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Review

ASSESSING THE TRAJECTORY OF BIPOLAR DISORDER EFFECTIVELY IN ORDER TO TREAT EFFECTIVELY

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SUMMARY

Accurate diagnosis of mood disorders, particularly depression and bipolar disorder, is essential for effective treatment planning and patient management. This article emphasizes the need for systematic symptom assessment and longitudinal analysis in facilitating the precise diagnosis and planning appropriate treatment interventions. By meticulously evaluating the symptomatology and delineating the longitudinal trajectory of the illness, clinicians can distinguish between unipolar depression and bipolar disorder, and therefore optimise patient outcomes.

The article describes the inherent complexities in diagnosing mood disorders. It describes the overlapping symptomatology and diagnostic challenges. Through a comprehensive review of literature and clinical insights, it argues for a structured approach to symptom assessment, focusing on both the current presentation and also retrospective evaluation of illness progression.

By elucidating the longitudinal trajectory of the illness, including the presence of episodes of high mood suggestive of bipolar disorder, clinicians can differentiate between mood disorders accurately.

The article discusses the implications of accurate diagnosis on treatment planning and patient prognosis. A precise diagnosis enables clinicians to plan treatment strategies to the specific needs of the individual, including pharmacotherapy, psychotherapy, or both. By addressing the underlying mechanisms and trajectory of the illness, clinicians can implement targeted interventions which reduce the risk of misdiagnosis and which optimize therapeutic outcomes.

Key words: *unipolar depression - bipolar spectrum - bipolar disorder – diagnosis - trajectory of illness - symptomatology*

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INRODUCTION

The risk of Suicide is high in patients with bipolar disorder, especially when in the depressive phase, in mixed states and in Rapid cycling patients (Agius 2023). Therefore, while identifying unipolar depression as a cause of suicide, it is important to also identify bipolar illness-both Bipolar I and Bipolar II as important causes of suicide (Agius 2023). This is especially so in the case of Bipolar II illness where the dominant polarity of the illness is the depressive phase, so that the illness might easily be understood to be unipolar depression. Often, however, bipolar disorder is often under-diagnosed and is often misdiagnosed as unipolar depression, either because the diagnosis is missed or because minor episodes of hypomania are considered by the clinician as being insufficient to prove the diagnosis of bipolar disorder (Agius 2023).

The above realities have, in the past, led one of us, Dr Mark Agius, to eventually develop an inventory of questions which he began to use in his daily practice with all his patients who presented with mood disorders. This inventory he called the Cambridge-Perugia Inventory.

UNDERDIAGNOSIS OF BIPOLAR DISORDER

It was recognised that Bipolar Affective Disorder is frequently under-diagnosed and misdiagnosed, particularly as unipolar depression (Bongards 2013). This has serious implications on treatment and outcome of the condition (Bongards 2013). We therefore reassessed the patients in the community team to examine whether it was possible to increase the sensitivity of diagnosis of bipolar affective disorder; to identify more cases and to identify them earlier, in order to be able to offer adequate treatment as early as possible.

Standards need therefore to be decided for the diagnosis of bipolar disorder based on the DSM criteria for the diagnosis of Bipolar I and Bipolar II illness (Bongards 2013). It was shown by Bongards et al. that it is possible to increase the sensitivity of bipolar affective disorder diagnosis and that this results in an increased number of diagnoses of Bipolar disorder, and a decreased number of diagnoses of unipolar depression (Bongards 2013). It was hoped that better identification, and therefore treatment, of bipolar affective disorder is likely to lead to better social and professional functioning of affected individuals (Bongards 2013).

THE CONCEPT OF THE BIPOLAR SPECTRUM

In the meantime, in the USA and in Europe, the Concept of the Bipolar Spectrum was being developed (Jain 2023). The concept that Bipolar Disorder was a spectrum of illness was first proposed in 1977 when a prospective study showed that people with cyclothymic mood disorder go on to develop unipolar depression (UPD) or Bipolar Disorder (Akiskal 1977). A further

study showed that 12% of patients in the study went on to develop Bipolar Disorder type II; having had a Unipolar Depression diagnosis 15 years earlier (Angst 2002).

Sub-threshold bipolar (or Cyclothymic) patients have also been seen to progress towards Bipolar Disorder, one study indicating a progression of 7% of such patients with Bipolar type II advancing to BPD type I, over 15years (Goldberg 2001).

