BIPOLAR DISORDER: THE IMPORTANCE OF CLINICAL ASSESSMENT IN IDENTIFYING PROGNOSTIC FACTORS - AN AUDIT.
Part 2: Mixed state features and rapid cycling

Norma Verdolini[1], Jonathon Dean[2], Sandro Elisei[3], Roberto Quartesan[3], Rashid Zaman[3,4] & Mark Agius[4,5]

[1]*School of Specialization in Psychiatry, Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, University of Perugia, Santa Maria della Misericordia Hospital, Perugia, Italy*
[2]*School of Clinical Medicine, University of Cambridge, Addenbrooke's Hospital Gonville and Caius College, Cambridge, UK*
[3]*Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, University of Perugia, Santa Maria della Misericordia Hospital, Perugia, Italy*
[4]*South Essex Partnership University Foundation Trust, Bedfordshire Centre for Mental Health Research in association with the University of Cambridge, Department of Psychiatry, University of Cambridge, UK*
[5]*Clare College Cambridge, The University of Cambridge, Cambridge, UK*

SUMMARY

Background: Rapid cycling in bipolar disorder complicates the clinical picture and worsens the long-term outcomes of bipolar disorder. Mixed states features do similarly and are known to present an increased risk to patients. Early recognition of these patterns can lead to better treatment strategies and improvement of the long-term course of the disease.

Method: We collected data from the clinical notes of 70 bipolar outpatients seen at an ASPA (initial assessment) clinic about socio-demographic and clinical characteristics.

Results: The sample comprised 16 bipolar I (22.9%) and 54 bipolar II (77.1%) outpatients; percentages reported in our results are of the sample for which the data was available. 71.7 % (33 patients) of the sample reported mixed states features and 32 patients (72.7%) are recorded to have more than 4 changes in mood in a year. There were no statistically significant correlations between mixed state features or rapid cycling and anhedonia, suicidal ideation, borderline symptoms, OCD symptoms, anxiety, positive psychiatric family history, current alcohol use, previous alcohol use, current illicit drug use, or previous illicit drug use. An almost significant correlation was found between mixed state features and anxiety. Assignation of a care coordinator did not seem to be associated with these prognostic factors.

Conclusions: The two subgroups of mixed state features and rapid cycling patients share very common clinical characteristics: high incidence of suicidal thoughts, high levels of anxiety, and high previous substance use – but low levels of current alcohol and drug use and high levels of features of atypical depression. These features of mixed state bipolar disorder and rapid cycling bipolar disorder should be identified during psychiatric assessment to identify useful information for prognosis.

Key words: *bipolar affective disorder – comorbidity - mixed affective states – rapid cycling*

* * * * *

INTRODUCTION

Rapid cycling is a common but underrecognized condition in bipolar disorder, and it constitutes a worsening of the primary disorder. In fact, rapid cycling affects a significant proportion of bipolar patients and is related to a longer course of illness, an earlier age at onset, more illegal drug and alcohol abuse, increased suicidality, and has a profound influence on strategic treatment design (Carvalho 2014). Early recognition of this pattern can lead to better treatment strategies and improvement of the long-term course of the disease. The aetiology of rapid cycling bipolar disorder remains unclear, but antidepressant use and hypothyroidism are implicated in a causal or triggering role. Furthermore, in terms of prognosis, a recent literature review (Carvalho 2014) concern rapid cycling bipolar disorder states that although this seems to constitute a general worsening in the course of bipolar disorder, it does not happen in a predictable manner and may instead represent a transitory phenomenon rather than a stable phase or feature of the disorder in the majority of cases.

The same authors (Carvalho 2014) reported on characteristics of rapid cycling and stated that the year prevalence of rapid cycling among all bipolar patients ranges from 5%–33.3% and from 25.8%–43% for lifetime prevalence.

Female bipolar patients have a higher prevalence of rapid cycling, and the proportion of females with bipolar disorder who demonstrate rapid cycling can be as high as 92% (Carvalho 2014). A number of factors might explain the relationship between rapid cycling and female gender, including hormonal changes associated with the menstrual cycle and the higher

prevalence of hypothyroidism. Furthermore, rapid cycling in type II bipolar disorder is also strongly related to female gender.

