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Negative Affective Features in 516 Cases of First Psychotic Disorder Episodes: Relationship to Suicidal Risk

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Abstract

Objectives: Plausible candidates of psychopathological phenomena that may associate with or anticipate suicidal risk, include negative affects, including admixtures of dysphoria, depression and anxiety described mainly in nonpsychotic disorders. We ascertained the distribution of such affective features in various first-episode psychotic disorders and correlated these and other clinical and antecedent features with intake suicidal status.

Methods: We evaluated 516 adult subjects in first-lifetime episodes of various DSM-IV-TR psychotic disorders. Blinded, protocol-guided, assessments of clinical features ascertained in SCID examinations, self- and family reports and clinical records supported analyses of associations of suicide attempts at first-psychotic episodes with antecedent and intake clinical characteristics, including negative affects and diagnoses, using standard bivariate and multivariate methods.

Results: Negative affective features in various combinations were prevalent (90%) and at >75% in both affective and nonaffective psychotic disorders; anxious depression was most common (22%). We identified antecedent and intake clinical factors preliminarily associated with suicide attempts. Factors remaining independently associated in multivariate logistic modelling (ranked by OR) were: (a) prior suicide attempt, (b) prior aggressive assault, (c) bipolar-mixed state or psychotic major depression diagnosis, (d) prior dysphoria, (e) intake dysphoric-anxiousdepression, (f) prior impulsivity, (g) previous affective instability, (h) previous nonpsychotic depression, (i) previous decline in vital drive, and (j) prior sleep disturbances.

Conclusions: Various types and combinations of negative affective features (especially anxious depression with and without dysphoria) were prevalent across nonaffective as well as affective first psychotic episodes and strongly associated with suicide attempts. These findings extend previous observations in nonpsychotic disorders.

Keywords: Antecedents; First-psychotic episodes; Mixed anxiety and depression; Prodromes; psychopathology; Suicidal risk

The unstable mixed states characterized by rapidly changeable and discordant shifts of mood and drive of depression, anxiety and dysphoria are expressions of dynamic instability, in the sense of Janzarik's, which makes them particularly susceptible to developing psychosis and aggression.

Introduction

Co-occurrence of anxiety and depression is prevalent in a variety of psychiatric disorders and may deserve consideration as a separate clinical entity [1,2]. Such combinations of negative affects have been proposed as useful predictors of poor treatment-response or adverse clinical outcomes including suicidal risk [3-8]. Most studies of such phenomena are limited to comorbid affective features in depressive or anxiety disorders, in classically defined neurotic, adjustment, and personality disorders, or in various general medical or neuromedical illnesses [1,9-12]. Notably, however, the prevalence and clinical implications of admixtures of negative affects in psychotic disorders, particularly early in their course, are little-studied [13].

Accordingly we evaluated the distribution of specific types of negative affects (combinations of anxiety, depression and dysphoria) among patient-subjects meeting DSM-IV-TR diagnostic criteria for a first-lifetime episode of an affective or non affective psychotic disorder requiring hospitalization. In addition, as a pilot test of the potential clinical value of identifying such affective features, we examined their association, along with diagnosis and other antecedent or current clinical features, with suicide attempts during the index initial psychotic episode.

Material and methods

Subjects and assessments

We studied 516 first-episode patient-subjects with a DSM-IV-TR psychotic-disorder at first lifetime psychiatric hospitalization who were enrolled in the *McLean-Harvard International First-Episode Psychosis Project* based at McLean Hospital and University of Parma in 1989–2003. Project protocols were reviewed annually and approved by the McLean Hospital Institutional Review Board and the Ethical Committee of the University of Parma Medical Center, through 2012, in full accordance with the 1975 Helsinki Declaration. All subjects

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provided signed, informed consent for study participation and for anonymous, aggregate reporting of findings. First-lifetime major episodes included both affective (manic, mixed, or depressive) and nonaffective psychoses (brief psychotic disorder, delusional disorder, psychosis not otherwise specified [NOS], schizoaffective disorders, schizophrenia, or schizophreniform disorder). Exclusion criteria were: (a) acute alcohol or drug intoxication or withdrawal, or any delirium; (b) previous psychiatric hospitalization, unless for detoxification or a non-psychotic syndrome; (c) documented mental retardation (WAIS-tested IQ <70) or other organic mental disorder; (d) index syndrome present >6 months; (e) any previous psychotic syndrome; or (f) previous treatment with an antipsychotic drug for a total of ≥4 weeks, or an antidepressant or mood-stabilizer for ≥3 months.

