in bipolar disorder, there is limited evidence regarding the long-term effectiveness of this drug in this particular situation. Further, valproic acid has been known to cause certain side effects, including drowsiness, weight gain, and tremor. While anticonvulsants have mood stabilizing properties that can be useful during manic episodes of bipolar disorder, they may or may not be used as the sole form of treatment for the illness. Other types of anticonvulsants that may be seen as part of a patient’s medical history include carbamazepine, lamotrigine, and topiramate.

Benzodiazepines are drugs that may be listed as part of medication use with bipolar disorder. Although not as common as some of the other drugs available, benzodiazepines are sometimes prescribed when the patient with bipolar disorder experiences symptoms such as anxiety, agitation, or insomnia during manic episodes. These drugs are not necessarily used as part of long-term treatment and they should be used in caution when substance use is present. In many cases, benzodiazepines may be administered as a temporary form of treatment until mood stabilizing medications take effect.

Lithium is a classic drug used as part of bipolar disorder treatment. Lithium is a mood stabilizing agent that is particularly effective in treating manic symptoms; it was developed as one of the first types of drugs used for bipolar mania. Patients who take lithium must have routine blood tests that check the levels of the drug within the bloodstream. Elevated levels can cause toxicity, while too low of levels are considered subtherapeutic. Serum lithium levels are also impacted by other factors such as dehydration, salt intake, and alcohol use.
Because depression is also part of bipolar disorder, antidepressants may be considered to combat these symptoms during depressive episodes, as well as in cases of treatment-resistant unipolar depression. Antidepressant drugs are somewhat controversial when used for bipolar depression because they can cause mood swings and alterations in mood levels that contribute to manic episodes. If antidepressants are used, they are often combined with other mood stabilizers to avoid rapid cycling and mania.\(^{73}\)

Antidepressants are commonly used as treatment for major depressive disorder, however, when patients undergo trials of antidepressant use but do not respond to therapeutic intervention, bipolar depression may be a possible cause. According to a study in *The British Journal of Psychiatry* people with higher rates of resistance to medication intervention for treatment of major depressive disorder may be considered for hidden bipolar disorder. The study showed that when individuals with depression are difficult to treat and do not respond to standard antidepressant therapy, they are more likely to require a change in diagnosis to bipolar depression when compared to those with major depression who are less difficult to treat and responded well to antidepressant therapy.\(^{75}\)

Major depressive disorder, sometimes referred to as unipolar depression to distinguish between it and depression associated with bipolar disorder, is often very difficult to treat and has high levels of treatment resistance. Many patients who undergo initial treatment for major depression do not recover adequately. Further, those who do not respond to initial trials of antidepressants may be more likely to fail additional medication trials with different types of drugs as well.\(^{76}\) When a patient does not respond to an initial trial of antidepressant therapy, options include adding a second form of medication to augment the original medication or changing the type of
medication and/or including a type of somatic therapy, such as electroconvulsive therapy, or adding psychosocial therapy, such as cognitive-behavioral therapy.

As such, a patient who presents for care of major depression may have tried one or more medications for treatment that have been considered ineffective. When assessing effectiveness of drug treatment interventions for major depression, it is important to keep in mind the fact that many patients who might have refractory depression are actually just undertreated. They may not have had the correct dose or timeline of antidepressant medications and have therefore not responded. With an increase in dosage or a change in medication, they may be more likely to respond and their condition becomes one of pseudoresistance.\textsuperscript{77}

To best determine whether a patient is experiencing true resistance to treatment, several factors must be considered when evaluating the effectiveness of previous therapies. Some factors are related to the prescribing clinician’s shortcomings on treatment, the patient not receiving the appropriate dose of a medication or where the dose prescribed is too low to make a difference in symptoms, the patient not taking the medication long enough to achieve therapeutic effects, or the patient being misdiagnosed.\textsuperscript{77} Additionally, patient factors, such as being unable or unwilling to take the medication as prescribed, the development of co-morbid substance use disorders, or other social or environmental changes that impact the ability to attain and continue with taking medications as prescribed can also affect the success of therapeutic interventions for major depressive disorder.
There are a multitude of classes of antidepressants used to control major depressive disorder, as well as their different types within each class. A clinician who is reviewing prior therapies for the treatment of depression may encounter any number of antidepressant medications or combinations thereof. While it is not possible to know all of the exact dosage requirements, side effects, and contraindications of each particular medication, the clinician should be familiar with major classes of antidepressant medications and how they work, as well as whether they are impacted by other types of therapy or treatments.

The most commonly prescribed types of antidepressants are selective serotonin reuptake inhibitors (SSRIs), which work by blocking the reabsorption of serotonin in the brain, which alters mood. These drugs may be more commonly prescribed because they cause fewer side effects and have limited interactions with other drugs when compared to some other forms of antidepressant medications. Examples of commonly prescribed SSRIs include fluoxetine, sertraline, paroxetine, and citalopram.

Tricyclic antidepressants (TCAs) are one the first types of drugs developed for the treatment of depression and are therefore some of the oldest forms of antidepressants available. These drugs work by blocking the absorption of serotonin and norepinephrine in the brain, as well as blocking some amount of dopamine reabsorption. However, they tend to cause more side effects when compared to SSRIs and so may be less commonly prescribed. Examples of TCAs include amitriptyline, clomipramine, doxepin, and trimipramine.

Monoamine oxidase inhibitors (MAOIs) work by affecting the enzyme that alters levels of the neurotransmitters dopamine, serotonin, and
norepinephrine, in the brain. These drugs are less commonly prescribed because they are more likely to cause side effects, particularly with certain foods. Because of the dangers of hypertension associated with MAOIs and foods that contain tyramine, these drugs are not routinely prescribed as a first choice for treatment of depression. However, they may be considered as a form of treatment if other classes of antidepressants have not been successful when considering refractory depression. Some examples of MAOIs that may be included within a patient’s history of antidepressant use include tranylcypromine, selegiline, phenelzine, and isocarboxazid.

Atypical antidepressants are those that do not necessarily fit into other categories of antidepressants. They may work by impacting brain neurotransmitters, but different brands of atypical antidepressants affect different neurotransmitters. For example, some drugs impact dopamine and norepinephrine levels, while others may impact serotonin levels. Some types of atypical antidepressants that may be seen include bupropion, trazodone, mirtazapine, and venlafaxine.\(^7\)

Some patients may also have undergone combination medication therapy, in which more than one drug is administered at the same time to achieve healthy effects of treatment. As an example, a patient with depression may have been prescribed an antidepressant as well as a prescription for a stimulant such as methylphenidate to improve motivation. Other adjunctive treatments that may be seen include the addition of antianxiety medications, such as buspirone, lorazepam, and chlordiazepoxide; or a benzodiazepine anticonvulsant, such as clonazepam. Some patients may have combinations of antidepressants, including SSRIs and TCAs that when taken together, provide an augmentative effect on depression.
Hormone treatment may also be an option for treatment of depression, and hormone supplements may be included as adjunctive therapy with some antidepressants. Adding triiodothyronine (T3) to an antidepressant prescription may serve to augment the antidepressant effects and to manage an unknown hypothyroid condition. Gih, et al., in Current Psychiatry, stated that literature reviews have shown that use of T3 as adjunct therapy with antidepressants may be able to achieve faster response rates for the management of depression when compared to monotherapy with SSRIs. Some patients may be more likely to continue taking T3 because it is well tolerated and has few drug interactions.

In addition to use of adjunctive medications, a patient with potentially treatment-resistant depression may have undergone some form of psychotherapy, with or without antidepressant medication use. Psychotherapy can take various forms and may include cognitive-behavioral therapy, in which the patient undergoes talk therapy to determine how negative and dysfunctional thinking patterns affect behavior and how to change these patterns of thought. Psychodynamic therapy focuses on specific circumstances in the past that are affecting the patient’s current behavior. Social skills training also may help to assist the patient with integrating positive behaviors into work and social relationships to effectively function in society. Psychotherapy, whether used as monotherapy or as an adjunct to antidepressant medications, may or may not be effective for some patients with severe depression. As with other types of medications, a review of effectiveness for this particular form of therapy, including the length of time in treatment, the experience level of the counselor or psychiatrist involved, and any progress that was made throughout the treatment course are important factors to consider when determining the appropriate direction to take in the patient’s treatment.
Somatic therapies are those that are therapeutic interventions beyond pharmacologic treatments. There is a range of somatic therapies that may be implemented as part of treatment for mood disorders, and these interventions should be considered as part of evaluating the effectiveness of a patient’s former or current treatments. Somatic therapies are medical therapies that are considered invasive or non-invasive. Examples of invasive techniques include electroconvulsive therapy and magnetic seizure therapy, as well as surgical approaches, while non-invasive therapies include such methods as transcranial magnetic stimulation and cranial electric stimulation.  

Electroconvulsive therapy is one of the most common forms of somatic therapy used for the treatment of depression associated with major depressive disorder and bipolar disorder. The patient undergoes several sessions of electroconvulsive therapy, in which electrodes are placed on the scalp and an electrical current passes through them to induce a seizure in the brain. The use of electroconvulsive therapy is further discussed later in this article, but it should be noted during the patient assessment whether he or she has undergone this procedure, how many times the therapy was performed, and whether it was beneficial (temporarily or permanently) in treating the symptoms.

Magnetic seizure therapy is another type of invasive technique used to treat major depressive symptoms associated with mood disorders. The process is considered invasive because it induces seizure activity within the brain. The procedure is very similar to electroconvulsive therapy, but according to some, it allegedly produces none of the same side effects. Magnetic seizure therapy (MST) is performed by delivering magnetic fields through a specialized machine that uses an item similar to a headset that is placed
over the patient’s head. The delivery of the magnetic pulses induces a seizure in the brain, which affects and decreases the patient’s depressive symptoms.\textsuperscript{68} It is thought that the magnetic pulses are able to reach certain areas of the brain to produce better symptom control when compared to electrical pulses delivered through electroconvulsive therapy.

In theory, MST offers better control of where seizures are induced in the brain when compared to electroconvulsive therapy, which affects larger regions. As a downside, delivery of magnetic pulses through MST requires specialized equipment that is not available in most healthcare centers that treat mental illnesses and that would otherwise provide electroconvulsive therapy. While the process is growing in popularity, it may take more time before MST is more utilized as part of treatment for depressive illnesses and before many healthcare providers see it included as part of a patient’s history of treatment.

Surgical procedures are obviously more invasive processes and their use may be a bit more limited as part of treatment when compared to some other standard forms of therapy. However, it is important to be familiar with some of the surgical procedures available for treatment of severe mood disorders, including severe depression and bipolar disorder. Vagus nerve stimulation is one type of surgical procedure that involves placement of a pulse generator in the patient’s body; it is typically implanted under the skin on the left upper chest. The pulse generator is attached by wires to the vagus nerve, where it delivers pulses of electricity. Each situation involves programming of the pulse generator to deliver a specific number of pulses over a certain time. Vagus nerve stimulation was originally used as treatment for epilepsy to control seizure activity; however, studies have shown that it is also beneficial as treatment for severe depression. The
electrical impulses are thought to affect brain neurotransmitters, including GABA, serotonin, and norepinephrine. It is approved for treatment among patients suffering from severe depression that has lasted two years or longer, and in cases where a person with depression has undergone at least four other types of treatments without success.  

