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Review

DEPRESSION, MOOD DISORDERS AND BIPOLAR SPECTRUM: ONE OR DIFFERENT DISEASES?

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SUMMARY

The concept of mixity is the essential cognitive cornerstone for quantifying and understanding unstable mood and restlessness, which are components of all mood disorders, diseases that always present fluctuations in mood, from the depressive component to the restless one and to the hypomanic and manic one. The GT-MSRS Mixed States Rating Scale becomes an essential means for early diagnosis.

Key words: *bipolar disorders - mixed states - GT-MSRS - mixed state rating scale*

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INTRODUCTION

Mood and anxiety disorders in their various diagnostic manifestations, including sub-threshold forms, involve approximately 20% of the entire population (Tavormina 2013, Akiskal 2000, 2005, Perugi et al. 2014); the component common to all these clinical forms is the presence of restlessness, agitation and internal tension, hyperactivity of thoughts and instability of mood (the oscillation of which, whether small or medium or high in intensity and frequency may be, is always present even when the mood appears "stable" in its depressive or manic phase). Also the comorbidity of mood disorders with the clinical manifestations of substance abuse, with eating disorders (with bulimic or anorexic symptoms) and, as already written, with the acute manifestations of anxiety (Gad, Pad, Ocd, Social Phobia) fall within the broad spectrum of unstable mood due to the presence of restlessness, hyperactivity of thoughts, internal tension and sleep disorders (Rihmer & Akiskal 2010, McElroy et al. 2005).

As I have had the opportunity to write several times in previous articles, even in the presence and persistence of depressive forms of mood we must speak of "unstable mood", in which restlessness is its main manifestation, with all its oscillatory characteristics typical of the mood tone. Depression therefore becomes only "a phase", not a pathology in itself, of a mood balance that presents instability, which for certain periods can remain (more or less long for weeks or months) along the depressive component, and then attenuate without going into a hyperthymic or hypomanic component, or even changing with an increase in the "restless" or "agitated" component, sometimes with underlying hyperthymia and/or irritability, with the almost constant presence of hyperactivity of thoughts and consequent difficulty in concentrating or maintain it, with sleep almost always disturbed in continuity and quality (non-restorative sleep), with a high frequency of presence of various somatic forms of tension-related origin (colitis, gastritis, headache), with frequent comorbidity with eating disorders, with anxiety diseases (Gad, Pad, OCD, Social Phobia) and with substance abuse (McElroy et al. 2005, Tavormina 2011, 2012, 2016, 2019).

Unstable mood, or mood in the "bipolar spectrum", therefore becomes the mood disorder that the clinician must treat (diagnose and treat correctly, prevent with adequate training and information campaigns), and not therefore "depression", whose term can be misleading as sometimes the depressive symptoms may not even be present in a clearly manifest and continuous way in the patient, or be masked due to the greater presence of prevalent tension-irritable, impulsive or in any case symptoms connected with restlessness (Akiskal et al. 2000, Akiskal & Benazzi 2006, Tavormina 2019).

DIAGNOSTIC SCHEMES

Analyzing Akiskal's scheme on the bipolar spectrum (Table 1), we see that he structures mood disorders into 7 diagnostic sub-types, as well as an eighth in which he inserts schizo-affective frameworks (Akiskal 1999).

Bipolar disorder type I is characterized by mood swings of notable intensity between severe mania and major depressive phases (Core manic-depressive illness).

Type II bipolar disorder is characterized by highly intense depressive phases alternating with spontaneous episodes of discrete hypomania: the so-called "sunny" bipolar people, with the presence of periods of hypomania lasting a few days characterized by cheerfulness and playfulness, intense search for sociality, increased sexual desire and behavior, talkativeness and logorrhea, confidence and optimism, disinhibition and carefree attitudes, reduced need for sleep, eutony and vitality and excessive involvement in new projects).

Between bipolar I and type II Akiskal inserts a disorder characterized by serious depression in a context of protracted hypomania, which he defines as "bipolar type I and ½".

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).

Following bipolar II, in Akiskal's scheme we find bipolar disorder type II and ½, characterized by pictures of depression superimposed on a cyclothymic temperament. It is a clearly unstable form, a "darker" bipolar type II with: dysphoric and irritable hypomania superimposed on an inter-episodic cyclothymic temperament ("rollercoaster" type trend, often interpreted or misdiagnosed as borderline personality disorder). Often comorbid with panic disorder and social phobia, as well as bulimia and borderline personality disorder.

Next we find bipolar disorder type III, characterized by a picture of depression with induced hypomania (for example, hypomania that occurs exclusively in association with antidepressants or other somatic treatments).

Next we find bipolar disorder type III and ½, characterized by significant mood swings that occur in the context of the use or abuse of substances or alcohol.