Hypomania often goes undiagnosed, due to the reduced impact on the patient's life. Patients tend to present in a euthymic condition or when experiencing depressive symptoms. Often a history of hypomania may be missed, or BPD type II (mixed state) may be misdiagnosed as an agitated depression (Akiskal 2005, 2010). This poses a very real risk to patients; undiagnosed patients with BPD may progress (or 'switch') to manic/hypomanic or mixed states as a result of treatment with potent antidepressants, such as, for example, venlafaxine. This may dramatically increases suicide risk in these patients (Agius 2013).

Thus, the Bipolar Spectrum can be described as a group of conditions (Tavormina 2007, Akiskal 1999), including Bipolar I (highs of Mania and lows of depression), Bipolar II (highs of Hypomania and lows, often very severe, of Depression), Bipolar III (Mania induced iatrogenically by antidepressants, given to depressed patients), Mixed Affective States, Cyclothymia (Patients in which the highs and lows are subsyndromal), as well as unipolar depression and specific temperaments.

This concept enabled patients with affective disorders to be classified into groups, and within those groups it became possible to identify the most appropriate and safest pharmacological treatment for those groups.

DEVELOPMENT TOWARDS AN INVENTORY OF SYMPTOMS TO ELICIT

At this point, the main change in the taking of the history of the patient consisted in specifically whether the patient had experienced episodes of high mood from time to time and assessing from the history the entity of these high mood episodes as well as the duration, which was expected to be at least four days of high mood.

However, it became clear that, while identifying that patients could have minor episodes of high mood was important, it became equally important to be able, through eliciting the past history of the patient, it was important to be able to elicit the trajectory of how the condition developed (Agius 2014).

This became important because we found that the reason bipolar disorder is often underdiagnosed in community mental health teams is often because of failure to assess the longitudinal trajectory of patients suffering from recurrent depression (Agius 2014).

We began to understand that, often, patients who might present, early in their lives, with episodes of unipolar depression, might in their late teens, or even afterwards, begin to suffer episodes of hypomania, so that their diagnosis changes from unipolar recurrent depressive disorder to bipolar II disorder, thus patients over time could 'move along the spectrum' (Rogers 2012, 2013). Thus, we were able to audit a sample of 146 representative patients and 112 bipolar patients from our team, examining the course of their illness and diagnosis (Rogers 2012). We were able to show that Bipolar disorder is under-diagnosed in the community and in secondary care (Rogers 2012). First manic or hypomanic symptoms usually follow first depressive symptoms by several years (μ=7.3, σ=7.9) (Rogers 2012). A diagnosis of bipolar also commonly follows manic or hypomanic symptoms by years (μ=7.6, σ=8.3) (Rogers 2012). Both psychiatrists and GPs under-diagnose bipolar disorder, but this study shows that it may be due to two factors: poor recognition by doctors and also conversion to bipolar disorder from major depressive disorder (Rogers 2012).

Others have described similar Progression along the bipolar spectrum, thus Alloy has described 57 individuals with an initial cyclothymia or bipolar disorder not otherwise specified (BiNOS) diagnoses, of which 42.1% progressed to a bipolar II diagnosis and 10.5% progressed to a bipolar I diagnosis, while of 144 individuals with initial bipolar II diagnoses, 17.4% progressed to a bipolar I diagnosis (Alloy 2012).

It needs to be said that our interest in the relationship between the Bipolar Spectrum and the trajectory of Bipolar Illness was lead by the work of Akiskal (2005, 1995, 1977) and of Angst (2010, 2002, 1995, 2000, 2002, 2013).

THE CAMBRIDGE-PERUGIA INVENTORY

Thus, we have demonstrated that when the systematic assessment of the trajectory of bipolar disorder is carried out in a community mental health team (Rogers 2012), the number of bipolar patients among the patients assessed by the team increases, but there remain a number of patients who do have unipolar depression; in other words, the assessment of the trajectory of mood disorder patients enables the discrimination between bipolar and unipolar depression (Bongards 2013).

We therefore have been able to develop a series of twenty-nine questions to be used in the history taking of all patients with potential affective states in order to demonstrate the developmental trajectory of the illness and assist the diagnosis. These also provide auditable points by which to assess the quality of our assessments. These twenty-nine questions we have called the Cambridge-Perugia Inventory for assessment of Bipolar Disorder (Agius 2015, 2013).

