The dynamic relationship between insight and suicidal behaviour in first episode psychosis patients over 3-year follow-up.

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Abstract

Background: Several studies have established the high risk of suicide in first episode psychosis (FEP). Between 15%-26% of FEP patients attempt suicide at least once before their first contact with psychiatric services and 2-5% die from suicide, particularly in the early stages of the illness. Also, many patients with schizophrenia spectrum disorders lack insight into having a mental disorder, which evolves over the illness course. However, the relationship between insight changes and suicidal behaviour in FEP remains poorly understood.

Method: Information about suicidal behaviour was available in a cohort of 397 FEP patients. Three dimensions of insight (into mental illness, into the need for treatment, and into the social consequences of the illness) were measured at: baseline, 1 and 3 years after the initiation of treatment. Survival analyses examined time to suicidal behaviour i) from insight at baseline, ii) the closest insight measure to the suicide attempt, and iii) changes in insight during the 3-year follow-up. The analyses were adjusted for a set of potential confounders.

Results: No associations were found between baseline insight dimensions and time to suicidal behaviour. However, poor insight at the evaluation closest to the suicide attempt was associated with increased the risk of suicide attempts. In addition, stability of insight (poor or good at both assessments) did not affect the risk of suicidal behaviour, while changes in either direction from the first to the third year were linked with an increased risk of suicidal behaviour, particularly worsening.

Conclusions: Insight in psychosis is a dynamic concept and we demonstrated the relationship between insight and suicide risk to be equally dynamic. Poor insight seems to increase the risk, especially when insight levels change. Hence, repeated insight assessment to detect change carried out in early psychosis may play a role in suicide prevention. Further research needs to clarify what underlies this and whether other variables, particularly previous suicide attempts and depression, may explain the apparent association of insight changes with risk of suicidal behaviour.

Keywords: suicidal behaviour; insight; first episode psychosis; schizophrenia.

Introduction

Suicide is a major cause of death among patients with schizophrenia. Previous literature confirmed the high risk of suicide in first episode psychosis (FEP) (Dutta *et al.*, 2010, Pompili *et al.*, 2007). Between 15% and 26% of (FEP) patients have attempted suicide at least once by their first treatment contact and from 2 to 11% of them attempt to end their lives over the first year of the illness (Melle *et al.*, 2006). In a previous report from our group we found that at baseline 37% of FEP patients had made a suicide attempt and 20% of them did so within a 3-year follow-up (Ayesa-Arriola *et al.*, 2015).

With regard to insight, it has been said that the majority of patients with schizophrenia deny having a mental disorder (Amador *et al.*, 1994, David, 1990). Even with more nuanced assessments, lack of insight has been strongly associated with greater psychotic symptomatology, treatment noncompliance, increased involuntary hospital admissions, psychosocial functioning impairment and poorer outcome (David, 2004). Poor insight leads to negative attitudes towards treatment, which is particularly important in FEP patients (Coldham *et al.*, 2002). Concerning the association between insight and suicide behaviuor, Foley and colleagues (Foley *et al.*, 2008) found that 47% of patients with a FEP reported suicidal ideation, and those who made a suicide attempt (9%) tended to have higher insight into having a mental illness than non-attempters.

Insight has been suggested to increase suicide risk via the so-called "demoralization syndrome", described by Drake and Cotton (Drake and Cotton, 1986) in people with schizophrenia when they become aware of their illness and its consequences (i.e. higher insight, greater risk of suicide). Variables such as previous suicide attempts (i.e. prior to first presentation) (Lopez-Morinigo *et al.*, 2014), depressive symptoms and negative beliefs about psychosis(Barrett *et al.*, 2010), may confound/mediate such an association, which has been replicated by a recent cross-sectional study of patients with psychotic disorders (Massons *et al.*, 2017). Hence there is evidence that insight may be associated with both good and poor outcomes (Belvederi Murri *et al.*, 2016, Mintz *et al.*, 2003), the so-called "insight paradox". Belvederi and colleagues (Belvederi Murri *et al.*, 2016) remarked that the association between insight and higher levels of depression and potentially suicidal behavior could be explained by potential confounders, such as the severity of psychotic symptoms, extrapyramidal symptoms, hopelessness, internalized stigma, self-esteem, socio-economic status and service engagement. It has also been suggested that the effect of insight on suicidal behaviour can go in opposite directions at different time-points, with insight at baseline increasing the risk and insight at follow-up decreasing it (Barrett *et al.*, 2015). These authors also suggested that the relationship depends on changes in insight (e.g. while gaining insight during treatment could be associated with reduced risk for suicide, losing insight could have the opposite effect) ie., the dynamics of insight (Ayesa-Arriola *et al.*, 2014). To the best of our knowledge, there is only one previous longitudinal FEP study from Norway that has examined the dynamics of insight, reporting that gaining insight may decrease the risk of suicidal behaviour (i.e. suicidal ideation and suicide attempts as a whole) (Barrett *et al.*, 2015). However, longer

term insight changes in FEP cohorts have not been investigated considering multiple insight dimensions and their associations with risk of suicidal behaviour.