Akiskal's scheme concludes with bipolar disorder type IV, describing a picture of depression superimposed on a hyperthymic temperament. It is the bipolar spectrum picture that is often the most serious and at risk, presenting depression superimposed on a stable hyperthymic temperament: a person with these characteristics is exuberant, varied and playful, hyper-optimistic and carefree, very self-confident and boastful, with a high level of energy, full of plans and activities, with broad interests, hyper-involved, uninhibited and risk-taking, with reduced need for sleep. He may suddenly slip into a deep depression, often resistant to treatment. This is an extremely risky condition because hyperthymic individuals are intolerant to any degree of depression, and certainly poorly tolerate the affective dysfunction associated with a mixed depressive state. Many strange suicides, or the suicides that we often read about in the newspapers (described: "a very successful and happy person, who had everything, put the gun in his mouth...") could well belong to this category (Akiskal 1999).

If we analyze the entire scheme with Akiskal's diagnostic subtypes, except for bipolar I disorder (and schizoaffective), all the other subtypes describe mixed mood pictures (bipolar types I and ½, type II, type II and ½, type III, III and ½ and type IV), in which the underlying characteristic is the co-presence of episodes-phases of depression interconnected and/or interspersed with other episodes-phases of hyperthymia-hypomania-cyclothymia, sometimes with comorbidity with anxiety disorders, eating disorders, substance abuse and personality disorders themselves: all of this falls within the different ways in which the bipolar spectrum manifests itself (Angst et al. 2003, Akiskal et al. 1977, Akiskal 2004).

In my scheme on the bipolar spectrum (Table 2), taking inspiration from Akiskal's fundamental scheme, I intended to simplify the description of the diagnostic subtypes of bipolarity by seeing them from the perspective of the clinician who observes patients with mood disorders: I took inspiration from the concept literal "spectrum", which, like that of light, presents that of mood,

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		

placing acute mania at the two ends and the so-called "unipolar" depression at the other, within them all the variations of mood fluctuations and various forms of instability (Tavormina 2013). That is to say, we find: agitated depression, dysphoric depression, mixed dysphoria, recurrent depression, cyclothymia, attenuated bipolar II disorder, rapidly cycling bipolar disorder. All these manifestations describe a state of constant rapid or cyclical fluctuation and instability of mood, which can be defined in the concept of "mixed state" of bipolar disorder; similarly, all the clinical descriptions made by Akiskal also underlie the "mixed state" of bipolar disorder (Tavormina 2019, 2021, Angst et al. 2003, Akiskal et al. 1977, Akiskal 2005, Akiskal & Benazzi 2005).

THE "MIXITY"

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, Tavormina et al. 2017).

The presence of a new rating scale, mainly focused on mixed states symptoms, is crucial; the first validating studies on "GT-MSRS" confirmed its great usefulness and practicality of use (Tavormina 2015, Tavormina et al. 2017, Cervone et al. 2022).

Furthermore, the creation of an "online calculator" in three languages (English, Russian and Italian) focused on this GT-MSRS scale (Smirnova et al. 2023), has made the use of this scale further accessible to everyone evaluation (website link: www.icern.org/calc/msrs_en/).

It is essential for the clinician to quantify, so to speak, the intensity of the discomfort of those who suffer from these mixed states (i.e. the "mixity"), in order to better understand the level of the discomfort itself. This Mixed States Rating Scale (GT-MSRS) easily highlights the intensity of the "mixity" to quickly direct towards the prescription of one or more mood regulators (Tavormina 2014, Tavormina et al. 2017, Cervone et al. 2022, Smirnova et al. 2023, Agius et al. 2007).

Already Akiskal and Benazzi perceived that there is a continuity between Major Depression and Bipolar Bisorder: "A normal-like distribution of the 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).

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; he said: "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".

CLINICAL CONSIDERATIONS

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. This description of the mixed states of about a century ago is almost completely comparable to contemporary ones.

All the previous statements and considerations do nothing but highlight even more how unstable mood, restless mood and therefore mixed bipolar states are extremely frequent, more than previously thought (Akiskal et al. 2000, Perugi et al. 2014, Tavormina 2021). The following statement by Maria Luisa Figueira simply outlines a symptomatic picture useful to the clinical doctor: “Despite its heterogeneity, mixed states usually include: affective instability, mood lability and irritability. Patients may even experience psychotic features, thought disorders, disorganized behavior and agitation” (Figueira 2009).

The use of the GT-MSRS Mixed States Rating Scale, as we have said, serves to highlight the intensity of the "mixity" of the subject suffering from a mood disorder, i.e. the intensity of the thymic malaise ; it cannot be quantified in any way except only with the description of the presence of the various symptoms (listed at the various points of the GT-MSRS scale), however the GT-MSRS itself also numerically quantifies the intensity of the discomfort from 2 to 19. Each type of mood disorder always presents a certain amount of "mixity" (Tavormina et al. 2017, Cervone et al. 2022), such that it can be stated that all these disorders fall within a single clinical picture which we can define as "unstable mood"; the exceptions are "Post-traumatic stress disorder" (PTSD) and "Maladaptation to a protracted stressful event", which do not fall within the bipolar spectrum despite the fact that the intensity of their discomfort can be equally quantifiable with the GT-MSRS scale (Tavormina 2019, 2021).

