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FROM THE TEMPERAMENTS TO THE BIPOLAR MIXED STATES: ESSENTIAL STEPS FOR THE CLINICIANS ON UNDERSTANDING THE MIXITY

Giuseppe Tavormina

"Psychiatric Studies Center" (Cen.Stu.Psi.), Provaglio d'Iseo, Italy

SUMMARY

The notion of "mixity" of the dysphoric phases of the bipolarity includes the most insidious symptoms of the bipolar spectrum of mood disorders: the overlapping between depression-restlessness-irritability-grief-tension-anxiety can cause worsening of the mood disorders and in the most acute phases may cause increased risk of major behavioural disruption including murder and suicide.

The "mixity" is a dynamic notion describing the presence of overlapping symptoms of mixed states, in an increasing intensity level. The early utilization of the rating scale on mixed states, "GT-MSRS", which can demonstrate the level of "mixity" of the mood disorder, can prevent this.

Mixed states occur in an average of 40% of bipolar patients over a lifetime;when considering bipolarity the notion of the "mixity" becomes the conceptual reference point of the diagnostic process.

Key words: *mixed states - bipolar disorders - mixity*

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INTRODUCTION

In 1978 Akiskal began to revolutionize the clinician's approach to the depression and mood disorders (Akiskal 1978); he wrote: ≪The diagnostic usage of the concept of "neurotic depression" may no longer be clinically meaningful, since it lacks sufficient phenomenological characterization and refers to a heterogeneous group of disorders. … Depressive disorders probably represent the most common group of psychiatric maladies for which physicians are consulted. It is the impression of many clinicians that the incidence of these disorders is on the rise. … Thus, a large percentage of depressed individuals is nowadays being assigned to the category of "neurotic depression.". Yet, neither the defining clinical characteristics nor the delimitation of this type of depression from other affective disorders is clearly formulated.≫

CLINICAL CONSIDERATIONS

Currently the knowledge of bipolar spectrum disorders and mixed states is well known by research and clinical psychiatrists, although we still often find inadequate approaches to these pathologies (diagnostic and therapeutic errors) that definitely interfere with people's mental health.

The mood in a person who is euthymic is stable. In mood disorders, the mood "swings" between depression and euphoria/irritability and therefore there is the "unstable mood"; in consequence of this we can understand that the depressive phases of the mood are only "moments of an instable mood". A depressive episode is in fact only one phase of a broader "bipolar spectrum of mood", in which instability of the mood is the main component (Tavormina 2013).

This introduces the concept of bipolar spectrum of mood (Table 1) (Akiskal 1996; Akiskal & Pinto 1999), that I revisited to make it more usable and simply for the clinicians (Table 2) (Tavormina 2007, 2013); all subtypes of the instability of the mood are inserted in this scheme: as the spectrum of the light (having in two opposite sides the white and black colours, and between them all other colours), at the same time this spectrum of the mood presents in the opposite sides the acute mania and the so called "unipolar depression", and between them all other types of the instability of mood; only PTSD and "Maladjustment to stressful events" are out of this scheme.

What are the temperaments? They are continuous kinds of presentation of the character's mood-peculiarities; they are subthreshold (sub-clinic) forms of the Bipolar Spectrum (Tavormina 2009).

They are: the Depressive Temperament; the Hyperthymic Temperament; the Cyclothymic - irritable Temperament (in which there also is the "Softly- instable Temperament": a "soft" cyclothymic temperament).

The person with Depressive Temperament is characterized by the presence of gloomy, humorless, or incapacity for fun; he is given to worry, or pessimistic cognitions, introverted, passive, or lethargic; he is a habitually long sleeper (more then 9 hours of sleep) or suffering intermittent insomnia, preoccupied with inadequacy, failure, and negative events; skeptical, self-critical, overcritical, complaining and guilt-prone.

The person with Hyperthymic Temperament is characterized by the presence of mental overactivity and overtalkative, he is cheerful, over-optimistic, or exuberant, warm, people seeking, extroverted, overconfident, self-assured, boastful, or grandiose; he is a habitual short sleeper (less then 6 hours of sleep), including weekends, full of plans and improvident activities, over-involved, uninhibited, stimulus seeking, or promiscuous.