There is data to suggest that rapid cycling is related to a greater number of total episodes and hospitalizations, to poorer long-term disease course, to comorbidities, and to more severe disability. Emil Kraepelin was the first to highlight a possible relationship between illness progression and cycle length. After his work, many authors provided definitions of the cycle and of rapid cycling (Dunner 1974) and suggested its influence on the course of bipolar disorder and treatment planning. For instance, it is stated that the concept of rapid cycling overlaps with other clinical phenotypes including mixed specifiers, which provides a source of diagnostic uncertainties. In fact, as we know, it can sometimes be particularly difficult to differentiate rapid cycling bipolar disorder from a truly severe mixed state.

Furthermore, rapid cyclers may not even achieve full remissions between episodes. This causes major disability and makes the clinical picture similar to a cluster B personality disorder (Mackinnon 2006), potentially resulting in incorrect diagnosis and inappropriate treatment.

As for mixed episodes, the updated DSM-V proposes a "with mixed features" specifier to be applied when at least three opposite symptoms are present during a mood episode and it may be applied to manic episodes in bipolar I, hypomanic episodes in bipolar I and II, mood depressive episodes experienced in bipolar I, bipolar II, bipolar disorder not otherwise specified (BD-NOS), and major (unipolar) depressive disorder. This addition arises from the manifest need to capture subthreshold non-overlapping symptoms of the opposite pole and to better account for the highly prevalent subsyndromal presentations that, under DSM-IV-TR classification, do not meet the criteria for any of the 3 bipolar diagnoses (Nusslock 2011, Pacchiarotti 2011).

This new classification seems to be increasingly popular compared to the traditional unipolar–bipolar dichotomy, and it is linked to Kraepelin's concept of a "mood spectrum" that varies from unipolar depression to pure mania at its extremes (Kraepelin 1899, Akiskal 2000, Perugi 2005, Angst 2010).

Looking at mixed state prognostic factors, a recent analysis (Pacchiarotti 2013) identified a specific mixed factor dimension that the authors termed *mixicity*, which includes anxiety, tension, suicidality, motor hyperactivity, and excitement. This *mixicity* dimension was found to be associated with a predominantly depressive polarity, more lifetime mixed episodes, poorer course of illness, and a higher frequency of previous antidepressant use. Moreover, the *mixicity* factor was associated with an anxious temperament and a premorbid temperament mainly characterized by anxiety and tension, supporting the hypothesis that mixed episodes result from an admixture of inverse temperamental factor and a manic syndrome, as proposed by some authors (Akiskal 1992, Perugi 2005).

Aims

As stated in part one of this research (Verdolini 2014), this paper examines the need to seek information about mixed state features and rapid cycling during clinical assessment to better consider the course and outcomes of bipolar disorder. The authors evaluate the presence of mixed states features and rapid cycling in a patient population, and we analyse the assignation of a care coordinator during the phase of assessment after initial presentationto secondary care, to understand if patients are referred to them in consideration of the importance of these two prognostic factors. Furthermore, we examine the possible correlations between mixed state and rapid cycling and ten other previously-identified prognostic factors: anhedonia, suicidal ideation, borderline symptoms, OCD symptoms, anxiety, positive family psychiatric history, current alcohol use, previous alcohol use, current illicit drug use, and previous illicit drug use.

METHOD

Participants

This study included 70 treatment-seeking adults diagnosed with bipolar disorder (16 bipolar I, 22.9%, and 54 bipolar II, 77.1%) at any mood state, assessed from 2011 to 2014 by a senior psychiatrist (M.A.) in his ASPA clinic (Assesment and Single Point of Access, or initial psychiatric assessment). Patients were aged between 18 and 65 years old and were assessed according to the ICD-10 criteria and DSM IV-TR criteria.

Procedures

Data was anonymously drawn from the archival ASPA dataset. Information drawn was socio-demographic (gender, age, ethnicity, occupation) and clinical in nature. Clinical data points extracted from the clinical notes were psychiatric diagnosis, psychiatric comorbidities, physical comorbidities, age at first depressive and hypomanic episodes (even if subsyndromal), eating and sleeping habits during depressive episodes, concentration, anhedonia, suicidal ideation, psychotic characteristics, whether the patient had rapid cycling or mixed state features, psychiatric family history, current and previous alcohol or illicit drug use, and assignation of a care coordinator.

