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COMPLETED SUICIDE IN BIPOLAR II PATIENTES AFTER THEIR FIRST HOSPITALIZATION

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Abstract:	INTRODUCTION Bipolar disorder, especially Bipolar II subtype, is a mental disorder that has one of the greatest risk of completed suicide (CS). OBJECTIVES To determine the rate and the risk factors of CS in a cohort of Bipolar II patients followed after their first hospitalization METHODS We recruited all Bipolar II patients (DSM-IV) who were hospitalized for the first time in our Psychiatric unit between 1996 and 2016. We collected clinical variables during their first hospitalization and identified all patients who CS during follow-up. We compared the baseline variables between Bipolar II patients who CS and the rest. RESULTS Out of a total of 59 bipolar II patients 6 (10 %) CS, at a mean of 13 years of follow-up (a rate 120 times higher than the General Population (GP)). The average age at CS was 45.3 years (range between 33 and 57 years old) and there was a 2-year gap on average between the first psychiatric hospitalization and suicide. CS was characterized by a violent act (5 out of 6 cases, 83 %. When we compared BP II patients who CS with the rest, only a history of previous violent suicide attempt (P<0.04) was detected as a risk factor significantly associated with CS. CONCLUSION Bipolar II patients CS early after first hospitalization and at a very high rate (120 times more than GP) almost always by violent methods. History of a previous violent suicide attempt is a predictor of completed suicide.
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Please find attached our manuscript entitled ***"COMPLETED SUICIDE IN BIPOLAR II PATIENTES AFTER THEIR FIRST HOSPITALIZATION"*** to be considered for publication in the Journal of Affective Disorders.

This manuscript represents original material and has not been published previously, has not being considered for publication elsewhere and has been approved by each author.

We hope this manuscript will be of your interest.

Yours sincerely,

Eduard Vieta

Highlights

- Bipolar disorder, especially Bipolar II subtype, is a mental disorder that has one of the greatest risk of completed suicide (CS).
- Bipolar II patients completed suicde early after first hospitalization and at a very high rate (120 times more than general population) almost always by violent methods
- The previous history of a violent suicide attempt is a powerful and significant predictor of CS in Bipolar II patients after their first Hospitalization

ABSTRACT

INTRODUCTION

Bipolar disorder, especially Bipolar II subtype, is a mental disorder that has one of the greatest risk of completed suicide (CS).

OBJECTIVES

To determine the rate and the risk factors of CS in a cohort of Bipolar II patients followed after their first hospitalization

METHODS

We recruited all Bipolar II patients (DSM-IV) who were hospitalized for the first time in our Psychiatric unit between 1996 and 2016. We collected clinical variables during their first hospitalization and identified all patients who CS during follow-up. We compared the baseline variables between Bipolar II patients who CS and the rest.

RESULTS

Out of a total of 59 bipolar II patients 6 (10 %) CS, at a mean of 13 years of follow-up (a rate 120 times higher than the General Population (GP)). The average age at CS was 45.3 years (range between 33 and 57 years old) and there was a 2-year gap on average between the first psychiatric hospitalization and suicide. CS was characterized by a violent act (5 out of 6 cases, 83 %. When we compared BP II patients who CS with the rest, only a history of previous violent suicide attempt ($P<0.04$) was detected as a risk factor significantly associated with CS.

CONCLUSION

Bipolar II patients CS early after first hospitalization and at a very high rate (120 times more than GP) almost always by violent methods. History of a previous violent suicide attempt is a predictor of completed suicide.

Key Words: Bipolar disorder; bipolar II; first hospitalization; violent suicide attempt.