Table 1. Akiskal's schema of bipolar spectrum

Bipolar ½ :schizobipolar disorder

Bipolar I : core manic-depressive illness

Bipolar I½ : depression with protracted hypomania

Bipolar II : depression with discrete spontaneous hypomanic episodes
(Bipolar II, "sunny" bipolars - hypomanic periods (2-3 days) characterized by cheerfulness and jocularity, people-seeking, increased sexual drive and behavior, talkativeness and eloquence, confidence and optimism, disinhibition and carefree attitudes, reduced sleep need, eutonia and vitality, and over-involvement in new projects)

Bipolar II½ :depression superimposed on cyclothymic temperament
(*Bipolar II½: Unstable, "darker" BP II* : dysphoric, irritable hypomania superimposed upon an inter-episodic cyclothymic temperament ("roller-coaster" course often misinterpreted or misdiagnosed as borderline personality disorder). Often comorbid with panic disorder and social phobia, as well as, bulimia and borderline personality disorder)

Bipolar III :depression with induced hypomania (i.e., hypomania occurring solely in association with antidepressant or other somatic treatment)

Bipolar III½ : prominent mood swings occurring in the context of substance or alcohol use or abuse

Bipolar IV : depression superimposed on a hyperthymic temperament
(*Bipolar IV : VERY DANGEROUS condition* - Depression superimposed on a stable hyperthymic temperament: exuberant, articulate and jocular, overoptimistic and carefree, overconfident and boastful, high energy level, full of plans and activities,... with broad interests, over involved, uninhibited and risk-taking, and an habitual short sleeper. And suddenly slip into deep (often) treatment-resistent depression. This is an extremely DANGEROUS condition because hyperthymic individuals are intolerant of any degree of depression, and certainly poorly tolerate the affective dysfunction associated with a depressive mixed state. Many mysteries about suicide, and suicides that one reads about in the newspaper [ie, "an extremely successful and happy person, who had everything, put the gun in his mouth"] may well belong to this category).

Table 2. Tavormina's schema of bipolar spectrum (with the possible evolutionism described after the arrow)

Acute mania	
1 Bipolar I	(➔dysphoric mania)
2 Bipolar II	(➔rapid cycling bipolarity, mixed disphoria)
3 Cyclothymia	(➔rapid cycling bipolarity)
4 Irritable Cyclothymia	(rapid cycling bipolarity)
5 Mixed Dysphoria	(depressive mixed state)
6 Agitated Depression	(➔ depressive mixed state)
7 *Cyclothymic temperament*	(➔mixed dysphoria, depressive mixed state, rapid cycling bipolarity, irritable cyclothymia, bipolar I-II)
8 *Hyperthymic temperament*	(➔agitated depression, bipolar II)
9 *Depressive temperament*	(➔ brief recurrent depression, agitated depression)
10 Brief recurrent depression	(➔ dysthymia, major depressive episode)
UnipolarDepression	

The Cyclothymic - Irritable Temperament is instead characterized by a byphasic dysregulation of the mood characterised by slight endoreactive shifts from one phase to the other, each phase lasting for a few days at a time, with infrequent euthymia, and typical symptoms such as mental overactivity, insomnia or bad quality of sleep, somatizations, considerable tension, irritability and internal restlessness as well as frequent substance abuse.

The Softly - instable Temperament is a soft cyclothymic temperament, characterised by: vague and fluctuating uneasiness, mood instability but of low grade, anxious traits and trait-state overlap. When it develops to up-threshold forms of bipolar disorder, this presents a better prognosis then cyclothymic temperament development (Tavormina 2009).

To clarify how important it is for the clinician to early catch the typology of the the temperament present at the origin of mood disorder visible in current events, Rihmer and Akiskal wrote in the following basic sentence some years ago: ≪Premorbid affective temperament types have important role in the clinical evolution of minor and major mood episodes including the direction of the polarity and the symptom formation of acute mood episodes. … They also significantly affect the long term course and outcome, including suicidality and other forms of self-destructive behaviours, such as substance abuse and eating disorders≫ (Rihmer & Akiskal 2009).

CLINICAL EVALUATIONS AND THE MIXITY

To identify early the type of temperament of the patient will clarify as better the understanding of the evolution of the mood disorders the clinician is going to treat, and also the choice of the best treatment (Tavormina 2010).

The main symptoms of the mixed states are (two or more; Tavormina 2016):
- depressed mood together with irritability,
- antisocial behaviour,
- substance abuse (alcohol and / or drugs),
- disorders of appetite,
- a sense of despair and suicidal ideation,
- anhedonia and widespread apathy,
- reduced ability to concentrate and mental over-activity,
- hyper/hypo- sexual activity,
- insomnia (or fragmented sleep),
- comorbidity with anxiety disorders (PAD, GAD, OCD, soc ph.),
- gastrointestinal disorders, headaches, and various somatisation symptoms (colitis, gastritis, diffuse muscle tension).