As well as establishing the earliest depressive or manic episode and the trajectory of the illness, the questions attempt to establish the presence of Mixed Affective states or Rapid cycling, and also the presence of co-morbidities including Migraine, Anxiety, Panic Disorder, Obsessive Compulsive Disorder, and Borderline Personality Disorder (Agius 2013, 2015).

We would suggest that, before a conclusion is reached as to the diagnosis of a patient with an affective disorder is made, all of these points should have been addressed in the history notes (Agius 2013, 2015).

It should be recorded that, before applying the inventory, we always carry out a PHQ-9 (Kroenke 2001, Sahni 2018) self-rating scale in order to identify whether the patient is suffering from symptoms of depression at present.

We describe the PHQ-9 and GAD 7 symptoms below in order to show how the symptoms of depression and anxiety had developed since the 1990s; in particular disturbances of sleep and appetite were acknowledged as being too little or too much, thus accepting atypical depression, which is linked with bipolar disorder.

When assessing depressive symptoms, it must be remembered that by definition, patients must have suffered the symptoms over two weeks in order that the depression be seen as a depressive episode. Thus the PHQ9 asks 'Over the last 2 weeks, how often have you been bothered by any of the following problems?' The symptoms asked about then are as follows:

- Little interest or pleasure in doing things;
- Feeling down, depressed, or hopeless;
- Trouble falling or staying asleep, or sleeping too much;
- Feeling tired or having little energy;
- Poor appetite or overeating;
- Feeling bad about yourself - or that you are a failure or have let yourself or your family down;
- Trouble concentrating on things, such as reading the newspaper or watching television;
- Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual;
- Thoughts that you would be better off dead or of hurting yourself in some way.

These symptoms are rated on a 0 to 3 scale. They are appropriate to identify whether the patient is presently suffering from a depressive episode including atypical depression, which may be linked with bipolar disorder.

We also carry out a GAD 7 (Ruiz 2011, Agius 2013) self-rating scale in order to assess symptoms of anxiety which the patient is presently is suffering from, since anxiety is a very frequent co-morbid condition with bipolar disorder.

Similarly to the PHQ9, the GAD7 asks 'Over the last 2 weeks, how often have you been bothered by any of the following problems?' The symptoms asked about then are as follows:

- Feeling nervous, anxious or on edge;
- Not being able to stop or control worrying;
- Worrying too much about different things;
- Trouble Relaxing;
- Being so restless it is hard to sit still;
- Becoming easily annoyed or irritable;
- Feeling afraid as if something awful might happen.

These symptoms are rated on a 0 to 3 scale. They are appropriate to identify whether the patient is presently suffering from anxiety, which is frequently linked with bipolar disorder.

We also ask the patient, as a preliminary to the main assessment, to fill out the Mood Disorder Questionnaire, even though our Inventory is more detailed assessment of Bipolar Disorder.

The Cambridge-Perugia Inventory is NOT designed to identify depression, and there are insufficient questions in it to assess eating, sleeping and risk of suicide in patients with depression, and these are covered by the PHQ9. Naturally, if suicidal thoughts are mentioned, a full assessment of risk of suicide must be carried out. The Cambridge-Perugia Inventory is designed to be used as a supplement after these preliminary questions listed in these three questionnaires have been addressed in order to identify bipolar disorder once these preliminary issues are addressed.

We append the basic rationale for each of the questions in this version of the Inventory.

THE CAMBRIDGE-PERUGIA INVENTORY FOR ASSESSMENT OF BIPOLAR DISORDER

Questions related to Diagnosis

Q.1 You are aware of how it feels when you are depressed. How old were you when you had your first depressive episode (treated or untreated)?

From experience, we often find patients report a primary depressive episode during their early to mid-teenage years. This is supported by research which has shown:

• BPD is known to be diagnosed on average 6 years prior to UPD (unipolar depression) (Weissman 1996).

• BPD diagnoses may take ~10years after onset BPD symptomatology (Hirschfeld 2003).

Q.2 After that, did you proceed to suffer recurrent depressive episodes?

Patients with recurrent depressive disorder may develop BPD Type II over time (Judd 2003, Goldberg 2001).

