Bipolar Disorder: A Concise Overview of Etiology, Epidemiology Diagnosis and Management: Review of Literatures

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Abstract

Bipolar affective disorder, or manic depressive Illness (MDI), is a common, severe, and persistent Mental Illness. This condition is a serious lifelong struggle and challenge. Bipolar affective disorder is characterized by periods of deep, prolonged, and profound depression that alternate with periods of an excessively elevated or irritable mood known as mania. Only one manic/hypomaniac episode is required to diagnose bipolar rather than unipolar disorder. Bipolar disorder is further characterized as type I or type II. Type I is diagnosed when at least one manic episode is identified.

Bipolar disorder occurs in approximately 1 percent of the population. Bipolar II disorder and Bipolar disorder not otherwise specified (NOS) account for another 2.5 percent of the population. Bipolar disorder is almost always recurrent and can be associated with severe illness-related Morbidity and increased medical mortality. About 10 to 20 percent of patients with bipolar disorder die of their illness by suicide.

Bipolar disorder is equally prevalent in men and women. It has an early age onset. The most common age of onset of bipolar disorder is 17 years. It is a highly disabling illness, and in fact a study.

Bipolar disorder is caused by bio psychosocial influences including genetic, perinatal, neuroanatomic, neurochemical and other biologic abnormalities. In addition psychological and socio environmental factors are associated with a greater risk of bipolar disorders. The role of genes in the susceptibility to mood disorders has long been supported by family, twin, and adoption studies. That mood disorders run in families is a common observation of patients and clinicians. However, genes clearly only contribute a predisposition that must interact with environmental factors in order to cause disease.

Treatment of bipolar disorders requires an integration of medical, psychological, and psychosocial inputs.

Keywords: Bipolar; Mania; Hypomania; Cyclothymia; Mood Stabilizers; Psychotherapy;

Background

Bipolar disorder is characterized by manic or hypomanic states: the patient is either depressed, euthymic (normal in mood), or hypomaniac/ manic. Bipolar disorder differs from unipolar disorder by including manic states. No matter how many times a patient is depressed; only one manic/hypomaniac episode is required to diagnose bipolar rather than unipolar disorder. Bipolar disorder is further characterized as type I or type II. Type I is diagnosed when at least one manic episode is identified. Usually recurrent depression also occurs, but in 5 to 10 percent of cases there are no diagnosable major depressive episodes, although almost always there will be minor depressive episodes. Bipolar disorder type II requires the absence of even one manic episode, and instead the occurrence of at least one hypomaniac episode and at least one major depressive episode. The critical difference between mania and hypomania, in current DSM-V nosology, is that mania requires significant social and occupational dysfunction, while in hypomania significant social and occupational dysfunction needs to be excluded. Durational criteria are less strict for hypomania (a minimum of 4 days) than for mania (a minimum of 1 week) [1].

Bipolar disorder is common and disabling [2]. The hallmark of the disorder is mood elevation (mania or hypomania) [1]. Patients with bipolar I disorder have episodes of mania and nearly always experience major depressive episodes. Patients with bipolar II disorder suffer both hypomaniac episodes and major depressive episodes.

It is one of the most severe of the psychiatric disorders. Bipolar disorder is among the most disabling and economically catastrophic medical disorders, ranked by the World Health Organization as one of the common illnesses contributing to the global burden of disease [3].

It carries a lifetime risk of around 2.6–7.8%, and its early onset and tendency to chronicity mean that its prevalence is relatively high. The social and economic impact of the illness is enormous, and its impact on sufferers and their families can be devastating [4, 5].

Bipolar disorder is a clinical diagnosis. It must be differentiated from other psychiatric and medical illnesses, as well as from disorders such as heavy metal toxicity, adverse effects of drugs, and vitamin deficiencies [1].
Treatment of bipolar disorders requires an integration of medical, psychological, and psychosocial inputs. The bulk of care occurs in an outpatient setting and is best carried out by a multidisciplinary team. Psychosocial rehabilitation is an essential part of treatment [1].

