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The co-occurrence of manic and depressive dimensions in early psychosis: a latent transition analysis

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Abstract

Background. Frequently associated with early psychosis, depressive and manic dimensions may play an important role in its course and outcome. While manic and depressive symptoms can alternate and co-occur, most of the studies in early intervention investigated these symptoms independently. The aim of this study was therefore to explore the co-occurrence of manic and depressive dimensions, their evolution and impact on outcomes.

Methods. We prospectively studied first-episode psychosis patients ($N = 313$) within an early intervention program over 3 years. Based on latent transition analysis, we identified subgroups of patients with different mood profiles considering both manic and depressive dimensions, and studied their outcomes.

Results. Our results revealed six different mood profiles at program entry and after 1.5 years follow-up (absence of mood disturbance, co-occurrence, mild depressive, severe depressive, manic and hypomanic), and four after 3 years (absence of mood disturbance, co-occurrence, mild depressive and hypomanic). Patients with absence of mood disturbance at discharge had better outcomes. All patients with co-occurring symptoms at program entry remained symptomatic at discharge. Patients with mild depressive symptoms were less likely to return to premorbid functional level at discharge than the other subgroups. Patients displaying a depressive component had poorer quality of physical and psychological health at discharge.

Conclusions. Our results confirm the major role played by mood dimensions in early psychosis, and show that profiles with co-occurring manic and depressive dimensions are at risk of poorer outcome. An accurate assessment and treatment of these dimensions in people with early psychosis is crucial.

Introduction

Early intervention programs for psychosis have been developed within the last 30 years. Intensive and specialized intervention in the early phase of psychosis improves symptomatic and functional outcomes, increases satisfaction and engagement in care, reduces the risk of suicide and relapse, and is superior to treatment as usual in various outcomes (Birchwood, Todd, & Jackson, 1998; Correll et al., 2018; Fusar-Poli, McGorry, & Kane, 2017; Galletly et al., 2016). Although specialized and integrated early intervention programs improve care in psychosis globally, there are still some challenges to resolve, such as further improving relapse prevention in the most difficult to treat patients, and the identification of patient sub-groups with specific treatment needs, in order to adapt early intervention strategies (Conus & McGorry, 2002; Dempster, Li, Sabesan, Norman, & Palaniyappan, 2021; Ramain, Conus, & Golay, 2021b). In this regard, mood symptoms may prove crucial in improving our understanding of the early course of first-episode psychosis (FEP) as they are notably associated with poor outcome and could help differentiate sub-groups of FEP patients with specific needs (Arrasate et al., 2014; Bebbington, 2015; Ramain et al., 2021b; Ramain, Conus, & Golay, 2022).

Mood symptoms are common in psychosis. The prevalence of depressive symptoms ranges between 14.15 and 44.80% after FEP. In addition, around 30% of FEP patients suffer from an

affective psychosis (Coentre, Talina, Góis, & Figueira, 2017; Kennedy et al., 2005; Ramain, Conus, & Golay, 2021a). Studies on early psychosis have highlighted the burden of manic and depressive dimensions. Indeed, patients with manic symptoms may hardly fully recover after a first episode (Conus et al., 2006; Conus & McGorry, 2002; Marwaha et al., 2021), and depressive symptoms are associated with long-term functional impairment (Alameda et al., 2017; McGinty & Upthegrove, 2020). Despite the burden of mood symptoms in early psychosis, their course over time and predictive values remain understudied (Arrasate et al., 2014; Ciompi, 2015).

Furthermore, literature on early psychosis investigated depressive and manic symptoms independently, with a large focus on first-episode mania (Arrasate et al., 2014; Conus & McGorry, 2002; Ratheesh et al., 2017). Nevertheless, the possible alternation of manic and depressive episodes in sub-groups of psychosis suggests that manic and depressive dimensions can interact (Strakowski et al., 1998). Depressive and manic symptoms may also co-occur, leading to poor quality of life and functioning (Bauer, Simon, Ludman, & Unützer, 2005). In sum, despite manic and depressive dimensions, and their possible co-occurrence, remain understudied in FEP, previous literature suggests that manic and depressive symptoms may be determinant in the course of early psychosis. There is a subsequent need for studies investigating the co-occurrence of mood dimensions and their impact in FEP.