Q.3 Looking back, when was your first hypomanic episode?

UPD has been proven occasionally to develop over time into BPD type II with the first episode of hypomania (Goldberg 2001).

Q.4 How long do the hypomanic episodes last?

The DSM Criteria (American Psychiatric Association 2000) suggest 4 days is diagnostic; and 2 days would be sub-syndromal. However, on investigation, often patients say that they are aware of a day when there is an upward shift in their mood, prior to full mania/hypomania, and another day where their mood is returning to their prior state.

Q.5 When you are high, hypomanic, do you find:

- You need less sleep?
- Experience racing thoughts?
- Talk quickly and hop from one though to another?
- Spend excessively perhaps accruing debt?
- Find you mix with lots of new people, or are more flirtatious than usual?
- Take more risks than usual?

Q.6 When you are depressed do you find you comfort eat?

This is common, as atypical depression is linked with BPD (Mitchell 2008).

Q.7 When you are depressed do you find you sleep a lot during the day?

Also common as atypical depression is linked with BPD (Ruiz 2011).

Q.8 When you are depressed can you concentrate?

Patients often experience difficulties with concentration and attention span when depressed (American Psychiatric Association 2000).

Q.9 When you are depressed, can you enjoy things?

Patients often experience anhedonia when depressed (American Psychiatric Association 2000).

Q.10 How long do your periods of depression last?

Often weeks or months; in BPD low moods last longer than high moods However, evidence suggests episodes of unipolar depression last longer (Mitchell 2008).

Q.11 When you are depressed, do you get suicidal thoughts?

In practice, patients are often forthcoming about their thoughts; suicidal ideation is a common aspect of BPD (American Psychiatric Association 2000).

Q.12 When you are depressed, do you ever get severe retardation (being slowed down), paranoia, or have hallucinations

Psychotic depression, including catatonia may be a concomitant of bipolar disorder (American Psychiatric Association 2000).

Questions related to Mixed States and Rapid Cycling

Q.13 Do you often get irritable or angry?

This is a common feature; often such irritability is linked with a mixed state (Agius 2010).

Q.14 Does it sometimes happen that your mood changes rapidly from high to low within a day?

These mixed affective episodes are one subtype of mixed affective state (Agius 2010).

Q.15 Do you sometimes find that you are happy and crying at the same time?

Dysphoric mania is a form of mixed affective state (Balázs 2006).

Q.16 Do you sometimes find that you are depressed and very irritable at the same time?

Agitated Depression is a form of mixed affective state (Balázs 2006).

Q.17 When you are in a mixed state, as we have just described, do you often find that you have marked suicidal ideation?

Patients are more likely to commit suicide when in a mixed state, and thus experience greater suicidal ideation (Balázs 2006).

Q.18 In one year, do you get 4 or more changes of mood; at least 2 highs and 2 lows?

Often patients find this to be the case, and it implies rapid cycling. Rapid cycling patients are moredifficult to treat and have increased suicidality (Ghaemi 2000).

Questions related to Co-Morbidities

Q.19 Do you suffer from migraine?

There are genetic links between BPD and migraine, so this may increase likelihood that BPD is the cause (Hirschfeld 2003).

Q.20 Do you suffer with anxiety or panic disorder?

Comorbid anxiety disorders are common in bipolar disorder (Ruiz 2011)

Q.21 Do you suffer from OCD symptoms?

OCD is often linked with BPD and such patients are particularly difficult to treat with medication (Merikangas 2007).

Q.22 You may have been told that you have 'borderline' symptoms but do you also have episodes of HIGH mood, lasting more than 4 days?

Borderline personality disorder patients have mood 'swings' from low to normal - not high (American Psychiatric Association 2000). Therefore if they have high moods lasting more than 4 days they are comorbid borderline/bipolar.

A Few other Questions related to the Possibility of Borderline Personality Disorder Co-Morbidity

- Do you tend to be Impulsive?
- Do you chronically feel 'Empty' Inside?
- Are your relationships very unstable?
- Do you fear being Abandoned by significant Others?
- Do you chronically feel bored?
- Do you tend to be very emotional?
- Do you have concerns about your identity? (Zimmerman 2013, Agius 2014, Crawford 2014).

Q.23 Do you suffer from irritable bowel syndrome (IBS) or colitis?