Title: COMPLETED SUICIDE IN BIPOLAR II PATIENTES AFTER THEIR FIRST HOSPITALIZATION

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INTRODUCTION

Bipolar disorder is perhaps the Mental Disorder with the highest risk of committing suicide (Plans L, Barrot C et al, 2019), reaching a suicide rate up to 30 times higher than the general population (Pompili 2013). Suicidal behaviour in bipolar disorder is influenced by multiple variables (Segura et al, 2019; Perugi et al, 2019; Squassina et al, 2020; Trepci et al, 2021). Although there is no coincidence between all the studies, many indicate an increased risk of completed suicide in Bipolar II Disorder versus Bipolar I Disorder (Rhimer 2002, Tondo 2007, Dennehy 2011, Sani 2011, Plans L, Nieto E et al. , 2019). However, there are no previous studies that analyze the risk factors for completed suicide in a specific cohort made up only of hospitalized subtype II bipolar patients followed long-term. As we know from previous studies, psychiatric hospitalization in itself suggests an additional severity and a greater risk of committing suicide in affective disorders (Hansson 2018, Baldesarini 2019) compared to affective patients who have not received hospitalization. Although there are quite a few studies focused on suicidal behavior in bipolar patients, including bipolar II patients, for the most part they focus on suicide attempts (Novik 2010, Pallaskorpi 2017, Bobo 2018, Karanti 2020) or on ideas, attempts and completed suicide jointly (Tondo 2007, Baldessarini 2019) and few do it only in completed suicide (Plans L, Nieto E. et al 2019) and hardly any do so in a specific sample of only Bipolar II patients. Bipolar II disorder is a valid and reliable diagnosis (Vieta, 2019) but has been understudied (Carvalho et al, 2020) and may be different from Bipolar I by many means (Almeida et al, 2020). For this reason, we consider of special interest the study of the prevalence and risk factors of completed suicide in a cohort of bipolar II patients followed up first-hand in the long term after their first hospitalization. In this group of patients, both because of their diagnosis and because of their follow-up after having required their first hospitalization, we hope to find a very high rate of risk of completed suicide.

OBJECTIVES

To determine the rate and risk factors for completed suicide (CS) in a cohort of patients with Bipolar II disorder followed up from their first psychiatric hospitalization.

METHOD

We selected all the patients diagnosed with Bipolar II according to DSM-IV criteria, residents of Manresa, a medium-size city at the core of Catalonia, Spain, and its suburbs who were admitted for the first time in their life to the Psychiatric Hospitalization Unit between 1996 and 2016. Clinical variables are systematically collected at first hospitalization using a specific chart format. The hospital is a public general hospital that provides healthcare to a specific catchment area of the Manresa area. After discharge, these patients were sent to the Outpatient Mental Health Center, where they are systematically followed-up for as long as needed. All completed suicides are reported and scrutinized. Using the SPSS statistical package and using the Chi-square test for qualitative variables and the Student's T- and Man Whitney U for quantitative variables (parametric and non-parametric respectively), we compared the baseline variables collected on the first admission between the patients who had bipolar II with SC and those without. In the same way, we compared other powerful evolutionary variables between the two groups of patients, such as rehospitalizations and non-lethal suicide attempts that occurred throughout the follow-up.

RESULTS

Out of the total of 59 bipolar II patients that made up the cohort, a total of 6 (10%) completed suicide, at a mean of 13 years of follow-up.

Table I summarizes the baseline characteristics of the 6 BP II who committed suicide. Of these, 66% were male and 33% had a history of violent suicide attempts. On the contrary, none of them had a family history of first degree of completed suicide and neither had any of them been treated with lithium. 83% of suicidal BPII patients were admitted for depression and 17% for hypomania.

When we compare bipolar II patients with CS at baseline with the rest, as we can see in Table II, we detected that only the previous history of a violent suicide attempt was significantly associated ($P < 0.05$) with CS in the tracing. On the contrary, if all the history of suicide attempts, including non-violent and less serious ones, are taken into account, the relationship was not significant since in both suicidal and non-suicidal groups the history of suicide attempts is around 50%. Other variables such as male sex are also

associated with CS in Bipolar II patients, although the difference did not reach statistical significance (P <0.08). It is noteworthy that there was no significant difference in either baseline cholesterol levels or age between BP II than CS and those without. Baseline comorbidity with personality disorder is frequent in the first admission in non-suicidal bipolar II patients, while CS is not found in bipolar II patients, although the difference does not reach significance (P <0.07).