The mixed states features we identified were: 1) presence of iritability and anger 2) rapid changes of mood within a day from high to low 3) dysphoria 4) coincidence of depression and irritability 5) marked suicidal ideation during a mixed state.

Statistical analysis

χ^2 tests were used to evaluate associations between categorical variables. All statistical analyses were performed with the statistical software package SPSS (version 21), using a significance level of p-value ≤0.05.

RESULTS

Sociodemographic profile

The sample comprised 27 males (38.1%) and 43 females (61.4%), with ages between 18 and 61 years old (mean 35, s.d. 12.305). 28 patients (40%) were unemployed and 26 patients (41.4%) were employed. Of those 26 patients, 12 (17.1%) were laborers, 7 (10%) were skilled employees, and 7 (10%) were professionals. 6 patients (8.6%) were students, 8 patients (11.4%) were housewives, and 2 patients (2.9%) were retired. Percentages reported in our results are of the sample for which the data was available.

The most represented ethnicity was Caucasian (66, 94.3%); other ethnicities were not significantly represented in the sample (2 Indian patients, 2.9%; 1 Caribbean patient, 1.4%; 1 Asian patient, 1.4%).

Clinical profile

In part one of our research, we focused on patients' age at onset, duration of depressive/hypomanic episodes, psychiatric and physical comorbidities, depressive episode features, psychiatric family history, and current and previous alcohol and illicit drug use of the bipolar disorder patients. Furthermore, we correlated the prognostic factors and then assessed whether the assignation of a care coordinator was dependent on these prognostic factors (Verdolini 2014). In this part, we turn our attention to features of mixed state and rapid cycling bipolar disorder.
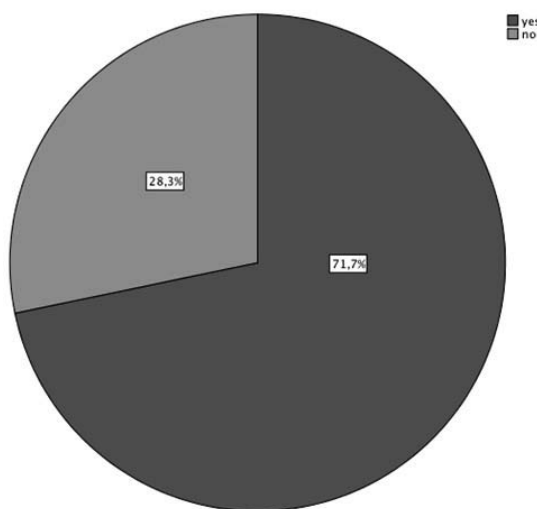

Figure 1. Patients with mixed state features

Mixed state features and rapid cycling

71.7 % (33 patients) of the sample reported mixed state features (see figure 1). Information about mixed state features was not available for 24 patients (34.3%).

32 patients (72.7%) reported rapid cycling features with more than 4 changes in mood in a year (see figure 2). Information was not available for 26 patients (37.1%).
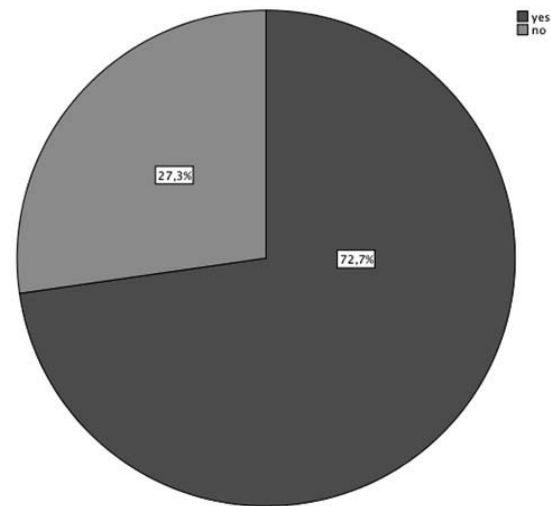

Figure 2. Patients with rapid cycling

We analysed the characteristics of the population on the basis of mixed state features and rapid cycling.

Gender

Mixed state: 19 females (57.6%); 14 males (42.4%).
Rapid cycling: 21 females (65.6%); 11 males (34.4%).