Etiology of bipolar disorders

Research has identified several factors that contribute to the risk of developing bipolar disorders. Bipolar disorder is a disease caused by biopsychosocial influences including genetic, perinatal, neuroanatomic, neurochemical and other biologic abnormalities. In addition psychological and socio environmental factors are associated with a greater risk of bipolar disorders [6, 7, 8].

Genetic factors

Different studies indicated that bipolar disorders have genetic transmission risks. Some of the evidence for genetic transmission of bipolar disorders are:

Family Studies: Studies indicate that bipolar disorders run in families. First degree relatives of people with bipolar I disorder are approximately 7 times more likely to develop bipolar I disorder than the general population. Remarkably, offspring of a parent with bipolar disorder have a 50% chance of having another major psychiatric disorder. One longitudinal study found that sub threshold manic or hypomanic episodes were a diagnostic risk factor for the development of subsequent manic, mixed, or hypomanic episodes in the offspring of parents with bipolar disorder. In fact, unipolar disorder is typically the most common form of mood disorder in families of bipolar probands. However, the rate of bipolar disorder is only slightly elevated in the families of unipolar probands. This familial overlap suggests some degree of common genetic underpinnings between these two forms of mood disorder [6].

Twin Studies: Twins who are reared together share the same environment, while monozygotic (MZ) twins share all their genes, while dizygotic (DZ) twins share on average only 50 percent. Twin studies compare the concordance rates in MZ and DZ twins. The concordance rate refers to the proportion of co-twins who are also affected or to the proportion of twin pairs where both twins are affected. Twin studies demonstrate a concordance of 3390% for bipolar I disorder in identical twins. As identical twins share 100% of their DNA, these studies also show that environmental factors are involved, and there is no guarantee that a person will develop bipolar disorder, even if they carry susceptibility genes [7, 8].

Adoption Studies: Adoption studies provide an alternative approach to separating genetic and environmental factors in familial transmission. Adoption studies have been conducted using a variety of experimental designs, but the most common is the adoptee as proband strategy. In this approach, probands are identified who have a mood disorder and were adopted at birth. Through this event, nature is separated from nurture. The rates of psychiatric illness are then determined in both the biological and adoptive parents. Numerous adoption studies prove that a common environment is not the only factor that makes bipolar disorder occur in families. Children whose biologic parents have either bipolar I disorder or a major depressive disorder remain at increased risk of developing an affective disorder, even if they are reared in a home with adopted parents who are not affected [7, 8].

Linkage Studies: Numerous linkage studies of bipolar disorder have implicated many different chromosomal regions. Bipolar disorder, especially bipolar type I (BPI) disorder, has a major genetic component, with the involvement of the ANK3, CACNA1C, and CLOCK genes [9, 15]. The evidence indicating a genetic role in bipolar disorder takes several forms.

Pregnancy and Birth Complications (Perinatal factors)

An association between obstetric complications, structural brain abnormality and early onset schizophrenia has been reported in a number of investigations [16, 17] and reviewed recently [12]. Although broadly defined or apparently unrelated, obstetric complications may share a common pathophysiology, namely foetal hypoxia [18]. Studies have demonstrated that patients with bipolar disorder have increased rates of obstetric complications and this was associated with an early illness onset [19]. By contrast, little research has been carried out into the relationship between obstetric complications and age of onset of bipolar affective disorder. However, increased risks of perinatal birth complications have also been reported in bipolar disorder [20-25]. The significance of such findings in the causation of bipolar disorder is still unclear. Scott’s review and metaanalysis of literature [24] failed to find a significant association between obstetric complications and bipolar disorder.