Regarding the characteristics of these patients at the time of CS, as can be seen in Table III, it should be noted that 83% (5 of the 6 cases) committed suicide by a violent method, 4 by hanging and 1 by jumping. The mean age at which the patients underwent CS was 45.6 years (range between 33 and 57), while the mean age at first admission was 43.3 years. Therefore, the average period between admission and CS was only 2.3 years. All the patients committed suicide in a depressive phase (without mixed elements) and in only 1 of them the depression was a psychotic depression. None of the 6 patients was treated with lithium carbonate either on admission or during their follow-up. Actually, they were receiving other treatments for their depressive phase (antidepressants, lamotrigine), except for 1 who had abandoned treatment and follow-up. Finally, it should be noted that the mean time since the last visit of the patients who committed suicide was about 2 and a half months, varying between only 3 days and a maximum of 6 months.

The premature mortality of Bipolar II patients who commit suicide determines a very significant difference (P <0.000) in the follow-up time of bipolar II patients than CS (2.3 years) compared to the rest of bipolar II patients in which, as we pointed out at the beginning and it can be seen in Table IV the mean follow-up was 13 years.

We can also see in Table IV the outcome of bipolar II patients who committed suicide, that none of these 6 patients required any re-admission after discharge from their first hospitalization until they committed suicide. The foregoing represents a significant difference (P <0.03) with respect to the rest of Bipolar II patients who did not commit suicide, since in this case more than 50% of the patients required re-admission. Furthermore, none of these 6 patients performed any type of non-lethal suicidal behavior in that period compared to the 26% of the bipolar II patients who did not CS who did, although in this case the differences were not significant.

DISCUSSION

Our study highlights the finding of a very high rate of completed suicide (6 out of 59, more than 10%) in bipolar II patients hospitalized for the first time in their lives followed-up as an outpatient for a mean period of 13 years, despite the availability of free-of-charge lifetime mental health care.

This percentage is almost three times the percentage of CS obtained in the same period in the cohort of Bipolar I patients (9 of 254, 3.5%), which represents a very significant difference in risk between both groups (Plans, Nieto et al 2019). This increased risk of CS is due to the fact that in Bipolar II patients the baseline hospitalization, the initial polarity and the dominant polarity are depressive. These marked CS risk differences between Bipolar II and Bipolar I patients no longer reach significance when a multivariate analysis is performed that includes the intermediate variables related to depression mentioned above (Plans L, Nieto E l 2019). It should not be forgotten that bipolar I patients are admitted 2 to 6 times more than those of Bipolar II according to studies (Tondo 2007, Del Osso 2015, Karanti2020) and that most of them do so in manic phases (which has little risk of suicide) and who spend much less time overall during their entire illness in depressive phases associated with suicide risk than Bipolar II patients. Therefore, the completed suicide rate obtained in our Bipolar II sample after their first hospitalization is not only the highest found in a clinical study (120 times more than the general population) but it is also 3 times higher than that of Bipolar I patients from the same cohort. Those high rates do not seem to be related to poor mental health care access but rather to the reliability of the data, given that all completed suicides in the region are reported and investigated.

In our study, it is highlighted that suicidal bipolar II at baseline differed from non-suicidal bipolar II in that they have previously made a violent suicide attempt. On the contrary, if we include less serious attempts, especially drugs, this association does not occur. These results are identical to those obtained in our global cohort of bipolar patients, which includes 80% bipolar I and 20% Bipolar II (Plans L, Nieto E, 2019). The association between violent attempts and Bipolar disorder is a fact differentiator compared to unipolar depressives (Guillaume 2010) and occurs especially in men (Zaalsman 2006, Rosso 2020). Thus, in our cohort, 83% of the bipolar II patients committed suicide, using a violent method and of the BPII who committed suicide, 33% had a history of violent attempt.

On the contrary, other risk factors that are detected in suicidal behavior in cohorts of Bipolar Disorders that include bipolar I and II do not appear in this group of bipolar II patients. In the case of depressive onset polarity, predominant depressive polarity (Popovic 2013; Pallaskorpi et al, 2019) or admission due to depressive symptoms, as it occurred in a high% of all hospitalized bipolar II patients, there were no significant differences between those with CS and those without.