Aims and hypotheses

The aim of the present study was to explore the long-term (3-year follow-up) relationship between insight and suicidal behavior in a large cohort of FEP patients. We hypothesized that: i) insight and its possible relationship with suicidal behaviour may vary along the different phases of the illness; ii) longitudinal insight changes are likely to affect suicide risk.

Methods

2.1. Study design and setting

This investigation was designed as an observational prospective study. Data were obtained from an ongoing epidemiological and three-year longitudinal intervention program of first-episode psychosis (PAFIP) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Spain (Pelayo-Teran *et al.*, 2008). In accordance with international standards for research ethics, this program, which is fully publicly funded by the regional Mental Health Services, was approved by the local institutional review board. Patients meeting inclusion criteria and their families provided written informed consent.

2.2. Subjects

All referrals to PAFIP between 2001-2010 were screened against the following inclusion criteria: age 15-60 years; living in the catchment area; experiencing their first episode of psychosis; no prior treatment with antipsychotic medication or, if previously treated, a total life time of adequate antipsychotic treatment of less than 6 weeks; meeting DSM-IV criteria (APA, 2000) for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. DSM-IV criteria for drug or alchohol dependence, mental retardation and having a history of neurological disease or head injury were exclusion criteria.

Three hundred and ninety seven patients met the inclusion criteria and were therefore included in the PAFIP program over this period (2001-2010). Baseline sociodemographic and clinical information was recorded for the total sample. Diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID-I) (First *et al.*, 1996), which was carried out by an experienced psychiatrist (BC-F) 6 months after the baseline visit. In particular, the baseline diagnoses of our FEP patients (i.e. six months after first contact) were as follows: schizophrenia (N = 224), schizophreniform disorder (N = 96), schizoaffective disorder (N = 5), brief psychotic disorder (N = 41), psychosis NOS (N = 29) and delusional disorder (N = 2).

2.3. Procedures

Premorbid and sociodemographic information was recorded from interviews with patients, their relatives and from medical records on admission. Sex, age, age at psychosis onset (defined as the age when the emergence of the first continuous [present most of the time] psychotic symptom occurred, and duration of untreated psychosis (DUP, defined as the time from the first continuous [present most of the time] psychotic symptom to initiation of adequate antipsychotic drug treatment), were collected. Premorbid social adjustment was measured by the Premorbid Adjustment Scale (PAS) (Cannon-Spoor *et al.*, 1982).

All participants received three years of PAFIP care. Besides their routine visits in order to check symptoms and compliance with treatment, patients were telephonically contacted to schedule face-to-face appointments at one and three years. Of 397 patients, 335 (84%) and 306 (77%) agreed to participate at 1 and 3-year follow-up assessments, respectively. The same senior consultant psychiatrist (BC-F) interviewed patients at baseline, at 1 and at 3-year follow-up. Clinical symptoms of psychosis were assessed by the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). SANS-SAPS dimensions of positive (scores for hallucinations and delusions), disorganized (scores for formal thought disorder, bizarre behaviour and inappropriate affect) and negative (scores for alogia, affective fattening, apathy and anhedonia) symptoms were calculated (Grube *et al.*, 1998). General psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS) (Flemenbaum and Zimmermann, 1973), and depressive symptoms severity was measured using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington *et al.*, 1992).

Information on suicidal behaviour

Suicidal behaviours, i.e. "potentially self-injurious behaviour for which the person intended to kill himself/herself" (Silverman *et al.*, 2007a, b), which encompasses suicide attempts and suicide completions, were taken from medical records, which provided information from patients, their families and medical staff. Information on suicidal behaviour was available for the whole sample (N= 397 patients). Sixty patients (15.11%) made a suicide attempt. Of these, six subjects (1.51%) completed suicide over the 3-year follow-up period. For more details, see (Ayesa-Arriola *et al.*, 2015).