Consequently, the aims of this study were to investigate (1) the co-occurrence of manic and depressive dimensions defining mood profiles in the early course of psychosis, (2) their trajectories over three years of treatment in early psychosis and, (3) their impact on functional and symptomatic outcomes in an early intervention in psychosis program.

Method

Sample and procedure

This is a prospective study on a cohort of FEP patients treated at the Treatment and Early Intervention in Psychosis Program (TIPP) that has been implemented by Lausanne University Hospital's Department of Psychiatry in 2004 (Baumann et al., 2013; Conus & Bonsack, 2004). Patients entering the program are aged 18–35, reside in the Lausanne catchment area and have crossed the psychosis threshold according to the Comprehensive Assessment of At-Risk Mental States scale (CAARMS; Yung et al., 2005) based on the *Psychosis Threshold* subscale. Patients are referred to other programs if they have been on antipsychotic medication for more than six months, have an intoxication-induced or organic brain disease-induced psychosis, or have an intelligence quotient below 70. The TIPP favors a bio-psycho-social approach and provides 3 yearlong psychiatric and case management follow-up including psychotherapy, psychoeducation, family support and therapy, cognitive assessment and remediation, social support, supported employment, psychological interventions for cannabis use, and pharmacological treatment. In line with international guidelines, atypical antipsychotics are a first-line pharmacological treatment used in order to minimize side effects (Baumann et al., 2013). Case managers fill out a specifically designed questionnaire for the TIPP with every patient. This includes items on socio-demographic characteristics, medical history, exposure to traumatic life events, psychopathology and usual functioning. Follow-up assessments are carried out at 2, 6, 12, 18, 24, 30 and 36 months, by a psychologist and a case manager, to explore various aspects of treatment: changes in psychopathology and treatment, functional status, insight and treatment adherence, as well as intermittent exposure to trauma, suicide attempts, forensic events and substance use. The study was approved by the Human Research Ethics Committee of the Canton of Vaud (protocol #2020-00272). The data generated during follow-up were only used if patients provided written informed consent; only five of them refused to have their clinical data used for research, yielding a highly representative sample of early psychosis patients.

Diagnostic assessment

The diagnoses result from an expert consensus built from discussions held at 18 and 36 months, based on the DSM-IV criteria and using information from patients' medical records provided by their treating psychiatrists and their case manager. We used the latest consensus diagnosis available.

Depressive and manic symptoms

Depressive and manic symptoms were assessed at 2, 6, 12, 18, 24, 30, 36 months follow-up. We measured the severity of depressive symptoms using the overall score of the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), and manic symptoms with the overall score of the Young Mania Rating scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978).

Outcomes at discharge

We considered scores at 36 months follow-up or 30 if not available, for the outcome measures at discharge. We used 8 items of the PANSS (delusion, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms, blunted affect, social withdrawal, lack of spontaneity; Andreasen et al., 2005)) following Andreasen's Criteria (score $\leqslant 3$) to determine symptomatic recovery. A PAS score equal or lower to the premorbid rating on four of the five PAS general scale's items defined functional recovery (Strakowski et al., 1998). The assessment of independent living recovery (head of household/living alone, with partner, or with peers/living with family with minimal supervision) was carried out using the Modified Vocational Status Index and working recovery (paid or unpaid full- or part-time employment/being an active student in school or university/head of household with employed partner (homemaker/full or part-time volunteer) using the Modified Location Code Index Independent living (Tohen et al., 2000). Insight recovery was defined as full insight at discharge. We assessed quality of life at discharge with the World Health Organization Quality Of Life scale ('The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization,', 1995). It measures satisfaction with life and self-esteem through 26 self-rated items with 5-point Likert scales ranging from 1 (low satisfaction) to 5 (high satisfaction).