Current diagnosis

Mixed state: Bipolar I – 9 patients (27.3%); Bipolar II – 24 patients (72.7%)
Rapid cycling: Bipolar I – 10 patients (31.3%); Bipolar II – 22 patients (68.8%)

Characteristics of patients with mixed state features

We extracted characteristics from the subset of 33 patients with mixed state features.

Average age of patient: 34.52 years (s.d. 11.798); average age at first depressive episode: 15.63 years (s.d.6.159); average age at first hypomanic/manic episode 19.19 years (s.d. 7.125); average duration of depressive episode 62.52 days (s.d. 83.646); average duration of hypomanic episode 13.72 days (s.d. 10.737).

We then identified patients in this subset with particular features of mixed state and with potential prognostic factors.

27 patients (84.4%) reported suicidal ideation; 21 patients (65.6%) reported anxiety features; 10 patients (31.3%) reported current alcohol use; 16 patients (50%) reported previous alcohol use; 9 patients (30%) reported present drug use; 19 patients (63.3%) reported previous drug use. 15 patients (46.9%) stated that they eat more during a depressive episode; 17 patients (53.1%) stated that they slept more in the day during a depressive episode; 31 patients (96.9%) reported anhedonia; 3 patients (9.4%) were noted to have symptoms of borderline personality disorder; 23 patients (76.7%) declared a positive psychiatric family history; 25 patients (92.6%) met the criteria for rapid cycling. 9 patients (27.3%) were assigned to a care coordinator.

Characteristics of the patients with rapid cycling

We extracted characteristics from the subset of 32 patients with rapid cycling features.

Average age of patient: 35.53 years (s.d. 11.846); average age at first depressive episode: 15.68 years (s.d.6.505); age at first hypomanic/manic episode: 18.95 years (s.d. 7.352); average duration of depressive episode: 35.84 days (s.d. 41.011); average duration of hypomanic episode: 14.44 days (s.d. 13.654).

We then identified patients in this subset with particular features of rapid cycling and with potential prognostic factors.

24 patients (82.8%) reported suicidal thoughts; 20 patients (64.5%) reported anxiety features; 9 patients (29%) reported present alcohol use; 14 patients (42.5%) reported previous alcohol use; 8 patients (27.6%) reported present drug use; 17 patients (58.6%) reported previous drug use. 16 patients (57.1%) stated that they eat more during a depressive episode; 18 patients (62.1%) stated that they slept more during the day during a depressive episode; 27 patients (93.1) reported anhedonia; 4 patients (13.3%) were noted to have symptoms of borderline personality disorder; 18 patients (62.1%) declared a positive psychiatric family history; 25 patients (89.3%) had mixed states features. 9 patients (28.1%) were assigned to a care coordinator.

In our analysis of features of atypical depression in patients with either mixed state features or rapid cycling, we noted that 50% (12 patients) of the sample reported finding eating comfortable and 54.2% (13 patients) reported sleeping more during the day in a depressive episode.

Antidepressant related relation

In our sample, 7 patients (77.8%) reported that anti-depressants caused an increase in their mood at some point during their life and 2 patients (22.2%) did not. This information was not available in most patients (61 patients, 87.1%). Of the 7 patients for whom anti-depressants caused mood increases, 5 (71.4%) reported rapid cycling and 6 (85.7) are recorded to have mixed state features.

Physical comorbidities

In part one of this research, we considered the physical comorbidities of the bipolar disorder population. In particular, we reported that 6 patients (9%) had thyroid problems. Of these, 4 (66.6%) reported hypothyroidism, 1 (16.7%) are noted to have hyper-thyroidism, and 1 (16.7%) is noted to have unspecified thyroid dysfunction.

Of these six, 2 patients (33.3%) showed mixed state features and rapid cycling, 4 (66.7%) reported no rapid cycling, and 3 (50%) reported no mixed state features (in 1 patient, information about mixed states was not available).

Correlation between prognostic factors

A comparison between mixed states and rapid cycling was done (χ^2=17.198, P≤0.005) but there was no statistically significant correlation. This is likely due to the low statistical power of our sample size.

A correlation between mixed states features and the 10 prognostic factors we identified was completed as well as a correlation between rapid cycling and the same 10 prognostic factors (see tab. 1 and 2).

An almost significant correlation was found between mixed states features and anxiety (χ^2=2.796, P=0.091).