Deep brain stimulation is an experimental form of surgery that is still being investigated for its potential as treatment for major depression, as well as obsessive-compulsive disorder. Deep brain stimulation (DBS) requires brain surgery that involves placement of electrodes within identified areas of the brain. A patient with severe depression who undergoes DBS may have electrode placement at a specific location that is different from another person who is undergoing DBS for treatment of obsessive-compulsive disorder. During electrode placement, the patient is awake and provides feedback to the surgeon. Once the electrodes are in place, the patient receives general anesthesia and wires are attached to the electrodes, which are then connected to generators that have been implanted in the patient’s upper chest. The generators are programmed to deliver electrical pulses through the wires to stimulate the specific areas of the brain near the electrodes.

An article in the *Cleveland Clinic Journal of Medicine* regarding the use of DBS in the management of treatment-refractory depression discussed the methods by which the process is effective. The procedure affects the subgenual cingulate region of the brain, which is known as Area 25 and is located in the cerebral cortex. Studies have shown that this area is often hyperactive in patients with severe depression. However, certain studies that have used positron emission tomography to specifically analyze this area have shown a reduction in the amount of activity in this area following
Because DBS is still investigational, a patient who is being treated for a mood disorder such as severe, refractory depression may not necessarily have this type of surgical intervention as part of his or her medical history. However, knowing and understanding the procedures that can be used to treat severe depression and their levels of effectiveness can better provide healthcare providers with more options for successful treatment.

Also developed for the management of severe depression, transcranial magnetic stimulation therapy is a non-invasive procedure that uses magnetic pulses to stimulate specific nerve cells within the brain. The theory behind the procedure is that certain areas in the brain are underactive when depression exists; with exposure through magnetic therapy, these areas can be stimulated to become more active and possibly reduce some symptoms of depression. The process is done in a physician’s office or clinic and does not require anesthesia. The patient can undergo the treatment and then resume normal activities without requiring any period of recovery. Most people must undergo more than one session as part of treatment. Although it may be used as part of treatment for a number of different neurological disorders, transcranial magnetic stimulation is currently only approved within the U.S. for treatment of major depression that has not responded to at least one trial of antidepressant medication.

Cranial electric nerve stimulation is a type of non-invasive somatic therapy that may be used for the management of certain mood disorders, including depression and anxiety. The process produces changes in the brain that are similar in effect to anxiolytic medications. Cranial electric nerve stimulation (CES) uses a small mechanism that delivers a current through electrodes that are attached to the head or clips connected to the earlobes. The low-amplitude current gently stimulates areas of the brain to relieve symptoms
of anxiety, depression, or insomnia. The product can be purchased by consumers and used at home individually. It has been approved by the U.S. FDA for use in the treatment of depression and anxiety for almost 40 years, although there are few clinical trials that have specifically found CES to be beneficial in treating severe mood disorders. Nevertheless, use of CES may be a part of a patient’s history as a treatment that was attempted for mood alterations.

The exact methods of what defines a condition to be treatment resistant can vary somewhat, based on literature samples and the work of reviewers who have attempted to define it. In the case of refractory mood disorders, such as major depression, the effectiveness of treatment, or lack thereof, can be determined based on the number of trials of medications the patient has attempted without success. The level of ineffectiveness is categorized according to stages, based on the level of refractoriness and resistance to treatment. According to Thase and Rush in the Journal of Clinical Psychiatry, levels of treatment resistance can be classified according to six different categories:

- **Stage 0**: Any trials of medication have been ineffective.
- **Stage 1**: Treatment with ≥1 type of major antidepressant has been ineffective.
- **Stage 2**: Treatment with ≥2 major antidepressants of different classes has been ineffective.
- **Stage 3**: Failed treatment with ≥2 major antidepressants of different classes, plus failure of a tricyclic antidepressant medication.
- **Stage 4**: Criteria of stage 3, plus failure of a monoamine oxidase inhibitor medication.
- **Stage 5**: Criteria of stage 4, plus a course of electroconvulsive therapy.
Other rating scales and criteria have also been implemented to assess levels of refractoriness for mood disorders beyond major depression. In the case of potential refractory bipolar disorder, the International Society on Bipolar Disorder (ISBD) has issued definitions regarding what constitutes treatment-resistant bipolar disorder and what signifies that a patient has reached a stage of recovery. In this case, recovery is defined as being in a stage of remission for at least eight weeks. Remission is defined as either the complete resolution of mood symptoms or resolution to the point that only 1 to 2 mood symptoms of mild intensity continue. However, because a patient with bipolar disorder tends to experience repeated episodes of the illness, it often takes a much longer period of time and different trials of medication and somatic therapies to determine whether a patient is considered to be non-responsive to treatment.

Throughout the course of mental illness, a patient’s condition may become progressively worse, resulting in an inability to adequately control symptoms through standard forms of therapy. In the case of bipolar disorder, affected patients may be more likely to develop refractory forms of the condition when more time has elapsed since the time of diagnosis and when efforts at treatment have been futile. A study by Rosa, et al., in *Acta Psychiatrica Scandinavica*, assessed patients diagnosed with bipolar disorder, who were following up after a year of treatment, to determine their levels of functional outcomes. According to the study, those patients who had their first symptoms related to an episode of bipolar disorder and earlier phases of the disease had better functional outcomes when compared to patients who had multiple episodes of bipolar disorder. The study showed that affected patients demonstrated changes in areas such as autonomy, interpersonal relationships, cognition, and leisure time. A patient who continues to
struggle with episodes of mania or depression associated with a mood disorder may have a greater chance of treatment resistance. It is therefore essential to determine the effectiveness of former and current therapies and medications to better understand what elements are effective and what needs to be changed.

Psychotic disorders such as schizophrenia may also have various patterns of effectiveness as part of treatment. For those who have been struggling with a psychotic disorder such as schizophrenia, the types and amounts of drugs administered may vary between different types of antipsychotic and mood stabilizer medication. Patients who develop refractory forms of the illness are more likely to suffer from treatment resistance with negative symptoms, which are defined in *Neuropsychiatric Disease and Treatment* as being primary or secondary. Primary negative symptoms are those that are actually a part of the disease process, such as the experience of delusions or hallucinations, while secondary symptoms are those that develop as a consequence of the disease process, such as drug withdrawal or depression. These types of symptoms, when present in the patient’s history, may be more resistant to treatment and difficult to control and may decrease the effects of treatment.

Schizophrenia may be classified as refractory and resistant to treatment according to various classification systems, each proposed by different authors. According to Ventura, *et al.*, in the *International Journal of Methods Psychiatry Research*, the effectiveness of schizophrenia treatment can be considered and treatment refractoriness classified according to several factors that indicate a resistance to treatment. The data included:
• Two or more trials of prescribed antipsychotic drugs, administered at doses similar to 400 to 600 mg chlorpromazine daily without any reduction in symptoms after 4 to 6 weeks of use.

• Failure to achieve occupational or social functioning within the last five years.

• A Brief Psychiatric Rating Scale (BPRS) score greater than 45. The BPRS is a simplified scale used to assess such symptoms as depression, anxiety, or hallucinations. It assesses and scores between up to 24 items that the patient may be experiencing, including somatic concerns, disorientation, blunted affect, or suspiciousness.

• At least 2 out of 4 items on the 4-Item Positive Symptom Rating Scale. This test assesses for factors such as suspiciousness, unusual thought content, hallucinations, and conceptual disorganization.62

A patient with schizophrenia who fits a profile consistent with the factors listed could be classified as having a treatment-resistant form of the disease, in which standard forms of treatment have been ineffective.63

As with some other portions of the assessment, understanding the patient’s history of treatments and past effective therapies could be challenging, depending on the patient’s current state of behavior and symptom manifestation. If refractory illness is present, the patient could still be suffering from acute disease symptoms that can impact cognitive or social functioning and that could limit the patient’s ability to communicate the information about treatment effectiveness. A list of therapies or past medications can be beneficial to best understand the timeline of treatments and if they produced any effects.
There are a number of treatments and medication types that may be part of a patient’s history of treatments to evaluate. Over the years, various forms of therapeutic interventions and numerous drugs have been used to treat psychosis. Although many of the drugs used are in similar classes, there have also been differences in specific formulations, such as introduction of first- or second-generation antipsychotic agents, with some drugs being used specifically as introductory regimens just after initial diagnosis and others being introduced later in the course of the illness after some other methods have not been effective. In many cases, an affected patient will have tried multiple modes of treatment simultaneously, such as use of one or more medications combined with psychosocial interventions.

The main body of medication types prescribed for treatment of psychosis, such as schizophrenia, is antipsychotic agents, which are classified as first generation or second-generation drugs. First-generation antipsychotics were developed earlier during the course of finding treatment for mental diseases that caused psychosis. Prior to their development, many people who suffered from psychotic disorders or schizophrenia were hospitalized in institutions and asylums for life. With the advent of antipsychotic drugs, however, patients with psychosis were able to experience many more stable periods of mental functioning and could successfully live in the community or at home with their families. First-generation antipsychotic drugs were the first agents to bring some of these dreams to reality for many.

There are a significant number of first-generation antipsychotic drugs available. These drugs, which are sometimes referred to as typical antipsychotics are primarily designed to control delusions and hallucinations that occur with psychosis. Unfortunately, they are also often ineffective in treating negative symptoms, which are often responsible for contributing to
the refractory state of psychotic illness. First-generation antipsychotics may further contribute to patient disability because they can cause motor dysfunction, such as extrapyramidal symptoms and tardive dyskinesia. Some types of first-generation drugs that may be found within some patient histories are chlorpromazine, haloperidol, fluphenazine, and trifluoperazine.

Second-generation antipsychotics, also known as atypical antipsychotics, were developed after first-generation agents and were initially met with success in symptom reduction. They help to reduce many symptoms of psychosis and do not lead to motor dysfunction or tardive dyskinesia. However, some of their side effects can cause significant health problems, in which they must be used with caution. Clozapine, as described, is one example of a second-generation antipsychotic that, while effective in many cases of refractory psychosis, can cause severe agranulocytosis and so it is not considered the first choice of drugs to consider for treatment. Some other second-generation antipsychotics can also cause metabolic side effects and may lead to changes in cardiovascular, gastrointestinal, musculoskeletal, or genitourinary functioning. For these reasons, these drugs may also need to be used with caution in certain conditions and might be included on a case-by-case basis. Other atypical antipsychotics may also be used as part of treatment; some examples include aripiprazole, olanzapine, quetiapine, and risperidone.

Despite the development of many specific formulations of first- and second-generation antipsychotics, they all have similar levels of efficacy and studies have shown that there are no major differences in effectiveness among the main brands of drugs. Their main methods of disease management include blocking dopamine receptors, which then inhibits some psychotic symptoms. While clozapine has been shown to be one of the most effective
antipsychotic drugs used for the treatment of refractory schizophrenia when compared to other available medications, a patient presenting for care of a possible treatment-resistant condition who requires a needs assessment may not have a history of clozapine use.

Most antipsychotic drugs are prescribed as monotherapy in that they are the main drugs taken for symptom management. However, there are some other classes of medications that may be prescribed as adjunct drugs which, while not as effective on their own, can support the actions of other drugs or can reduce some of the side effects seen in other drugs. When evaluating the types of medications patients with psychosis have used and determining their overall effectiveness, many patients may present with histories of using different classes of drugs in addition to antipsychotic medications. Anticonvulsants are one form of drug that are commonly prescribed as adjunct medications to support antipsychotics. Anticonvulsants such as carbamazepine and lamotrigine are some of the more commonly prescribed kinds. They are sometimes included with antipsychotic agents to offset impulse control problems or aggression seen with some patients with psychosis.64

Antidepressants may also be part of psychosis treatment; while these drugs do not treat psychosis in and of themselves, they are useful adjuncts to antipsychotics. Some drugs such as fluoxetine or citalopram may be prescribed because they are often helpful in controlling some negative symptoms associated with psychosis. While some patients may not have antidepressant use found in their medication histories (upon review of the effectiveness of former treatments), antidepressants could be an item to consider when evaluating refractory psychosis in order to better reduce negative symptoms that are often associated with treatment resistance.
Antidepressants have also been shown to reduce some cravings when used as part of comorbid substance use disorders, and are more commonly seen with some mental health illnesses such as bipolar disorder.

