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PSYCHOPATHOLOGICAL AND THERAPEUTIC TRAJECTORIES OF INPATIENTS AFFECTED BY MIXED STATES AND BIPOLAR SPECTRUM DISORDERS

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SUMMARY

In clinical practice, mental health professionals face diagnostic and therapeutic challenges daily. The diagnostic identification of mixed states allows the management of diagnostic and therapeutic trajectories appropriately. In our study, we evaluated 484 patients at a psychiatric rehabilitation center. The initial pre-admission diagnosis of the mixed state of 3.71% (at baseline) increased to 32.23%. The observation period was three years. The therapeutic efficacy of the pharmacological association of Antidepressants (Ads) or Second Generation Antipsychotics (SGAs) with a mood stabilizer (sodium valproate, lithium, lamotrigine, gabapentin, and pregabalin) was evaluated. An improvement in psychopathological symptoms was observed in different groups analyzed. The most significant differences were observed with the association SGAs + mood stabilizer [olanzapine + valproate sodium (p=0.005); risperidone + pregabalin (p=0.072)] and SSRIs + mood stabilizer [escitalopram + valproate sodium (p=0.005), vortioxetine + mood stabilizers (valproate or gabapentin). However, these are preliminary data and are under evaluation.

Key words: *Mixed state - bipolar disorders - Second Generation Antipsychotics - mood stabilizers - GT-MSRS*

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INTRODUCTION

Mixed states, with their potential for major behavioral disruptions, continue to pose a significant challenge for clinicians regarding diagnostic classification and therapeutic management. The ongoing debate on mixed states has revealed contradictions and controversies and underscored the gravity of the situation. The term "mixed state" refers to a mood disorder where the simultaneous presence of depressive and manic symptoms is observed (Verdolini et al. 2015). The overlapping of depression-restlessness-irritability-grief-tension-anxiety can exacerbate mood disorders and, in the most acute phases, may lead to an increased risk of major behavioral disruption, including murder and suicide (Tavormina 2019).

The issue of diagnostic collation of mixed states, as defined in the DSM-5, is that it places them as subtypes of manic or depressive episodes. However, it is strongly argued that mixed depression and mixed mania should have their own distinct diagnostic identity (Franza et al. 2016). The DSM-5 currently indicates mixed states with specifiers, but a shift towards a categorical gradient is necessary to ensure this disorder receives the attention it deserves (Akiskal 1996).

To qualify for the mixed characteristics specifier, a person must meet the diagnosis of one polarity (e.g., mania or depression) and have at least three symptoms of the other polarity during most days of the current or most recent episode. In the ICD-11 (WHO 2022), mixed states (MS) are described as a separate episode rather than a specifier of depression or mania. Correct identification of mixed states is crucial as it can help identify possible diagnostic and therapeutic trajectories, empowering mental health professionals to provide more effective care. A review by Natale and colleagues (2022) attempted to clarify the essential points of the mixed state (MS). In the DSM-5, the concept of a specifier with "mixed characteristics" allowed the co-presence of expansive or depressive symptoms during a depressive episode to be assessed. In the ICD-11, mixed states are defined as "the presence of several symptoms seen in manic and depressive episodes consistent with those co-occurring and alternating very rapidly."

Various studies have evaluated the frequency of mixed features specifiers in patients who had initially been given a different diagnosis (agitated depression, dysphoric depression, recurrent depression, schizoaffective disorder, etc.). The mixed features specifier criteria were fulfilled by 16% of patients with first-episode depression. This finding suggests that the extension of this specifier to depression is not just a helpful step, but a promising avenue for understanding the symptom profile of patients with depression (Grover et al. 2023).

The problem of identifying mixed states is fundamental for their management. Koukopoulos et al. (2007) raised the problem of identifying the criteria that lead to a hasty diagnosis of resistant depression. The existing criteria can lead to a misdiagnosis of this disorder. The presence of symptoms such as psychomotor agitation, marked insomnia, highly expressed emotionality, and explosive crying fits in a hyperthymic or cyclothymic temperament should lead to the diagnosis of a "mixed state" (Tavormina et al. 2015, 2017). The therapeutic implications oriented towards the administration of mood stabilizers or second-generation antipsychotics (SGA) are evident (Dargél et al. 2022). Epidemiological data support these considerations from a prevalence of 7% to 12% of MS, according to the DSM, a frequency of 47% is reached with the inclusive criteria of Koukopoulos. A multicenter study (Mineo et al. 2022) demonstrated an overlap of the DSM-5 criteria and the "mixed-depression" criteria, according to Koukopoulos. The high frequency of mixed states in patients previously diagnosed with bipolar disorder (BD) or major depressive disorder (MDD) has been highlighted by several studies (Cervone et al. 2022). About half of patients with major depressive episodes fulfill the DSM-5 criteria for depression with anxiety features or the Koukopoulos criteria for mixed depression, and many of these patients fulfill both diagnoses. Patients with both diagnoses are a heterogeneous group that includes people whom the current diagnostic criteria cannot fully differentiate (Tundo et al. 2023).