Table 1. Correlation between mixed states features and the other prognostic factors

	Anhe-donia	Suicidal thoughts	Anxiety	OCD	Borderline symptoms	Family history	Present alcohol use	Previous alcohol use	Present illi-cit drug use	Previous illi-cit drug use
Mixed states features	χ^2=2.233 P=0.196	χ^2=0.000 P=0.680	χ^2=2.796 P=0.091	χ^2=0.243 P=0.482	χ^2=1.306 P=0.350	χ^2=0.443 P=0.382	χ^2=0.421 P=0.379	χ^2=0.243 P=0.440	χ^2=2.218 P=0.137	χ^2=0.632 P=0.325

Table 2. Correlation between rapid cycling and the other prognostic factors

	Anhe-donia	Suicidal thoughts	Anxiety	OCD	Borderline symptoms	Family history	Present alcohol use	Previous alcohol use	Present illi-cit drug use	Previous illi-cit drug use
Rapid cycling	χ^2=0.920 P=0.332	χ^2=0.002 P=0.672	χ^2=1.856 P=0.155	χ^2=0.007 P=0.655	χ^2=1.625 P=0.271	χ^2=1.772 P=0.169	χ^2=0.629 P=0.328	χ^2=0.601 P=0.332	χ^2=0.549 P=0.378	χ^2=0.231 P=0.453

Care coordinators

17 patients (24.3%) of the 70 patients with bipolar disorder were assigned to a care coordinator (see figure 3).
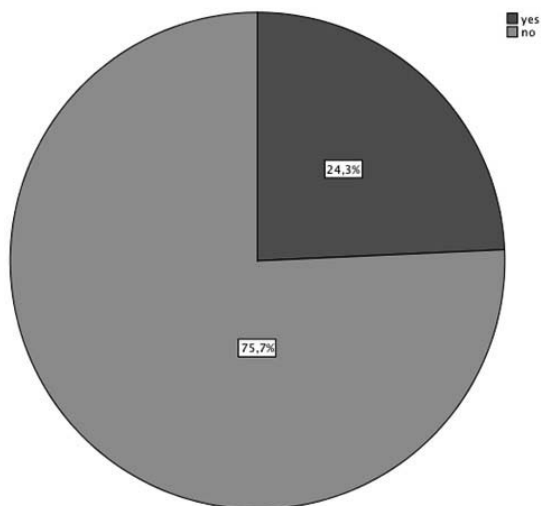

Figure 3. Care coordinators

We have evaluated whether there were any statistically significant differences between patients who had been assigned a care coordinator and those who had not on the basis of the presence of mixed states features and rapid cycling, but no statistically significant differences between the two groups of patients were found: mixed states features/care coordinator (χ^2=0.056, P=0.541), rapid cycling/care coordinator (χ^2=0.611, P=0.359).

DISCUSSION

The results obtained from our sample of bipolar patients seem to reflect those of the previous literature, though there are some key differences.

In our sample, we noted a high percentage of patients who demonstrated both rapid cycling and mixed state features. That highlights the strong correlation and overlap between these two subtypes.

In the review mentioned above, the authors (Carvalho 2014) reported that the year prevalence of rapid cycling among all bipolar patients ranges between 5%–33.3% and 25.8%–43% for lifetime prevalence. Though we did not record lifetime prevalence, the percentage of rapid cycling among our sample of bipolar patient was higher than expected at 72.7%.

The recognized overall mean global prevalence of mixed state features in bipolar disorder is 31% (McElroy 1992), but the prevalence based on the narrow definitions of ICD-10 and DSM-III/IV is reported to be between 6.7% and 28%, and is up to 66% when using broader definitions (Cassidy 2008). In our sample, the percentage of mixed state features among our bipolar patients was again particularly high at 71.7%.

We surmise that our sample of patients with bipolar disorder reported unexpectedly high percentages of both rapid cycling and of mixed state features when compared to previous literature because we utilised a relatively broad definition of these subtypes for diagnosis.

Carvalho (Carvalho 2014) underlined the need for broader diagnostic definitions and provided his own, stating "the course of bipolar disorder is rarely that symmetrical and typical, consequently a more pragmatic approach to rapid cycling and mixed states is needed; as for rapid cycling, we can consider a cycle as the period of time that starts with an episode of any polarity and lasts until the recurrence of the disorder with the emergence of another mood episode of any polarity".