Lithium is a mood stabilizer that is often used to treat bipolar disorder and the significant behaviors that occur during manic episodes. It can also be useful in managing depressive episodes associated with bipolar disorder and in reducing suicidal ideation. Lithium is sold under several different brand names. Despite the fact that lithium has been in use as a mood stabilizer for over 50 years, the drug is not necessarily effective in the management of psychosis, such as with cases of schizophrenia. According to a study in *Schizophrenia Research*, lithium is ineffective when used alone for treatment of psychosis, and it may be limited in its use as an adjunct therapy in these cases as well.

Electroconvulsive therapy may be included as part of a patient’s treatment history when assessing for effectiveness of techniques. In some cases, electroconvulsive therapy can be very beneficial, however, for some patients with psychosis, it has been shown to be ineffective in managing symptoms. When used as adjunct treatment with antipsychotic medications, it may be successful, particularly with associated catatonia. The patient who presents for treatment and assessment of possible refractory psychosis should be evaluated for a history of electroconvulsive therapy as part of treatment and how well the process worked in managing psychotic symptoms.

Because psychosis is involved with an elevated degree of noncompliance with medication regimens, it is important to implement psychosocial interventions for the patient and the patient’s family to support the continued use of prescribed medications. Psychosocial treatments may
involve cognitive-behavioral therapy, and educational elements that provide ongoing education and support about the patient’s disease and possible consequences of non-adherence. Other interventions that may also be used as part of disease management and that should be evaluated for effectiveness include social skills training, community integration measures, and cognitive remediation, which involve teaching the patient compensatory strategies to support certain cognitive areas, such as with memory or attention.

Family members may benefit from group therapy that allows them to meet with others who have loved ones suffering from psychotic illnesses as these meetings can provide further support for coping with their situations and with continuing to manage their loved ones’ illnesses. Because family members or close friends are often involved with the care and the illness management of those with psychosis or severe mood disorders, appropriate support and help is required to keep patients on track with adherence to medication and treatment requirements. When assessing the effectiveness of previous therapeutic interventions that have been attempted, consideration should be given to the patient’s caregivers and the elements of treatment they have attempted as well. Although family support is not always directly related to treatment-resistant manifestations of a mental illness, lack of family support or ineffectiveness of therapy provided for the patient’s primary caregivers can contribute to a lack of compliance in managing the disease and a greater propensity for treatment failure.

When assessing a patient who suffers from psychosis and who may be experiencing a refractory condition of the disease, evaluation of past and current treatments and therapies is necessary to determine their effectiveness and to guide the clinician toward future decisions for provision
of care. By evaluating effectiveness, the healthcare provider is better able to understand what methods have been unsuccessful, what may have partially worked, and what could be continued for treatment with some modification. Sometimes, the methods of treatment, particularly when dealing with refractory forms of the disease, are developed by trial and error, as different patients respond to different forms of therapy and medication. What one patient may consider to be an effective treatment, another may struggle with through the timeline of taking a drug or pursuing a therapeutic intervention.

Another factor to consider is that with some forms of mental illness, a treatment that did not work in the beginning of the course of the disease is not only no longer useful because of its ineffectiveness, but it can also be detrimental if the patient continues to try the treatment long after it is certain not to work. This can prolong the patient’s chances of receiving treatment that could be much more beneficial for his or her situation and may further progress in terms of disease severity. For example, when first diagnosed with schizophrenia, a patient may have started on a course of a first-generation antipsychotic drug that may have helped resolve some of hallucinations, but that otherwise left the patient with extrapyramidal side effects, poor impulse control, and feelings of anger and hostility. Although the patient may not have achieved the desired effects of using a single antipsychotic medication, he or she might continue to use the drug in the hope of eventually experiencing improvement. On the other hand, the patient’s condition may only progressively worsen so that by the time treatment is sought for disease resistance, the course of the patient’s disease has advanced in severity and it is much more difficult to manage.
A review of the effectiveness of treatments the patient has tried in the past is essential to determine what elements of his or her condition can be managed and what should be changed as part of the treatment plan. The decision to start a new medication or to change a medication type or dosage is not only dependent on the severity of the illness, but also the duration of symptoms and evidence of the lack of effective treatments. Many drugs used for the management of mood and psychotic disorders work in similar manners, and there is often not one agent that is supposedly superior to all of the rest. Therefore, when one drug of a particular class and mechanism of action has been ineffective, the decision must be made as to whether to continue with another agent with the same mechanism, to change drug classes to use medications with different mechanisms of action, or to include adjunct therapy in the course of treatment. There is no evidence that determines that one of these processes is better than any of the others. The choice of which direction to take for treatment is not always easy, nor is it clear for the healthcare provider.

**Polypharmacy And Drug-Drug Interactions**

Polypharmacy is common for the management of mental illnesses. Many patients who have been diagnosed with a mental illness will be prescribed at least one medication to control symptoms and may have more drugs prescribed to combat some of the side effects or to act as adjunct medications. The combinations of drugs that are taken by patients under study at any one time is substantial. This is particularly true among patients who may have refractory forms of mental illness and who have tried multiple methods of combatting their symptoms through medication use.

A drug-drug interaction occurs when one drug taken by a person changes the effect, duration, or other outcomes of another drug. A drug interaction
occurs when more than one drug is in the body; their presence causes an increase or a decrease in the effects of one or both drugs available. The term is referred to as a drug-drug interaction because it involves two or more drugs affecting each other; other interactions, such as the effect of food on drug availability in the body are known as drug-nutrient interactions. When drug-drug interactions occur and drug effects are increased or decreased, the effects are typically undesirable and the affected person does not attain the benefits of one or both of the drugs.

Drug-drug interactions may be manifested in multiple ways, depending on the point of their effects in the body. They may cause a number of adverse effects, such as cardiac dysrhythmias, seizures, delirium, or even sudden death. Unfortunately, in some cases, what appears to be an ineffective drug treatment regimen or the appearance of a worsening of the disease is actually a result of a drug-drug interaction. These interactions do not always manifest as obvious effects, and instead may appear as poor tolerability or they may cause the healthcare provider to misdiagnose the situation.

Antipsychotic medications are the initial form of treatment for schizophrenia; these drugs have been shown to provide relief of psychotic symptoms and better behavioral control when given to affected patients, including a reduction in instances of delusions and hallucinations when used appropriately. Antipsychotic drugs are also likely to be administered concomitantly with other medications, as clinicians have found that adjunct therapy through use of other drugs, such as antidepressants, anticonvulsants, or benzodiazepines, may better control some symptoms of psychosis. Unfortunately, the more drugs prescribed for a particular condition, the greater the chances of the individual experiencing an
interaction between the drugs in the body, which can lead to a range of symptoms that may include actual medical illness or ineffectiveness of the therapy.

Many drugs administered to combat symptoms of psychosis cause serious side effects. These effects may be detrimental enough that the affected patient no longer wants to continue taking the medication. Additionally, the patient needs to take other types of medications to combat some of the side effects. An example is when a patient develops headaches after using a prescription for an antipsychotic medication. The affected person may need to start taking pain relievers to control headaches so that he or she can continue to derive benefits from the psychiatric medicine. Regrettably, many patients do not want to continue to add more and more medications to their drug regimens and may be more likely to discontinue certain forms of treatment. While actual psychotic symptoms may be resolved with the administration of medication, other problems can develop instead; including suicidal ideation, cognitive impairment, or poor social functioning. Many patients who take antipsychotic drugs struggle with changes in affect, losing their ability to express emotion or becoming lethargic and dull in character.

Drug interactions that develop when more than one drug is administered for management of refractory mood disorders or psychosis may occur between two different types of the same class of medications, such as with two different kinds of antipsychotics. In this case, a person who takes two drugs that are in the same class — and that potentially have very similar effects in the body — can experience a drug interaction because of augmentation of the drugs’ effects. Interactions could also develop when more than one drug is administered to control varying symptoms; for instance, a drug-drug interaction could develop when the patient takes more than one drug for
symptoms, such as one drug for the treatment of depression and one for psychosis.

Antidepressants, which are also commonly administered for management of mood disorders, are another type of drug that may be susceptible to drug-drug interactions when combined with other medications. As an example, serotonin syndrome may be more likely to develop when a patient takes more than one type of antidepressant medication, which impacts serotonin levels in the brain. The serotonin, of which reabsorption is normally blocked with certain types of antidepressants, can build up in the body, leading to symptoms that can range from mild to life threatening. The condition can develop rapidly and can cause hyperreflexia, muscle rigidity, tachycardia, fever, and diaphoresis. Serotonin syndrome can develop as a result of a pharmacokinetic interaction, a pharmacodynamic interaction, or both. In order to best prevent the development of this type of reaction, the healthcare provider should be familiar with the types of drugs that can potentially cause a drastic rise in serotonin concentrations. While this may include many SSRI antidepressants, it also includes other drugs that are not necessarily used for depression, including some antipsychotic medications (reserpine, droperidol), appetite suppressants (phentermine), mood stabilizers (carbamazepine, lithium), pain medications (fentanyl, meperidine) or illicit drugs (LSD, cocaine, ecstasy).  

Monoamine oxidase inhibitors, in addition to causing interactions that can lead to serotonin syndrome, can also cause hypertensive reactions in which the patient’s blood pressure reaches dangerously high levels. The patient with a hypertensive drug reaction may develop symptoms such as severe headache, tachycardia, fever, disorientation, blurred vision, or symptoms of stroke. Combining MAOIs with some other types of medications may lead to
hypertensive reactions; some drugs to use with caution include serotonin-norepinephrine reuptake inhibitors (SNRIs), TCAs, as well as some stimulant drugs such as methylphenidate, pseudoephedrine, and atomoxetine. Because some drugs that are stimulants can impact neurotransmitter levels in the body, which is somewhat similar to the effects of MAOIs, the resultant elevation in neurotransmitters such as norepinephrine can cause dangerously high blood pressure.

The combination of MAOIs with some other medications used for management of mental illness, such as with sedatives or benzodiazepines, can increase their sedative effects and can make the patient very drowsy. The patient may have an opposite effect of taking the MAOI with a stimulant or another antidepressant, and, instead of a hypertensive crisis may develop a drop in blood pressure to dangerously low levels.

As discussed, during the assessment process, the clinician should assess the patient’s use of concomitant medications that could potentially cause interactions. This includes medications prescribed by other providers, as well as over-the-counter preparations and illegal drugs. When prescribing medication for the treatment of mental illness, the healthcare provider should understand that psychiatric drugs do not necessarily interact with other medications because of their therapeutic use; rather, drug interactions develop because of pharmacokinetic and pharmacodynamic properties.

