Identifying predictors of outcome of mania

# Age at the onset of a first episode of psychotic mania is not a determinant of short-term outcome in a specialised early psychosis treatment setting

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## Summary

Numerous publications have shown that the outcome of bipolar disorder is worse than previously thought, with poor outcomes evident from the first episode of mania. Although the manic syndrome usually resolves rapidly in the vast majority of patients, functional outcome often lags behind. In this context, it is important to study the outcome of mania in various settings and to identify predictors of outcome in order to identify sub-groups of patients with specific needs. In this study, we explored the outcome of 118 patients with a first episode of psychotic mania (FEPM) treated at EPPIC, Melbourne, Australia, and, more specifically, the impact of age at onset (<21 years and ≥21 years) of this first episode on 18-month outcome. Globally, patients had a good level of premorbid functioning in spite of high rates of exposure to sexual and physical abuse and of cannabis use. After presenting with very intense symptoms and low functioning at entry to the service, outcome was rather good, which suggests that adequate treatment provided in a specialised setting allows a favourable outcome after FEPM. The good quality of this treatment may explain why we did not find any difference in outcome when comparing subgroups defined by age at onset of FEPM.

Philippe Conus

## Introduction

Although manic episodes usually resolve rather rapidly under available treatments [1, 2], the global outcome of patients with bipolar disorder is usually not as favourable. Indeed, 60% of patients still display general symptoms such as anxiety and depression 6 months after a manic episode [1], and over the long term, patients with bipolar disorder spend about 40% of their time with depressive symptoms [3, 4]. In addition, they display cognitive impairment, high rates of comorbidities and a rate of suicide 20 times higher than the general population [5].

Many authors have also insisted on the importance of the gap between syndromal remission (disappearance of the manic syndrome) and functional recovery (return to previous level of functioning and activity). In a sample of chronic bipolar disorder patients, Dion et al. [1] observed that whereas 80% of patients had recovered from their manic syndrome after 6 months, only 43% had a job and only 21% worked at premorbid level by that time. Similarly, Conus et al. [2] found that 6 months after a first episode of psychotic mania (FEPM), 90% of patients had reached syndromal remission but only 40% had returned to premorbid level of functioning. Considering this poor global evolution even after a first manic episode, it seems important to explore factors influencing outcome in order to develop strategies that may improve it. Various correlates of outcome have been identified [6], such as sociodemographic characteristics, cognitive performance, symptomatology, presence of comorbid personality disorder [7, 8], substance abuse [9, 10], psychotic features [9, 10] and Schneiderian symptoms [11, 12].

Along with these factors, there are suggestions that younger age at the time of the onset of bipolar disorder could also be a risk factor of poorer evolution [5, 6]. Various hypotheses have been proposed to explain this observation, such as a difference in the illness mechanisms underlying variations in age at onset, impact of the developmental issues to be faced at the time of onset, or specific treatment needs of younger patients that may not met by current practices [13]. However, the majority of data regarding this issue stem from

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studies conducted in samples of chronic patients. Exploring this question in samples of patients going through the early phases of bipolar disorder allows avoidance of various confounding factors such as recall bias, selection bias towards patients with poorer and chronic outcome, effect of long-term medication and impact of relapses through the kindling effect. In a sample of 87 patients with a first episode of psychotic mania FEPM, we observed that lower age at entry to the clinical programme, family history of bipolar disorder and comorbid substance use were predictors of poorer functional outcome [2]. These results were in line with data stemming from the Suffolk county study [12] where, along with the presence of Schneiderian symptoms and childhood psychopathology, a younger age at onset determined a poorer outcome in 126 patients hospitalised with FEPM. However, these studies did not explore the issue of age at onset specifically. In addition, none of them applied evidence-based age cut-offs resulting from solid data to define early, intermediate and late onset of bipolar disorder. Finally, they were conducted in samples of manic patients who had provided informed consent to enter the study, which implies an important bias towards milder forms of mania.

Considering these limitations and the important need for more research to identify predictors of poorer evolution in the early stage of bipolar disorder, we decided first to study premorbid, baseline and 18-month outcome characteristics in a sample of FEPM patients aged 15 to 29. Secondly, we wanted to compare these variables between subgroups defined by their age at onset of the first manic episode, in order to see if a younger age at onset (defined as onset before age 21) was linked with poorer outcome than in patients where the onset occurred after age 21.