Statistical analysis

First, we performed a latent profile analysis (LPA) for the beginning, middle and end of the program. Depressive and manic symptoms, respectively MADRS and YMRS scores, were used as

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indicators. To guarantee model statistical identification and deal with missing data, each LPA was estimated using depressive and manic symptom scores of two neighboring assessment (2 and 6 months, 12 and 18 months, 30 and 36 months) with measurement invariance imposed across the two depressive symptom respectively the two manic symptom indicators. The best solution was determined using the Bayesian information criterion (BIC) coefficient, which balances model fit and model complexity, i.e. the number of parameters (Schwarz, 1978).

Second, we performed a latent transition analysis (LTA). Given the meaning of the classes was very close between each three LPA, we also imposed longitudinal measurement invariance in the LTA model. While reducing the total number of model parameters, it also ensured the meaning of the classes would stay the same between the beginning, middle and the end of the program, thus facilitating interpretation.

Finally, in order to compare scores from the different classes at discharge, we used a Bayesian model comparison approach. This represents an elegant alternative to the classic problem of multiple comparisons and enables evaluations to support the null hypothesis (Golay et al., 2020; Golay, Morandi, Silva, Devas, & Bonsack, 2019; Noël, 2015). The first model was the homogeneous model (1, 2, 3, 4), stating that the four groups did not differ and were issued from the same distribution. It corresponds to the null hypothesis in the classical statistical testing framework. Another model was the heterogeneous model: (1) (2) (3) (4) (i.e. all the groups were different from each other and were issued from four different distributions). All other possible combinations, which adds up to 15 – for instance (1, 2, 3), (4) or (1, 3), (2, 4) – were also estimated. For continuous variables, the best possible Gaussian model (μ, σ2) was determined by use of the BIC (Schwarz, 1978). For nominal variables, the best multinomial model was determined using the exact likelihood with a uniform prior on all parameters (Noël, 2015). An equal prior probability of 1/15 was assumed for all models so that no model was favored. The Bayes factor was also computed (Kass & Raftery, 1995) and provided a comparison between the best model and the homogenous model. A Bayes factor of 4 indicates that the best model was 4 times more likely to be true than the homogenous model. Values over 3 are generally considered sufficiently important to favor one model over another (Jeffreys, 1961; Wagenmakers, Wetzels, Borsboom, & Van Der Maas, 2011).

All statistical analyses were performed using the Mplus statistical package, version 8.3, IBM SPSS, version 26, the AtelieR package for R (Noël, 2013) and the Bayes R2STATS group models calculator (Noël, 2018).

Results

Patient sample

The sample consisted of 313 patients (Mean age = 24.8; S.D. = 4.81), and included a majority of males (65.5%). Among these patients, 56.9% met diagnostic criteria for schizophrenia, 12.5% for schizophreniform or brief psychotic disorder, 9.9% % for schizoaffective disorder, 8.0% for bipolar disorder with psychotic features, 3.2% for major depressive disorder with psychotic features, and 9.6% for other psychotic disorders.

Characteristics of the different LPA solutions (Table 1)

A six-class solution was chosen for the first LPA (2–6 months corresponding to the beginning of the program) based on its lowest BIC and clinical interpretability. The first class consisted of patients with moderate depression (MADRS score 20–34). The second class consisted of patients without any mood disturbance (MADRS and YMRS scores <12). The third class consisted of patients with hypomania (YMRS score 12–19). The fourth class consisted of patients with co-occurring manic and depressive symptoms (MADRS score 20–34 and YMRS score 12–19). The fifth class consisted of patients with severe depression (MADRS score >33) and the sixth class with mania (YMRS score >20). For the LPA performed in the middle of the program (12–18 months), BIC indicated a six-class solution similar to the classes observed in the first LPA. The LPA performed at the end of the program (30–36 month) revealed a four-class solution with a similar interpretation, but no class including patients with severe depression or mania.

Table 1. Characteristics of the three latent class analysis solutions

Number of classes	Entropy	BIC
Beginning (2–6 months)		
1	–	4823.006
2		4774.360
3		4750.420
4		4731.229
5		4729.334
6		**4729.125**
7		4730.291
Middle (12–18 months)		
1		4630.792
2		4515.393
3		4498.492
4		4493.853
5		4486.680
6		**4484.543**
7		4498.322
End (30–36 months)		
1		3603.448
2		3561.489
3		3529.455
4		**3527.091**
5		3528.941

Note. BIC, Bayesian information criterion; a, one class is empty. The best class was determined on the basis of the lowest BIC coefficient and is indicated in bold.