**Pharmacokinetics of Drug-Drug Interactions**

A discussion of the types of drug interactions that can occur when more than one medication is needed involves explaining the differences between pharmacokinetics and pharmacodynamics as branches of pharmacology. Pharmacokinetics is sometimes referred to as “what the body does to a
drug.” It describes how a drug is absorbed, distributed, metabolized, and excreted after it has been taken. A pharmacokinetic drug-drug interaction is therefore one in which a certain type of drug affects one or more of these processes in the body. For instance, taking two drugs together could cause a pharmacokinetic interaction in which one drug affects the absorption of the second drug.

Absorption describes the movement of the drug into the bloodstream. When a drug is administered orally, absorption most often involves passage of the drug through the gastrointestinal mucosa and into circulation. The drug is first dissolved from its original state; this may occur very rapidly, or in some cases as “extended release” where the drug’s action is to dissolve very slowly and release its contents over a longer period. Drug absorption of oral medications can be affected by several factors, including amount of gastric secretions in the intestinal tract, the pH level along the gastrointestinal tract, the presence of mucus or bile, and whether the lining of the epithelial membranes are intact.

If the drug is given as a subcutaneous or intramuscular injection, it is absorbed into circulation by passing through the epithelium and into the nearby capillaries to enter the bloodstream. Some drugs absolutely must be administered in this method and cannot be taken orally because they will not be absorbed in the gastrointestinal tract. An example of this situation is with the administration of insulin, which must be given subcutaneously or intravenously. The rate of absorption after subcutaneous or intramuscular administration is affected by factors such as blood flow to the site, and the presence of scar tissue or local inflammation.
With oral drug administration, a drug-drug interaction that causes a disruption in absorption typically occurs when the medication is poorly absorbed in the gastrointestinal tract. Much absorption occurs in the small intestine through the gastrointestinal mucosa. Some drugs alter the pH of the gastrointestinal tract, thereby affecting the absorption of other drugs when the two are taken together. Because the pH of the gastrointestinal tract must remain within a specific range for drugs to be dissolved and absorbed, an alteration in the pH caused by administration of one drug can impact the absorption of another. Some drugs, when taken together, may cause complexes that are poorly absorbed in the gastrointestinal tract. These complexes may be made up of a combination of the drug and metal ions that are not absorbed well, or the drugs themselves may bind together and neither one is absorbed. The solution is often to eliminate one of the drugs, if possible, or to increase the time interval between administration so that one does not affect the absorption of the other.

Note that drug absorption is only affected when drugs are taken by certain routes; for example, through oral administration. When taken orally, a drug enters the gastrointestinal tract where it is absorbed as an early part of pharmacokinetics. However, when a drug is administered intravenously, absorption is already complete, as it directly enters the bloodstream and does not need to pass through the gastrointestinal mucosa or other tissues first. Many people who take antipsychotics and other drugs to stabilize their mental health when refractory psychosis or mood disorder symptoms are present take medications via the oral route, which requires absorption and could lead to drug-drug interactions with other substances. However, there are some people who temporarily may benefit from intravenous drug administration, which would change the potential for a drug-drug interaction that causes a disruption in drug absorption.
Diffusion occurs after the drug has reached the bloodstream; diffusion describes the distribution of the drug to various organs or tissues. The components of the drug travel through the bloodstream to reach their appropriate points. Medication may be distributed to the intracellular or extracellular spaces. It can directly enter certain cells if it is designed to do so; alternatively, some drugs are designed to stay within plasma or other extracellular fluid. Problems with drug distribution can occur when there are issues with the drug reaching the appropriate areas, such as through decreased blood flow or plasma protein binding.

Albumin is the main type of protein found in plasma and it can bind to many different types of medications. Drugs may also bind to other types of plasma proteins as well, including α-1-acid glycoprotein, which acts as a carrier to certain kinds of drugs within plasma. Each drug varies in terms of its affinity for certain proteins; some medications have very high affinities and bind easily to plasma proteins, while others possess lower affinity rates. When drug-drug interactions occur that affect drug distribution, it is often because one drug displaces another in its ability to bind to plasma proteins. If one drug has a higher affinity for plasma protein sites, it can displace a second drug and bind to the site instead. When a drug is not bound to protein in the bloodstream, it then becomes a free agent and can travel to other parts of the body instead of going to the area where it is needed for most for its therapeutic effects. Some drugs may collect within certain tissue areas as well.

The process of drug metabolism removes the potentially harmful effects of a drug in the body. Metabolism inactivates drugs and prevents them from building up to the point of toxicity. Most medications are metabolized in the liver; when drug-drug interactions occur that affect a drug’s metabolism,
they often take place in or around the liver. The process of metabolism occurs when the liver enzymes convert the drug components into metabolites, which are then prepared for excretion from the body. These metabolites are water soluble and can be easily excreted by the kidneys.

The metabolic process can take one of many forms, including through oxidation, reduction, hydration, hydrolysis, or conjugation, among others, in which the drug is basically readied for eventual excretion through the renal system. Drug-drug interactions that affect drug metabolism typically develop when the rate of metabolism is affected. If the rate is too slow, the drug may not be metabolized quickly enough and can build up within the body to toxic levels. Alternatively, the drug interaction may increase the metabolic rate of the drug too much so that it is excreted quickly and the drug does not exert its effects on the body.

A pharmacokinetic drug interaction occurs between the simultaneous administration of venlafaxine and bupropion for the treatment of depression. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor, while bupropion inhibits dopamine and norepinephrine. An article in *The Journal of Clinical Psychiatry* considered the effects of the use of these two drugs by examining a case of a patient with severe depression who did not respond adequately to venlafaxine when used in isolation. The prescribing provider added bupropion to treatment when considering that the two drugs were part of different pharmacodynamic categories and impacted different types of neurotransmitters. Instead of simply replacing the initial drug, the addition of the second drug augmented the effects of the first drug hence adding a therapeutic benefit to the total combination drug treatment.
The article showed that bupropion inhibits the enzyme cytochrome P4502D6, which is needed to convert venlafaxine into its metabolite. However, the enzyme does not act on the metabolite of venlafaxine, and a significant amount of it ends up being excreted in the urine with a small percentage being metabolized by a different type of enzyme. Alternatively, when the enzyme is inhibited, such as by bupropion when it is present, venlafaxine levels rise, fewer metabolites are created from the venlafaxine, and there is less urinary excretion. The affected patient ends up experiencing many of the adverse effects associated with the drug.

In other situations, such as when serotonin syndrome develops because of a pharmacokinetic interaction, there may be alterations with the body’s ability to metabolize serotonergic antidepressants. These drugs are metabolized by the work of cytochrome P450 (CYP450) enzymes, however, when another drug is taken simultaneously that inhibits CYP450, the individual is at risk of serotonin syndrome from elevated circulating serotonin levels in the body.

When there is reduced blood flow, such as in the case of an aging liver or when liver disease is present, the liver may not work quickly enough to metabolize drugs at an appropriate rate. If the liver is attempting to metabolize more than one drug at a time, one drug may use up the work of the liver enzymes more than another, leading to prolonged half-lives and the potential for toxicity. Although drug metabolism primarily occurs in the liver, the enzymes needed for metabolism are also located in other areas of the body and could potentially perform some of the same measures; such areas with these enzymes include the skin, the brain, the lungs, and the kidneys.

Excretion occurs when the drug is removed from the body, and most excretion occurs in the urine; however, some drugs may be excreted
through such processes as sweat, feces, or saliva. The drug enters the renal system through the bloodstream as either the actual drug or its metabolite. It circulates through the glomerular filtration system in the kidneys in a manner similar to other electrolytes and substances in the bloodstream as they are filtered through the renal system. Clearance describes the rate of drug elimination from the body. The drug’s clearance is calculated as the amount of the drug that has been excreted in the urine minus the amount that was reabsorbed in the kidneys. Some types of drugs are more readily reabsorbed in the kidney tubules, which means that less is excreted in urine.

Drug interactions occur at the site of tubular secretion, in which wastes are removed from the blood. Two or more drugs may compete at the site of tubular secretion, and one drug may block the excretion of another, causing decreased renal clearance. A percentage of drugs are also excreted through the bile from the liver. The liver breaks down the drugs into metabolites, which are then excreted into the bile, which eventually travels to the intestines. A small portion of the leftover metabolites may recirculate and return to the liver as well. In the intestinal tract, the drug may also be reabsorbed and may complete the cycle of pharmacokinetics again.

Clozapine is associated with a number of potential pharmacokinetic drug interactions when it is taken with other medications. It should be used with caution when taken with other drugs that bind to the same enzyme for metabolism, such as certain antidepressants, phenytoin, carbamazepine, or St. John’s wort, as these drugs may compete for activity of the same enzymes. While no specific interactions have been observed so far, clinicians recommend the concomitant use of these types of drugs to be done with caution to avoid changes in plasma levels of clozapine.
Drugs that have long elimination patterns and that take a long time to be excreted from the body can cause extended symptoms of drug-drug interactions when they occur. If toxicity develops with these types of drugs, the patient may suffer from symptoms associated with the drug interaction for a longer period, even though he or she may have stopped taking the drug when the effects occurred because of the long elimination time.85

The prescribing provider cannot be expected to know all of the possible types of drug interactions, although access to a comprehensive drug guide that can explain many of the pharmacokinetic effects of drugs prescribed is important. More commonly prescribed drugs are also more clearly understood and their effects can be easily recognized with greater familiarity. Because many patients do take at least one medication for the management of psychiatric illnesses, understanding the basic dynamics of many of the commonly prescribed drugs is helpful to provide thorough and safe treatment and to reduce the risk of pharmacokinetic interactions.

**Pharmacodynamics of Drug-Drug Interactions**

Pharmacodynamic drug-drug interactions occur when two or more drugs have the same effects on receptor sites. In these cases, there is little to no effect on drug absorption, distribution, metabolism, or excretion; instead, competing drugs cause an interaction when their actions result in similar or opposite receptor activities. Pharmacodynamics is sometimes described as “what the drug does to the body,” instead of “what the body does to the drug,” which explains pharmacokinetics. Many drugs activate receptor points found at various locations within the body and exert either agonist effects, in which they bind to the receptors, or antagonist effects, which are those that block the work of receptors.12
When a pharmacodynamic reaction occurs, both drugs may have agonist properties and therefore compete with the same receptor sites whereby one drug may become ineffective in binding to the appropriate receptors and working properly. Alternatively, both drugs might also be receptor antagonists, which typically block the work of other agonist drugs or other properties in the body. The administration of more than one drug of the same class and with the same effects produces synergy, which occurs when the effects of the drug are increased because of the effects or work of the other drug.

According to Palleria, et al., in the Journal of Research in Medical Sciences, pharmacodynamic drug-drug interactions can be classified according to one of three different groups; those having a direct effect at the site of the receptor, interfering with biological or physiological control processes, and having either an additive or an opposed pharmacological effect. In the case of serotonin syndrome as previously discussed, the condition may also develop as a result of a pharmacodynamic interaction when two drugs potentiate each other. The drugs can affect the amount of serotonin found in the synaptic space between two neurons. When more than one drug is used that affects serotonin, such as by increasing serotonin release, decreasing reuptake of serotonin, or decreasing serotonin metabolism, then each drug can increase the total concentration of serotonin found in the synapses. If an SSRI antidepressant medication is taken with another drug that works as a serotonin agonist, the two drugs then work in combination to compound the effects, leading to the negative symptoms of serotonin syndrome.