Diagnoses were based on baseline and 2 year SCID-P assessments, followed by best estimate, investigator-consensus that considered all available information, with diagnoses updated to meet DSM-IV-TR criteria in 2011–2012; final diagnoses were considered here except to note comparisons of bipolar-I disorder patients presenting in mania versus a mixed manic depressive state [14]. Assessments of antecedent features and first-psychotic episode phenomena also involved best-estimate procedures based on all available information from the SCID-P assessments, medical records, and clinical narratives from interviews of family members and primary treating clinicians (all with diagnoses removed). In addition, to guide recording of clinical phenomena and to develop comprehensive and systematic symptom inventories for each case, we followed the *Manual for Assessment & Documentation of Psychopathology* (AMDP system) [15] and the *Bonn Scale for the Assessment of Basic Symptoms* (BSABS) [16]. These assessments were made without preconceptions about the nature or timing of antecedent or presenting psychopathological phenomena in relation to type of presenting episode. The first author (PS) carried out comprehensive reviews of all available documents providing information about antecedent and first-episode clinical phenomena for all 516 first-episode psychotic subjects in random order over a three-year period, while held blind to initial and later diagnoses [17,18].

Data analysis

We compared subjects with a suicide attempt associated with the index, first-episode of psychotic illness vs. subjects without suicidal behaviours at intake, as regards final diagnoses, various types of negative affects parenthesis anxiety,, depression, dysphoria or their combinations), as well as various antecedent clinical characteristics preceding the index episode of psychotic illness. We tested continuous variables statistically by ANOVA (*F*) methods, and categorical measures by contingency tables (χ^2). Measures preliminarily associated with suicidal behaviour at intake, based on bivariate comparisons were entered, stepwise, into logistic, multivariate regression modelling to identify factors independently associated with high suicidal risk, based on Odds Ratios (OR) with their 95% confidence intervals (CI). Averages are means with standard deviations (±SD) unless stated otherwise. Statistical analyses used standard commercial programs (Stata-9®, Stata Corp., College Station, TX; Statview-5®, SAS Institute, Cary, NC).

Results

Subjects and diagnoses

The 516 subjects meeting DSM-IV-TR criteria for a first-lifetime psychotic episode included 285 (55.2%) men and 231 (44.8%) women, of average intake-age of 31.5±13.6 years. Initial diagnoses ranked: bipolar mania (n=150), bipolar mixed manic-depressive episode (n=84), major depressive episode (n=80), unspecified psychosis (psychosis-NOS, n=74), schizophrenia (n=48), brief psychotic disorder (n=37), delusional disorder (n=22), schizophreniform disorder (n=20), and schizoaffective disorder, depressed type (n=1). By 24 months of follow-up, final diagnoses ranked: type-I bipolar disorder (BD-I, n=244), schizoaffective disorder (n=61), recurrent major depressive disorder (recurrent MDD, n=52), schizophrenia (n=49), psychosis-NOS (n=38), brief Psychotic disorder (n=22), delusional disorder (n=18), unspecified bipolar disorder (BD-NOS, n=8), and schizophreniform disorder (n=2). Diagnoses changed in 111 (21.5%) of cases but no diagnostic changes were required after two years of follow-up. A total of 22 subjects (4.26%) refused to continue to two years or otherwise were lost to follow-up, which averaged 5.84±3.23 years from intake.

Distribution of negative affect-types by final diagnoses

We identified 7 types of negative affects at intake and determined their prevalence among final DSM-IV-TR diagnoses, as well as between BD-I patients presenting in mania versus mixed states (Table 1). Their prevalence in descending order, ranked: (a) the combination of anxiety and depressive features (22.1%), (b) dysphoria (16.4%), (c) the combination of anxiety, depression, and dysphoria (16.0%), (d) depression with dysphoria (12.6%), (e) anxiety only (8.50%), (f) depressive symptoms only (7.29%), and (g) anxiety with dysphoria (6.88%). A total of 89.7% of subjects had one of these 7 negative affective presentation-types, and only 10.3% had none (Table 1); no subject had more than one type of negative affect or combination. The finding that nearly 90% of first-episode psychotic disorder patients had some form of negative affect at intake indicates broad distribution across DSM-IV-TR diagnoses, not limited to affective psychotic disorders. Distribution of total negative affects by final diagnosis ranked: (1) recurrent MDD, BD-NOS and brief psychotic disorder (all at 100%); (2) psychosis-NOS (92.1%); (3) schizoaffective disorder (90.2%); (4) BD-I (somewhat greater among those presenting in manic-depressive mixed states [95.2%] than in pure mania [84.7%]) and delusional disorder (both at 88.9%); (5) schizophrenia (75.5%), and (6) schizophreniform disorder (50.0%; Table 1).