Depressive and manic dimension trajectories over the 36 months follow-up (Table 2)

Our results suggested that 38.3% of patients had not any mood disturbance from the beginning to the end of the program. Among patients who had not any mood disturbance at the end, 15.3% of patients had moderate depression, 8.6% had hypomania, 2.2% had severe depression, and 0.9% had severe mania at the beginning. 12.8% of patients remained moderately depressed

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Table 2. Depressive and manic dimension trajectories over the 36 months follow-up ($N = 313$)

Beginning	End	*N*	%
Absence of mood disturbance	Absence of mood disturbance	120	38.3
Moderate depression	Absence of mood disturbance	48	15.3
Moderate depression	Moderate depression	40	12.8
Hypomania	Absence of mood disturbance	27	8.6
Moderate depression	Hypomania	15	4.8
Severe depression	Absence of mood disturbance	7	2.2
Co-occurrence	Hypomania	6	1.9
Absence of mood disturbance	Hypomania	5	1.6
Severe depression	Co-occurrence	3	0.9
Mania	Absence of mood disturbance	3	0.9
Absence of mood disturbance	Moderate depression	2	0.6
Severe depression	Hypomania	2	0.6

Note. The trajectories are presented according to their frequency of occurrence in the cohort.

from the beginning to the end of the program, while 4.8% transited from moderate depression to hypomania. Moreover, among patients who transited to hypomania at the end, 1.9% had co-occurring manic and depressive symptoms, 1.6% had not any mood disturbance, and 0.6% had severe depression at the beginning. 0.9% of patients had severe depression at the beginning but co-occurring manic and depressive symptoms at the end. 0.6% of patients had not any mood disturbance at the beginning but were moderately depressed at the end.

Transition matrices between the beginning and the end of the program (Table 3)

All patients with mania at the beginning of the program had not any mood disturbance at the end of the program. A majority of patients (58.7%) with severe depression at the beginning of the program had not any mood disturbance at the end, but some of them developed hypomanic symptoms (16.7%), and others co-occurring manic and depressive symptoms (25%). Nearly all patients without any mood disturbance at the beginning of the program did not display mood symptoms at the end, only few of them had a moderate depression (1.6%) or hypomania (3.9%). While nearly half of patients with moderate depression at the beginning of the program had not any mood disturbance at the end, 38.8% of them remained moderately depressed and 14.6% presented hypomanic symptoms. Despite 64.3% of patients with hypomania at the beginning of the program had not any mood disturbance at the end, 35.7% of them remained hypomanic at the end. Three-quarters of patients with co-occurring manic and depressive symptoms at the beginning of the program had a moderate depression at the end of the program, the 23.1% remaining had hypomanic symptoms at the end.

Comparison of outcomes between groups of mood profiles at discharge (Table 4)

Globally, patients without any mood disturbance at discharge had a better outcome at the end of the program. Indeed, patients without any mood disturbance had better symptomatic and functional recovery, a better working recovery, as well as better quality of environment and social relationships than the other groups. Patients with hypomania at discharge had poorer insight recovery than the other groups. Patients with moderate depression at discharge had a lower rate of return to premorbid functional level. Patients with moderate depression or co-occurring manic and depressive symptoms had a poorer quality of physical and psychological health than patients without any mood disturbance or hypomania. All groups had a similar independent living recovery.