Neurotransmitters (Biochemical factors)

Multiple biochemical pathways likely contribute to bipolar disorder, which is why detecting one particular abnormality is difficult. A number of neurotransmitters have been linked to this disorder, largely based on patients responses to psychoactive agents as in the following examples. The blood pressure drug reserpine, which depletes catecholamines from nerve terminals, was noted incidentally to cause depression. This led to the catecholamine hypothesis, which holds that an increase in epinephrine and nor epinephrine causes mania and a decrease in epinephrine and nor epinephrine causes depression. Drugs used to treat depression and drugs of abuse (e.g., cocaine) that increase levels of monoamines, including serotonin, nor epinephrine, or dopamine, can all potentially trigger mania, implicating all of these neurotransmitters in its etiology. Other agents that exacerbate mania include L-dopa, which implicates dopamine and serotonin uptake inhibitors, which in turn implicate serotonin. Evidence is mounting of the contribution of glutamate to both bipolar disorder and major depression. A postmortem study of the frontal lobes of individuals with these disorders revealed that the glutamate levels were increased [26].

Recent life events and bipolar disorder (Environmental factors)

Overall, studies of life events have found that bipolar individuals experience increased stressful events prior to first onset and recurrences of mood episodes. Moreover,
most studies have found that negative life events precede the manic/hypomaniac as well as the depressive episodes of bipolar individuals. Numerous studies indicate that from 20% to 66% of bipolar patients experienced at least one stressful event rated as independent of their behavior in the 1–3-month period prior to onset of a mood episode. In addition, psychosocial stressors are the major causes of relapse in bipolar patients [27, 28].

Epidemiology

Global prevalence of Bipolar disorder

Bipolar disorder was equated with classic manic depressive (i.e., bipolar I) disorder, and the lifetime prevalence of bipolar disorder was found to be approximately 1%. However, if the diagnosis of bipolar II disorder (major depression with hypomania, but not with mania) is much higher lifetime prevalence rates of the broadly defined bipolar disorders, up to at least 5%, were reported. The recent results of the National Comorbidity Survey Replication has shown that the lifetime prevalence estimates were Studies also indicate differences in lifetime prevalence estimates for bipolar disorder type I (BPI) (1.0%), bipolar disorder type II (BPII) (1.1%), and sub threshold bipolar disorders (2.44.7%) [29].

Socio demographic factors

The gender ratio in bipolar disorder (all subtypes combined) is approximately 1:1. However, among bipolar II patients and in special subpopulations (mixed/dysphoric mania, mixed depressive episode, winter depression, bipolar depression with atypical clinical features, and rapid cycling bipolar disorder), women are overrepresented. Looking at the depression–mania continuum as a whole spectrum, there is a clear trend: The higher the depressive component, the higher the proportion of women. Consequently, in the rare cases of unipolar mania (manic episode without any major or minor depression), men are markedly overrepresented. The gender differences in lifetime prevalence rates are more marked than in 1-year and current prevalence rates, which may be attributable—at least in part—to the stronger male tendency to forget previous episodes and deny emotionally negative events [30].

Diagnosing of bipolar disorders (Current Diagnostic Criteria- DSM-5)

Seven bipolar disorder categories are included in DSMV: bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder [1].

Bipolar I disorder

The bipolar I disorder criteria represent the modern understanding of the classic manic depressive disorder or affective psychosis described in the nineteenth century, differing from that classic description only to the extent that neither psychosis nor the lifetime experience of a major depressive episode is a requirement. However, the vast majority of individuals whose symptoms meet the criteria for a fully syndromal manic episode also experience major depressive episodes during the course of their lives (table 1).

Bipolar II disorder

Bipolar II disorder, requiring the lifetime experience of at least one episode of major depression and at least one hypomaniac episode, is no longer thought to be a “milder” condition than bipolar I disorder, largely because of the amount of time individuals with this condition spend in depression and because the instability of mood experienced by individuals with bipolar II disorder is typically accompanied by serious impairment in work and social functioning (table 2).

Cyclothymic disorder

The diagnosis of cyclothymic disorder is given to adults who experience at least 2 years (for children, a full year) of both hypomaniac and depressive periods without ever fulfilling the criteria for an episode of mania, hypomania, or major depression (table 3).