We considered the following features of mixed state: 1) presence of irritability and anger 2) rapid changes of mood within a day from high to low 3) dysphoria 4) co-presence of depression and irritability 5) marked suicidal ideation during a mixed state.

In our sample, females seemed to show more rapid cycling and mixed features than males did, which is in line with previous literature (Jenner 1967). In our sample of patients, we saw that the subset of patients with mixed state and rapid cycling showed an average age and an age of onset for first depressive and hypomanic episodes that were similar to the rest of the population of our sample (Verdolini 2014).

However, they presented interesting durations of depressive and hypomanic episodes. The subset with rapid cycling reported a duration of depressive episodes that was an average of 23.4 days shorter than that of our general bipolar disorder population (35.84 days, s.d. 41.011 vs 59.23 days, s.d. 73.971).

On the other hand, the subset of patients with mixed state features is recorded to have an average duration of depressive episodes (62.5 days, s.d. 83.646) longer than both that of our general bipolar population and our rapid cycling subgroup. It might be possible that our patients were more likely to remain in a state of agitated or atypical depression rather than in a state of mixed mania.

Both the mixed state subset and the rapid cycling subset reported shorter hypomanic episodes than those of the general bipolar population (mixed states: 13.72 days, s.d. 10.737; rapid cycling 14.44 days, s.d. 13.654; general bipolar population: 15.11 days, s.d. 16.613). This is particularly interesting because the subsets of mixed state and rapid cycling share very common clinical characteristics: high levels of suicidal ideation; high levels of anxiety; high previous alcohol and illicit drug use with low current levels of alcohol and drug use, and high levels of features of atypical depression.

Both the rapid cycling subgroup and the mixed state subgroup reported low percentages of assignment of care coordinators during the assessment period. We might again conclude that patients' clinical state was not considered in the assignment of a care coordinator. This is highlighted in the absence of statistically significant correlations between the presence of a care coordinator and these two subsets of bipolar disorder.

Comorbid borderline personality disorder was reported in 6 patients. Of these six, it is interesting that 4 (66.7%) reported rapid cycling and 3 (50%) reported features of mixed state bipolar disorder.

We identified overlap between the two groups, with the mixed state group reporting a high percentage of rapid cycling (92.6%) and the rapid cycling group reporting a high percentage of mixed state features (89.3%).

Previous research has suggested a sharp increase in suicidal ideation for patients with bipolar disorder who are both rapid cycling (Carvalho 2014) and who have features of mixed state (González-Pinto 2010). Gonzàles-Pinto's previous work (Gonzàles-Pinto 2007) discovered that high anxiety scores are found among patients with previous mixed states and that in mixed state, these anxiety symptoms were associated more heavily with depression scores than with mania scores (Gonzàles-Pinto 2007, Swann 2009). In our sample, we identified an almost significant correlation between mixed states features and anxiety ($\chi^2=2.796$, P=0.091).

We suspect that the links between suicidal ideation in depressive episodes, urgency associated with anxiety in mixed state, and possible disinhibitory effects of antidepressant treatment could account for the particularly high suicide risk in this population. This allows us to identify a potentially prognostic factor of anxiety in a depressive episode, and this also allows us to lend support to recommendations to avoid antidepressant treatment in these patients unless strictly in tandem with mood stabilisers (Akiskal 2005). In grossly simplified terms, it might be that depression provides the suicidal thought, the urgency and stress associated with anxiety provides the distress to turn thought into action, and antidepressants initiate or potentiate a mixed state that provides the energy to follow through.

This might also be considered in light of the aetiology of rapid cycling bipolar disorder, which seems to be particularly linked to previous antidepressant use (Carvalho 2014). In our sample, 7 patients of the bipolar population reported elated moods in association with treatment with antidepressants. Of those, 5 (71.4%) reported rapid cycling and 6 (85.7%) reported mixed state features – we acknowledge that we do not have enough patients to reach significance.

Previous research has also identified high percentages of substance misuse in patients with both rapid cycling (Carvalho 2014) and mixed state features

(Azorin 2012). In our sample, patients reported high levels of previous substance use but diminished current use; we view this in consideration of possible triggering effects substances might have on the initiation of cycling and mood instability in a population that is already at risk of these.