The availability of assessment scales aimed at identifying mixed states is necessary. The "G.T. Mixed State Rating Scale, GT-MSRS" (Tavormina et al. 2014, 2015, 2017) is a useful, easy to administer and repeatable tool. The pharmacological treatment of mixed state also presents a challenge for clinicians. The available guidelines agree in indicating the use of antidepressants only as a third line and for a short time due to the risk of turning towards expansive forms. Mood stabilizers are indicated as first-line drugs in patients with M.S., together with second generation antipsychotics (SGAs) (Maina et al. 2017). Among the former, lithium, valproate, and lamotrigine are indicated. Several studies suggest using gabapentin and pregabalin in these disorders (Fountoulakis et al. 2012, Stahl et al. 2017, Ng et al. 2021, Lähteenvuo et al. 2023, Taipale et al. 2024).

Our study aimed to evaluate the percentage of mixed-state diagnoses compared to the admission diagnosis and the pharmacological trajectories at discharge in patients hosted in a psychiatric rehabilitation centre.

METHOD

In an observational study, patients admitted to our facility have been selected between January 2019 and June 2024. During this period, the results of 484 patients [(mean age: 40.88 (±SD: 11.59)] were recruited, with a balanced gender distribution of 198 females [(mean age: 39.67 (±SD: 11.31)] and 286 males [(mean age: 42.96 (±SD: 11.99)]. During the process of psychiatric rehabilitation, the initial therapy and diagnosis of these patients were evaluated and modified in several cases. The diagnoses and hospitalization therapies were recorded using the admission model developed by psychiatrists and the multidisciplinary team of the Local Health Authority (A.S.L.), which plays a crucial role in proposing hospitalization in psychiatric rehabilitation centers. After the team has drawn up the Individual Therapeutic Rehabilitation Project (or P.T.R.I.), the patient can access the Psychiatric Rehabilitation Center.

Participants

Four hundred eighty-four patients were selected from the guests from 18 to 70 y.o. with diagnosis at the time of admission of depressive syndrome, affective disorder, bipolar disorder, recurrent depressive disorders, schizoaffective disorder, and personality disorders according to the DSM-5 criteria. Patients with confirmed diagnoses of schizophrenic spectrum disorders after clinical and instrumental evaluation were excluded.

However, these patients were monitored during the hospitality period and re-evaluated for possible reinsertion into the analyzed group.

Patient assessment

According to the routine clinical management regulations of patients upon admission to the facility (T0 or baseline), the following assessment scales to all patients are administered:

Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham 1988); Global Assessment of Functioning (GAF) (APA 1994); Clinical Global Impressions (CGI) (Guy 1976).

Patients with schizophrenia spectrum disorder are administered the Positive and Negative Syndrome Scale (PANSS)(Kay et al. 1987); patients with bipolar disorder are administered the Young Mania Rating Scale (YMRS) (Young et al. 1978), in manic episode, or the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960). These scales are subsequently re-administered after 3 months (T1), after 6-12 months (T2), after one year (T3) and after 2 or 3 years (T4). If the patient has been discharged, the missing times are not recorded.

All patients were administered the G.T. Mixed States Rating Scale (GT-MSRS) (Tavormina 2014) after admission and at the times described above (T1, T2 and/or T3). All patients were administered pharma-

cological therapies (SGAs: olanzapine, risperidone, paliperidone, aripiprazole; Mood stabilizers: lithium, sodium valproate, gabapentin, lamotrigine, pregabalin). If necessary, some patients were administered benzodiazepines or hypnotics.