Clinical features associated with suicide attempts

Among the 516 subjects suicidal ideation was identified at baseline in 196 cases (37.9%), and suicide attempts prior to first hospitalization for a first-lifetime psychotic episode occurred in 100 (19.4%). Suicidal ideation without suicidal attempt was reported at baseline in 142 (27.5%) of cases. The distribution of suicide attempts, by final diagnosis (and for initial presentation of BD-I cases in either mixed or manic episodes), ranked: BD-NOS (37.5%), recurrent MDD (32.7%), initial bipolar-mixed episode (31.0%), schizoaffective disorder (21.3%), brief psychotic disorder (18.2%), BD-I (17.6%), psychosis-NOS (15.8%), delusional disorder (11.2%), schizophrenia (10.2%), initial bipolar mania (9.33%), and schizophreniform disorder (0.00%). In order to test the potential clinical value of the presence of negative affects, we evaluated their associations as well as associations of final diagnosis and other current or antecedent clinical factors with suicide attempts during index first psychotic episodes. Suicide attempts were identified in 100 subjects (19.4%) and absent in the remaining 416 (80.6%). In preliminary, bivariate testing, we identified a total of 12 factors associated with suicide attempts. They were of three types (ranked by relative association within-types; Table 2): (a) 8 antecedent factors (assaultive acts, suicide attempts, dysphoria, unstable or rapidly labile affects, evidence of impulsivity, non-psychotic depression, decreased vital drive, and sleep disturbances), (b) 2 affective presentations at

Diagnosis	Subjects (n)	Anxious Depression	Dysphoric Anxious Depression	Dysphoria	Anxious Dysphoria	Depressive Dysphoria	Anxiety	Depression	Any Negative Affects	No Negative Affects
Major depression	52	30 (57.7)	13 (25.0)	0 (0.00)	0 (0.00)	5 (9.62)	0 (0.00)	4 (7.69)	52 (100)	0 (0.00)
Bipolar-NOS	8	4 (50.0)	2 (25.0)	0 (0.00)	0 (0.00)	1 (12.5)	0 (0.00)	1 (12.5)	8 (100)	0 (0.00)
Schizophreniform	2	1 (50.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.0)	1 (50.0)
Psychosis-NOS	38	10 (26.3)	6 (15.8)	5 (13.2)	1 (2.63)	4 (10.5)	7 (18.4)	2 (5.26)	35 (92.1)	3 (7.89)
Schizoaffective	61	15 (24.6)	8 (13.1)	7 (11.5)	3 (4.92)	8 (13.1)	7 (11.5)	7 (11.5)	55 (90.2)	6 (9.84)
Brief psychosis	22	5 (22.7)	4 (18.2)	2 (9.09)	2 (9.09)	2 (9.09)	5 (22.7)	2 (9.09)	22 (100)	0 (0.00)
Bipolar-I **All cases* [Initial mania] [Initia mixed]**	244 [150] [84]	36 (14.8) 10 (6.67) 22 (26.2)	38 (15.6) 10 (6.67) 25 (29.8)	57 (23.4) 51 (34.0) 6 (7.14)	23 (9.43) 17 (11.3) 5 (5.95)	34 (13.9) 17 (11.3) 17 (20.2)	16 (6.56) 14 (9.33) 2 (2.35)	13 (5.33) 8 (5.33) 3 (3.57)	217 (88.9) 127 (84.7) 80 (95.2)	27 (11.1) 23 (15.3) 4 (4.76)
Schizophrenia	49	7 (14.3)	6 (12.2)	8 (16.3)	3 (6.12)	6 (12.2)	3 (6.12)	4 (8.16)	37 (75.5)	12 (24.5)
Delusional	18	1 (5.56)	2 (11.1)	2 (11.1)	2 (11.1)	2 (11.1)	4 (22.2)	3 (16.7)	16 (88.9)	2 (11.1)
***All cases* (n [%])**	494	109 (22.1)	79 (16.0)	81 (16.4)	34 (6.88)	62 (12.6)	42 (8.50)	36 (7.29)	443 (89.7)	51 (10.3)

[*] Including 10 cases that were re-diagnosed by 2 years after intake. Diagnoses (final, at two years of follow-up, based on all available information, except that presentation of bipolar-I disorder as mania or manic-depressive mixed states is based on initial presentation at intake). Data are in descending strength of association for anxious-depression.