## Patients and methods

### Sample and setting

The First Episode Psychosis Outcome Study (FEPOS) [14] is a file audit study conducted in all 786 FEP patients treated at the Early Psychosis Prevention and Intervention Centre (EPPIC) between January 1998 and December 2000 [14–24]. During these 3 years, EPPIC provided a comprehensive specialist treatment programme for young people aged 15–29 years experiencing their first episode of psychosis. The programme's catchment area of about 900,000 inhabitants at the time of the study covered the North and Western regions of Melbourne, Australia [14]. Among these 786 patients, 118 had a diagnosis of FEPM, and they are the subjects of the current study.

### Materials and procedure

Previous publications provide a detailed description of the study procedure and methodology [14–24]. We used the Early Psychosis File Questionnaire [14] to assess consecutive medical files systematically. All the data derive from notes taken by clinicians and from medical documents produced during the entire treatment phase. In particular, pretreatment variables derive from information gathered retrospectively by clinicians when assessing patients. The research and ethics committee of Melbourne allowed access to all files provided data were anonymised, which permitted the inclusion of all patients in the study with very limited selection bias.

Pretreatment characteristics included the following variables: past history of DSM-IV [25] diagnosis of psychiatric disorder, of substance use disorder, of suicide attempts, of forensic issues, of exposure to sexual or physical abuse, family history of psychiatric disorder, premorbid adjustment based on the Global Assessment of Functioning (GAF; [26]), age at the onset of psychotic symptoms, age at the onset of manic symptoms and duration of untreated psychosis (age of entry into EPPIC subtracted from age at first sustained positive psychotic symptoms longer than a week duration).

At service entry, clinical diagnoses were based on DSM-IV criteria based on the clinical description and on the elements mentioned in medical documents. Illness severity was rated with the Clinical Global Impressions-Severity of Illness Scale [27] and the Clinical Global Impressions-Bipolar Illness (CGI-BP; [28]). Insight was rated on a three-point scale (0 'absence of insight; 1 'partial insight – perception of being ill but persistence of illogical explanations'; and 2 'full insight'). Global functioning was assessed using the GAF.

Treatment information included suicide attempts, inpatient admissions, medication non-compliance (≥1 week without taking medication) and service engagement. At service discharge, the final file DSM-IV clinical diagnoses were recorded, based on clinical descriptions and on all the elements (medical reports, symptom description, discharge summaries, etc.) found in the file. Outcome characteristics were based on symptom severity, which was determined using CGI-S, CGI-BP, on the insight scale and on the final GAF score to assess discharge functional status.

### Validity of diagnoses

The validity of the FEPOS diagnoses was established by the following procedure. Between 1998 and 2000, 230 of the 786 patients treated at EPPIC were included in prospective trials. Their main and comorbid diagnoses were defined within 6 weeks of admission using the

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Structured Clinical Interview for DSM-IV (SCID-I/P25). The SCID and FEPOS diagnoses of 115 patients randomly selected within this sample of 230 were compared. The calculated kappa values revealed a very good concordance for both psychosis diagnoses (kappa = 0.80) and comorbid substance abuse diagnoses (kappa = 0.74).

### Inter-rater reliability

Inter-rater reliability was established by comparing baseline ratings given independently by both main investigators (ML and PC) in a randomly selected sample of 40 files stratified by time, on the following scales: CGI, CGI-BP, GAF and insight. Analysis revealed a good to very good inter-rater reliability with kappa values ranging from 0.80 to 0.90 (CGI-S: 0.87, CGI-BP mania severity score: 0.89, CGI-BP depression severity score: 0.87, GAF score: 0.88, Insight score: 0.89).