Study Procedures

At admission during the first visit, patients signed a written information. All patients gave their consent to the management of their pathologies during hospitalization. After accessing the facility, the patient receives treatment for the entire duration of hospitalization. Doctors can modify the treatment according to their clinical judgment and the evaluation of the results of the administered scales. During the department meetings attended by the entire healthcare team (doctors, psychologists, nurse educators, psychiatric rehabilitation technicians, and social workers), the diagnostic and therapeutic path is evaluated, and new diagnostic and therapeutic trajectories are defined. Statistical significance was ascertained by t-tests or repeated measures ANOVA (to test multiple groups) with EZAnalyze 3.1 Excel Platform. Student's t-tests were used to compare the results of administered scales in any group. Demographic variables and evaluation questions were subjected to descriptive analysis.

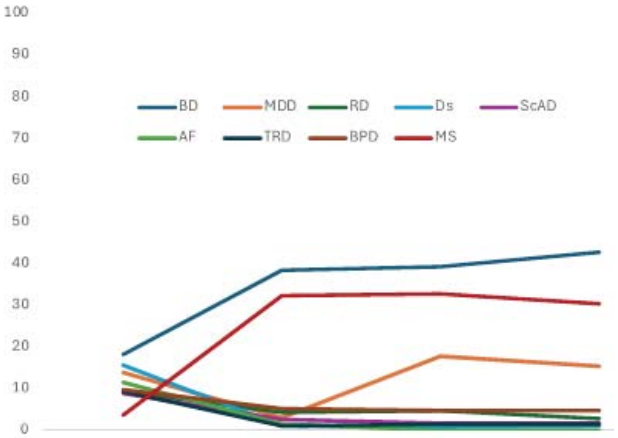
RESULTS

The results are shown in Tables 1, 2 and 3, and in figure 1. The results show a percentage of change in the diagnosis formulated following the administration of the GT-MSRS. The percentage of mixed status diagnoses increased from 3.71% (T0) to 32.23% (T1) in the selected patient group compared to the initial diagnosis. In T1, T2 and T3 the percentage of mixed

Table 1. Epidemiological inpatients diagnoses at T0

	Total 484	%	Females 198	Males 286
BD	88	18.18	25	63
MDD	67	13.84	32	35
RD	45	9.30	24	21
Ds	75	15.50	28	47
ScAD	43	8.88	28	15
AF	56	11.50	22	34
TRD	45	9.28	20	25
BPD	47	9.71	12	35
MS	18	3.71	7	11

Legend: BD: Bipolar disorder type I, type II; MDD: Major Depressive Disorder RD: Resistent Depression; Ds: Depressive syndrome; ScAD: SchizoAffective Disorder; AF: Affective Disorder; TRD: Treatment-resistant Depression; BPD: Borderline Personality Disorder or other; MS: Mixity State



Legend: BD: Bipolar disorder type I, type II; MDD: Major Depressive Disorder RD: Resistent Depression; Ds: Depressive syndrome; ScAD: SchizoAffective Disorder; AF: Affective Disorder; TRD: Treatment-resistant Depression; BPD: Borderline Personality Disorder or other; MS: Mixity State

Figure 1. Percentage (%) diagnoses in T0 vs Tn

status remained unchanged. The percentage of BD diagnoses also increased (from 18.18% in T0 to 38.25% in T1). The percentage of other initial diagnoses dropped [(e.g., schizoaffective disorder (ScAD), affective depression (AD), treatment-resistant depression (TRD), and borderline personality disorder (BPD)] from T0 to T1, remaining virtually unchanged in the other periods analyzed. A shift toward MS or BD diagnoses was observed. Substantial diagnosis modifications allowed the modification of pharmacological therapies, which contributed significantly to the improvement of the patient's symptoms.

The group of patients after having modified the initial diagnosis following the reassessment with the GT-MSRS, observed an improvement in the overall score of the scales analyzed (see tables and graphic). It is interesting to note that the most significant results were obtained when a mood stabilizer was added to the therapy with antidepressants alone or SGAs alone.

Significant improvements in patient symptoms were achieved through substantial diagnosis modifications, which in turn allowed for the modification of pharmacological therapies.

Notably, the most significant improvements were observed when a mood stabilizer was introduced to the therapy, particularly when the initial diagnosis was modified following reassessment with the GT-MSRS. The most significant results were obtained when a mood stabilizer was added to the therapy with antidepressants alone or SGAs alone.