Another example of a potential pharmacodynamic drug interaction is a prolongation in the Q-T interval, as seen on an ECG. The Q-T interval is associated with the action potential of heart muscle cells in the ventricles.
With the heart’s conduction system, the heart muscle cells are depolarized and then repolarized through a series of steps during the time the electrical impulses pass through different areas of the heart muscle, stimulating the heart to contract. There is also a continuous flow of various electrically-charged ions as they move in and out of cells throughout this process. The action potential describes the flow of ions as they move across cell membranes. In order for the ions to cross the cell membranes, they must utilize certain protein channels. When these channels do not work properly, it then affects the rate at which ions are able to pass and subsequently affects the action potential and leads to prolonged Q-T intervals.

The Q-T interval is measured on the ECG and is calculated from the beginning of the QRS complex to the end of the T-wave. The interval represents depolarization and repolarization of the ventricles; by the end of the T-wave, the impulse conduction has returned to baseline to prepare for the next contraction of the heart. Prolongation of the Q-T interval can lead to life-threatening cardiac dysrhythmias, including torsades de pointes, a type of ventricular tachycardia that can lead to sudden death.87

Prolongation of the Q-T interval can develop as a drug interaction when the drugs affect the cell membrane channels that affect the movement of ions and the cells’ action potentials. For example, use of haloperidol (Haldol®) as treatment of schizophrenia has been known to block certain cell membrane channels, affecting ion transport. It can lead to a prolonged Q-T interval that can be delayed by 15 to 30 ms.87 A combination of haloperidol and the antipsychotic droperidol, which may also affect ion channels in the cell membrane, may cause intense effects of Q-T interval prolongation and subsequent cardiac arrhythmias.
Some antidepressants have also been associated with an increased risk of prolonged Q-T intervals, particularly tricyclic antidepressants. The TCAs can affect action potential by blocking sodium channels in the cell membrane, which could cause changes in the Q-T interval. The effect can be further enhanced when the drug is administered with some types of antidepressants, such as amitriptyline or imipramine, which can affect potassium ion channels in the cell membrane. Some examples of other antidepressants that have been associated with changes in the Q-T interval include citalopram and escitalopram. Other drugs that are not used as part of psychiatric treatment but that instead may be taken concomitantly to control a coexisting medical disorder may also lead to changes in Q-T interval. When taken during the course of treatment for mental illness, the pharmacodynamic drug interactions that can result can cause dangerous heart arrhythmias. Examples of such drugs include cisapride which is used to treat gastroesophageal reflux, some fluoroquinolones used as antibiotic therapy, terfenadine and astemizole used as antihistamines, and antiarrhythmic agents used to manage or prevent cardiac arrhythmias, which include quinidine, procainamide and disopyramide.

Any patient who is at risk of prolonged Q-T intervals and who takes any of these medications should be closely monitored throughout therapy to reduce the risk of serious complications associated with cardiac arrhythmias. Risk factors for development of torsades de pointes from drugs that prolong Q-T intervals include female gender, advanced age, electrolyte imbalances, hepatic or renal dysfunction, underlying cardiac abnormalities, and use of diuretic medications or digitalis. Prolonged Q-T intervals and torsades de pointes can often spontaneously resolve after short periods. However, with continued changes in the rhythm abnormality, the patient can develop a
ventricular arrhythmia that is life threatening and that requires rapid treatment to prevent sudden death.

Anticholinergic toxicity is another type of pharmacodynamic reaction that could occur, particularly when multiple drugs are prescribed for management of mental illnesses. Anticholinergic medications work by blocking the activity of the neurotransmitter acetylcholine in the brain. Acetylcholine plays a significant role in various body processes and acts not only as a neurotransmitter, but is also considered to be a local cell signaling agent and a hormone. The two major types of receptors for acetylcholine include the muscarinic receptors and the nicotinic receptors. Most of the anticholinergic effects that occur with administration of these types of drugs happen because of activity at the level of the muscarinic receptors.

There is a wide variety of anticholinergic drugs prescribed in medicine today, primarily because muscarinic receptors are found throughout the body and are easily affected by these medications. Outside of the central nervous system, peripheral muscarinic receptors can be found in the heart, lungs, gastrointestinal tract, the eyes, and the skin. Drugs that are considered to be anticholinergics may be prescribed for various medical conditions associated with these areas and include 1) antiemetics such as dimenhydrinate or scopolamine, 2) antihistamines such as clemastine, brompheniramine, or hydroxyzine, 3) antiarrhythmics such as disopyramide, or 4) muscle relaxants such as cyclobenzaprine.

Additionally, many anticholinergic drugs are administered for the management of mood disorders, such as depression, or as antipsychotic agents because of their effects on the central nervous system. Examples include tricyclic antidepressants such as amitriptyline, amoxapine, or
imipramine, and antipsychotics such as clozapine, olanzapine, and quetiapine, as well as other anti-Parkinson drugs and antispasmodics. With a general increase in the availability and prescription of anticholinergic medications, the potential for pharmacodynamic interactions that can lead to toxicity is great. In most cases, the pharmacodynamic effects occur because of additive effects on the muscarinic receptors; occasionally, pharmacokinetic effects may also develop as drug interactions.

Symptoms of anticholinergic toxicity can range from mild to severe. General symptoms may be difficult to detect and may not necessarily be diagnosed as a type of drug interaction. Such symptoms can include dry mouth, blurred vision, urinary retention, and constipation. Alternatively, the patient with this type of toxicity can also develop severe tachycardia with widened pulse pressures, poor muscular tone resulting in coordination problems and ataxia, gastric ileus, and cognitive changes, such as somnolence, hallucinations, or possibly coma.

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with a number of pharmacodynamic drug interactions that can cause potentially serious complications when these drugs are taken with some other medications. Research has shown that simultaneous administration of NSAIDs and SSRIs can increase a person’s risk of gastrointestinal bleeding. Administration of each drug tends to potentiate the other. NSAIDs are well known for their risks of gastrointestinal irritation and bleeding, while SSRIs can reduce the transport of serotonin into the platelets, such that the patient’s risk of bleeding is further increased. Other types of antidepressants, such as TCAs and MAOIs are not associated with the same bleeding risks.
There are a number of other examples of the combinations of drugs causing pharmacodynamic interactions that lead to synergistic effect. A review by Bleakley in the journal *Progress in Neurology and Psychiatry* discussed the effects of antipsychotic drugs in particular and conferred that when two drugs are administered during the same time period and both have similar effects, they often potentiate each other, even if the drugs are from different classes. For example, one of the side effects of clozapine is constipation; if clozapine is administered with another drug that is also known to slow gastrointestinal motility, such as codeine, then the patient is more likely to suffer from constipation because of the pharmacodynamic effects.\(^\text{91}\)

Alternatively, drug interactions can have oppositional effects in which the two drugs cancel each other out when taken together and the patient derives no benefits of the medications. An example of this situation is the combination of an antipsychotic medication with levodopa. Antipsychotic drugs commonly act as antagonists to dopamine; however, levodopa’s main purpose is to raise the levels of dopamine in the central nervous system. When the two drugs are taken together, their effects negate the other and the patient may not achieve symptom control.\(^\text{91}\) Even worse, the patient may appear to be suffering from a relapse of a mental illness or may be accused of noncompliance with drug therapy when in fact the patient is experiencing a pharmacodynamic reaction of opposing drug interactions.

Based on the understanding of the various effects of drugs and their abilities to interact with others in various ways, it is important to consider possible drug interactions when prescribing and administering medication, whether for psychiatric illnesses or for somatic conditions. Being aware of risk factors and common reactions, and seeking advice during situations in which the outcome may not be entirely clear, is essential to prevent potentially
harmful interactions between certain medications and to help the patient to be able to achieve the fullest potential for symptom control.

**Electroconvulsive Therapy (ECT)**

Electroconvulsive therapy is a clinical procedure used for the treatment of various mood disorders. It is considered by some to be one of the most effective treatment measures for the management of severe depression; however, among some cohorts, ECT is also extremely controversial. It was initially introduced during the 1930s and developed for the treatment of schizophrenia, during a time when there were no medications available for the treatment of psychotic symptoms. Later, as antipsychotic medications were developed and prescribed, the use of ECT for the treatment of psychosis declined, however, it remains in use today for a number of different mental health conditions.

Electroconvulsive therapy involves application of an electrical current that passes through the brain; the length of application of the current may last anywhere from 0.2 to 8 seconds in length. The current induces a seizure in the brain, which is essential to be therapeutic. The exact mechanism of how the electrical stimulus and the resulting seizure impacts mental health and behavior is not entirely clear.

Several theories have emerged as to the nature of how ECT can affect the brain and can change moods and behavior associated with refractory mood disorders. Some theories developed historically when clinicians were first conducting ECT procedures and seeing the results, but the mechanisms of action according to their theories were later disproven. Among some examples of these theories was the idea that ECT produces an amnesic effect and, thereby, erases some of a patient’s bad memories and feelings,
or that the fear of experiencing a seizure through ECT forced a reduction in symptoms.

Today, the exact mechanisms of why ECT provides a therapeutic benefit for a person with severe depression or psychosis still remain somewhat unclear. Other theories have suggested that there is a seizure threshold that must be reached during ECT in order for the process to be effective. This is based on previous opinions that suggested by inducing generalized seizure activity through ECT is what allowed the procedure to be effective. However, later research has shown that this is not necessarily true. Although seizure activity is a very important component of ECT, it does not seem to be the ultimate sole cause of treatment.98 Despite its controversies, ECT has been used to effectively treat severe depression and other forms of mental illness for over 75 years.92

Electroconvulsive therapy is administered on an outpatient basis in a suite designed specifically for the treatment; it may also be given to hospitalized patients who are already inpatients receiving treatment in psychiatric institutions or rehabilitation centers. The procedure is most often done in the morning, since the individual is typically required to remain NPO prior to starting. The patient is monitored before, during, and after the procedure, and consent for the procedure is required prior to starting the ECT.

At the beginning of the process, the patient is connected to a hemodynamic monitor to evaluate heart rate, blood pressure, and oxygen saturations throughout the entire session, and an electroencephalogram is in place to monitor brain activity. The effectiveness of the ECT is measured while monitoring the patient occurs as the current is being delivered. Effectiveness is measured as convulsions, an increase in heart rate, and seizure activity in
the brain.\textsuperscript{16} The patient is given general anesthesia, such as with methohexital, which is short acting so that it will wear off shortly after the procedure is complete. The anesthesia is administered intravenously and takes effect almost immediately. Once the patient is under anesthesia, he or she is also given succinylcholine, a neuromuscular blocking agent, and atropine, which controls secretions and prevents aspiration during the procedure. Oxygen is also required, both before and after the procedure, because of the effects of the succinylcholine. Although muscle blockade is used to control seizure activity, some motor convulsions can still be observed. The administration of succinylcholine is done to avoid injury from severe convulsions.

The electrical current is administered through electrodes either on one side of the brain or it is delivered to both sides. During the ECT, the patient is monitored for 1) motor convulsions, which should last a minimum of 20 seconds, 2) tachycardia, which must occur for at least 30 to 50 seconds, and 3) a brain seizure as monitored through electroencephalogram, which must last between 30 and 150 seconds. These parameters are pre-determined and should occur during the process in order for it to be considered therapeutic.\textsuperscript{16}

Following the ECT, the patient goes through a period of recovery, in which he or she is monitored closely for complications from the procedure. Once the patient is physically stable, without respiratory complications and breathing spontaneously, and the effects of the anesthesia have worn off, the patient can then be moved from the procedure area to another location. Most people are disoriented for a short period after undergoing ECT and may need to be reoriented to the current surroundings during the recovery time. A small percentage of people emerge from the sedation provided for ECT as
agitated, which requires administration of further medications, such as benzodiazepines. Side effects of ECT are usually mild and can be managed with over-the-counter pain relievers, such as acetaminophen.\textsuperscript{15} Typical side effects include headache and muscle aches from the seizure.