Discussion

In this study, we investigated the co-occurrence of mood dimensions and their impact on symptomatic and functional outcomes in a cohort of FEP patients. In this regard, we identified latent sub-groups based on depressive and manic dimensions and explored their evolution and outcomes at the end of the program. Results of LTA revealed six mood profiles at the beginning of the program: a subgroup of patients without any mood disturbance, one with moderate depressive symptoms, one with co-occurring manic and depressive symptoms, one with hypomanic symptoms, one with severe depressive symptoms, and one with severe manic symptoms. These profiles evolved at the end of the program into four different profiles: one without any mood disturbance, one with moderate depressive symptoms, one with co-occurring manic and depressive symptoms, and one with hypomanic symptoms. These results suggested that manic and depressive dimensions can co-occur at a moderate level (Co-occurrence profile), but not at a severe level (severe depressive or manic profile). They also showed that mood dimensions have an important impact in the early course of psychosis. Indeed, the subgroup without any mood disturbance at discharge had better outcomes, especially regarding psychotic symptomatic recovery, functional and working recovery, as well as quality of environment and social relationship at discharge.

In line with previous literature, our results suggested that either depressive or manic symptoms worsen prognosis in early psychosis (Bauer et al., 2005; Ciompi, 2015; Conus et al., 2006; Marwaha et al., 2021; Morrissette & Stahl, 2011). In addition, our results

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Table 3. Transition matrixes between the beginning and the end of the program

				End of the program			
			Total	Moderate depression (MADRS score 20–34)	Absence of mood disturbance	Hypomania (YMRS score 12–19)	Co-occurrence (moderate depression and hypomania)
Beginning of the program	Moderate depression (MADRS score 20–34)	*n* =	103	**40**	48	15	0
		% within beginning		**38.8**	46.6	14.6	0.0
	Absence of mood disturbance	*n* =	127	2	**120**	5	0
		% within beginning		1.6	**94.5**	3.9	0.0
	Hypomania (YMRS score 12–19)	*n* =	42	0	27	**15**	0
		% within beginning		0.0	64.3	**35.7**	0.0
	Co-occurrence (moderate depression and hypomania)	*n* =	26	20	0	6	**0**
		% within beginning		76.9	0.0	23.1	**0.0**
	Severe depression (MADRS score >33)	*n* =	12	0	7	2	3
		% within beginning		0.0	58.3	16.7	25.0
	Mania (YMRS score >20)	*n* =	3	0	3	0	0
		% within beginning		0.0	100	0.0	0.0

Note. Cells in bold indicates stability.

showed that 94.5% of patients without any mood disturbance at the beginning of the program had not any mood disturbance at the end, suggesting a stability of the absence of mood disturbance profile: on this basis, it seems possible to identify FEP patients with a risk of enduring mood symptoms early in treatment. Reciprocally, our results suggest that identification of mood symptoms at the beginning of treatment justifies their treatment and may even deserve the development of specific interventions.

However, treating mood dimensions at the beginning of early intervention program would require assessing and adjusting treatment of mood dimensions accurately, as previously suggested (Lambert, Conus, Lambert, & McGorry, 2003; Ramain et al., 2021a). Unfortunately, our results also revealed that, while all patients with manic symptoms, and a majority of patients with hypomanic (64.3%) or severe depressive symptoms (58.3%) at the beginning of the program did not have any mood disturbance at the end, none of the patients with co-occurring manic and depressive symptoms at the beginning were free of mood disturbance after 3 years. Indeed, they had moderate depressive (76.9%) or hypomanic (23.1%) symptoms at discharge. These results suggested that pure manic/hypomanic or severe depressive forms, contrary to mild mood symptoms, are probably well identified, and appropriately treated leading to the resolution of mood disturbance at the end of treatment. However, results also showed that all patients with co-occurrence profile at the beginning remained symptomatic at the end, suggesting the need to improve assessment and specific treatment for patients with co-occurring manic and depressive dimensions, even under threshold of a florid manic or severe depressive episode (Bauer et al., 2005; Berk, 2007; Marneros, Röttig, Wenzel, Blöink, & Brieger, 2004; Ramain et al., 2021a). Further studies on FEP investigating depressive and manic dimensions together, rather than independently, are also required.