At 2-year follow-up, 22 subjects were lost including one death from accidental fall 4 months after discharge, 9 with only baseline assessment and 12 who refused to participate into follow up assessments.

Table 1: Types of affective features at first lifetime episodes of affective or nonaffective psychotic disorders in 516 patients.

Factor	Suicide Attempts (%)		Risk Ratio	*F* or χ^2	*p*-value
	Present **(n=100)**	***Absent*** **(n=416)**			
Antecedent Factors					
Aggressive assaults	27.0	3.61	7.47	59.0	<0.0001
Suicide attempt	47.0	6.73	6.98	105.2	<0.0001
Dysphoria	49.0	25.5	1.92	21.2	<0.001
Unstable affects	42.0	24.0	1.75	13.0	<0.001
Impulsivity	66.0	42.6	1.55	17.8	<0.001
Depression (nonpsychotic)	50.0	35.1	1.42	7.60	0.001
Decreased vital drive	57.0	44.0	1.30	4.69	0.03
Sleep disturbances	50.0	39.2	1.28	3.89	0.05
Affect Types at Presentation					
Dysphoric-anxious-depression	31.0	13.0	2.38	19.0	<0.001
Absence of mania	85.0	73.1	1.16	4.72	0.03
Any negative affects	99.0	88.0	1.12	10.9	0.001
First Episode Type					
Major depression	28.0	12.5	2.24	14.8	<0.001
Bipolar-mixed state	26.0	13.9	1.87	8.60	0.003

Factors are ranked by risk-ratio (prevalence among cases that made a suicide attempt or not during the index illness episode).

Table 2: Clinical features preceding suicide attempts at first-lifetime major episodes in 516 psychotic disorder patients.

intake (the combination of anxiety and depression with dysphoria, and presence of any negative affect), and (c) 2 intake diagnostic factors (presenting in major depression or a manic-depressive mixed-state).

Multivariate modeling of factors associated with suicidal risk

We used stepwise, multivariate logistic modeling to test factors preliminarily associated with suicide attempts (Table 2). Ten of these remained significantly and independently associated with suicide attempt, ranking by Odds Ratio: (1) prior suicide attempt, (2) prior assaultive behavior, (3) in a mixed bipolar disorder state or in a major depressive episode at intake, (4) previous dysphoria, (5) the combination of dysphoria anxiety and depression at intake, (6) prior impulsivity, (7) previous unstable affects, (8) previous non-psychotic depression, (9) previously decreased vital drive, and (10) previous sleep disturbances (Table 3).

Discussion

The main finding of this study is that admixtures of anxious and depressive symptoms, with or without dysphoric features, were identified in 90% of 516 patient-subjects diagnosed with first lifetime DSM-IV-TR psychotic episodes, with prevalences of >=50% (all >75% except in schizophreniform disorder) in both nonaffective and affective psychotic disorders (Table 1). It is also noteworthy that combinations of negative affects were strongly and independently associated with suicide attempts during the index psychotic episode, even when additional risk factors were considered (Table 3). The additional correlated or risk factors were as expected from previous studies of factors associated with suicidal risk, including prior suicide attempts and aggressive assaults, a history of depression, impulsivity, affective instability, decreased vital drive and sleep disturbances [19]. Of note, prior dysphoria also was a risk factor, whereas current pure dysphoria was not, evidently owing to

Risk Factor	Odds Ratio [95% CI]	*z*-score	*p*-value
Prior suicide attempt	12.3 [7.09–21.3]	8.96	<0.001
Prior aggressive assault	9.89 [5.02–19.5]	6.62	<0.001
Bipolar-mixed or depression at intake	3.27 [2.08–5.12]	5.16	<0.001
Prior dysphoria	3.11 [1.89–4.40]	4.50	<0.001
Dysphoric-anxious-depression at intake	3.01 [1.81–4.22]	4.23	<0.001
Prior impulsivity	2.62 [1.66–4.14]	4.13	<0.001
Prior unstable affects	2.29 [1.45–3.61]	3.56	<0.001
Prior depression (nonpsychotic)	1.85 [1.19–2.87]	2.73	0.005
Prior decreased vital drive	1.62 [1.04–2.52]	2.16	0.03
Prior sleep disturbances	1.55 [1.00–2.41]	1.96	0.04

Factors ranked by Odds Ratio.