Often, patients who receive ECT are scheduled to have the procedure several times, and they may be prescribed a series of up to 12 treatments for management of severe depression or schizophrenia. Once the number of ECT sessions has been determined by the healthcare provider, the patient typically receives 2 to 3 sessions per week until the total amount has been achieved.

In cases where ECT is indicated, it has been shown to be an effective form of treatment for such conditions as severe depression and schizophrenia. Despite its controversial nature, it may be implemented in cases where other treatments, such as through medications or therapy, have failed to relieve symptoms. The reasons why the public is often skeptical of ECT are varied. Because clinicians do not entirely understand how the process works, many have rejected it as a valid form of treatment, often forgetting that there are various other types of drugs or procedures whose mechanisms are also not entirely clear but that continue to be used for treatments.

Another reason why ECT is often viewed with suspicion is because it appears barbaric in nature. The process of inducing a seizure, when seizure activity is normally prevented or treated, seems as if it would do more harm than good. Again, there are other procedures and surgical processes that also often seem barbaric and cruel and yet they are commonly performed as part of medical treatments to manage or even cure some diseases. By educating the public about the benefits of ECT and its success in treating patients with
various forms of mental disorders, the procedures may be more likely to be accepted by the public and by prescribing providers.

**Candidates for ECT**

Not all patients with mental illnesses are good candidates for ECT. Instead, it should be reserved for those conditions that are refractory to other types of treatments such as through medications. Additionally, ECT should not be performed on someone who cannot physically tolerate the procedure and the medications used throughout. The U.S. FDA has approved the official use of ECT for the management of six different mental illnesses, including depression, both unipolar and bipolar forms, schizophrenia, schizoaffective disorder, bipolar disorder, for both manic and mixed states, schizophreniform disorder, and catatonia. It is most commonly used for the treatment of unipolar severe depression, particularly when other trials of medications for treatment have not been effective. It is more likely to be implemented in cases where a patient’s mental health status has put him or her at risk, such as in cases of suicidal or homicidal ideation, or severe psychotic episodes that lead to agitation and aggression.

The main candidates for ECT are those whose mental health conditions have so affected quality of life that they are unable to function normally in social, occupational, or relational contexts. In the case of major depressive disorder, a patient may be suffering from such severe depression that he or she is unable to continue to function normally in society. Unfortunately, in many cases, ECT is only recommended after the patient has undergone at least one trial of prescription antidepressants that have failed. In cases where the patient is not in imminent danger, ECT is still often looked upon as a late resort for treatment when other measures are unsuccessful, rather than seeing it for its success. Again, this may be due to the controversies
associated with the process, which may prompt healthcare providers to consider other alternatives that seem “safer” or those that are more benign. In reality, ECT is very successful in the treatment of severely depressed patients and in those who have otherwise been diagnosed with treatment-resistant depression. According to the International Society for ECT and Neurostimulation, ECT has a success rate of 60 to 90 percent in the treatment of mental illnesses.\textsuperscript{93}

Beyond those who receive ECT for treatment of depression, the process may be administered for many other forms of mental health disorders and issues, including severe obsessive-compulsive disorder, Parkinson’s disease, post-partum depression, aggressive forms of dementia, refractory epilepsy, severe autism with aggressive behavior, and some chronic pain syndromes.\textsuperscript{93} In many cases, aggression, agitation, or even violence is often present before the patient is offered ECT. It is commonly given as a second choice of treatment after drug use when instead ECT could be quite successful for helping many to achieve remission from mental illness symptoms.

Patients who receive ECT as treatment for bipolar disorder are much more infrequent when compared to those who receive the treatment for depression. However, use of ECT in patients with bipolar disorder has also been shown to be an effective form of treatment. A clinical data review by Palma, \textit{et al}, in \textit{Depression Research and Treatment} looked at the administration of ECT in patients who experienced mixed states of bipolar disorder with both symptoms of depression and mania. The study showed that patients who suffered from mixed episodes of bipolar disorder were effectively treated with ECT and experienced asymptomatic periods that would be similar to relapses of those with depressive or manic polarities.\textsuperscript{94}
Although most of the patients required maintenance ECT treatment and some necessitated hospitalization, the overall prospect of using ECT as treatment for this specific type of mental illness was considered positive.

Mixed mood states are associated with more severe forms of bipolar disorder when compared to manic or depressed states; they are also more commonly connected to other comorbidities, including substance use disorders, cognitive impairments, and traumatic brain injuries when compared to other forms of bipolar disorder. Mixed states of bipolar disorder can be very difficult to treat and are often considered refractory conditions when affected patients have failed to respond to standard mood stabilizing medications or antipsychotics. A patient with a diagnosis of bipolar disorder and who suffers from frequent episodes of mixed states, particularly someone who has been considered as “treatment resistant”, could be considered for ECT as a valid form of treatment when compared to other possible management options.

Electroconvulsive therapy has also been shown to be effective in the treatment of psychoses, such as with diagnosed schizophrenia. Studies indicate that ECT is more effective than psychotherapy when used in patients with schizophrenia and is equally effective as pharmacotherapy through antipsychotic medications. Supplementing antipsychotic drugs with ECT for patients with acute and chronic schizophrenia has also been shown to be more beneficial when compared to antipsychotic use alone.

Refractory schizophrenia may be more likely to be considered for treatment with clozapine, as this drug is often one of the first choices of antipsychotics to use in this specific patient population. However, a certain percentage of patients with treatment-resistant schizophrenia also do not respond to clozapine; between 45 and 70 percent of patients with refractory
schizophrenia may fail to show adequate improvement in symptoms. Because clozapine is a typical first option in the line of treatment in these cases, when a patient does not respond to it, options for adequate treatment may become even more limited. In cases where severe cases of schizophrenia do not respond to standard medications and where patients are suffering, sometimes intensely from their symptoms, ECT could be implemented.

The addition of ECT to the administration of clozapine for schizophrenia treatment may provide synergistic effects, and some studies have shown that combining these two types of treatment provides much better results when compared to using either treatment alone. A study by Petrides, et al., in *The American Journal of Psychiatry* conducted a randomized, controlled trial of patients with refractory schizophrenia who had either not responded to clozapine or who were considered “partial responders,” in that they experienced some symptom management with clozapine after use for 12 weeks. The findings showed that 50 percent of patients who received ECT combined with clozapine therapy showed a 40 percent reduction in symptoms, and 60 percent of participants responded with at least a 20 percent reduction in symptoms. Unfortunately for some patients with treatment-resistant forms of the disease, use of clozapine may come as a last resort. When even clozapine does not cause symptom abatement, inclusion of ECT alongside clozapine treatment could cause a reduction in negative symptoms and could lead to further success in treatment.

Catatonia is a common manifestation associated with a variety of psychiatric and somatic illnesses. Catatonia describes a state of unresponsiveness to external stimulation; the affected person is conscious and awake, yet does not act on outside stimulation. A patient with catatonia may demonstrate
mutism or may repeat words or phrases, which are often those heard in surroundings, as well as exhibit negativism, posturing, rigidity, stupor, and automatic obedience. Catatonia also often causes a state of waxy flexibility, in which the person is immobile and does not change positions; however, the person’s body is not necessarily in a “frozen” state of no movement, and the extremities or body could be moved or repositioned by another person. Catatonia is commonly seen with schizophrenia, however, it may develop in affiliation with other types of mood disorders, as well as some toxicity syndromes or neurodevelopmental disorders.96

In addition to its methods of treating other forms of mental illness, ECT has also been a useful treatment for some mental illnesses that produce catatonic states. In particular, it should also be considered early on as a form of management among patients with catatonia that is refractory to pharmacological treatment. The most common form of treatment for catatonia, regardless of the underlying cause, is administration of benzodiazepines on a short-term basis, approximately 4 to 10 days, until the patient responds. In cases where a patient experiences a catatonic state that is refractory to treatment, ECT may be considered as an effective form of treatment as well.

A review in the World Journal of Psychiatry studied cases of patients with catatonia who were treated with ECT when they were otherwise unresponsive to benzodiazepine treatment. The review showed that observational studies reported between 80 and 100 percent success rates in relieving symptoms of catatonia through ECT.96 The study showed that ECT was effective in treating all forms of catatonia, regardless of whether the underlying cause was associated with mental illness or another somatic disorder.
The effects of ECT have obviously been shown to be beneficial for many patients who otherwise have little hope of recovery through traditional methods of medical treatment. The appropriate candidates for ECT are often those whose mental health states are either putting them in danger of harm, who suffer so much with mental illness symptoms that their level of functioning has greatly declined, or that have not responded to other conventional methods of treatment. Although patients with such severe conditions are often chosen to undergo ECT as a form of treatment and often do respond well, ECT may also be successfully used among other patients struggling with mental illness and, in many cases, it should be employed earlier in the course of their illness to prevent symptom progression past the point of attainable recovery.

**Potential for Regression**

Although ECT has been shown to be beneficial in many cases of treatment for mental disorders, there are some risks associated with the process. However, what were once considered contraindications to the practice of ECT have now been relegated to risk factors that should be considered when determining the overall benefits of treatment. This change in viewpoint has come about with the continued development and practice of the technique to refine the process.

Because the process of performing ECT requires anesthesia, patients who are unable to tolerate the drugs associated with the procedure would be at risk of being unable to tolerate the process at all. Electroconvulsive therapy also places a greater amount of stress on the heart and the circulatory system, such that when the process induces a seizure, the cardiac workload is temporarily increased and there is a rise in catecholamine levels. Therefore, anyone with a history of such conditions as ischemic heart
disease or an identified aneurysm should undergo some form of treatment or surgery for these medical conditions prior to having ECT to avoid life-threatening complications.

The brain and nervous system are also placed under stress during the ECT procedure because of the accompanying seizure activity. The brain requires an increase in oxygen during this time and there is an increase in intracranial pressure that occurs as well. Those patients who have medical conditions that would preclude them from having ECT because of a risk of complications must be under thorough consideration to weigh the benefits against the risks of the procedure. If medical complications develop because of ECT in these cases, the patient may have the benefit of experiencing relief of psychiatric symptoms but may also have developed new symptoms and medical consequences instead.

There are some patients who initially benefit from undergoing ECT but who eventually develop symptoms of their underlying mental illness again after a period of time. In these cases, the patient must consider undergoing another round of ECT to control symptoms again, or may consider an alternative form of treatment. As with other methods of treatment discussed in this article, ECT is not considered a cure for mental illness, but it can place a patient with a mental disorder into a state of remission. It is known that ECT often requires more than one session in order for it to be effective; however, guidelines for long-term maintenance of ECT to maintain a state of remission are unclear. There is therefore potential for patient regression into illness when there is a lack of understanding about when and how often to conduct follow-up ECT. There are high rates of relapse associated with ECT, particularly within the first six months following treatment.
In some cases, ECT followed by a course of medications, such as antidepressants or antipsychotics, has been beneficial and has prevented patient regression from lapsing back into acute states of mental illness. Shortly after the introduction of many major antidepressants, for instance, many clinicians performed ECT on severely depressed patients for a few sessions and then prescribed medication to maintain follow up for the long-term duration of treatment. Unfortunately, many patients experienced relapse after several months or years, despite continuing with antidepressant medications for treatment. Researchers soon discovered that ongoing ECT at routine intervals is often necessary to maintain a state of balance and to prevent disease regression.