This is another common co-morbidity. There may be immunological links, in association with levels of inflammation, between these conditions and BPD (Merikangas 2007)

Q.24 Do you suffer muscular tension?

This is another common co-morbidity (American Psychiatric Association 2000).

Q.25 Do you have a family history of BPD, suicide, or psychosis?

Patients often report that a family member spent periods of time as an inpatient, or that their relative suffered with depression. However, they are often unaware of the concept of mania.

Q.26 Do you drink alcohol to excess?

Many persons who suffer from depression use alcohol. Alcohol is a depressant. On the other hand there may be other causes of the depression. Other substances such as cocaine cause euphoria and depression when withdrawn. Cannabis has many effects on mood, often complicating diagnosis (Khantzian 1985).

A few more questions to complete the picture

Q.27 Do you find episodes of high/low mood are particularly associated with different seasons?

BPD Type I is worst in summer, and BPD Type II is worst in winter (Shapira 2004).

Q.28 Do you think of yourself as creative?

Patients with BPD are often very creative individuals.

Q.29 Have antidepressants ever caused your mood to become high?

BPD often presents with mania/hypomania caused by antidepressants: BPD type III (iatrogenic) (Agius 2010).

IMPLEMENTING THE INVENTORY

By the end of my (Dr.Agius') career, this was how the inventory was being delivered to patients; *My consultations were now designed as teaching consultations, because for me there was the need to teach senior medical students to take a psychiatric history while a senior doctor guided them.*

The consultation was carried out with two students; one to write the notes, while the other led the consultation and the doctor guides him or her and gives explanations to the patient. Add to these the patient and the patient's family, and the whole group ends up sitting in a circle. This completely changes the dynamic of the consultation. Add to this that the patient has agreed before entering the room that they will work with the students, and to work in this way and the group became a teaching and learning group where everyone shares information and learns about the illness, and everyone tries to solve a common problem. Furthermore each consultation lasts an hour of allocated time. The PHQ9, GAD7 and Mood disorder questionnaire are filled out before the consultation starts and the Inventory is used within the group so that all the points are covered (Agius 2014).

WHY IS FULL ASSESSMENT AND DIAGNOSIS OF BIPOLAR DISORDER IMPORTANT?

One reason that full assessment and diagnosis of bipolar disorder is important is that misdiagnosis and late diagnosis of bipolar disorder is very common.

Misdiagnosis of bipolar disorder is common; it is a well established phenomenon in the literature. It has been shown that the first symptom of Bipolar Disorder in at least 50% of patients is depression (McElroy 1998, Agius 2013). Long-term follow-up studies (12.8 years) by Judd et al. (2003) found that patients with Bipolar Disorder were symptomatic, (that is, in a depressed, manic, hypomanic or in a mixed state) for approximately 47% of their lives, mostly with depressive symptoms (Agius 2013). Yet, misdiagnosis is, a very common problem (Agius 2013). The Depressive and Bipolar Support Alliance (DBSA) found that large-scale retrospective studies (Benazzi 2003) indicated that the most frequent misdiagnosis was unipolar depression, and also that more than >35% of misdiagnosed patients reported experiencing Bipolar Disorder symptoms for about 10 years prior to diagnosis of bipolar disorder (Hirschfeld 2003, Agius 2013). These findings are supported by Ghaemi et al. (2000) who showed that patients wait 9 years, on average, for a Bipolar Disorder diagnosis (Agius 2013). Hirschfield et al. (2003) have shown that the Mood Disorder Questionnaire (MDQ) overall positive screen rate, for Bipolar Disorder, was 3.7% across a population of 83,358 US citizens over 18years old (Agius 2013). Of those for whom the MDQ suggested Bipolar Disorder, only 19.8% had previously received a diagnosis from a physician, 31.2% had a unipolar depression diagnosis, and 49.0% had no Bipolar or unipolar diagnosis. Positive screens for bipolar disorder were highest amongst young adults from lower socioeconomic areas in this study (Agius 2013).