Moreover, our results showed that patients with mild depressive symptoms at discharge had a lower rate of return to premorbid functional level than the other subgroups. They also showed that displaying a depressive component was associated with poorer quality of physical and psychological health. These results may confirm previous findings that a depressive dimension, even under depression diagnostic threshold, has a negative impact on outcome (Alameda et al., 2017; Fiedorowicz et al., 2021). It also supports the idea that some patients develop a poorer outcome via an affective pathway (Alameda et al., 2020; Alameda, Conus, Ramain, Solida, & Golay, 2022; van Os et al., 2020). Contrary to previous studies (Alameda et al., 2022; Calderon-Mediavilla et al., 2021), we did not observe a significant association between

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Table 4. Comparison of outcomes between groups of mood profiles at discharge

	(1) Moderate depression ($n = 62$)	(2) Absence of mood disturbance ($n = 205$)	(3) Hypomania ($n = 43$)	(4) Co-occurrence ($n = 3$)	Best model[a]	Bayes factor against null hypothesis [b]	Probability of the model to be true[c]
Symptomatic recovery, % (*n*)	25.0 (10)	69.6 (71)	34.2 (13)	0.0 (0)	(1, 3, 4) (2)	1 120 684.4816	0.3506
Insight recovery, % (*n*)	69.6 (32)	65.4 (89)	42.9 (15)	66.7 (2)	(1, 2, 4) (3)	6.5437	0.2863
General functional recovery, % (*n*)	20.0 (11)	57.5 (88)	29.3 (12)	0.0 (0)	(1, 3, 4) (2)	399 792.8051	0.3583
Premorbid adjustment recovery, % (*n*)	28.6 (10)	50.0 (55)	46.4 (13)	66.7 (2)	(2, 3, 4) (1)	2.8226	0.2132
Independent living recovery, % (*n*)	57.1 (28)	65.5 (93)	60.5 (23)	66.7 (2)	(1, 2, 3, 4)	1.0000	0.2580
Working recovery, % (*n*)	16.3 (8)	39.0 (55)	21.1 (8)	0.0 (0)	(1, 3, 4) (2)	60.5788	0.3423
Quality of life, M (S.D.)							
Quality of physical health	22.03 (4.460)	26.80 (4.165)	25.14 (5.112)	19.00 (2.828)	(1, 4) (2, 3)	92.3229	0.5025
Quality of psychological aspects	18.55 (3.293)	22.63 (3.436)	21.70 (3.263)	17.50 (4.950)	(1, 4) (2, 3)	353.0749	0.6286
Quality of social relationships	9.17 (2.517)	11.03 (1.793)	10.11 (3.127)	10.00 (2.828)	(1, 3, 4) (2)	3.1402	0.2341
Quality of environment	27.94 (5.778)	31.49 (5.018)	24.42 (6.215)	25.50 (3.536)	(1, 3, 4) (2)	755.3846	0.3177

Note.
[a]Based on BIC coefficient.
[b]Bayes factor comparing the best model to the homogeneous model (1, 2, 3, 4).
[c]Compared to all possible models.

depressive symptoms and psychotic symptomatology. However, to our knowledge, this is the first study that investigated the co-occurrence of manic and depressive dimensions in early psychosis, considering the impact of the relative expression of both dimensions at the same time, rather than separately.

Our results should be considered with some degree of caution considering several limitations. First, due to too many missing data, we were not able to include analysis of medication. Second, the prospective realistic design of the follow-up did not allow to control for all the confounding factors possibly explaining for the appearance of mood disturbance and its variation (e.g. trauma, cannabis use). Third, the methodology used did not allow us to differentiate outcome of patients without any mood disturbance since the beginning of the program, from those of patients remitted from a mood disorder at the end. Fourth, because the size of several sub-groups at the beginning of the program was very small, we were not able to include robust results about the prediction of outcomes at discharge based on latent class profiles of the beginning of the program.

Conclusion

This study investigated the co-occurrence of manic and depressive dimensions in FEP and their impact on outcome. Based on transition LTA, we identified subgroups of patients with different mood profiles considering the relative expression of manic and depressive symptoms. Our results showed that the subgroup of FEP patients without any mood disturbance at the end of the program had better outcomes. They also revealed that the co-occurrence of manic and depressive dimension, as well as a depressive component under threshold, may require specific treatment adjustment in early intervention. Further studies investigating both manic and depressive dimensions together in FEP are required.

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Conflict of interest. The authors declare that there is no conflict of interest.

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