Cholesterol levels during the first admission do not differentiate between bipolar II patients who completed suicide, which coincides with recent studies (Park 2013) in that, contrary to older studies, cholesterol levels are similar in patients who complete suicide and those who don't.

The issue of sex deserves a separate mention since, although the difference is not significant as in other studies (Isometsa 2014, Hansson et al) due to the small size of the sample, a clear trend ($P < 0.08$) to the increase of the risk of completed suicide in bipolar men (20% commit suicide versus 5% of women).

Regarding the family history of suicide that is related to an increased risk of suicide attempts (Romero 2007) and completed suicide (Schaffer 2014), it should be noted that none of the Bipolar II patients in the sample (both suicidal and non-suicidal) had this antecedent. This result could be due to the small sample size. But at least, in our global cohort of 313 bipolar I and II patients, (Plans L, Nieto E, 2019) the significant association between first degree family history and completed suicide occurs at the expense of patients with Bipolar I Disorder.

Comorbidity with personality disorder in our study tends to be associated, although it does not reach significance ($P < 0.07$), with a lower risk of CS. Previous studies indicate an increased risk of suicidal behavior in bipolar patients with a personality disorder (Schaffer 2014), but the significant association occurs with suicide attempts (Undurraga 2012), while in the case of CS there is no significant increase in the risk of suicide in bipolar people with Personality disorder (Schaffer 2014)

A remarkable fact is that suicidal bipolar II patients commit suicide quite early after discharge (mean of 2.3 years) of course much earlier than the mean time that the bipolar I disorders of our cohort carried out, which was 9 years. Most bipolar II patients were admitted for a depressive phase, and patients who commit suicide after hospitalization do

so much more quickly when admission was for depression than when it was for mania (Isometsa 2014).

On the other hand, the bipolar II patients who committed suicide did not require any rehospitalization or underwent any TA from the moment of discharge to the completed suicide. This occurs because they carried out violent suicidal behavior early on, which determines the completion of the suicide. Thus, previous studies coincide in the higher lethality of suicide attempts in bipolar II patients, in which there is a lower percentage of patients who make repeated suicide attempts (Tondo 2020) and a lower proportion of patients with suicide attempts with respect to those who commit suicide (Tondo 2007) than in Bipolar I or unipolar depressives.

Finally, it must be noted that none of the CS patients was on lithium. Lithium has antisuicidal properties, and is nevertheless underused (Del Matto et al, 2020; Carvalho et al 2020). Other treatments may not protect against suicide (Antolin-Concha et al, 2020).

CONCLUSIONS

Bipolar II patients followed up after their first hospitalization mostly commit suicide by a violent method and at a rate 120 times higher than that of the general population, and they do so early (average 2.3 years after discharge) without being hospitalized again or having made any non-fatal suicide attempt after discharge.

The previous history of a violent suicide attempt is a powerful and significant predictor of CS in Bipolar II patients after their first Hospitalization.

LIMITATIONS

-Limited sample size, especially regarding the number of patients that make up the group that commited suicide, which means that some risk factors such as sex do not reach significance

-Data can be extrapolated only to patients with the characteristics of the sample that only includes Bipolar II patients hospitalized for the first time in their life and does not include outpatients or patients hospitalized several times

-Another limitation is that we have collected variables prospectively and retrospectively, with variable reliability (but mostly high),

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TABLE I: BASELINE CHARACTERISTICS (DURING FIRST ADMISSION) OF THE 6 BIPOLAR II PATIENTS WHO COMPLETED SUICIDE

Nº	**SEX**	**AGE ING.**	**PHASE ING**	**TA PREVIEW**	**FAMIL. SC**	**LITIO ING.**
1	MAN	49	HYPOMANIA	NO	NO	NO
2	MAN	31	DEPRESSION	YES, SERIOUS AND VIOLENT	NO	NO
3	WOMAN	54	DEPRESSION	YES, SERIOUS AND VIOLENT	NO	NO
4	WOMAN	51	DEPRESSION	NO	NO	NO
5	MAN	28	DEPRESSION	YES, SERIOUS AND VIOLENT	NO	NO
6	MAN	47	DEPRESSION	NO	NO	NO