Management of bipolar disorders

Although mood stabilizers are the mainstay of the treatment for bipolar disorders, research has found that psychosocial interventions, including psychotherapy, can augment the clinical improvement. Just as pharmacological agents are used to treat presumed chemical imbalances, no pharmacological strategies must treat no biological issues. The complexity of bipolar disorders usually renders any single therapeutic approach inadequate to deal with the multifaceted disorder. Psychosocial modalities should be integrated into the drug treatment regimen and should support it. Patients with bipolar disorders benefit more from the combined use of mood stabilizers and psychosocial treatment than from either treatment used alone [36].

Pharmacological managements

A number of medications are used to treat bipolar disorder [31, 39] including:

- Mood stabilizers
- Anti-psychotics
- Anti-depressants
- Anti-anxiety medications

Most people with bipolar I or bipolar II will need mood stabilizers to control their manic or Hypomaniac episodes. Commonly used mood stabilizers include:

- Tegetrol (carbamazepine)
- Depakote (divalproex sodium., valproic acid)
- Lamictal (lamotrigine)
- Lithobid (lithium)

Antipsychotic drugs may also be used to control episodes of depression or mania, especially when delusions or hallucinations...
are occurring. Examples of drugs in this class include:

- Abilify (aripiprazole)
- Saphris (asenapine)
- Symbyax (olanzapine and fluoxetine)

### Table 1: DSM-V Diagnostic Criteria for bipolar I disorder

<table>
<thead>
<tr>
<th>DSM-V Diagnostic Criteria for bipolar I disorder</th>
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<tbody>
<tr>
<td>For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.</td>
</tr>
</tbody>
</table>

#### Manic Episode

A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 Week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

#### Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2 week period and represent a change from previous functioning; at least one of the symptoms is either (1) Depressed mood or (2) Loss of interest or pleasure.

**Note:** Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful).
   - Note: In children and adolescents, can be irritable mood.

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   - Note: In children, consider failure to make expected weight gain.

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
   - Note: Do not include symptoms that are clearly attributable to another medical condition.

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self reproach or guilt about being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

**B.** The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**C.** The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

**Note:** During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1. Inflated self esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non goal directed activity).
7. Excessive involvement in activities that have a high potential for painful consequence (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

**D.** The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

### Bipolar I Disorder

#### A.

Criteria have been met for at least one manic episode (Criteria AD under “Manic Episode” above).

#### B.

The occurrence of the manic and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizoaffective disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
Table 2: DSM-V Diagnostic Criteria for bipolar II Disorder

<table>
<thead>
<tr>
<th>DSM-V Diagnostic Criteria for bipolar II Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>For a diagnosis of bipolar II disorder, it is necessary to meet the following criteria for a current or past hypomanic episode and the following criteria for a current or past major depressive episode:</td>
</tr>
</tbody>
</table>

**Hypomanic Episode**

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable), represent a noticeable change from usual behavior, and have been present to a significant degree:

1. Inflated self esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment).

**Note:** A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

**Bipolar II Disorder**

A. Criteria have been met for at least one hypomanic episode (Criteria AF under “Hypomanic Episode” above) and at least one major depressive episode (Criteria AC under “Major Depressive Episode above”).

B. There has never been a manic episode.

C. The occurrence of the hypomanic episode(s) and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

D. The symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Table 3: DSM-V Diagnostic Criteria for Cyclothymic Disorder

<table>
<thead>
<tr>
<th>DSM-V Diagnostic Criteria for Cyclothymic Disorder</th>
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</thead>
<tbody>
<tr>
<td>For at least 2 years (at least 1 year in children and adolescents) there have been numerous periods with hypomanic symptoms that do not meet criteria for a hypomanic episode and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode.</td>
</tr>
</tbody>
</table>

A. During the above 2year period (1 year in children and adolescents), the hypomania and depressive periods have been present for at least half the time and the individual has not been without the symptoms for more than 2 months at a time.

B. Criteria for a major depressive, manic, or hypomanic episode have never been met.

C. The symptoms in Criterion A are not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

D. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism) course.