In the analyzed group, the most significant differences were observed with the association SGAs + mood stabilizer [olanzapine + valproate sodium (T1 vs T3: P - Unadjusted: 0.019; P - Bonferroni: 0.188) or lithium (T1 vs T3: P – Unadjusted: 0.0005; P - Bonferroni: 0.0098);

Table 2. Epidemiological data and percentages inpatients diagnoses at T0, T1, T2, T3

	T0		T1		T2		T3	
Total	484	%	484	%	293	%	293	%
BD	88	18.18	186	38.43	115	39.25	125	42.66
MDD	67	13.84	67	3.06	43	17.68	45	15.36
RDD	45	9.30	21	4.34	14	4.78	8	2.73
Ds	75	15.50	5	1.03	2	0.68	3	1.02
ScAD	43	8.88	12	2.48	5	1.71	5	1.71
AD	56	11.50	7	1,45	0	0.00	0	0.00
TRD	45	9.28	5	1.03	4	1.37	4	1.37
BPD	47	9.71	25	5.17	14	4.78	14	4.78
MS	18	3.71	156	32.23	96	32.76	89	30.37

Legend: BD: Bipolar disorder type I, type II; MDD: Major Depressive Disorder RDD: Recurrent Depressive Disorder; Ds: Depression; ScAD: SchizoAffective Disorder; AD:Affective Disorder; TRD: Treatment-resistant Depression; BPD: Borderline Personality Disorder; MS:Mixity State

Table 3. G.T.- MSRS Data T0 -T1 - T2 - T3

	T0 (18 pts)		T1 (156 pts)		T2 (96 pts)		T3 (89 pts)	
	Mean Total	± SD	Mean Total	± SD	Mean Total	± SD	Mean Total	± SD
GT-MSRS	7.944	4.196	8.628	4.249	7.768	3.611	6.886	2.806
BPRS	45.89	11.347	42.32	10.456	39.87	9.899	36.876	8.982
CGI	4.25	0.851	3.65	0.988	3.4	0.754	2.75	1.217
GAF	47.04	10.461	45.89	9.895	44.45	8.89	43.34	8.567

SD - Standard Deviation; The ANOVA results indicate that at least two of the repeated measures differed significantly

risperidone + pregabalin (T1 vs T3: P - Unadjusted: 0.007; P - Bonferroni: 0.072)] and SSRIs + mood stabilizer [escitalopram + valproate sodium (T1 vs T3: P - Unadjusted: 0.005; P - Bonferroni: 0.005). Results in terms of efficacy were also observed, including the association between vortioxetine and mood stabilizers (valproate or gabapentin). However, these are preliminary data and are under evaluation.

CONCLUSIONS

The results of our observational study are limited by the difficulty of a "clean" evaluation of pharmacological treatment and the necessary intake of other drugs or cognitive and educational rehabilitation techniques. Being an observational study, it lacks the comparison evaluation with a healthy control group. However, it is a real-world study carried out on patients during their daily rehabilitation activity. The results have highlighted that the diagnosis of mixed state is more frequent than expected, a finding of significant importance for the field of mental health. This diagnosis can help improve therapeutic management and identify the necessary trajectories to improve the efficacy and effectiveness of an integrated multidisciplinary treatment. The strategic and combined use of different pharmacological groups (SGAs + mood stabilizers or ADs + mood stabilizers) represents the indispensable therapeutic strategy for the treatment of mixed states. Finally, we would like to mention the study by Smirnova et al. (2023) of the PC program on "Multilingual IBM-PC Online Calculator for early diagnosis of Mixed Affective State", based on the Giuseppe Tavormina Mixed States Rating Scale (G.T.-MSRS): translated into three languages (Russian, English, and Italian language versions), it is accessible online, allowing the evaluation of mixed states online (https://icern.org/calc/msrs_en/).

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Contribution of individual authors:

Francesco Franza: design of the study protocol, statistical design, interpretation of the data & writing manuscript, final version evaluation.

Giovanna Celia: literature research, reviewed and corrected the manuscript.

Wilma Angela Renata Di Napoli & Maurilio Giuseppe Maria Tavormina: literature research, first draft, writing manuscript.

Andreana Franza: literature research, first draft, writing manuscript, statistical design, interpretation of the data, approval of the final version.

Barbara Solomita: design of the study, sample collecting, literature research, statistical design, interpretation of the data.

Francesca Pagnotta: bureaucratic and legal observations, reviewed and corrected the manuscript.

Giuseppe Tavormina: literature research.

All authors approval of the final version of the article for its submission.

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