TABLE II: BASELINE COMPARISON (DURING THEIR FIRST ADMISSION) BETWEEN BIPOLAR II PATIENTS WHO USED SUICIDE AND THOSE WHO DID NOT

BASAL VARIABLES (On first admission)	CS (N=6)	NCS (N=53)	P CS vs NCS
QUALITATIVE (Chi Square)			
Any previous suicide attempt	3 (50%)	31 (58,5%)	P= NS
Previous violent suicide attempt	2 (33%)	2 (3,8%)	P<0.048
First degree family history with CS	0 (0%)	0 (0%)	P= NS
Male Gender	4 (66%)	15 (28,3%)	P<0.08 (NS)
Depressive onset polarity	6 (100%)	48 (88,7%)	P=NS
Depressive phase	5 (83%)	31 (58,5%)	P=NS
Absence of psychotic symptoms	6 (100%)	45 (85%)	P =NS
Comorbidity with Personaltiy Disorder	0 (0%)	22 (41.5%)	P<0.07 (NS)
Comorbidity with substance abuse	2 (33%)	19 (33%)	P=NS
Any comorbidity	4 (66%)	31 (60%)	P=NS
Lithium treatment	0 (0%)	16 (30,2%)	P=NS
Treatment with antiepileptics (lamotr / valp)	3 (50%)	29 (54,7%)	P=NS
Antidepressant treatment	5 (83%)	30 (57%)	P=NS
QUANTITATIVE (Student's t)			
Age	43,33	43,17	P=NS
Cholesterol level	178	177	P=NS
Duration of first admission in days	24	19	P=NS

TABLE III: FINAL CHARACTERISTICS OF THE 6 BIPOLAR II PATIENTS BEFORE CONSUMING SUICIDE

PAT. Nº	MOOD STATE AT CS	AGE OF SUICIDE	METHOD CS	PREVIOUS TREATMENT BEFORE CS	DAYS UNTIL CS SINCE LAST APPOINTMENT AND PROFESSIONAL
1	DEPRES.	49	CAR GAS	Lamotrigine+olanzapine	30 - PSYCHIATRIST
2	DEPRE.SP	33	HANGING	Lamotrigine+Risperidone	3 - EMERGENCIES. PSYC
3	DEPRES.	57	HANGING	Venlafaxine+mirtazapine	125-GENERAL DOCTOR
4	DEPRES.	51	PRECIPITAT	Fluoxetine+quetiapine	22- PSYCHIATRIST
5	DEPRES.	33	HANGING	Stopped treatment	180-GENERAL DOCTOR
6	DEPRES.	49	HANGING	Lamotrigine+citalopram	63 - PSYCHIATRIST

TABLE IV: FOLLOW-UP COMPARISON BETWEEN BIPOLAR II PATIENTS WHO COMPLETED SUICIDE AND THOSE WHO DID NOT

FOLLOW UP VARIABLES	CS (N=6)	NCS (N=53)	P CS vs NCS
QUALITATIVE (Chi-square)			
Some re-entry	0 (0%)	27 (50,9%)	P<0.03
Some non-lethal suicide attempt	0 (0%)	14 (26,4%)	P=NS
QUANTITATIVE (Mann-Whitney U)			
Mean years of follow-up	2,3 hasta SC	13,2	P<0.000
Mean number of re-admissions	0	1,63	P< 0.024
Mean number of days of re-hospitalization	0	35,8	P< 0.029
Mean number of days of rehospitalization M	0	0,29	P=NS
Mean number of days of rehospitalization Mx	0	8,27	P=NS
Mean number of days of rehospitalization D	0	18,96	P<0.06 (NS)
Average number of non-fatal suicide attempts	0	0,36	P=NS

Conflict of interest:

Dr. Nieto has served as speaker for Janssen.

Dr. Benabarre has served as speaker for Lundbeck and Janssen.

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