The population of patients who receive ECT for treatment of mental illness has evolved over time. Where ECT was once used more commonly as a form of treatment for depression or psychosis, particularly prior to the development of many psychiatric drugs, it was often found to be successful in treating many negative symptoms and rates of relapse were slower. Currently, ECT is more commonly used in complex cases where patients have failed trials of different medications or are otherwise unresponsive to other treatment methods. They may respond to ECT initially, but because of the complexity of their situations, they are less likely to maintain a stable state and are more likely to regress after ECT. They may also be less likely to even achieve a full state of remission at all and may instead only reach partial remission that is at greater risk of early regression. As a result, rates of relapse and regression after ECT continue to increase over time.

A review by Jelovac, et al., in *Neuropsychopharmacology* looked at the long-term effects of ECT and rates of relapse of patients who had undergone the therapy for treatment of mental illness. Among patients who only had ECT
and no other continuation therapy, 50 percent had relapsed back to their prior mental states within three months of ECT and 80 percent had relapsed within six months.\textsuperscript{99} This suggests that without ongoing treatment with ECT or another form of pharmacotherapy, there are little to no lasting effects of ECT and affected patients are most likely to return to their former states. The review also showed that when pharmacotherapy was included as part of follow-up for ECT but without continued ECT, 34 percent of patients had relapsed within six months, and 51 percent had relapsed by 12 months.

Based on some of these findings, it may seem that continued ECT would be more beneficial than ECT followed by pharmacotherapy. However, when the researchers in the study looked at data about patients who had continued ECT, the rates of relapse were similar to those who followed up with medication. Approximately 37 percent of patients who had follow-up ECT treatments relapsed within six months after their initial therapeutic intervention. The relapse rate was 45 percent at six months for those patients who underwent ongoing ECT treatments within pharmacologic intervention.\textsuperscript{99} These findings do not accurately predict an adequate number of ECT treatments or an appropriate timeframe for delivery of ECT after the initial sessions in order to promote ongoing remission. In other words, some patients may prevent regression by going through routine sessions of ECT and one or more psychiatric medications to maintain wellness; in other cases, some patients may not regress even with very little follow up.

Beyond the timing and rate of ECT administration as part of follow up to prevent relapse, there are other factors that can affect a patient’s propensity for regression after undergoing ECT. Patients who have comorbid disorders, including substance use disorders, and the type and use of prescribed medications for treatment during follow up, are all factors involved. When
comorbidities are present and the patient must manage physical illnesses or other psychiatric diagnoses during the recovery period, there is a greater likelihood of regression following ECT. A larger number of factors to manage during the course of recovery results in greater difficulties in maintaining mental health. For example, a patient with severe depression and alcohol use disorder may undergo ECT as part of treatment for depressive symptoms and suicidal ideation. Following six sessions of ECT, the patient enters a state of remission from depressive symptoms but continues to struggle with alcohol use. Despite receiving adequate treatment and ongoing pharmacological therapy, the patient may be more likely to regress in a depressive disorder in the setting of a co-occurring substance use disorder. As with the difference in mental health conditions and presenting symptoms and manifestations, each patient will respond to the effectiveness of ECT differently and each course of treatment to prevent regression must be tailored to the individual needs of each patient.

**Psychiatric Advance Directives (PAD)**

Individuals with a mental illness are often seen as incompetent and unable to make decisions for themselves. They may eventually be at the mercy of others who must decide what is best for their health and safety. While this can be true for many with mental illnesses, particularly in cases where psychosis is present and the affected person is out of touch with reality, not all people with mental health disorders are incapable of making decisions. For those with mental health diagnoses, it is important to not only be a part of the decision-making process required as part of care, but also to play a role, if possible, on the interdisciplinary team that is discussing and planning for the best forms of the patient’s treatment management.
Caregivers of patients with mental health diagnoses also may struggle with little control over how their loved one is treated and how the illness is managed. Also, the caregivers of patients who suffer from psychoses should be aware of their state’s laws regarding treatment, such as through administration of medication or performing certain therapeutic procedures. While it may seem as if some patients with mental health diagnoses are involuntarily committed for psychiatric care, mental health patients do have rights regarding their treatment and they can set up guidelines for treatment in advance of any mental health crises that may occur. A patient without any kind of directive for care may be given medication or treatments, even if the patient disagrees with the process. This is typically because a person with a severe mental illness such as psychosis is often considered incompetent to make decisions about needed care during a time of crisis. However, if the patient has an advance directive in place, the healthcare provider must follow the stipulations set forth according to the plan of care that the patient devised.³

In most states, a patient with a mental illness who is experiencing psychotic symptoms is considered as someone who is unable to make appropriate decisions regarding their care. When no legal directives are in place, a psychotic patient would most likely be considered incompetent by a court of law and would be ordered to undergo treatment for psychiatric care. This decision is most often made because the court system would consider that psychiatric treatment is in the patient’s best interest, whether he or she conveys that the care is wanted or not.

Alternatively, if a patient has a psychiatric advance directive in place, the patient’s desires have been defined ahead of time and he or she may be able to refuse treatment if so wished. A psychiatric advance directive (PAD) is
developed as a type of plan for a patient with a mental health diagnosis. The PAD is actually a legal document that is drawn up with the help of an attorney and is signed by the patient. It contains specific instructions regarding the patient’s preferences for mental health treatment. The document follows in the footsteps of a medical advance directive, including a durable power of attorney or living will that stipulates a patient’s specific desires regarding care in the event that he or she is unable to communicate what is wished. According to the Patient Self-Determination Act, any healthcare facility that receives Medicare funding must ask all incoming patients if they have an advance directive in place, and if not whether they would like more information about developing a medical advance directive.

A psychiatric advance directive follows the same course as the medical directive, however, providers are not necessarily required to ask patients about their psychiatric advance directives; the laws differ between the states. The PAD is written during a time when the patient is able to make healthcare decisions and is competent to do so. The idea behind the psychiatric advance directive is that if the patient ever reaches the point of being no longer competent enough to make independent healthcare decisions because of a mental illness, the advance directive will be in place and will dictate the appropriate decisions for the patient. A PAD offers peace of mind for those who may worry about what would happen if the time comes when the patient is unable to make independent decisions related to healthcare. It also allows the patient to feel more in control because the health plan is established and made known in advance.

Although a patient with refractory psychosis or a mood disorder often benefits from treatments and experiences relief of many psychotic symptoms, if a PAD has been developed that refuses medication or
treatment, the patient cannot be forced to have the treatment against his or her will. However, because the patient has been proactive in defining preferences for health care and a PAD is in place, it does not mean that a PAD is universally accepted in all situations. In fact, psychiatric advance directives are somewhat controversial and are not approved for use in all states. Some people believe that a patient with a psychiatric illness is incapable of declaring his or her own interests for care, particularly if the patient has been hospitalized for mental illness in the past. This erroneous belief sometimes holds true even though the patient is considered mentally competent when completing the PAD.

Additionally, some patients develop advance directives that go against conventional forms of treatment, often because they have tried various methods of symptom management or they have been hospitalized a number of times. When these patients seem to need care but a PAD is in place that allows for refusal of involuntary hospitalization, it may seem that the PAD is working against the patient’s best interests. What was once developed as a declaration of the patient’s wishes instead becomes a fight over the best course of treatment in the current moment in these situations. There are several arguments over why a PAD should be a legally accepted document and the differences between a psychiatric advance directive and a medical advance directive, which are otherwise accepted as part of care in healthcare institutions.

**Advantages of a PAD**

There are a number of advantages of developing a PAD prior to requiring mental health treatment. Proponents of psychiatric advance directives state that patients who have developed the documents feel a sense of autonomy over making decisions regarding their own care. This is often true in cases
where a patient struggles with such severe mental health issues that he or she is otherwise unable to function in a normal capacity within society, which can be demoralizing. Additionally, a patient who has attempted to treat a mood or psychotic disorder with medications or somatic therapies and who has a treatment-resistant form of mental illness may feel frustrated and powerless over his or her situation. By developing a PAD, the patient may have a greater sense of control over some elements of care, and may feel helpless in one less area of life.

The PAD is also designed to be a communication tool between the patient and the patient’s caregivers. While the patient most often develops it according to his or her desires for treatment, an effective advance directive should be developed within the context of collaboration between the patient and the physician. Because the healthcare provider is the person prescribing treatments and guiding much of the care, the provider’s input over whether or not a patient should receive certain services or should avoid other situations is valid in developing the PAD. Not all people agree with this position, though, and there are some who believe that the patient should solely develop an advance directive because the care decisions directly affect his or her own treatment and psychiatric care. However, in the interest of communication between all parties involved, development of a PAD through the guidance of a healthcare provider with the patient and family not only provides direction for the basic decisions to be made, but the provider will also already know what care to provide if the patient becomes incapacitated.

The PAD is a useful communication tool in cases where an unfamiliar healthcare provider who would otherwise not know or understand the patient’s wishes for care is seeing the patient. In this type of situation, the PAD is an intercessory tool that can guide the healthcare provider in making
care decisions. For example, when caring for an unfamiliar patient with schizophrenia, a healthcare provider would need to access medical records and review background information regarding the patient’s previous care to better determine how to proceed with care in the current situation. Often, these situations occur in emergency departments where physicians must make rapid treatment decisions on short notice for people that are otherwise unfamiliar to them.

There is little time to access the patient’s medical history or to perform a thorough and comprehensive assessment when determining whether to admit a psychiatric patient to the hospital during a time of crisis. The presence of a PAD, however, can dictate some of the course of care because it communicates the patient’s wishes even while the patient is unable to do so. A PAD does not replace a patient’s medical history or record as part of the assessment, but its usefulness as a communication tool is significant.

The PAD is usually mobile, in that it can be taken and transported between providers and healthcare facilities to whichever location the patient needs care. This process also eases facilitation of communication between different providers and caregivers because the document is often readily available. In addition to guidelines for standard treatment measures, the PAD may also contain other important information, including emergency contact information for a caregiver or family member. This also provides a method of communicating important information about who to contact if there is any question about the appropriate methods of caring for the patient.

Unfortunately for many patients with mental health conditions, involuntary hospitalization or treatment is a reality. A patient may not wish to undergo psychiatric treatment nor be hospitalized, but without a PAD in place, the
patient may not have a choice in the decision if seen by providers and treatment teams as incompetent. An added benefit of developing a PAD before the time of a crisis is that it avoids involuntary hospitalization and treatment when the patient would otherwise refuse. In-hospital treatment and rehabilitation are excellent situations for providing care and treatment for mental illness and for keeping some people within a safe environment when they would otherwise harm themselves or others. Conversely, a patient who does not wish to be hospitalized may be less cooperative with treatment and may not benefit from the situation at all if it is against the patient’s will, which then becomes a costly endeavor that could be avoided if the patient’s wishes were upheld.

Finally, a patient who has developed a PAD that outlines a course of treatment is more likely to be compliant with his or her own directions for treatments, including with medication use or other therapy. When a person feels a measure of control over making choices for healthcare, he or she may also be more likely to follow through with those choices made independently rather than following the orders of someone else. By keeping the patient involved and allowing for an ability to make one’s own care decisions, a PAD can support treatment compliance and potentially lead to greater numbers of patients who enter remissive states and those who have treatment success.