The description of these symptoms leads us to evaluate the notion of the“mixity”. The mixity is a dynamic notion describing the presence of overlapping symptoms of mixed states, in an increasing intensity level (Tavormina 2019); this component is an essential part of the mixed states. This knowledge is fundamental for the clinician in making a correct diagnosis and therapy and its intensity is put in evidence by the rating scale GT-MSRS (Tavormina 2014).

The dysphoric component of mood (mixed states) is quite frequent among all the subtypes of the bipolar spectrum: mixed states include approximately 30% of all mood spectrum disorders (Tavormina 2010, 2013, Akiskal 2000, Perugi et al. 2014).However they are pathologies which are often underestimated or, worse, not diagnosed or treated inappropriately (Agius et al. 2007, Tavormina & Agius 2007, Tavormina 2018).

Clinicians find great difficulties in making a correct diagnosis of mixed states of the mood disorders: this is because the patients mainly focus their own symptoms on depressive uneasiness, inducing the clinicians to frequently prescribe antidepressants drugs alone or together with benzodiazepines: inadequate treatments inducing (or increasing) the dysphoria (Tavormina 2018).

The “mixity” of depressive phases (that are the most insidious symptoms of overlapped depression-restlessness-irritability) can cause increased risk of suicidality (Akiskal 2005). The intensity of these symptoms can be shown using the rating scale for mixed states “GT-MSRS”, an easy rating scale to administer to the patient structured in eleven items (and 7 sub-items), to demonstrate the level of the mixity (a score from 2 to 6: medium-light level; a score from 7 to 12: medium level; a score from 13 to 19: high level); (Tavormina 2014, 2015) (Table 3).

The presence of a new rating scale, mainly focused on mixed states symptoms, is crucial; thefirst two validating studies on “GT-MSRS” confirmed its great usefulness and practicality of use (Tavormina 2015, Tavormina et al. 2017).

None of other actual rating scales for mood disorders, despite being very useful (the “Bech-Rafaelsen Mania Scale”; the “Manic-State Rating Scale, MSRS”; the “Mood Disorder Questionnaire, MDQ”; the “Young Mania Rating Scale, YMRS”), are specific to all typologies of symptoms of the mixed state disorders, and so are too generic (as the MDQ) or too specific only for mania and bipolar I or II (all the others).

TREATMENT

A Hyperthymic Temperament can evolve into agitated depression or bipolar II; a Depressive Temperament can evolve into brief recurrent depression or agitated depression; a Cyclothymic - Irritable Temperament can instead evolve into mixed dysphoria, or depressive mixed state, or rapid cycling bipolarity, or irritable cyclothymia, or bipolar I-II.

A careful diagnosis of the patient's temperament and complete clinical history, as well as the full family history, facilitates the clinical's understanding of the diagnostic subtype of the bipolar spectrum; then the use of the evaluation scale GT-MSRS highlights which symptoms are most evident in the current clinical picture; consequently there will be the choice of the best drug therapy to be adopted (mainly: the utilization of mood-stabilisers); (Tavormina & Agius 2012, Tavormina 2016).

Very often, an inadequate treatment (to use long time benzodiazepine or antidepressants alone) causes an increase in instability and the development in the patient of dyphoric-mixed states (Tavormina 2018).

In consequence of this, my suggestions for the clinicians are to not use, or at least use rarely and for short periods, the antidepressants alone and/or in combination with oral benzodiazepine, or also long term benzodiazepine alone; both in order to avoid an increase in instability and the development in the patient of the dyphoric-mixed states.

One observation from the first validating study (Tavormina 2015): the four diagnoses of “Recurrent Depression” and “Major Depression” emerged in that study scored within the “medium level” of the rating scale GT-MSRS, showing how the symptoms of mixity are diffused within all mood disorders sub-types. Therefore, the prescription of mood stabilisers together with antidepressants, even in patients with a diagnosis of major depression or recurrent depression, is crucial for a good treatment.