Insight assessment

The short version of the Scale to Assess Unawareness of Mental Disorder (SUMD) (Amador *et al.*, 1994) was used to measure three insight dimensions: insight into mental illness, insight into need for treatment, and insight into social consequences of illness. 'Poor' insight at baseline, 1 and 3-year follow-up was defined as SUMD scores greater than 1, and a score of 1 designated 'good insight'(Ayesa-Arriola *et al.*, 2011). Out of 397 patients, SUMD information at the three insight assessments was available for 270 (See study flowchat in **Figure 1**). Of these 270 FEP patients, 58 individuals (21%) presented with good into mental illness insight over the three assessments and 64 (23%) showed poor insight (i.e. those with no insight changes). However, in 84 individuals (31%) insight

was poor at baseline improved at either of the follow-up assessments, specifically in 43 subjects (16%) at 1-year and in 41 individuals (15%) at 3-year follow-up; in 22 individuals (8%), insight was good at baseline assessment but decined in 13 patients (5%) at 1-year and in 9 participants (3%) at 3-year follow-up. Finally, 42 individuals (15%) changed their insight at 1 year-follow up assessment and changed again at 3-year follow-up, 22 (8%) in the order good-poor-good, and 20 (7%) poor-good-poor.

Statistical analysis

The Statistical Package for Social Science, version 19.0 (SPSS Inc., Chicago, IL, USA), was used for statistical analyses. All tests were two-tailed and the significance level was set at 5%.

First, bivariate analyses (chi-square, ANOVA) were used to detect differences between those with/without insight assessment in sociodemographic and clinical variables. Second, Kaplan–Meier survival analyses for time to suicide attempt by each initial insight dimension group were performed. Log-rank tests were used to compare median time to suicide attempt between patients with a good and a poor insight in each dimension. Third, the Kaplan-Meier survival analysis and the log-rank test were used to compare time to suicidal behaviour by the most proximal insight measures. Fourth, multivariable Cox-regression (enter method) models were carried out to examine the relationship between suicidal behaviour and insight levels, whilst controlling for significant variables in bivariate analyses. Finally, in order to explore the influence of dynamic aspects of insight in time to suicide attempt, changes in insight over the three assessments (baseline, 1-year and 3-year follow-up) were considered in additional survival Kaplan-Meier analyses for each of the insight dimension. The hazard ratio of time to suicide attempt and 95% confidence intervals (CI) values were also calculated. For non-suicide attempters, the censoring date was the last face-to-face contact with staff or the end of the study, whichever came sooner.

Results

No significant differences between patients who did and did not complete the insight assessments were found in relevant variables such as age, sex, duration of illness or clinical severity. However, as showed in **Table 1**, those with all the insight measures available had significantly more years of education, a larger proportion of them were unmarried and they were less frequently cannabis users than those without all the insight data. See Ayesa-Arriola *et al.,* 2015 for more detailed information about the total sample (N=397), including the differences between suicide attempters and non attempters.

Kaplan-Meier curves of the three SUMD insight dimensions at baseline in relation to suicidal behaviour are presented in **Figure 2**. No significant relationships between baseline insight measures and risk of suicidal behaviour were found. Interestingly, when the insight measurement closer to the suicidal behaviour was considered, a significant relationship emerged for insight into mental disorder (Chi Square = 8.874; p = 0.003), insight into the need of treatment (Chi Square = 11.406; p = 0.001) and insight into the

social consequences (Chi Square = 9.362; p = 0.002)), i.e. poorer insight scores, greater suicide risk. (**See Figure 3**)).

When analysing insight changes across the follow-up evaluation (dynamic insight) and time to suicidal behaviour, dynamic insight into mental disorder (Chi Square = 8.235; p = 0.083) and dynamic insight into the need of treatment (Chi Square = 9.404; p = 0.052) only showed a tendency, whereas insight into the social consequences resulted in a significant effect (Chi Square = 15.34; p = 0.032). Specifically, 22 (38% in the suicide behaviour group) individuals with stable good insight attempted to end their lives during the follow-up, and 21 subjects (37%) with stable poor insight during the first two years, particularly within the first 200 days under our care. When insight declined 5 individuals (9%) attempted to end their lives between the second and the third year of follow-up and when insight improved at that point 3 individuals (5%) made a suicide attempt. The 6 individuals (10%) who presented inestability in the insight assessment showed suicidal behaviour proximal to 3-year follow-up.