**Patient Competence**

In the interest of upholding patient autonomy, the patient with a mental illness should be the person to fill out the psychiatric advance directive. Often, this is done with a partner, such as family member or caregiver, as well as in consultation with the healthcare provider, if the patient desires.
Because it is the patient determining the course of the advance directive, the PAD is then drawn up according to his wishes and inclinations.

A patient who completes a psychiatric advance directive should be mentally competent to be able to finalize the paperwork. However, the statistics of whether or not this is true in all situations are not actually available. In an ideal situation, a patient with a psychiatric diagnosis can make decisions independently, with the help of others if necessary, to best determine a course of treatment during a time when the patient is mentally competent and stable. In reality, there may be many patients who file PADs at various times that have been drawn up during periods where the patient was incapacitated or under the direction of another person so that the actual document does not necessarily reflect the patient’s desires. Establishing competence is difficult and can be tedious prior to developing an advance directive. This is one of the reasons why PADs are seen as controversial and have not been adopted in all states. When a patient who is mentally incompetent because of a psychiatric illness presents for care and has a PAD in place, there is often a question of whether the patient was truly mentally competent at the time of the document’s development to be able to accurately state his or her desires for care.

Controversy exists about other factors related to PADs as well. A healthcare provider who cares for an unfamiliar patient with a mental illness in an emergency situation may determine that the patient needs inpatient hospitalization. However, the patient’s PAD may state that hospitalization is not wanted and that the patient wants to refrain from all treatment involving medication. The provider must assume that the PAD was completed during a time when the patient was mentally competent to make decisions, even if the patient currently is not. It is therefore very difficult to uphold the
stipulations of the PAD during a crisis when the directions seem medically inappropriate and do not meet the patient’s needs for care. Healthcare providers are often stuck in situations over which they have no control; they have a duty to provide help to the patient and to uphold the patient’s safety and health, yet they are given documents that may say otherwise.

Elbogen, et al., in the journal Law and Human Behavior discussed the issue of patient competence when completing a PAD and used a definition to describe a patient’s appropriate mental state in regards to having the ability to fill out a PAD and to have it notarized. According to the authors, a patient’s competence is the ability to “understand, appreciate, reason, and make choices in the context of life decisions.”¹³⁶ In this manner, the patient should be able to understand what is desired and convey it through a document that expresses the patient’s desire. The patient should also be able to comprehend the significance of the document, such that it is a legal entity that is notarized and will be put into place when psychiatric treatment is required. The patient should not only have the mental ability to write the document at the time of signing the PAD, but to also understand what treatment decisions mean.

When developing any document that considers the care and treatment of a patient with a mental health disorder, it must be recognized that there is a difference in the definitions of competence and capacity. “Competence” is actually a legal term, and “incompetence” describes a condition where an individual lacks the ability to understand healthcare decisions. In cases of the law, when a person is not deemed competent to make decisions, the person is often placed under the care of a guardian. Alternatively, “capacity” describes the ability to understand an individual’s actions and the effects of those actions. When describing competency, it can then be said that it is the
 establishment of a person’s level of capacity.¹³⁸ When a person with a mental illness is filing a PAD for care, it must be established that he or she has the capacity to understand the decisions being made, and the person’s competence determines the capacity to do so.

Because there are no specific standards in place that state the exact point of what determines mental competence to make decisions regarding psychiatric advance directives, when a patient is filing a PAD to direct his or her care, it is often assumed that the patient is competent to make independent choices. Even within a court of law, when a person commits a crime, the person must prove a condition of incompetence to avoid standing trial or receiving sentencing for having committed a crime. It is a similar situation with developing a PAD. Most patients who choose to go through the process of filing paperwork for an advance directive are thought to be competent enough to do so because there is no process in place that specifically states otherwise that is general enough to include all people. Instead, the decision of whether a patient is incompetent when developing a PAD is actually determined on an individual basis.

In theory, many patients who have been diagnosed with a mental illness have stated that they would want a PAD as a source of guidance for their care if they become incapacitated. Approximately 70 percent of patients with mental illness have expressed the desire for a PAD; however, only about 10 percent of the same population have actually completed one.¹³⁶ These statistics are not too far off from those of patients describing medical advance directives as well. Many people see the benefit of them but do not necessarily go through the time and measures needed to file an advance directive.
Until psychiatric advance directives become more common as part of patient declarations for care, they will most likely continue to be viewed as controversial. The very nature of mental illness is frightening and confusing for some anyway. When working with patients who have mental illnesses, there are those who choose to be suspicious of their intents for care, when in reality, most people who go through the process of filing a psychiatric advance directive are taking time to articulate their wishes for their own care during a time when they are unable to control anything else.

**Applicable Laws**

While recognized as a legal entity, psychiatric advance directives are not carried out in all situations. Although all 50 states have laws in place regarding medical advance directives, not all states have accepted the validity of psychiatric advance directives. Currently, there are at least 25 states that have laws in place regarding psychiatric advance directives. Some states allow for psychiatric advance directives of various forms, although they are not specifically named as such. In some locations, mental health directives fall under the umbrella of medical advance directives. The differences between state laws partly stem from the controversy surrounding PADs and their ability to dictate a patient’s care if the person filing the form was mentally competent to make the decision.

According to the Due Process Clause of the 14th Amendment, every person has the right to be safe from denial of life, liberty, or property by the government by authorization of the law. The Due Process Clause includes the right to refuse medical treatment, even if it is a lifesaving procedure. This right is afforded to all people who are competent to make such decisions, and is often revoked in situations where the affected person cannot decide for their own best interests. Examples include the care of
infants and young children, who would be unable to understand any of the processes needed to make their care decisions, persons with dementia, who may not be aware of the appropriate decisions for their care, and persons with mental illness that precludes rational thought.

Under general medical direction, a person can make decisions regarding medical care and treatment in an advance directive, which must be upheld when the person presents for care at a healthcare facility. A classic case regards Nancy Cruzan, a 25-year-old woman who was involved in a car accident in 1983 that left her in a persistent vegetative state. After five more years, her parents requested that the feeding tube be discontinued, but the state of Missouri took the case to court, saying that they had no evidence of Nancy’s wish to die. The case of *Cruzan v. Director, Missouri Department of Health*, which went to the Supreme Court, decided that it was acceptable to require clear and convincing evidence of a patient’s wishes to remove life support. In other words, in medical cases involving a patient’s inability to communicate desires for care, the patient should have an advance directive in place for making major decisions, particularly the removal of medical treatment.

This case speaks to the accountability of medical advance directives, but does not necessarily address psychiatric advance directives. Because of the Patient Self-Determination Act of 1990, more and more members of the psychiatric care community have become proponents of PADs, stating that patients with mental illnesses should be afforded the same rights for treatment.

The specific laws regarding PADs not only vary between states but there are also minor differences regarding execution of the PAD that vary between
states. For example, some states determine that when filling out a PAD, the document must be witnessed by two different people, while in other states, this does not apply. In Alabama, where PADs are legally binding documents, they are valid until the patient revokes them; in Montana, the PAD may have an expiration date. In many states, the patient may develop a plan of psychiatric care with the use of an agent; this may mean determining a healthcare proxy as someone to make care decisions for the patient if he or she becomes incapacitated or as someone who will work with the patient to complete the necessary documentation to file the PAD in the first place. Various states allow for PADs under the general provisions of medical advance directives, while some others do not.139

The Americans with Disabilities Act (ADA), which was developed in 1990, is designed to protect those with disabilities from being discriminated against in regards to employment, government activities, or those activities of local businesses. The law applies to those with physical disabilities as well as those with mental disabilities. This includes protection for those who have a history of mental impairment or who have previously sought treatment for a mental health disability.140 Those with mental health issues are protected under the Act and cannot be discriminated against on the basis of their mental health status. This means that businesses and the government must make accommodations for those with mental disabilities and that they cannot treat people with these types of disabilities differently than they would treat other members of the general public.

In the case of Hargrave vs. State of Vermont, a woman with a history of paranoid schizophrenia and who had multiple hospitalizations signed a durable power of attorney in which she appointed another person to make healthcare decisions for her if she became incapacitated. The state of
Vermont does not have laws in place specifically regarding PADs, so she filed under a type of medical advance directive that allows for a power of attorney for healthcare. In the document, the patient refused all psychiatric treatment with medications, including antipsychotic, neuroleptic, psychotropic, or psychoactive medications, as well as ECT. In 1998, the state of Vermont had filed Act 114, which required caregivers to obey the choices of the power of attorney for committed individuals with mental health diagnoses for 45 days. It was assumed that after 45 days, if the affected patient had not shown improvement in mental health status, the law could then override the advance directive and administer medications or provide hospitalization involuntarily to a patient. The patient in the case sued the state of Vermont for violating her rights under the Americans with Disabilities Act, stating that under Act 114, she was facing discrimination. The court sided with the patient and determined that Act 114 was a violation of her rights.

Despite the advances in legal proceedings regarding the rights of patients with mental illnesses, the right to refuse treatment can still be limited in some other situations. When a patient is considered a threat to self or to others, such as with imminent suicidal or homicidal tendencies, the patient can be involuntarily hospitalized. The concept of obligating an individual to be hospitalized, to take medication, or to be restrained or secluded is known as forced treatment. In many cases, forced treatment is not an isolated event and could have been dealt with prior to its circumstances by implementing other interventions. The process is not only a violation of a patient’s human rights, but it is also degrading and sets the stage for others to deem mental illness as a threatening or dangerous condition.

Because patients with mental illnesses often experience periods of mental competence and times of mental incapacity because of their conditions, the
decision of whether or not to hospitalize someone against his or her wishes because of the danger of harm is usually done on a case-by-case basis and according to the patient’s exhibiting symptoms and behaviors in the situation. A patient may be more likely to be involuntarily hospitalized or to receive some form of treatment that is unwanted if the patient does not have a psychiatric advance directive or any other type of care plan in place, if the patient presents for care because of a mental illness.

Fortunately, because of the nation’s history in legal cases where others have gone to court to defend their rights to treatment, many people with mental illnesses today are able to file some form of care planning to describe their wishes for treatment or to determine a healthcare proxy who will make decisions for them if they become incapacitated. Although not all states specifically allow for PADs, they do all have some measures in place that govern medical advance directives, which could be used for management of mental illness as well. Continued education for the public and the healthcare sectors regarding the important of psychiatric advance directives and their benefits is essential to prompt continuing acceptance of this important type of document in the care of the psychiatric patient.

Summary

There have been many advances in the treatment of various types of mental illnesses, including the use of psychotherapy, some forms of somatic interventions, and pharmacological interventions. A patient who receives a diagnosis of a mental illness today has more options for care and treatment than at any other point in history. Despite the success of many therapeutic interventions, there are still many who have developed refractory forms of their illnesses, which are unresponsive to standard forms of treatment. The reasons for why some illnesses are resistant to treatment are many. They
stem from various sources, including patient noncompliance to treatment regimens, comorbidities of other physical or mental illnesses, or failure to attain adequate and successful treatment at all.

Through the process of caring for patients who have refractory mental health disorders, the clinician must continue to consider the best options that will most likely provide successful results. This may mean choosing some of the first-line options that have worked for a lot of other people in the past, or in some cases, it may mean trying something new. Unfortunately, successful treatment of resistant mental illnesses often comes down to a process of trial and error. Despite this fact, healthcare providers can continue to learn and explore those measures that are promising, sometimes even considering treatments that have otherwise been deemed as controversial. Without continued support, education, and advocacy for treatment of mental disorders, the concept of psychiatric illness will remain in the dark and those afflicted with mental disorders will continue to suffer beyond their own control.

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