### Choice of cut-off regarding early and late age of onset

In recent years, the observation of an important heterogeneity within bipolar disorder samples regarding clinical presentation and outcome has led to the emergence of research aimed at identifying indicators and characteristics that may delineate more homogeneous subgroups of bipolar disorder patients, and age at onset of the disorder has come out as a potential candidate to do so. In order to avoid choosing arbitrary cut-offs, various groups have conducted analyses in large patient samples and determined cu-toffs based on data. For example, Azorin et al. [29] conducted an admixture analysis in a sample of 1082 patients diagnosed with bipolar disorder and reported the existence of three subgroups based on age at onset, with cut-offs between early and intermediate, and intermediate and late onset at 20 and 30 years, respectively. In a comprehensive review on this issue, Geoffroy et al. [30] confirmed the presence of three subgroups (early, intermediate and late onset) with cut-offs points at age 21 and 34. The choice for a cut-off at age 21 to identify a specific subgroup with early onset received additional support from Preisig et al. [31]. Indeed, this group found that heritability of bipolar disorder was present only in offspring of patients with onset before age 21, the heritable risk for children of parents with onset of bipolar disorder occurring later than age 21 being similar to the control population. Based on these elements, we

**Table 1:** Comparison of premorbid and baseline characteristics between FEPM patients with onset before or after age 21.

| Variable | | Age of onset of mania | | OR | 95% CI of OR | | p-value |
|---|---|---|---|---|---|---|---|
| | | <21 years (n = 38) | 21 years and older (n = 59) | | LCI | UCI | |
| **Pretreatment variables** | | | | | | | |
| Gender male | % (n) | 55.3 (21) | 57.6 (34) | 1.01 | 0.48 | 2.50 | 0.819 |
| Years in school | M (SD) | 11.0 (1.5) | 11.3 (1.4) | 1.17 | 0.89 | 1.55 | 0.277 |
| Premorbid GAF | M (SD) | 76.2 (8.8) | 73.5 (11.5) | 0.98 | 0.94 | 1.02 | 0.228 |
| Past history of suicide attempt (yes) | % (n) | 7.9 (3) | 3.4 (2) | 0.42 | 0.07 | 2.62 | 0.351 |
| Forensic history (yes) | % (n) | 16.2 (6) | 22.0 (13) | 1.46 | 0.50 | 4.25 | 0.488 |
| Past history of sexual trauma | % (n) | 10.5 (4) | 22.0 (13) | 2.40 | 0.72 | 8.02 | 0.154 |
| Past history of physical trauma | % (n) | 10.5 (4) | 18.6 (11) | 1.95 | 0.57 | 6.64 | 0.286 |
| **Diagnostic variables** | | | | | | | |
| Past history | | | | | | | |
| – Substance use disorder (yes) | % (n) | 65.8 (25) | 71.2 (42) | 1.29 | 0.54 | 3.08 | 0.57 |
| Current history | | | | | | | |
| – Substance use disorder (yes) | % (n) | 60.5 (23) | 57.6 (34) | 0.89 | 0.39 | 2.04 | 0.777 |
| – Cannabis (yes) | % (n) | 55.3 (21) | 39.0 (23) | 0.52 | 0.23 | 1.18 | 0.118 |
| – Polysubstance (yes) | % (n) | 7.9 (3) | 13.6 (8) | 1.83 | 0.45 | 7.38 | 0.396 |
| **Baseline variables** | | | | | | | |
| Severity of symptoms at entry | | | | | | | |
| – CGI-S severity score | M (SD) | 5.9 (0.8) | 5.6 (0.8) | 0.67 | 0.39 | 1.15 | 0.150 |
| – CGI-BP depression | M (SD) | 1.3 (0.9) | 1.2 (0.9) | 0.92 | 0.58 | 1.46 | 0.719 |
| – CGI-BP mania | M (SD) | 5.2 (1.3) | 5.0 (1.3) | 0.89 | 0.64 | 1.23 | 0.482 |
| Functional level at entry | | | | | | | |
| – GAF | M (SD) | 29.0 (10.0) | 32.0 (10.1) | 1.03 | 0.99 | 1.08 | 0.155 |
| – Studying or working (yes) | % (n) | 63.2 (24) | 72.9 (43) | 1.57 | 0.65 | 3.76 | 0.313 |
| Insight at entry (no) | % (n) | 71.1 (27) | 75.9 (44) | 1.28 | 0.51 | 3.32 | 0.600 |

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**Table 2:** Comparison of treatment and outcome characteristics between FEPM patients with onset before or after age 21.