Altamura et al. (2010) reported, in a study of 320 patients, that patients with a longer DUI showed a higher frequency of suicide attempts ($Z = -2.11$, $P = 0.035$), a higher number of suicide attempters ($\chi^2 = 4.13$, $df = 1$, $P = 0.04$), and a longer duration of illness ($Z = -6.79$, $P < 0.0001$) when compared to patients with a shorter DUI. Moreover, patients with a longer DUI had a depressive first episode more frequently than patients with a shorter DUI ($\chi^2 = 11.28$, $df = 2$, $P = 0.004$) These results were seen to indicate a potential association between a longer DUI and a worse outcome in Bipolar disorder, particularly in terms of suicidality, and confirm the clinical relevance of early diagnosis and pharmacological intervention with mood stabilizers in BD.

Drancourt et al reported on 501 patients with Bipolar Disorder (Drancourt 2013), They found that the mean duration of untreated bipolar disorder was 9.6 years (SD 9.7; median 6) (Drancourt 2013). The median duration of untreated bipolar disorder was for 6 years (Drancourt 2013). The median duration of untreated bipolar disorder for those with a hypomanic onset (14.5 years) exceeded that for depressive onset (13 years) and manic onset (8 years) (Drancourt 2013). Early onset bipolar disorder cases had the longest duration of untreated bipolar disorder ($P < 0.0001$) (Drancourt 2013). Thus, earlier age at onset and depressive onset were associated with a longer duration of untreated bipolar disorder (Drancourt 2013). An extended duration of untreated bipolar disorder was associated with more mood episodes ($P < 0.0001$), more suicidal behaviour ($P = 0.0003$), including a greater risk of suicide attempts and a trend towards greater lifetime mood instability including rapid cycling and possible antidepressant-induced mania (Drancourt 2013). The authors commented that the duration of untreated bipolar disorder will only be significantly reduced by more aggressive case finding strategies (Drancourt 2013). They suggested that reliable diagnosis, especially for Bipolar-II patients, and initiation of appropriate treatments is currently delayed by insufficient awareness of the early, polymorphous presentations of Bipolar Disorder, by a lack of systematic screening as well as by failure to follow established guidelines (Drancourt 2013).

Pantovic et al. (2014) reported in a study of 127 patients with bipolar disorder that the average duration of untreated bipolar disorder was between 130 and 108 months. Patients with a longer duration of untreated bipolar disorder presented with higher number of mood episodes, a higher number of inpatient treatments, and required a significantly higher dose of lithium in the remission period.

Medeiros et al. (2016) studied One hundred and fifty-two Brazilian psychiatric outpatients. The mean age and mean duration of untreated bipolar disorder were, respectively, 38.9 and 10.4 years (Medeiros 2016). An extended duration of untreated bipolar disorder was associated with early onset of Bipolar Disorder ($p = 0.001$), depression as first mood episode ($p = 0.04$), and presence of Bipolar Disorder in a first-degree relative ($p = 0.012$) (Medeiros 2016). Additionally, a longer duration of untreated bipolar disorder was associated with poorer clinical outcomes, such as elevated rates of rapid cycling ($p = 0.004$) and anxiety disorders ($p = 0.016$), as well as lower levels of current full remission ($p = 0.021$) (Medeiros 2016).

Zhang et al. (2017) studied 555 patients with bipolar disorder in Chinese hospitals. Short duration of untreated bipolar disorder was two years or shorter while long duration of untreated bipolar disorder was over two years in duration (Zhang 2017). The mean duration of untreated bipolar disorder was 3.2 years; long duration of untreated bipolar disorder accounted for 31.0% of the sample (Zhang 2017). Long duration of untreated bipolar disorder was associated with longer duration of illness, diagnosis of Bipolar Disorder type II, and earlier misdiagnosis of BD for major depressive disorder or schizophrenia (Zhang 2017).

Ahmed et al. studied 216 Egyptian in-patients who had bipolar I disorder and presented in a manic state (Ahmed 2021). The patients were divided into 2 groups based on duration of untreated bipolar disorder: Group A, with a duration of untreated bipolar disorder of less than 4 months; and Group B, with a duration of untreated bipolar disorder of more than 4 months (Ahmed 2021). It was found that A longer duration of untreated bipolar disorder was associated with negative clinical outcomes including more frequent episodes, more symptom severity, longer hospital admission, a higher risk of suicide, more residual symptoms (Ahmed 2021). The patients with longer duration of untreated bipolar disorder also had a lower socioeconomic state (Ahmed 2021).