Mixed states features and rapid cycling are more represented in bipolar II than in bipolar I, and borderline personality disorder traits are more represented in rapid cycling and mixed state features subgroups. With this in mind, we surmise a possible relationship between these symptomatological conditions at both a biological and a psychodynamic level. This is in particular consideration of the link that Perugi et al. (Perugi 2011) found between atypical depression, borderline personality disorder, and bipolar II. Might it therefore be possible to consider atypical depression as a Kraepelinian subgroup of mixed state (Vampini 2014)? If we assume so, we can state that the cyclothymic diathesis matrix proposed by Perugi et al. (Perugi 2011) correctly identifies these conditions as linked. This, needless to say, has an important impact on prognosis and the treatment of atypical depression with antidepressants; we reiterate our support of recommendations that patients with rapid cycling or mixed state features should not receive antidepressant treatment unless in conjunction with a mood stabiliser.

In addition, this would suggest that the "with mixed features" specifier of the new DSM-V can help clinicians recognize subthreshold mixed episodes not only in patients with bipolar disorder but also in patients with unipolar depression, allowing for more accurate detection of patients who do or do not truly have bipolar disorder.

The aetiology of rapid cycling bipolar disorder remains unclear, but antidepressant use and hypothyroidism are implicated in a causal or triggering role (Carvalho 2013). In our sample of 70 patients, 7 patients reported elation in association with antidepressant treatment, and 5 (71.4%) of these patients demonstrated features of rapid cycling and 6 (85.7) mixed state. We also previously reported that 6 patients of our general bipolar population had thyroid abnormalities, of which 4 (66.6%) reported hypothyroidism, 1 (16.7%) are noted to have hyperthyroidism, and 1 (16.7%) is noted to have unspecified thyroid dysfunction,and 2 (33.3%) of those were noted to have both mixed state features and rapid cycling. However, our small sample size does not allow us to reach valid conclusions on this topic.

RECOMMENDATIONS, LIMITATIONS, AND CONCLUSIONS

There were limitations to our study. The small sample size and consequently reduced statistical power of the study are limitations; all of the patients in this

study are outpatients at the ASPA clinic seen by only one of the senior psychiatrists (M.A.) of the clinic; that mostly one psychiatrist is involved is a limitation as well, as this may produce a bias as a result of a single clinician's preponderance towards particular questions.

Our paper would like to represent a pilot study for further analysis of the importance of mixed state features and rapid cycling as prognostic factors for bipolar disorder. Further research will allow health services to distribute resources on a community level more effectively.

On the basis of our results, we would like to provide some preliminary recommendations

1) All psychiatric assessments of bipolar disorder should include identification mixed state features and rapid cycling when present in order aid treatment and prognostication.

2) Broader classifications of mixed state and rapid cycling are needed to distinguish subthreshold presentations.

3) Information about previous antidepressant treatment should be recorded in clinical notes, and antidepressant treatment in patients with mixed state features and rapid cycling should be avoided if not in conjunction with mood stabilisers.

4) The collection of information about physical comorbidities is an important part of psychiatric assessment, and clinicians should have a low threshold to perform thyroid hormone screens in patients with bipolar disorder because of the impact that a comorbidity of thyroid disorder has on the aetiology of rapid cycling.

5) Cessation of substance misuse in adolescents and young adults with bipolar disorder must be a key goal for clinicians in light of the known effects on the aetiology of mixed state and rapid cycling.

References

1. *Akiskal HS: The distinctive mixed states of Bipolar I, II and III. Clin Neuropharmacol 1992; 15, Pt. A.*

2. *Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H & Hirschfeld R: Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord 2000; 59(Suppl. 1):S5–S30.*

3. *Akiskal HS, Benazzi F, Perugi G & Rihmer Z: Agitated "unipolar" depression re-conceptualized as a depressive mixed state: Implications for the antidepressant-suicide controversy. J Affect Disord 2005; 85:245-258.*

4. *Angst J, Cui L, Swendsen J, Rothen S, Cravchik A, Kessler RC et al.: Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. Am J Psychiatry 2010; 167:1194–1201.*

5. *Azorin JM, Kaladjian A, Adida M, Fakra E, Belzeaux R, Hantouche E et al.: Self-assessment and characteristics of mixed depression in the French national EPIDEP study. J Affect Disord 2012; 143:109–117.*