Finally, a Cox Regression analysis including the most recent insight measures in the three SUMD dimensions together with significant variables in univariate analyses (sex, premorbid adjustment, cannabis use, living in urban vs. rural areas, living alone vs. with family, previous attempts and depression) was conducted. The model was significant in predicting suicide attempts (Chi Square = 269.844, p < 0.001, log-likelihood = 409.964). Previous suicide attempts [hazard ratio (HR) 0.045 confidence interval (CI) 0.021-0.095; p < 0.001], poor premorbid adjustment [hazard ratio (HR) 0.465 confidence interval (CI) 0.25-0.865; p = 0.016] and depression severity [hazard ratio (HR) 0.5 confidence interval (CI) 0.255-0.977; p = 0.043] were the significant predictors of suicidal behaviour. When removing depression from the model, insight did not emerge as significant predictor of risk of suicide. All the predictors included in the Cox-regression model are shown in **Table 2**.

Discussion

In this study we investigated the relationship between insight and suicidal behavior in a large FEP patients sample over a 3-year follow-up. In contrast to the commonly held view among clinicians, no baseline insight dimension was associated with risk of suicidal behavior over the follow-up. However, when the closest insight assessment to the suicidal event was considered, poor insight increased the risk. Consistent with our hypotheses, changes in insight into having a mental illness in both directions (i.e. improvement and impairment) over the second and third year of the illness increased the risk. Our findings therefore suggest that there is a time-related effect of insight on risk of suicidal behaviour in early psychosis, which deserves some comment.

The controversial relationship between insight and suicide risk in early psychosis has attracted much research interest, particularly in the last three decades, with overall mixed findings (Lopez-Morinigo *et al.*, 2012). One replicated finding is that good insight in the first weeks or months after the psychotic illness onset increases the risk of suicide, which is probably due to reactive depressive symptomatology emerging as coping strategy

Commented [DA11]: what is the n for each of these graphs?

Commented [DA12]: I am not sure about this analysis. Because you have to take patients who have made suicide attempts only, rather tan the whole cohort, it makes the results look bad – especially early in the course of follow-up when most of the attempts occur! Also, I think the numbers are too small to show well on hte survival plot for the 'dynamic insight' cases. Is there another way to analyse the data? Is it useful to look at Odd ratios for suicidal behaviour in 3 groups: stable good insight; stable por insight and unstable insight?
RAA: In the initial anlyses we had 8 groups of dynamic insight; due to the same reasons you suggest, groups were reduced to 5; in both cases, exclusively insight about the social consequences resulted significant; we could try with 3 groups, but in this case we will miss the directions of the changes.

Commented [DA13]: does it imporve the model to use a single combined insight (total) score? Also should report results with and without depression included. for example, maybe insight looks like a predictors when depression is not included in the model...
RAA: We have never used a total score...To be honest I don't know how to compute the three measures of insight just in one.
RAA: removing depression from the models, even removing previous attempts, did not show insight as a significant predictor, neither with the 3 dimensions nor including dimensions one by one. In all the analyses, premorbid adjustment was the monst (an only) significant predictor.

Commented [DA14]: this is far too strong! It is a frequent claim but with little supporting evidence
RAA: OK

during the diagnosis process (Lysaker *et al.*, 2013). Lysaker and colleagues suggested that early insight may imply a negative change in self-image (switching from a healthy person to an ill one) or the awareness of the consequences of a mental disorder and the subsequent stigma. Conversely, good insight at follow up is suggested to be a protective factor for suicidal behaviours in psychotic disorders (Barrett *et al.*, 2015). Although some patients may become depressed after acknowledging the clinical handicaps of their disorder, treatment-related changes in awareness are generally associated with a positive outcome, including decreased suicide risk (Bourgeois *et al.*, 2004). Our results showed that good insight into the illness, into the need of medication and into the social consequences over the follow-up behaved as protective factor. Furthermore, it was poor insight the predictor of suicidal behaviour. This was relatively contrary to our expectations based on the so-called demoralization syndrome (Drake and Cotton, 1986). Howevever, recent research (Barrett *et al.*, 2015, Bourgeois *et al.*, 2004, Pijnenborg *et al.*, 2013) appears to suggest that 'gaining insight reduces suicide risk in psychosis', which is supported further by our results.