Table 3. G.T. Mixed States Rating Scales or G.T. MSRT (Tavormina 2014)

Self-administered rating scale		
Has there ever been a period of time during last three months when you frequently were and/or presented/felt	Yes	No
1) Hyperactivity (euphoria) quickly alternating with periods of psychomotor retardation (apathy)? If Yes, for how many days/weeks?	Yes	No
2) Depressed mood togheter with irritability and/or internal tension? If Yes, for how many days/weeks?	Yes	No
3) Substance abuse (alcohol and/ or drugs)? If Yes, for how many days/weeks?	Yes	No
4) Disorders of appetite? If Yes, for how many days/weeks?	Yes	No
5) A sense of despair and suicidal ideation?	Yes	No
6) Anhedonia and widespread apathy?	Yes	No
7) Delusions and hallucinations?	Yes	No
8) Hyper or hypo-sexual activity? If Yes, for how many days/weeks?	Yes	No
9) Insomnia (or sleep fragmentation) or hypersomnia? If Yes, for how many days/weeks?	Yes	No
10) Reduced ability to concentrate and mental overactivity? If Yes, for how many days/weeks?	Yes	No
11) Gastrointestinal disorders (colitis, gastritis), headaches, and various somatic symptoms (muscolar tensiouness; tachicardia)? If Yes, for how many days/weeks, and what of those symptoms?	Yes	No
Additional point Could it be considered that, at the age of about 18-20 years (if you are more then 20 years old; if you are younger, please consider the answer as "during actual last years"), you were (choose only one of these three following answers): - a person of very lively character-hyperactive and extremely cheerful? or - a person who always tended to be tense and irritable? or - a person always tended to be taciturn, solitary and melancholy, and also with anxiety simptoms (panic, fobia between persons, claustrophobia)?		
Scores *- The "Additional Point" helps to focus about the Temperaments;* *- Mixed states diagnosis if at least two YES are present;* *- Double scores in the points 1-2-3-4-8-9-10-11 if at least 50% of the month is involved;* *- Medium-light level of mixed state: from 2 to 6 scores;* *- Medium level of mixed state: from 7 to 12 scores;* *- High level of mixed state: from 13 to 19 scores.* The positive result following to "G.T. MSRT" will conduct to do a generic diagnosis for mixed states sub-types of bipolar spectrum disorders (following Akiskal's scheme or Tavormina's scheme for bipolar disorders). The clinician will need of special care to do the correct sub-diagnosis of sub-group of mixed state.		

Already Akiskal and Benazzi perceived that there is a continuity between Major Depression and Bipolar Bisorder:≪ A normal-like distribution of the HIG scores between BP-II and MDD would support a continuity, because distinct disorders should not have an overlap of symptoms, and because intra-depression hypomanic symptoms in MDD should not be present if hypomania and MDD were independent categories≫ (Akiskal & Benazzi 2006).

And also in past century, in 1921, Emil Kraepelin described the mixed states: ≪Very often we meet temporarily with states which do not exactly correspond either to manic excitement or to depression, but represent a mixture of morbid symptoms of both forms of manic-depressive insanity≫ (Kraepelin 1921). He thus specified six types of mixed states, based on various combinations of manic and depressive mood, thought, and behaviour. These were: depressive or anxious mania, excited

depression, mania with poverty of thought, manic stupor, depression with flight of ideas, and inhibited mania.

The following sentence of Hagop Akiskal (from the conference on: "Melancholia: Beyond DSM, Beyond Neurotransmitters" - May 2-4th 2006, Copenhagen) can confirm what is written above: "Melancholia as defined today is more closely aligned with the depressive and/or mixed phase of bipolar disorder. Given the high suicidality of many of these patients, the practice of treating them with antidepressant monotherapy needs re-evaluation".

The consequences of the lack of recognition and treatment of bipolar mood disorder can be:

- reduction in the expectation and/or the quality of life (personal, family and work),
- increased loss of working days,
- increased use of health care resources, including for concurrent diseases,
- the mood can become chronic and the clinical picture can get worse,
- higher risk of suicide.

CONCLUSIONS

The motto of every clinician must be: "a correct treatment follows a correct diagnosis".

We can remark once again that, in consequence of all described, the "instability of mood", more than the "depression", is the main issue which the clinician needs to deal with in a patient with mood disorder; that the depressive episode is only one phase of a broader "bipolar spectrum of mood"; that the utilization of mood stabilisers is the first choice of drugs to prescribe to these patients (Tavormina 2016).

When considering the bipolarity, the notion of the mixity becomes the basic starting point on talking on mixed states and approaching its diagnostic process (Tavormina 2019).

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Correspondence:
Giuseppe Tavormina, MD
President of "Psychiatric Studies Center" (Cen.Stu.Psi.)
Piazza Portici, 11 – 25 050 Provaglio d'Iseo (BS), Italy
E-mail: dr.tavormina.g @libero.it