| Variable | | Age of onset of mania | | OR | 95% CI of OR | | p value |
|---|---|---|---|---|---|---|---|
| | | <21 years (n = 38) | 21 years and older (n = 59) | | LCI | UCI | |
| **Treatment and outcome variables** | | | | | | | |
| Length of time in service (weeks) | M (SD) | 59.1 (35.1) | 64.8 (29.2) | 1.01 | 0.99 | 1.02 | 0.380 |
| Admitted to hospital (yes)[a] | % (n) | 89.5 (34) | 86.4 (51) | 0.79 | 0.22 | 2.87 | 0.723 |
| Number of admissions[a] | M (SD) | 1.3 (0.8) | 1.3 (1.1) | 0.94 | 0.61 | 1.45 | 0.795 |
| Non-compliance with treatment (yes)[a] | % (n) | 57.1 (20) | 56.4 (31) | 0.94 | 0.40 | 2.23 | 0.888 |
| Substance use disorder (SUD)[a, b] | | | | | | | |
| – No SUD | % (n) | 42.1 (16) | 35.6 (21) | | | | |
| – Remitted SUD (decreased or stopped) | % (n) | 47.4 (18) | 44.1 (26) | 0.76 | 0.42 | 1.40 | 0.384 |
| – Persistent SUD (increased or no change) | % (n) | 10.5 (4) | 20.3 (12) | 1.93 | 0.82 | 4.53 | 0.131 |
| Suicide attempt in treatment (yes)[a] | % (n) | 7.9 (3) | 6.8 (4) | 0.72 | 0.15 | 3.55 | 0.685 |
| Insight at discharge (no)[a,c] | % (n) | 2.6 (1) | 6.8 (4) | 3.22 | 0.32 | 31.98 | 0.319 |
| Severity of symptoms at discharge | | | | | | | |
| – CGI-S severity score[a,d] | M (SD) | 2.0 (1.1) | 2.3 (1.2) | 1.52 | 1.00 | 2.32 | 0.051 |
| – CGI-BP mania[a,e] | M (SD) | 1.3 (0.9) | 1.5 (1.0) | 1.54 | 0.87 | 2.72 | 0.141 |
| – CGI-BP depression[a,f] | M (SD) | 1.4 (0.9) | 1.5 (1.0) | 1.07 | 0.68 | 1.68 | 0.786 |
| Functional level at discharge | | | | | | | |
| – GAF[a,g] | M (SD) | 70.7 (14.6) | 70.0 (13.6) | 0.98 | 0.95 | 1.02 | 0.269 |

[a] Covariate was time in service; [b] based on multinomial logistic regression with "no substance use" as the reference category for the dependent variable; [c] covariate was also insight at service entry; [d] covariate was also CGI-S at service entry, unadjusted means and standard deviations are reported; [e] covariate was also CGI-BP mania at service entry, unadjusted means and standard deviations are reported; [f] covariate was also CGI-BP depression at entry, unadjusted means and standard deviations are reported; [g] covariate was also GAF score at entry, unadjusted means and standard deviations are reported

chose age 21 to distinguish patients with early onset from the others within our sample of patients aged 15 to 29.

### Data analysis

A series of logistic regression analyses were conducted with age at onset (<21 years vs ≥21 years) as the dependent variable, and the individual premorbid and service entry variables as predictors. From these analyses, odds ratios (ORs) and the 95% confidence intervals (CIs) of the ORs were derived. The Wald statistic (z) was used to determine significance of predictors. For the treatment and discharge variables, adjusted ORs and 95% CI of the adjusted ORs were reported, controlling for entry characteristics and time in service. Multivariate logistic regression with forward stepwise variable selection (based on the likelihood ratio) was used to determine which factors best differentiated subgroups according to age at onset of FEPM. Variables included in the equation were those that were different by age at onset in the univariate analyses at the p <0.100 level.

## Results

Precise and reliable data regarding age at the time of onset of the first manic episode was available in 97 of the 118 patients with FEPM: we hence conducted the data analysis within this restricted subgroup of patients. This subsample of 97 was composed of a majority of males (56.7%, n = 55), who had studied on average for 11.2 years (standard deviation [SD] = 1.5) and had an average premorbid GAF of 74.6 (SD = 10.6). A history of forensic issues was present in 19.8% (n = 19) of patients, and 5.2% (n = 5) had a history of suicide attempt, 17.5% (n = 17) a past exposure to sexual abuse and 15.5% (n = 15) a past exposure to physical abuse. Assessment revealed that 69.1% (n = 67) had a past history of substance abuse and that 58.8% (n = 57) were still actively abusing substances at baseline, 45.4% (n = 44) reporting cannabis abuse and 11.3% (n = 11) reporting polysubstance abuse.