Table 4: Most commonly used mood stabilizers and indications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications or preferred to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Euphoric, pure(classic )mania, no psychosis, no rapid Cyclic previous good personal or family response and sequence of mania-depression-euthymia.</td>
</tr>
<tr>
<td>Valproate</td>
<td>Irritable mania, mixed episode, rapid cycling, secondary mania, comorbid substance use, severe with psychosis</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>History of trigeminal neuralgia, comorbid post traumatic stress disorders, comorbid substance issues, Severe mania( with psychosis), comorbid anxiety and panic attack, comorbid migraine headache, Irritable mania</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>FDA approved for acute and maintenance treatment for mania.</td>
</tr>
</tbody>
</table>
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- Latuda (lurasidone)
- Zyprexa (olanzapine)
- Seroquel (quetiapine)
- Risperdal (risperidone)
- Geodon (ziprasidone)

An antidepressant may also be used to manage depressive episodes, in conjunction with a mood stabilizer or an antipsychotic.

Finally, Benzodiazepines Diazepam, Lorazepam, Clonazepam or another type of anti anxiety medication may be used.

Psychosocial interventions

Psycho education and more formal psychotherapy can improve outcome when used in conjunction with maintenance pharmacotherapy. Adjunctive psychosocial therapies should be considered early in the course of illness to improve medication adherence, identify prodromes of relapse, decrease residual symptoms (particularly depressive) and suicidal behavior, and help move patients towards a comprehensive functional recovery [40–46]. For bipolar disorders Psychological and social (psychosocial) interventions are important in addition to continuing on medication. These may include:

Psycho education: Psycho educational interventions include any discrete programme involving interaction between an information provider and service users or their careers which has the primary aims of offering information about the condition and the provision of support and management strategies. Complex psycho education was defined as any group programme involving an explicitly described educational interaction between the information provider and the patient/carer as the prime focus of the intervention [47, 48]. Patients/carers should be provided with information, support and different management strategies, including: illness awareness, treatment compliance, early detection of prodromal symptoms and relapse, lifestyle regularity.

Cognitive behavioral therapy (CBT): A structured and collaborative therapeutic approach, CBT is a discrete psychological intervention which aims to make explicit connections between thinking, emotions, physiology and behavior with respect to current or past problems, primarily through behavioral experiments and guided discovery. CBT seeks to achieve systemic change through the reevaluation of perceptions, beliefs or reasoning thought to cause and maintain psychological problems. The aim is to help the individual normalize and make sense of their psychotic experiences, and to reduce the associated distress and impact on functioning. Targeted outcomes include symptom reduction, relapse reduction, enhancement of social functioning, development of insight, amelioration of distress, and the promotion of recovery [49, 50].

Family intervention: Family intervention is a discrete psychological intervention with a specific supportive, educational or treatment function which involves problem solving/crisis management and/or intervention with the identified service user. Family intervention for individuals diagnosed with bipolar disorder has developed out of the consistent finding that the emotional environment within a family was an effective predictor of relapse. In this context, ‘family’ includes people who have a significant emotional connection to the individual, such as parents, siblings and partners. Different models of family intervention aim to help families cope with their relative’s problems more effectively, provide support and education for the family, reduce levels of distress, improve the ways in which the family communicates and negotiates problems, and try to prevent relapse by the service user [51]. Family sessions with a specific supportive or treatment function based on systemic, cognitive behavioral or psychoanalytic principles, which must contain at least one of the following psycho educational intervention, problem solving/crisis management work and intervention with the identified patient.

Interpersonal and social rhythm therapy (IPSRT): Interpersonal and social rhythm therapy (IPSRT) was defined as discrete, time limited, structured psychological intervention derived from an interpersonal model of affective disorders [52, 53]. It focuses on:

- Working collaboratively with the therapist to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current symptoms, feelings states and/or problems
- Seeking to reduce symptoms by learning to cope with or resolve these interpersonal problem areas

Seeking to improve the regularity of daily life in order to minimize relapse.

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