Table 3: Multivariate logistic regression model: Clinical features preceding or associated with suicide attempts at first-lifetime major episodes of 516 psychotic disorder patients.

the possibly seemingly paradoxical, but strong association of dysphoria with mania and grandiosity, with a relatively low suicidal risk [20]. In contrast, the strong association of suicidal risk with mixed manic-depressive illness as well as with major depression with psychotic features at intake underscores the relationship of negative affect and depression with suicidal risk [19]. Suicidal risk probably is further increased by elements of anger, agitation, aggression, and impulsivity associated with bipolar disorder [21]. The association of negative affects with suicidal risk has been noted previously in nonpsychotic disorders [6,7], and the present findings (Table 3) extend the relationship to psychotic disorders, whether affective or nonaffective in type. Psychotic disorders have a substantially increased risk of suicide, especially early in the illness-course [22-24]. Indeed, in psychotic disorders, suicide represents a major cause of excess mortality, in addition to comorbid medical disorders and potential toxic effects of psychotropic drugs [25-27]. However, most research on suicide risk in psychotic disorders has focused on schizophrenia, and far less is known about other forms of psychotic illness [21,23,24]. These considerations strongly encourage further efforts to identify practical, readily ascertained risk factors for suicide that can be found early in the broad range of non-affective and affective psychotic disorders. The present findings also highlight the particular importance of anxiety and depression in association with dysphoria as risk factors for suicide (Table 3). Dysphoria may be especially important when combined with other negative affects. It has been proposed as a fourth dimension of affective polarity in addition to anxiety, depression, and mania [28]. It overlaps with elements of depression and anxiety, but is usually marked by tension, disquietude, anger, irritability, and anguish [28]. Dysphoria can also be associated with rapidly changing affective states and may contribute to risk for perceptual disturbances, conceptual disorganization, psychotic perplexity, as well as aggression and other violent outcomes in psychotic disorders, including suicide [28-30]. Moreover, the complex interplay of anxiety, depression and dysphoria in contributing to suicidal risk during psychotic episodes as well as antecedent characteristics (Table 3) encourage Continued searches for biological contributions to risk. Recent trends in linking clinical phenomena to psychobiological factors include an endophenotype strategy aimed at quantifying measures that reflect stable characteristics or traits that may represent genetically-influenced aspects of brain function [31-33]. Promising candidate endophenotypes for suicide risk include trait aggression-impulsivity, disadvantageous decision-making or deficits in risk-assessment, early onset of major depression and excessive stress responses with exaggerated cortisol release, as well as possible dysfunctions of serotonin neurotransmission [32,33]. We also found that nonpsychotic depression and deficits of vital drive, as well as sleep disturbances predicted suicidal behaviors occurring even several years later. In general, we propose that two important phenomenological dimensions may characterize antecedent phases of suicidal first-psychotic episode patients, including an impulsive-irritable-angry-aggressive-depressed cluster and an anergic-lethargic-anhedonic-depressed construct. These psychopathological dimensions may suggest theoretical models for suicide research and prevention that focus on fundamental aspects of vitality, psychomotor activity and aggression, sleep, as well as mood or affective states [34]. In addition to antecedent characteristics and affective presentations as risk factors for suicidal behavior, suicidal psychotic subjects were most likely to meet diagnostic criteria for bipolar mixed-states or psychotic major depression (Table 3). These mood-states, though separated by current nosological conventions, may be closely related in that manic-depressive mixed-states appear to have more in common with psychotic major depression than with mania [18,35,36,37]. This study is limited in the numbers of subjects and of suicide attempts in some psychotic disorders. In addition, most manifestations of negative affects and suicidal risk both were assessed in the presenting episode, tending to limit testing of the predictive value of the negative affects. There also are risks of incomplete or inaccurate determinations and estimates of earlier psychopathology. Despite these limitations, the study supports the view that negative affects with admixtures of features of anxiety and depression, perhaps especially when combined with dysphoria, are both very common in first-episode psychotic disorders, are not limited to affective psychotic disorders, and are strongly associated with suicidal risk.

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Co-authors Baldessarini, Indic, Khalsa, Maggini, and Salvatore have no relevant disclosures; none is currently engaged in industry-supported research, participates in pharmaceutical speaker bureaus, nor do they or any immediate family members hold equity positions in biomedical or pharmaceutical corporations. Dr. Tohen was an employee and minor stock holder of Eli Lilly & Co. until 2008, as is his wife currently, and he occasionally serves as a consultant to that company.

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