Psychiatria Danubina, 2016; Vol. 28, Suppl. 1, pp 9-12 *Conference paper*

AN APPROACH TO TREAT BIPOLAR DISORDERS MIXED STATES

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SUMMARY

Very often clinicians meet great difficulties in making a correct diagnosis of mood disorders which they are assessing, above all when mixed states are present: this because the patients mainly focus on their own symptoms of depressive uneasiness; mixed symptoms can insidiously infiltrate into the mood and life of the patients causing a chronic and worsening clinical state. It is essential not to forget that the depression is only one phase of a broader bipolar mood disorder, and this has to be the illness to be treated by psychiatrists and, generally, by clinicians managing an appropriate polytherapy with mood-stabilisers and antidepressants.

Key words: *bipolar disordes - mixed states - treatment of mixed states*

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INTRODUCTION

Very often clinicians meet great difficulties in making a correct diagnosis of mood disorders which they are assessing, above all when mixed states are present: this because the patients mainly focus on their own symptoms of depressive uneasiness (inducing the clinicians to frequently prescribe antidepressant drugs alone or together with benzodiazepines), inducing them to prescribe these inadequate treatments and not take note of the real problem of increasing dysphoria consequent on these treatments.

The above reasons are why mixed symptoms can insidiously infiltrate into the mood and life of the patients causing a chronic and worsening clinical state.

It is essential to remark once again what has been described in previous papers: that 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; this relates to the important notion, that the depressive episode is only one phase of a broader "bipolar spectrum of mood" (Tavormina 2007, 2013, 2014).

When the mood quickly "swings" between depression and euphoria-irritability-hypomania or there is overlap between these conditions, we are dealing with a mixed state, even if the depressive symptoms seem to be prevalent: this then requires the clinician to carefully consider an appropriate pharmacotherapy.

The symptoms to note carefully on diagnosing mixed states are (at least two of these to be present at the same time Tavormina 2013, 2014):

- overlapping depressed mood and irritablity;
- presence of agitation and restlessness, irritability and aggression and impulsivity;
- reduced ability to concentrate and mental overactivity;
- high internal and muscular tension, gastritis, colitis, headaches, or other somatic symptoms (for ex.: increasing of eczema or psoriasis);
- comorbidity with anxiety disorders (PAD, GAD, Social phobia, OCD);
- insomnia (mainly fragmentary sleep and/or low quality of sleep);
- disorders of appetite;
- a sense of despair and suicidal ideation;
- hyper/hypo-sexual activity:
- substance abuse (alcohol and/or drugs);
- antisocial behaviour.

The "mixity" of depressive phases (that are the most insidious symptoms of overlapped depression-restlessness-irritability) can cause increased risk of suicidality (Akiskal 2007); besides, the co-presence of various types of somatisation symptoms, as well as the abuse of substances, should suggest the possibility of a "mixed state" of the bipolar spectrum (Tavormina 2013, 2014).

The "G.T. Mixed States Rating Scale", or "G.T. MSRS" (Tavormina 2014), a self-administered rating scale structured with 11 items (7 among them present also sub-items) can help the clinician to make a diagnosis of mixed state; if a patient is positive on the "G.T. MSRS", this will suggest a "generic" diagnosis for a mixed state in the bipolar spectrum, based on the full-spectrum scheme described by Akiskal (Akiskal 1999) or Tavormina (2007, 2013). Subsequently the clinician will need to carefully make a correct sub-diagnosis of the sub-groups of mixed state.

The pharmacological therapy of mixed affective states consists of a polytherapy with mood-stabilisers (mainly: lithium, carbamazepine, valproate, gabapentin, oxcarbazepine, lamotrigine, topiramate, olanzapine, asenapine, loxapine, pipamperone) and antidepressants (mainly: SSRIs, SNRIs and Bupropione), (Tavormina 2013). The clinician should never use antidepressants alone without mood-stabilisers when treating mixed states (or benzodiazepine alone), in order to avoid an increase in dysphoria (Tavormina 2010, Agius 2011).

STEPS FOR THE CLINICIANS

First step

It is essential at the beginning of the clinical interview to evaluate the present clinical situation which led the patient to consult the psychiatrist, and to assess what had led up to the present situation, including when the first symptoms of mood disturbance started, even though the first symptoms might have been very attenuated. In order to make a correct diagnosis of disturbance of mood within the bipolar spectrum it is essential to evaluate carefully the longitudinal psychiatric history of the patient, with particular attention to any sub-threshold symptoms and careful evaluation of the patient's temperament and the family psychiatric history (Tavormina 2007).

Second step

It is essential to use the "G.T. Mixed States Rating Scale" (or "G.T. MSRS") administering it to the patient, to conduct (or not) the clinician to a "generic" diagnosis for a mixed state in the bipolar spectrum (Tavormina, 2015). Within the full-spectrum already described in my past papers (Tavormina 2007, 2012), the dysphoric-mixed component of unstable mood is usually present in Irritable Cyclothymia (following from, and/or developing to, rapid cycling bipolarity), in Mixed Disphoria (typical depressive mixed state), in Agitated Depression and in the Cyclothymic Temperament.