The purpose of using the GT-MSRS Rating Scale is to direct the clinician to an early prescription of mood stabilizers once a mood disorder in the bipolar spectrum and a mixed state has been diagnosed (Agius et al. 2007, Tavormina & Agius 2007, Smirnova et al. 2023). The GT-MSRS scale does not give an exact diagnosis but highlights the intensity of the patient's thymic discomfort (the intensity of the "mixity"), guiding the doctor to think about mixed states, to ascertain the intensity of the discomfort and to evaluate the inclusion of one or more mood regulators in the therapy, once towards a complete diagnosis of the type of mixed picture to be treated.

The application of the GT-MSRS scale will highlight the score relating to the intensity of the patient's thymic discomfort ("mixity"), which is a consequence of the presence of the symptoms listed in the 11 points of the scale. Clinical practice has led to highlighting which mood regulators can be more effective and more tolerable both in the acute phase and in long-term maintenance treatment, and a considerable scientific literature supports all this (Vieta 2005, De Leon 2001, Yatham et al. 2002, Fountoulakis et al. 2012, Betzler 2017, Tavormina 2016), i.e. about the use of therapy or polytherapy with mood stabilizers. Regarding the use of polytherapy, what was stated by Vieta during the 5th IRBD Congress in Lyon (2005) is very important: “Polipharmacy is not necessarily good or bad: should be the result of reasonable balance between efficacy and tolerability, and should be evidence- and experience-based. Poly-pharmacy is often needed during acute episodes; some patients may keep well on monotherapy, but they are likely to be a minority”.

Table 3 highlights what emerged from the 2016 article (An approach to treat bipolar disorder mixed states, Tavormina 2016), regarding the use and effectiveness of mood stabilizers for the various diagnostic subtypes of mixed states. Furthermore, the high presence of somatic (Tavormina 2011) gastro-intestinal symptoms (colitis and gastritis), or also migraine, in patients with mixed states has found great clinical efficacy in the use of Gabapentin (Tavormina 2016, Perugi et al. 1999, Carta et al. 2003, Lee et al. 2005, Sator-Katzenschlager et al. 2005), or even the use of other mood stabilizers with Gaba-ergic function (for ex.: Valproate). The mood stabilizers effective in bipolar mixed states are summarized in table 4 (Tavormina 2016, Vieta 2005, De Leon 2001, Yatham et al. 2002, Fountoulakis et al. 2012, Betzler 2017). The concomitant use of antidepressants must always be done with great care, almost always with low doses, to be prescribed mainly in the presence of emotional lability,

Table 3. Mixed states treatment: steps of choice of the mood stabilisers (Tavormina 2016)

	1st step	2nd step	3rd step	4st step
Cyclothymic Temperament	Valproate (or Gabapentin)	Gabapentin + Valproate		
Agitated Depression	Gabapentin	Gabapentin + Valproate	Gabapentin + Valproate + Olanzapine	
Mixed Disphoria	Carbamazepine (or Valproate)	Carbamazepine (or Valproate) + Gabapentin	Carbamazepine + Valproate + Gabapentin	adding Olanzapine (or other atypical)
Rapid cycling bipolarity	Carbamazepine (or Valproate) + Gabapentin	Carbamazepine + Valproate + Gabapentin	adding Olanzapine (or other atypical)	
Irritable Cyclothymia	Carbamazepine (or Valproate) + Lithium	Carbamazepine + Valproate + Lithium	adding Olanzapine (or other atypical)	

Table 4 - Mood stabilisers to use (Tavormina 2016)

Anticonvulsants	
	Valproate
	Carbamazepine
	Gabapentin
	Oxcarbazepine
	Lamotrigine
	Topiramate
Lithium	
Atypical	
	Olanzapine
	Asenapine
	Loxapine
	Pipamperone

comorbidity with anxiety diseases (GAD, PAD, OCD, Soc phobia), persistent apathy; the concomitant use of BDZ is however not recommended for long periods (Tavormina 2019, Vieta 2005, Fountoulakis et al. 2012).

CONCLUDING REMARKS

Despite some international papers having written some reflections about the usefullness of the antidepressants on mixed states, the first validating studies of the rating scale on mixed states "G.T.MSRS" (Tavormina 2015, Tavormina et al. 2017, Cervone et al. 2022), can confirm that small dosages of antidepressants added to more than one mood stabiliser will allow the patients to achieve a good mood balance when there is the presence of emotive lability or sadness. Future studies are in project to give additional details and scientific evidence on these points.

The consequences of the lack of recognition and treatment of a mood disorder can lead to a higher risk of suicide, 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; and to the mood disorder becoming chronic and the clinical picture becoming worse.

When considering the mood disorders, the bipolarity and the notion of "mixity" become the basic starting point on talking on mixed states and approaching the diagnostic process; the mood disorders are part of the bipolar spectrum, the concept of mixity represents the essential cognitive cornerstone for quantifying and understanding unstable mood and restlessness. The knowledge of all the symptomatologic equipment is equally fundamental for the clinician for a correct diagnostic-therapeutic approach by clinicians managing an appropriate polytherapy with mood-stabilisers and low dosage of antidepressants.

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