Scott et al. (2022) carried out a systematic review of the papers on duration of untreated bipolar disorder and found that while the peak age at onset of Bipolar Disorder is 15-25 years, diagnosis and guideline recommended interventions such as mood stabilizers are likely to be delayed until the age of 25-35 years except for a minority of individuals who have access to early intervention services (Scott 2022).

Di Salvo et al. (2023) reported, in a study of of 897 patients with Bipolar disorder that, of these, Six-hundred and sixty patients (75.5%) presented with a long Duration of untreated illness of over 2 years and and a mean Duration of untreated illness of 15.7 years (Di Salvo 2023). There was an association of long Duration of untreated illness with bipolar II disorder (p: 0.016), with a lower age at onset ($p < 0.001$), and a depressive predominant polarity (p: 0.018), as well as depressive polarity onset ($p < 0.001$) (Di Salvo 2023). These patients also had a longer duration of illness ($p < 0.001$), a tendency to increased lifetime suicide attempts (p: 0.045) and also current medical comorbidities (p: 0.019) (Di Salvo 2023). Therefore this study confirms the association between long Duration of

untreated illness and higher risk of suicide attempts in patients with Bipolar Disorder (Di Salvo 2023) as well as demonstrating the association between long Duration of untreated illness and higher rates of comorbid medical conditions (Di Salvo 2023).

There therefore seems to be a consensus in the literature that there is, at the present time, a marked delay in diagnosis of bipolar disorder, and that this has important effects in terms of an increased risk of suicide in patients, and poorer outcome in terms of increased number of relapses and hospitalisations, longer hospitalisation, increased symptom severity, increased rapid cycling, and increased residual symptoms.

There are some other effects of long duration of untreated bipolar disorder; Galimberti et al. (2020) has reported that prolonged duration of untreated illness is associated with more severe cognitive impairment during depression, particularly but not only in bipolar disorder. Fico et al. studied the correlation between response to mood stabiliser and duration of untreated bipolar disorder (Fico 2021). They observed that Patients with a longer duration of untreated bipolar disorder showed poorer response to lithium ($Z = -3.196$; $p < 0.001$), but not to valproate or lamotrigine (Fico 2021). They suggested that poor functioning in Bipolar disorder be the result of multiple affective relapses, rather than a direct effect of duration of untreated bipolar disorder (Fico 2021). They suggested that a timely diagnosis with subsequent effective prophylactic treatment, such as lithium, may prevent poor functional outcomes in real-world patients with BD (Fico2021). With regard to illicit drug use Kvitland et al. (2016) have shown that Long duration of untreated mania seems to increase the risk for later cannabis use (Kvitland 2016).

Full assessment and diagnosis of bipolar disorder is important because a correct diagnosis of the patient is important in order that the treatment can be appropriate. While antidepressants are an appropriate treatment for patients with unipolar depression, it is mood stabilisers which is the appropriate treatment for patients with bipolar disorder. Lithium in particular is a very appropriate treatment for Bipolar I patients, and is also known to be effective in preventing suicide.

Recently, the NICE guidelines for bipolar patients have been changed in the UK to approve the treatment of bipolar depression with antipsychotics such as Quetiapine, Olanzapine and an Olanzapine and Fluoxetine combination (NICE 2014). Patients with Bipolar II illness, who suffer long periods of depression, require these antipsychotic drugs, but, because their episodes of hypomania are rare and, when they occur seem to be a welcome break from depression, often lasting only a few days, they are easily considered to suffer from unipolar depression and treated inappropriately with antidepressants alone, leading to failure of the treatment. Other undiagnosed bipolar patients, treated with antidepressants alone, may switch to mania or hypomania. Hence it is of great importance that an appropriate diagnosis is made of patients with symptoms of depression in order that they are prescribed the right treatment. This should lead to a better opportunity of recovery, and a reduced risk of self harm or suicide. We should add, of course, that patients with depressed mood should also be offered appropriate psychological therapy.

CONCLUSION

This article underscores the imperative of systematic symptom assessment and longitudinal analysis in the accurate diagnosis of depression and bipolar disorder. Through a comprehensive understanding of symptomatology and illness trajectory, clinicians can establish a foundation for informed decision-making and personalised treatment planning. By differentiating between mood disorders accurately, clinicians can enhance patient care and improve long-term outcomes.

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