The full-spectrum of the mood has been structured putting acute mania and unipolar depression in opposite sides of a chart, and between them all the different typologies of instability of mood, with all the fluctuations of the mood-waves, described as the following sub-types: Bipolar I, Bipolar II, Cyclothymia, Irritable Cyclothymia (or rapid cycling bipolarity), Mixed Dysphoria (or depressive mixed state), Agitated depression, three temperaments (Cyclothymic, Hyperthymic and Depressive temperament), Brief recurrent depression, and Unipolar depression (Tavormina 2007).

In the Table 1 there are depicted the main symptoms (corresponding to the items of the "GT-MSRS") present in the mixed states diagnosis (data followed from the paper "Clinical utilisation of the G.T.-MSRS, Tavormina 2015); furthermore, the Table 2 shows the percentage of intensity of the level of "GT-MSRS" (data followed from the same paper "Clinical utilisation of the G.T.-MSRS").

Table 1. Mixed states diagnosis: percentage of evidence of the symptoms

	Irritable Cyclothymia	Rapid cycling bipolarity	Mixed Disphoria	Agitated Depression	Cyclothymic Temperament
Euphoria with apathy	X	X	X		X
Depress. with irritability	XXX	XXX	XXX	XX	X
Substance abuse	XX	XX	XX		
Dis. of appetite		X	XX	X	
Suicidal ideation	XX	XXX	XX		
Chronic anhedonia			XX	XXX	
Delus./allucinat.	X				
Hyper-hypo sexual act.	XX	XX	XX	XX	
Hynsomnia/hypersomnia	XXX	XXX	XXX	XX	X
Mental overactivity	XXX	XXX	XXX	XXX	X
Somatic symptoms	XX	XX	XX	XX	X

Table 2. Mixed states diagnosis: percentage of intensity of the level of "GT-MSRS"

	Irritable Cyclothymia	Rapid cycling bipolarity	Mixed Disphoria	Agitated Depression	Cyclothymic Temperament
Level of "GT-MSRS"	H	H	H/M	M/H	L

Table 3. Mixed states treatment: steps of choice of the mood stabilisers

	1st step	2nd step	3rd step	4th 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

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

Third step

It is essential to have defined the diagnosis of the mixed state, and thence to choose the adequate mood stabiliser/s (Table 4), adding a small dosage of antidepressant in consequence of the intensity of the depressive symptoms measured both by the GT-MSRS and the clinical interview. The paper "A long term clinical diagnostic-therapeutic evaluation of 30 case reports of bipolar spectrum mixed states" (Tavormina 2013) showed that small dosages of antidepressants (in this study the following antidepressants has been used: Escitalopram, Sertraline, Paroxetine, Venlafaxine) are important, together with one or more mood stabilisers, to allow a good mood balance of the patients. The presence of emotive lability, or sadness or apathy suggests the need for small dosages of antidepressants, which when in presence of mood regulators will not prolong mixed states but only reduce the emotive lability and the sadness (Tavormina 2013).

The Table 3 shows the steps to use the mood stabilisers in the different types of mixed states. Eventual side effects, which may that force us to change drug, will induce the clinician to replace it with another drug of the same group; the paper "A long term clinical diagnostic-therapeutic evaluation of 30 case reports of bipolar spectrum mixed states" (Tavormina 2013) described all other different properties of the safety of the mood stabilisers.

Fourth step

In consequence of the diagnosis of mixed states and their symptoms presented in the patients, the clinicians has to select the mood stabiliser more indicated to be used. The high presence of severe somatic symptoms (such as colitis and gastritis) may induce the clinician to prescribe Gabapentin as first choice: Gabapentin has already been successfully used in chronic pelvic pain (Sator-Katzenschlager 2005) and irritable bowel sindrome (Lee 2005); Gabapentin has been used as a mood regulator with efficacy and tolerability (Carta 2003, 1999), and in my clinical experience with efficacy and tolerability also in presence of somatic symptoms (Tavormina 2013). The addition of Valproate and/or Carbamazepine is useful if there is a high presence of mental overactivity and confusion with reduced ability to concentrate (Tavormina 2013); finally, adding also Olanzapine if there is a serious insomnia with a long term utilisation of BDZ (this, to be progressively reducted until it is discontinued, and to use subsequently only occasionally when it is necessary), (Tavormina 2013). It is known that all mood regulators (and above all the anticonvulsants) have to be used carefully in women of childbearing age.

Eventual side effects, which may cause us to change any kind of medication, will induce the psychiatrist to replace the drug with another one of the same group, (Tavormina 2013).

CONCLUDING REMARKS

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.

It is essential not to forget that the depression is only one phase of a broader bipolar mood disorder, which is the fundamental illness to be treated by psychiatrists by clinicians managing an appropriate polytherapy with mood-stabilisers and antidepressants. Despite some international papers having written some reflections about the usefullness of the antidepressants on mixed states, my clinical experience (Tavormina 2013, 2014) and the first study to validate the rating scale on mixed states, the "G.T.MSRS" (Tavormina 2015), 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.

Acknowledgements: None.

Conflict of interest: None to declare.

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