At baseline, patients displayed a high intensity of symptoms with an average CGI of 5.7 (SD = 0.8), an average mania score of 5.0 (SD = 1.3) on the CGI-BP, and an average GAF score of 30.8 (SD =10.1). As expected, 74.0% (n = 71) had no insight when entering treatment. During the 18-month treatment period, 87.6% (n = 85) of patients needed admission to hospital at least once and 7.2% (n = 7) attempted suicide. At the end of treatment, CGI severity score had dropped to 2.2 (SD = 1.2), CGI-BP mania score to 1.4 (SD = 0.9), average GAF score had risen to 70.2 (SD = 13.9), and only 5.2% (n = 5) of patients had not developed insight. Rate of substance abuse had evolved, 45.4% (n = 44) of patients having either decreased or stopped abusing substances.

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We report the results of the comparison between FEPM patients with onset before and after age 21 in table 1 for pre-morbid and baseline variables and in table 2 for treatment and outcome variables. Based on our analysis, we did not identify any statistically significant difference between both groups.

## Discussion

The analysis of the characteristics of this FEPM sample revealed various interesting findings. First, these patients had relatively good premorbid functioning, with an average of 74.5 on the evaluated premorbid GAF and an average of 11.2 years of study. Second, despite this relatively good premorbid functional level, close to one in five had had issues with justice. In addition, 17.5% had suffered sexual abuse and 15.5% physical abuse. Various publications have mentioned this high rate of exposure to trauma in early psychosis patients [32–34], as well as in patients with a first episode of mania [35]. Clinicians treating such patients must therefore explore this issue adequately in order to adapt treatment and to monitor suicide risk. Third, our data analysis revealed that two patients in three had a past history of substance use disorder and that more than one in two were still actively using substances when entering treatment. Considering the impact of substance abuse on outcome in first episode psychosis [36], clinicians must address this issue, especially because of the non-negligible potential for decrease or interruption of substance use following a FEPM, as suggested by our observation that 44% of patients had decreased or stopped abuse of substances by the end of the treatment phase. Fourthly, despite very intense symptoms and low functioning when entering the programme, as revealed by the CGI, CGI-BP and GAF scores, this group of patients displayed a rather favourable outcome. Indeed, they displayed a good level of recovery marked by an average GAF score of 70 at the end of the treatment phase, and only a small number of patients failed to develop insight over time. Globally, these elements suggest that well-conducted treatment in this specialised setting that pioneered early intervention and where clinicians are well-prepared to face the specific issues at stake when illness manifests during youth, allow, on average, a favourable outcome after a FEPM. The good quality of this treatment may explain why we did not find any difference in outcome when comparing subgroups defined by age at onset of FEPM. Indeed, our analysis revealed that, in our sample, patients did not differ in any of the variables we compared.

Various limitations must however be taken into account when considering these results. First, as EPPIC provides treatment exclusively to patients aged between 15 and 29, this sample does not include very early onset patients who might have a poorer outcome than those where the onset occurs later. Secondly, our sample also excludes patients older than 29 at baseline, which may also contribute to the limitation of differences as they may become more accentuated when including older patients. Thirdly, the data stem from a file audit, which may limit to some degree their validity data. However, we did everything to validate rating and to complete missing data with the clinicians who had been in charge of the patients when there was a doubt. In addition, we were able to include all patients treated at EPPIC during the treatment period and could therefore work on the data of a highly representative sample of patients. Fourth, as EPPIC offers treatment exclusively for first episode psychosis, our sample includes only first episode mania with psychotic features. Because psychotic features are a predictor of poorer outcome [9–12], the results may differ if patients with non-psychotic first episode mania were also included. Finally, the sample size is limited, which may contribute to the fact that some differences may not reach statistical significance.

Despite these limitations, this study reveals that FEPM patients, although they present with very severe psychopathology and functional impairment, have a good potential for symptomatic and functional recovery if treated at a specialised centre where clinicians have the capacity to address the specific issues such patients are dealing with. On the other hand, although the results of other studies suggest that age at onset of bipolar disorder correlates with outcome, this was not the case in the particular setting of our study.

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**References**
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