But far more interesting are the results concerning changes in insight increased risk of suicide attempts. A recent paper has identified three post-hospitalization trajectories of suicidal ideation in FEP over a 2-year follow-up, namely a continuous increase in 11% of 376 patients, an increase and fast decrease in 57% and a subclinical low suicidal ideation trajectory in 32% (Madsen *et al.*, 2016). Similar to the suicide rates showed in our previous research (Ayesa-Arriola *et al.*, 2015), Madsen and colleagues reported that 40% of patients experienced frequent suicidal ideations which persisted or increased during the first years of treatment. However, few other studies have examined changes in insight and its relationship with suicidality. Barrett el al., (Barrett *et al.*, 2015) explored the dynamicity of insight and suicidal behaviors in FEP patients over a one-year follow-up. Their results indicated that gaining insight during treatment was associated with reduced risk of suicidality, while losing insight had the opposite effect. Our results are in full agreement with this study (Barrett *et al.*, 2015) using a larger FEP cohort followed-up over a more prolonged (3 years) period. Specifically, we found that good insight into having a mental disorder, which could be achieved as a function of treatment over a 3-year follow-up in our early intervention programme in 37% of the patients, decreased the risk of suicide. Interestingly, changes in insight, particularly between the 2- and 3-year follow-up, increased the risk for suicide, which suggests that a disruption in the beliefs about the illness should warn clinicians about an increased risk.

Hence, what causes changes in insight (e.g. medication discontinuation, psychotic symptoms exacerbation vs. amelioration, relapsing, hospitalizations and/or discharges close in time to suicidal behavior) may be determinant factors for suicide prevention. Failure to adhere to medication is a common problem in early psychosis, when the consequences of relapsing can be particularly devastating, including taking one's life. Some authors found that even relatively short gaps in medication coverage increase the risk of relapse (Masand *et al.*, 2009). Suicide prevention strategies, particularly in early psychosis, should therefore focus on ensuring medication compliance. In other words,

there seems to be a time-effect of insight on suicidality in FEP patients, which may be conceptually part of the so-called "insight paradox" in addition to depression (Belvederi Murri *et al.*, 2016, Mintz *et al.*, 2003). The role of previous suicide attempts and depression together with poor premorbid adjuntment in the increased risk of suicide attempts was also replicated by our study (Massons *et al.*, 2017).

Finally, insight did not have an independent significant effect on time to suicidal behaviour when variables such as premorbid adjustment, depression and previous suicide attempts were considered in the model. In a recent paper Massons et al., (Massons *et al.*, 2017) found that suicidality in psychosis was linked with two insight dimensions: awareness of mental illness and awareness of the social consequences. However, in the multivariable regression analyses only depression and previous suicidal behaviour were the significant predictors of suicidality, hence the mediators of the association of suicidality with insight. Similar to previous research, our results indicate that more depressive symptoms and negative beliefs about others increased the risk for suicidality in FEP patients (Barrett *et al.*, 2010). Therefore, managing depression and counteracting negative beliefs about psychosis while monitoring insight may reduce the risk for suicidal behaviour in patients with psychotic disorders.

Limitations

Our findings should be interpreted with some caution due to the study limitations. Suicidal behavior information was recorded retrospectively from clinical records in a large sample of 397 FEP patients and the attrition rate was high on data on insight at 1- and 3-year follow-up, which resulted in a final sample of 270 individuals with all the three insight measures. When comparing those who completed insight assessments with those who did not (see table 1), groups did not differed in clinical measures or suicidal behaviours rates, although education years, cannabis use and marital status varied between both groups, which may have added some noise to the data. Another methodological issue concerned the time from the insight measurement (baseline, 1-year or 3-years) to the suicidal event, during which insight levels may have changed further. In addition, we could not evaluate what contributed to insight changes (e.g. stopping taking the medication, psychotic symptoms exacerbation, relapsing and hospitalization close in time to suicidal behavior) which warrants further research. It might be challenged for clinicians to recall (and distinguish between causes) this relevant information, specifically in patients in whom depression and poor social adjustment are common features.

Conclusions

Insight in psychosis is a dynamic concept and the relationship between insight and suicidality was proved to be dynamic as well. This relationship was found to change over time, showing both improvements and impairments of illness recognition over the second and third year of the illness after first presentation with psychosis an increase in suicide risk. Hence, insight reassessment in early psychosis may help to identify those patients at a higher risk of suicide. Clinical interventions in FEP patients should include an adequate

assessment of insight and risk of suicidal behavior, Insight should also be monitored over time in order to tailor interventions according to illness phase. Interventions aimed to improve insight are likely to result in better outcomes, including a reduced risk of attempting suicide.

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