6. *Carvalho A, Dimellis D, Gonda X, Vieta E, McIntyre RS & Fountoulakis KN: Rapid Cycling in Bipolar Disorder: A Systematic Review J Clin Psychiatry 2014; 75:e578–e586.*

7. *Cassidy F, Yatham LN, Berk M & Grof P: Pure and mixed manic subtypes: a review of diagnostic classification and validation. Bipolar Disord 2008; 10:131–143.*

8. *Dunner DL & Fieve RR: Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 1974; 30:229–233.*
    doi:10.101/archpsyc.1974.01760807013PubMed

9. *González-Pinto A, Aldama A, Mosquera F & González Gómez C: Epidemiology, diagnosis and management of mixed mania. CNS Drugs 2007; 21:611–626 .*

10. *Gonzalez-Pinto A, Alberich S, Barbeito S, Alonso M, Vieta E, Martinez-Aran A et al.: Different profile of substance abuse in relation to predominant polarity in bipolar disorder: the Vitoria long-term follow-up study. J Affect Disord 2010; 124:250–255.*

11. *Jenner FA, Gjessing LR, Cox JR, Davies-Jones A, Hullin RP & Hanna SM. A manic depressive psychotic with a persistent forty-eight hour cycle. Br J Psychiatry. 1967; 113:895–910. doi:10.192/bjp.13.501.895PubMed*

12. *Kraepelin E: Psychiatrie. Ein Lehrbuch für Studierende und Ärzte, Klinische Psychiatrie. Verlag von Johann Ambrsius Barth, Leipzig, Germany, 1899.*

13. *Kraepelin E: Manic-Depressive Insanity and Paranoia. Edinburgh, Scotland: Livingstone; 1921.*

14. *Mackinnon DF & Pies R: Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. Bipolar Disord 2006; 8:1–14. doi:10.1/j.139-5618.206.0*

15. *McElroy SL, Keck PE Jr., Pope HG Jr., Hudson JI, Faedda GI & Swann AC: Clinical and Research Implications of the Diagnosis of Dysphoric or Mixed Mania or Hypomania. Am J Psychiatry 1992; 149:1633-1644.*

16. *Nusslock R & Frank E: Subthreshold bipolarity: diagnostic issues and challenges. Bipolar Disord 2011; 13:587-603.*

17. *Pacchiarotti I, Mazzarini L, Kotzalidis GD, Valentì M, Nivoli AMA, Sani G et al.: Mania and depression. Mixed, not stirred. J Affect Disord 2011; 133:105-113.*

18. *Pacchiarotti I, Nivoli AMA, Mazzarini L, Kotzalidis GD, Sani G, Koukopoulos A et al.: The symptom structure of bipolar acute episodes: In search for the mixing link. J Affect Disord 2013; 149: 56-66.*

19. *Perugi G & Akiskal HS: Emerging concepts of mixed states: a longitudinal perspective. In: Marneros, A., Goodwin, F.K. (Eds.), Emerging Concepts of Mixed States: A Longitudinal Perspective. 2005, Cambridge University Press, Cambridge, UK, pp. 45–60.*

20. *Perugi G, Fornaro M & Akiskal HS: Are atypical depression, borderline personality disorder and bipolar II*

disorder overlapping manifestations of a common cyclothymic diathesis? World Psychiatry 2011; 10:45-51.

21. Swann AC, Steinberg JL, Lijffijt M & Moeller GF: Continuum of depressive and manic mixed states in patients with bipolar disorder: quantitative measurement and clinical features. World Psychiatry 2009; 8:166-172.

22. Vampini C & Nifosì F: Gli stati misti bipolari: evoluzione del concetto e implicazioni per la cura e la ricerca. (Bipolar mixed states: evolution of the concept and implications for the treatment and research). J Psychopathol 2014; 20:92-106.

23. Verdolini N, Dean J, Quartesan R, Elisei S, Zaman R, Agius M: Bipolar disorder: the importance of clinical assessment in identifying prognostic factors. Part 1. Psychiatr Danub 2014 (Article in press).

Correspondence:

Norma Verdolini
School of Specialization in Psychiatry, Division of Psychiatry, Clinical Psychology and Rehabilitation
Department of Medicine, University of Perugia, Santa Maria della Misericordia Hospital
Perugia, Italy
E-mail: norma.verdolini@libero.it